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

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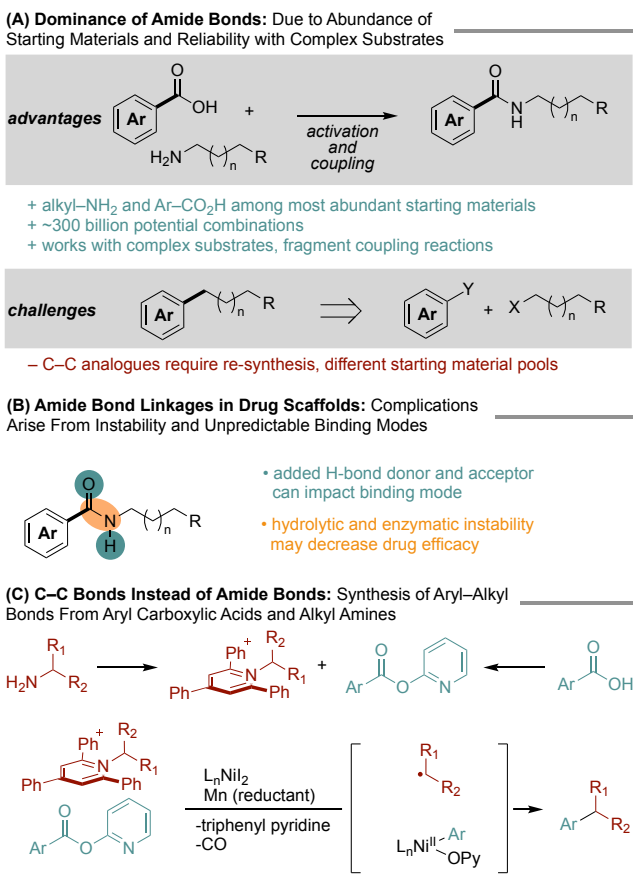
ABSTRACT: Carbon–heteroatom bonds, most often amide and ester bonds, are the standard method to link together two complex fragments because carboxylic acids, amines, and alcohols are ubiquitous and the reactions are reliable. However, C–N and C–O linkages are often a metabolic liability because they are prone to hydrolysis. While C(sp^2)–C(sp^3) 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^2)–C(sp^3) 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 $CO_{(g)}$, 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.

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).[1] 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.[2-5] 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 C(sp^2)–C(sp) bonds had stability issues.[6] These challenges have motivated the exploration of C(sp^2)–C(sp^3) linkages in PROTACs, despite extra steps often needed in the synthesis of these structures.[7]

A method to access C(sp^2)–C(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[8] or aryl boron reagents[9] can be high yielding and general, but translation to C(sp^2)–C(sp^3) bond formation has been challenging. Couplings with alkylzinc,[10] organosilicon,[11] and alkyl organoboron reagents[9d,12] 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[13] or arylboron reagents.[14]

A potential solution is the coupling of a carboxylic acid ester with an amine-derived (via *N*-alkyl pyridinium salts[15]) or alcohol-derived (via alkyl halide) alkyl radical source under nickel-catalyzed conditions (Scheme 1C).[16] Cross-electrophile coupling reactions of aryl halides with various alkyl radicals to form C(sp^2)–C(sp^3) bonds have the broad generality needed,[17] but the use of aryl carboxylic acid esters under these conditions has been demonstrated to make ketone products, not alkylated arenes (Scheme 2A).[18] 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).[19,20,21]

Scheme 1. A New Approach to the Utilization of Carboxylic Acid and Amine Substrate Pools in Synthesis.



