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## Formation of C(sp<sup>2</sup>)–C(sp<sup>3</sup>) Bonds Instead of Amide C–N Bonds from Carboxylic Acid and Amine Substrate Pools by Decarbonylative Cross-Electrophile Coupling

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### Abstract

Carbon–heteroatom bonds, most often amide and ester bonds, are the standard method to link together two complex fragments because carboxylic acids, amines, and alcohols are ubiquitous and the reactions are reliable. However, C–N and C–O linkages are often a metabolic liability because they are prone to hydrolysis. While C(sp<sup>2</sup>)–C(sp<sup>3</sup>) linkages are preferable in many cases, methods to make them require different starting materials or are less functional-group compatible. We show here a new, decarbonylative reaction that forms C(sp<sup>2</sup>)–C(sp<sup>3</sup>) bonds from the reaction of activated carboxylic acids (via 2-pyridyl esters) with activated alkyl groups derived from amines (via *N*-alkyl pyridinium salts) and alcohols (via alkyl halides). Key to this process is a remarkably fast, reversible oxidative addition/decarbonylation sequence enabled by pyridone and bipyridine ligands that, under reaction conditions that purge CO<sub>(g)</sub>, lead to a selective reaction. The conditions are mild enough to allow coupling of more complex fragments, such as those used in drug development, and this is demonstrated in the coupling of a typical Proteolysis Targeting Chimera (PROTAC) anchor with common linkers via C–C linkages.

### Graphical Abstract

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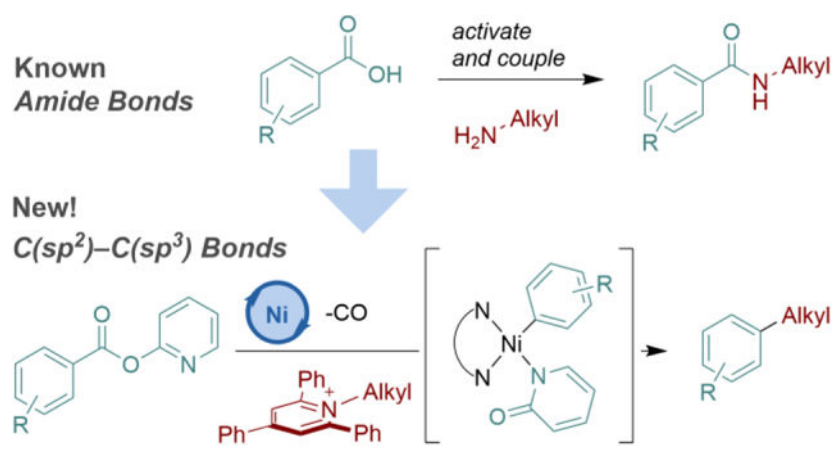
The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Supporting Information

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Additional tables of optimization data, full experimental procedures, characterization data, copies of NMR spectra. (PDF)  
X-ray Crystallography Data (CIF)



Chemical biology and drug discovery rely upon a small suite of reactions capable of joining together two functionalized molecules. Of the strategies available, carbon–heteroatom bond formation, especially amide bond formation, is by far the most common (Scheme 1A).<sup>1</sup> Reactions to form amides (and esters) are favored because of the ubiquity of carboxylic acids, alcohols, and amines in bioactive molecules and the tolerance of these reactions for complex functionality.<sup>2–345</sup> However, the instability of esters and amides to hydrolysis and metabolism can be limiting, as can the propensity of the amide to unpredictably alter binding properties (Scheme 1B). In a systematic survey of linkages used in PROTACs, it was found that C–N, C–O, and  $\text{C}(\text{sp}^2)\text{-C}(\text{sp})$  bonds had stability issues.<sup>6</sup> These challenges have motivated the exploration of  $\text{C}(\text{sp}^2)\text{-C}(\text{sp}^3)$  linkages in PROTACs, despite extra steps often needed in the synthesis of these structures.<sup>7</sup>

A method to access  $\text{C}(\text{sp}^2)\text{-C}(\text{sp}^3)$  bonds directly from starting materials used for amide bond formation is highly desirable, but suitable reactions have not yet been reported. Coupling aryl carboxylic acids and their derivatives with aryl halides<sup>8</sup> or aryl boron reagents<sup>9</sup> can be high yielding and general, but translation to  $\text{C}(\text{sp}^2)\text{-C}(\text{sp}^3)$  bond formation has been challenging. Couplings with alkylzinc,<sup>10</sup> organosilicon,<sup>11</sup> and alkyl organoboron reagents<sup>9d,12</sup> have been reported, but these reagents have limited stability, low commercial availability, and their syntheses have limited functional group compatibility. The need for better approaches has partially driven exploration of methods to convert aryl carboxylic acids to aryl halides<sup>13</sup> or arylboron reagents.<sup>14</sup>

A potential solution is the coupling of a carboxylic acid ester with an amine-derived (via *N*-alkyl pyridinium salts<sup>15</sup>) or alcohol-derived (via alkyl halide) alkyl radical source under nickel-catalyzed conditions (Scheme 1C).<sup>16</sup> Cross-electrophile coupling reactions of aryl halides with various alkyl radicals to form  $\text{C}(\text{sp}^2)\text{-C}(\text{sp}^3)$  bonds have the broad generality needed,<sup>17</sup> but the use of aryl carboxylic acid esters under these conditions has been demonstrated to make ketone products, not alkylated arenes (Scheme 2A).<sup>18</sup> The mechanistic challenge to be solved is how to convert an aroyl electrophile to an aryl electrophile; if this could be overcome, coupling to a wide array of alkyl electrophiles should be possible (Scheme 2).<sup>19–2021</sup>

We conducted mechanistic studies on the feasibility of key steps in the proposed catalytic cycle to better understand how to favor cross-product formation over ketone formation (Scheme 2). While decarbonylation of acylnickel(II) intermediates is a known side reaction in ketone synthesis, avoiding ketone formation entirely can be challenging, because oxidative addition and radical addition are usually faster than decarbonylation (Scheme 2A).<sup>14f,18</sup> First, we studied the rate of decarbonylation by reacting equimolar amounts of (dtbbpy)Ni<sup>0</sup>(COD) (**1**) and 4-trifluoromethylbenzoic acid 2-pyridyl ester (**2**) in THF at rt (Scheme 2B). Within 15 min, we obtained a 56% isolated yield of (dtbbpy)Ni(Ar)(OPy) (**3**), formed as the major product, along with (dtbbpy)Ni(CO)<sub>2</sub> (**4**) (33% NMR yield). The identity of the decarbonylated species (**3**) was confirmed by single-crystal X-ray diffraction, revealing the pyridone ligand to be *N*-bound. The bond angles and lengths were otherwise not remarkable.<sup>22</sup> In contrast, the reaction of 4-methylbenzoyl bromide with **1** resulted in an 89% NMR yield of the corresponding acylnickel(II) species (similar to **5**, Br instead of 2-pyridone).<sup>14f,23,24</sup>

Second, we tested the reversibility of the oxidative addition and decarbonylation steps, by exposing **3** (100 mM, 1.0 equiv) to <sup>13</sup>C-labelled CO(<sub>g</sub>) (20 mM, 0.2 equiv) and monitoring the reaction by NMR (Scheme 2C). We observed formation of a new <sup>13</sup>C-labelled acylnickel(II) complex (**5**). Upon exposure to additional <sup>13</sup>CO(<sub>g</sub>), **5** was further transformed into nickel(0) complex **4** (6% NMR yield with 0.2 equiv CO, 15% NMR yield with 1.0 equiv CO, along with 51% of Ni(<sup>13</sup>CO)<sub>4</sub>,<sup>25,26</sup> see SI for details) and <sup>13</sup>C-labelled **2** (7% NMR yield with 0.2 equiv CO, 24% NMR yield with 1.0 equiv CO, see SI for details). This demonstrates that the decarbonylation and oxidative addition steps are fast and reversible at rt.<sup>27</sup> This finding implies that 1) CO must be efficiently removed from the system to avoid ketone formation and 2) nickel(0) binds CO with high affinity.<sup>28</sup> We surmised that heating the reaction and maximizing reaction headspace may be required to liberate bound CO from the nickel catalyst and to dilute the concentration of CO in the reaction flask, respectively.<sup>29</sup>

Third, to study the reactivity of the new pyridone-ligated acylnickel(II) species in cross-electrophile coupling, we combined **3** with protected alkyl iodide **6** (1 equiv) under reducing conditions at rt, 60 °C, and 110 °C (Scheme 2D). We observed good yields of cross-product at all three temperatures, with a 93% yield in 20 min at 110 °C.

These results show that the pyridone ligand accelerates decarbonylation of an acylnickel(II) complex compared to a bromide, and the pyridone ligand may stabilize the resultant acylnickel complex.<sup>30</sup> These findings are in agreement with previous reports, where more basic ligands, such as fluoride and imide anions, are less likely to generate a cationic nickel complex, instead favoring CO release from a putative nickel(II) complex.<sup>14f,24c</sup>

Optimization of the nickel-catalyzed coupling of 2-pyridyl 1-naphthoate (**12**) with *N*-(3-phenylpropyl) 2,4,6-triphenylpyridinium tetrafluoroborate (**13**) illustrated three key points (Table 1). First, 2-pyridyl esters provided the highest yield of cross-product and were better at avoiding ketone than acid fluorides<sup>9</sup> and more reactive than phenyl esters<sup>10,12</sup> (entries 1–3). 2-pyridyl esters are also more stable and more functional-group compatible than acid fluorides.<sup>31</sup> Second, ligand identity had a profound effect on the reaction outcome:

bipyridines provided primarily the decarbonylation product and terpyridines provided primarily ketone (entries 1, 4–5, For additional ligand data, see Supporting Information Figure S3). Third, lower temperatures resulted in larger amounts of ketone side-product (entry 6) unless an N<sub>2</sub> sweep was used (entry 7).<sup>32</sup> The yield was improved by using 1.5 equiv of the alkyl pyridinium salt (entry 9). Besides ketone, the majority of the aryl mass-balance was Ar–H.

The substrate scope of the resulting reaction is broad (Scheme 3). Electron-rich (**16**, **20**, **28–30**, **32**), electron-poor (**15**, **17**, **19**, **21–26**), and sterically hindered (**16**, **20**, **27**) aryl and heteroaryl carboxylic acid esters worked similarly well. The coupling of aryl carboxylic acid pyridyl esters with electrophiles derived from amines (*N*-alkyl pyridinium salts) and from alcohols (alkyl bromides and iodides) work comparably for primary alkyl groups, but alkyl iodides give the best results with secondary alkyl groups (**25**, **29–30**, **32**). Functional-group compatibility is high, despite the higher temperature, and esters, acetals, nitriles, tertiary amines, -Cbz, -Boc, and -BPin groups were all tolerated. A few functional groups were not tolerated, such as isoxazole and a terminal epoxide, due to ring opening (see Figure S9). Very hindered carboxylic acids, such as 2,4,6-trimethylbenzoic acid, provided only ketone product. The abundance of amines, carboxylic acids, and alcohols allowed for easy access to products derived from complex starting materials, such as advanced pieces of mosapride (**17**), an atorvastatin side chain (**21**), and substrates derived from glucose (**30**), uridine (**31**), hydroxyproline (**29**, **32**), telmisartan (**27**) and febuxostat (**28–30**). Major side products observed in cases with lower yields were aryl dimer and ketone. For these preparative scale reactions (0.5 mmol), we found that sweeping the headspace with N<sub>2(g)</sub> and using a condenser to avoid solvent loss reduced the amount of ketone formed.<sup>32</sup>

PROTACs are a rapidly growing area of interest in biomedical research and drug development with at least 15 PROTACs entering clinical trials recently.<sup>33,34</sup> These heterobifunctional molecules are comprised of an E3 ligase anchor that recruits the human proteasome, a warhead that targets a protein of interest, and a linker of appropriate conformational flexibility that joins these two components together (Scheme 3B, left). Due to ease of synthesis, the linker junction points are most commonly carbon–heteroatom bonds,<sup>6a</sup> which can present issues with hydrolytic and enzymatic stability, such as in amide bonds.<sup>6b</sup> The introduction of C(sp<sup>2</sup>)–C(sp<sup>3</sup>) bond linkages in PROTACs has been shown to improve their stability and protein degradation ability<sup>35</sup> but is less explored due to limited synthetic approaches to access this motif.<sup>34</sup> We sought to evaluate the compatibility of this new decarbonylative carbon–carbon bond forming reaction with typical PROTAC fragments (Scheme 3B).

The most common anchor in PROTACs is immunomodulatory imide drugs (iMiDs) that recruit the cereblon (CRBN) E3 ligase, of which thalidomide is the most representative example.<sup>36</sup> Notably, approximately 1% of published CRBN anchors contain a C(sp<sup>2</sup>)–C(sp<sup>3</sup>) bound linker,<sup>37</sup> which are generally prepared through Songashira coupling, followed by reduction of the alkyne.<sup>34</sup> In a more direct approach, Novartis applied cross-electrophile coupling to lenalidomide-derived aryl bromides with alkyl tosylates,<sup>7</sup> but the analogous thalidomide scaffolds were not assessed.

We prepared the 4- and 5- carboxylic acid substituted thalidomide<sup>6a,38</sup> 2-pyridyl esters and coupled them to common linkers to form carbon–carbon linked PROTAC anchor fragments (Scheme 3C). We recognized the acidic imide N–H could present issues with formation of Ar–H from protonation of the intermediate arylnickel(II). Under modified reaction conditions, thalidomide carboxylic acid derivatives were coupled to linker fragments bearing a protected amine (**33**, **37**), carboxylic acid (**34**, **38**), alcohol (**35**, **39**), and piperidinyl (**36**, **40**) functionality, which provide a handle to further link a variety of relevant warheads. These results enable a complementary, single-step approach in PROTAC development to access more stable analogues of common amine/amide-based linkages. This decarbonylative strategy is rapid and could be applied to library synthesis of PROTACs.<sup>39</sup> We anticipate that this new chemistry will expand the types of synthetically accessible linkages in PROTAC development, potentially leading to greater clinical success.

In conclusion, we have reported how controlling a remarkably facile decarbonylation step has enabled the development of a reaction that might otherwise seem impossible: the coupling of activated carboxylic acids with activated amines that “edits out” the amide bond. We anticipate further advancements in activation strategies, catalysts, and coupling partners will allow a wide variety of new reactions to be developed based upon this work. As this system represents a facile method to produce an arylnickel(II) intermediate from an uncommon aryl source, we anticipate that reactions that couple 2-pyridyl aryl carboxylic acid esters with additional radical coupling partners (e.g., redox active esters, sulfones), alkyl organometallic reagents, and alkenes are now all possible. Further work in this area is ongoing in our group and will be reported in due course.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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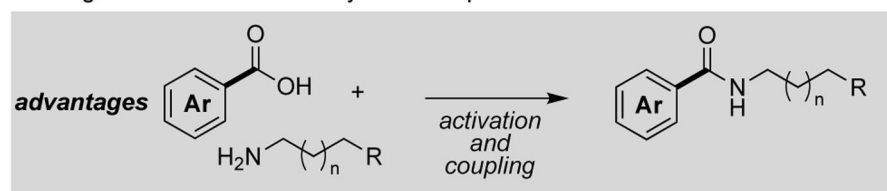


Nickel-Alkyl Bonds of Monoalkyl- and Dialkylnickel(II) Complexes, NiR(Y)L<sub>2</sub> and NiR<sub>2</sub>L<sub>2</sub>. Preparation of Ni(COR)(Y)L<sub>2</sub> from NiR(Y)L<sub>2</sub> and Selective Formation of Ketone, Diketone, and Aldehyde from NiR<sub>2</sub>L<sub>2</sub>. *Bull. Chem. Soc. Jpn* 1981, 54, 2161–2168.

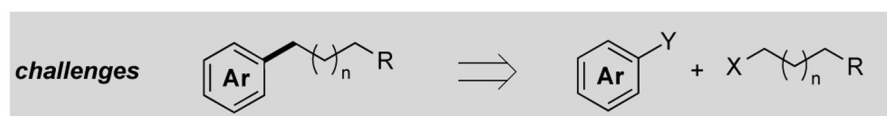
- (27). This data also explains why carbonylative cross-electrophile coupling chemistry with nickel is so challenging: CO can displace ligands and form less reactive (L)Ni<sup>0</sup>(CO)<sub>2</sub> and even Ni<sup>0</sup>(CO)<sub>4</sub> with even 1 equiv of CO. See references 14b and 23. There are limited examples of carbonylative cross-coupling with nickel catalysis, see: Wang, Q.; Chen, C., Nickel-Catalyzed Carbonylative Negishi Cross-Coupling Reactions. *Tetrahedron Lett.* 2008, 49, 2916–2921.
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- (31). We had previously attempted to synthesize the aroyl fluoride derivatives of compounds S8 and S9 (see SI section 4.3) and found that these aroyl fluorides decomposed on silica. This is in agreement with other reports on limited stability of some aroyl fluorides, see: Munoz SB; Dang H; Ispizua-Rodriguez X; Mathew T; Prakash GKS Direct Access to Acyl Fluorides from Carboxylic Acids Using a Phosphine/Fluoride Deoxyfluorination Reagent System. *Org. Lett.* 2019, 21, 1659–1663. [PubMed: 30840474]
- (32). A control reaction (see SI Section 4.1) revealed that a slightly lower yield could be achieved at 80 °C by sweeping the reaction headspace with N<sub>2</sub>.
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**(A) Dominance of Amide Bonds:** Due to Abundance of Starting Materials and Reliability with Complex Substrates

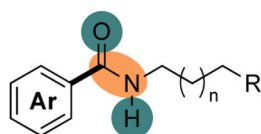


- + alkyl-NH<sub>2</sub> and Ar-CO<sub>2</sub>H among most abundant starting materials
- + ~300 billion potential combinations
- + works with complex substrates, fragment coupling reactions



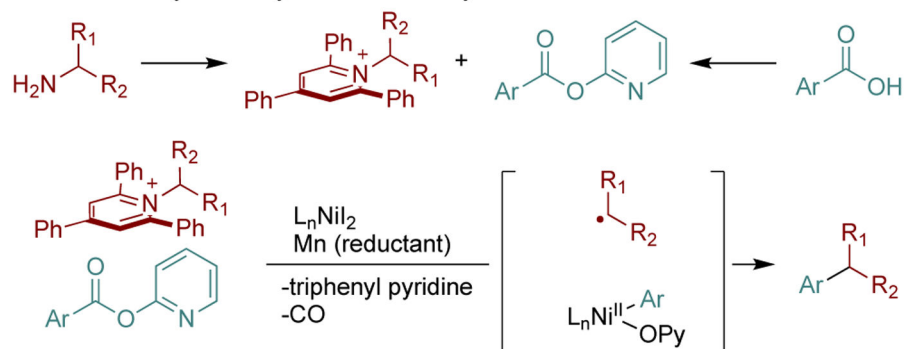
- C-C analogues require re-synthesis, different starting material pools

**(B) Amide Bond Linkages in Drug Scaffolds:** Complications Arise From Instability and Unpredictable Binding Modes



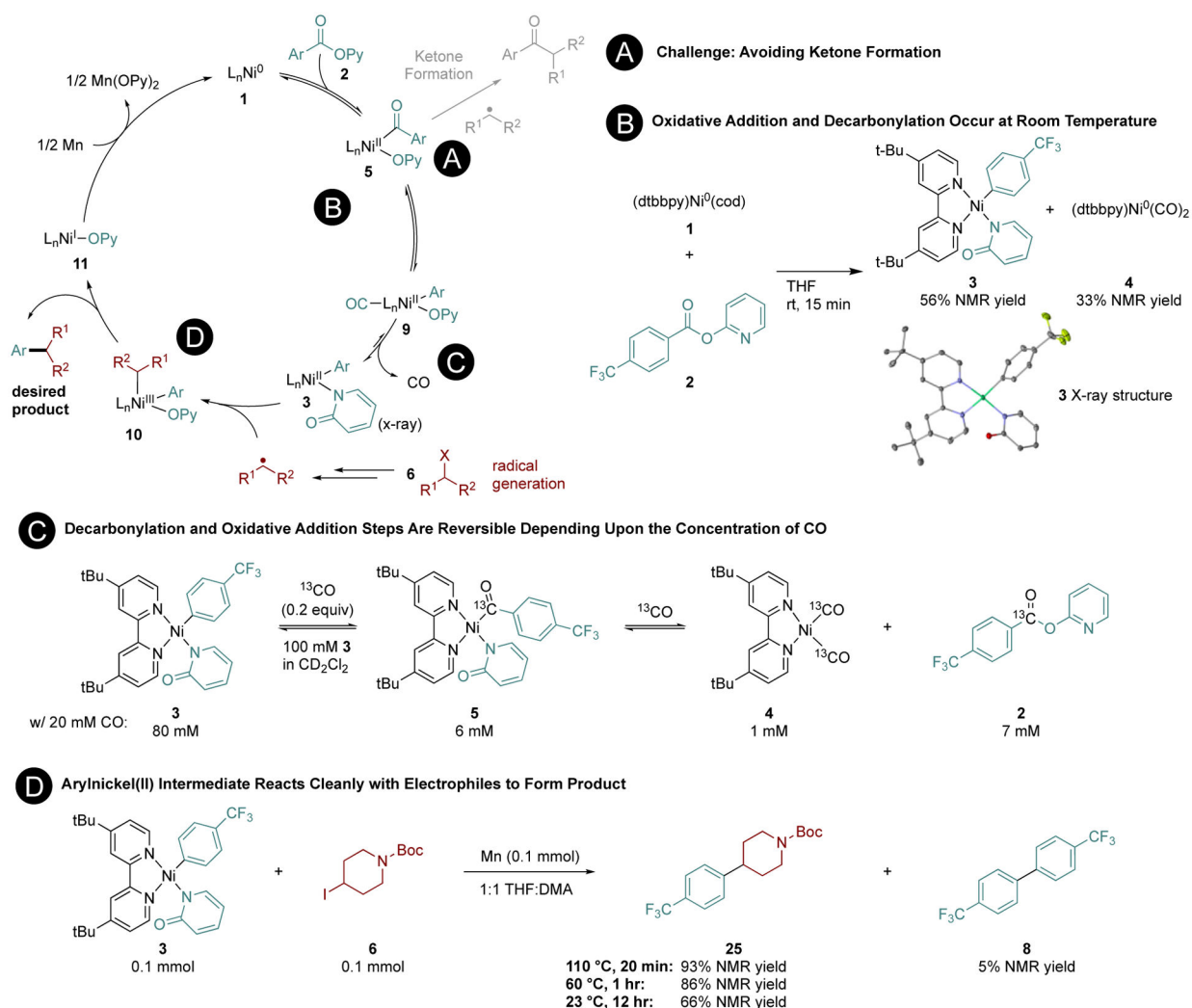
- added H-bond donor and acceptor can impact binding mode
- hydrolytic and enzymatic instability may decrease drug efficacy

**(C) C-C Bonds Instead of Amide Bonds:** Synthesis of Aryl-Alkyl Bonds From Aryl Carboxylic Acids and Alkyl Amines



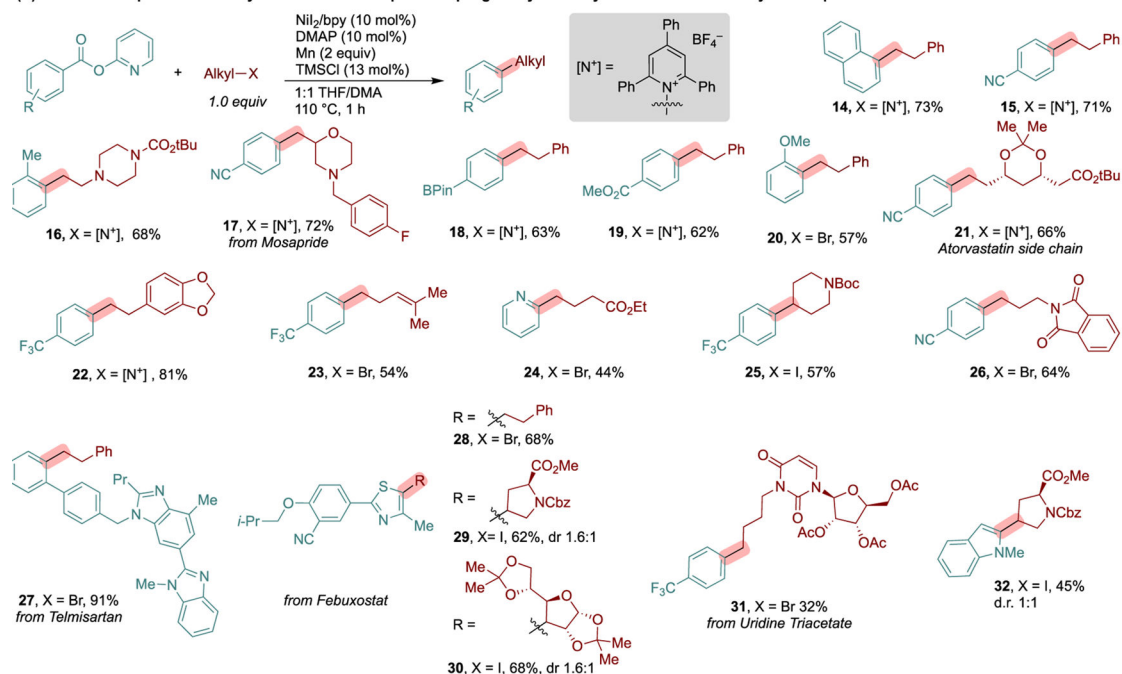
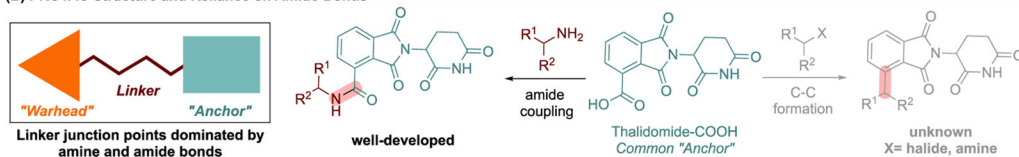
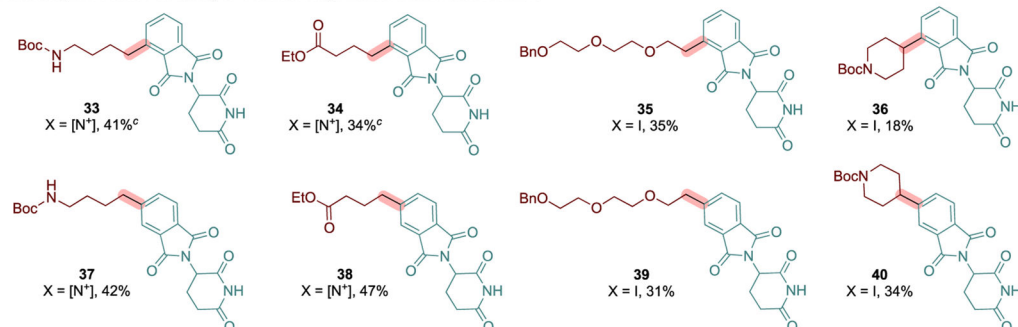
**Scheme 1.**

A New Approach to the Utilization of Carboxylic Acid and Amine Substrate Pools in Synthesis.



**Scheme 2.** Mechanistic Proposal for Decarbonylative Coupling of 2-Pyridyl Aryl Carboxylic Acid Esters with Alkyl Radical Donors.<sup>a</sup>

<sup>a</sup>For experimental details, see Supporting Information page S19.

**(A) Substrate Scope for Decarbonylative Cross-Electrophile Coupling of Aryl Carboxylic Acid Esters with Alkyl Electrophiles<sup>a</sup>****(B) PROTAC Structure and Reliance on Amide Bonds****(C) Decarbonylative Cross-Coupling to Generate Alkyl-Linked Thalidomide Anchors<sup>b</sup>****Scheme 3.**

Substrate Scope for the Cross-Coupling of 2-Pyridyl Aryl Carboxylic Acid Esters with Alkyl Radical Donors.

<sup>a</sup>Reaction conditions: X = Br, I: Ar-CO<sub>2</sub>Py (0.5 mmol), Alk-X (0.5 mmol), NiI<sub>2</sub> (50 μmol), bpy (50 μmol), DMAP (50 μmol), Mn (1 mmol), TMSCl (62.5 μmol), 1:1 THF/DMA (3.0 mL), 110 °C, 1 h. X = [N<sup>+</sup>]: Alk-[N<sup>+</sup>] (0.6 mmol, 1.2 equiv) was used in place of alkyl-Br/I; DMAP and TMSCl were omitted. <sup>b</sup>Reaction conditions: thalidomide-CO<sub>2</sub>Py (125 μmol), Alk-I or Alk-[N<sup>+</sup>] (1.5 equiv), NiI<sub>2</sub> (25 μmol), L2 (25 μmol), Mn (0.25 mmol), 1:1 DMA/THF (1.0 mL), 110 °C, 2 h. Yields are isolated unless otherwise noted. <sup>c</sup>NMR yield

with  $\text{CH}_2\text{Br}_2$  internal standard. Samples of analytically pure cross-product were obtained by reverse phase preparative HPLC.

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