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

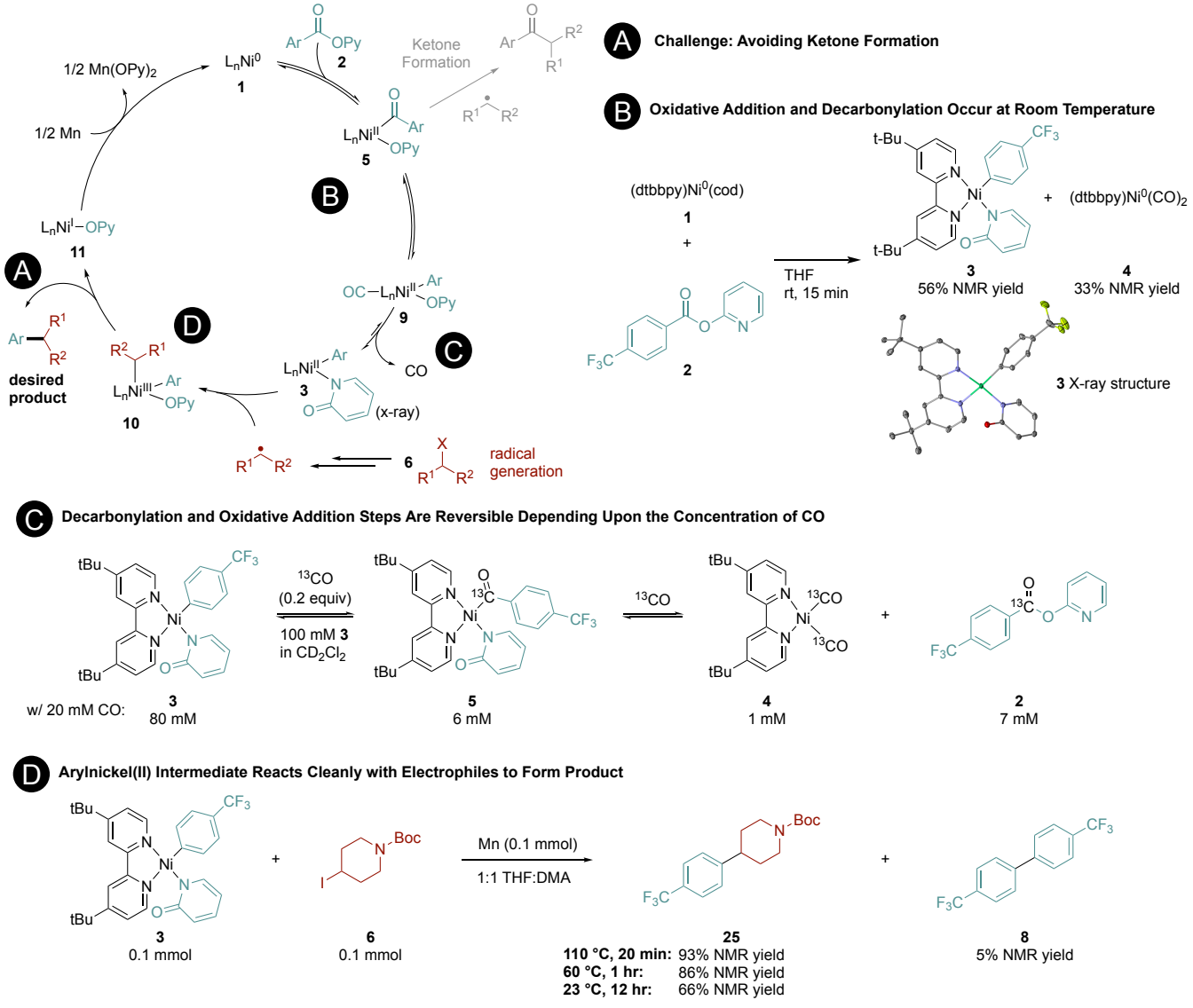
decarbonylation of aroylnickel(II) intermediates is a known side reaction in ketone synthesis, avoiding ketone formation entirely can be challenging, because oxidative addition and radical addition are usually faster than decarbonylation (Scheme 2A).[14f, 18] First, we studied the rate of decarbonylation by reacting equimolar amounts of (dtbbpy)Ni^0(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)$Ni(CO)_2$ (**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.[22] 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).[14f,23,24]

Second, we tested the reversibility of the oxidative addition and decarbonylation steps, by exposing **3** (100 mM, 1.0 equiv) to ^{13}C-labelled $CO_{(g)}$ (20 mM, 0.2 equiv) and monitoring the reaction by NMR (Scheme 2C). We observed formation of a new ^{13}C-labelled acylnickel(II) complex (**5**). Upon exposure to additional $^{13}CO_{(g)}$, **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 $Ni(^{13}CO)_4$,[25,26] see SI for details) and ^{13}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.[27] 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.[28] 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.[29]

Third, to study the reactivity of the new pyridone-ligated arylnickel(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 arylnickel complex.[30] These findings are in agreement with previous reports, where more basic ligands, such as fluoride and imide anions, are less likely

Scheme 2. Mechanistic Proposal for Decarbonylative Coupling of 2-Pyridyl Aryl Carboxylic Acid Esters with Alkyl Radical Donors.[a]

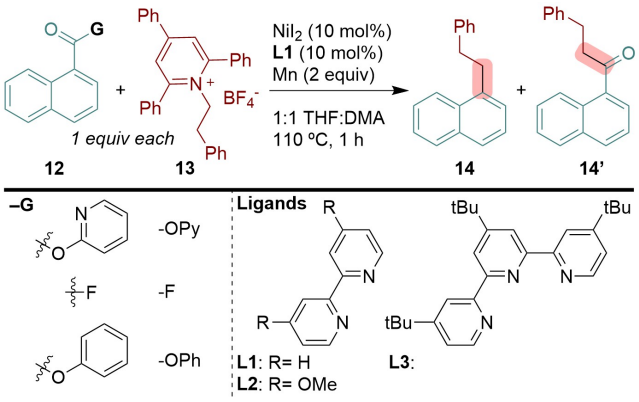


[a]For experimental details, see Supporting Information page S19.

to generate a cationic nickel complex, instead favoring CO release from a putative nickel(II) complex.[14f,24c]

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[9] and more reactive than phenyl esters[10,12] (entries 1–3). 2-pyridyl esters are also more stable and more functional-group compatible than acid fluorides.[31] 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_2 sweep was used (entry 7).[32] 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.

Table 1. Optimization of the Catalytic Reaction.[a]



Entry[b]	Change in conditions from scheme	G	**14** (%)[c]	**14'**(%)[c]
1	None	OPy	65	<2
2	Different **G** on **12**	F	56	4
3[d]	Different **G** on **12**	OPh	0	0
4	**L2** instead of **L1**	OPy	66	<2
5	**L3** instead of **L1**	OPy	<2	47
6	90 °C instead of 110 °C	OPy	56	11
7[e]	80 °C, N_2 sweep	OPy	50	4
8[f]	Zn instead of Mn	OPy	11	4
9	1.5 equiv of **13**	OPy	79	<2

[a]For further optimization and side products, see supporting information figures S3-6. [b]Aryl ester (0.125 mmol), *N*-alkyl pyridinium salt (0.125 mmol), Mn (0.25 mmol), NiI_2 (0.0125 mmol), and ligand (0.0125 mmol) were stirred in THF/DMA (1:1, 1 mL) at 110 °C for 1 h. [c]GC yield using 1,3,5 trimethoxybenzene as internal standard. [d]Quantitative recovery of aryl ester starting material after reaction. [e]Reaction on 0.5 mmol scale.[32] [f]Unreacted CO_2Py observed as majority of mass balance.

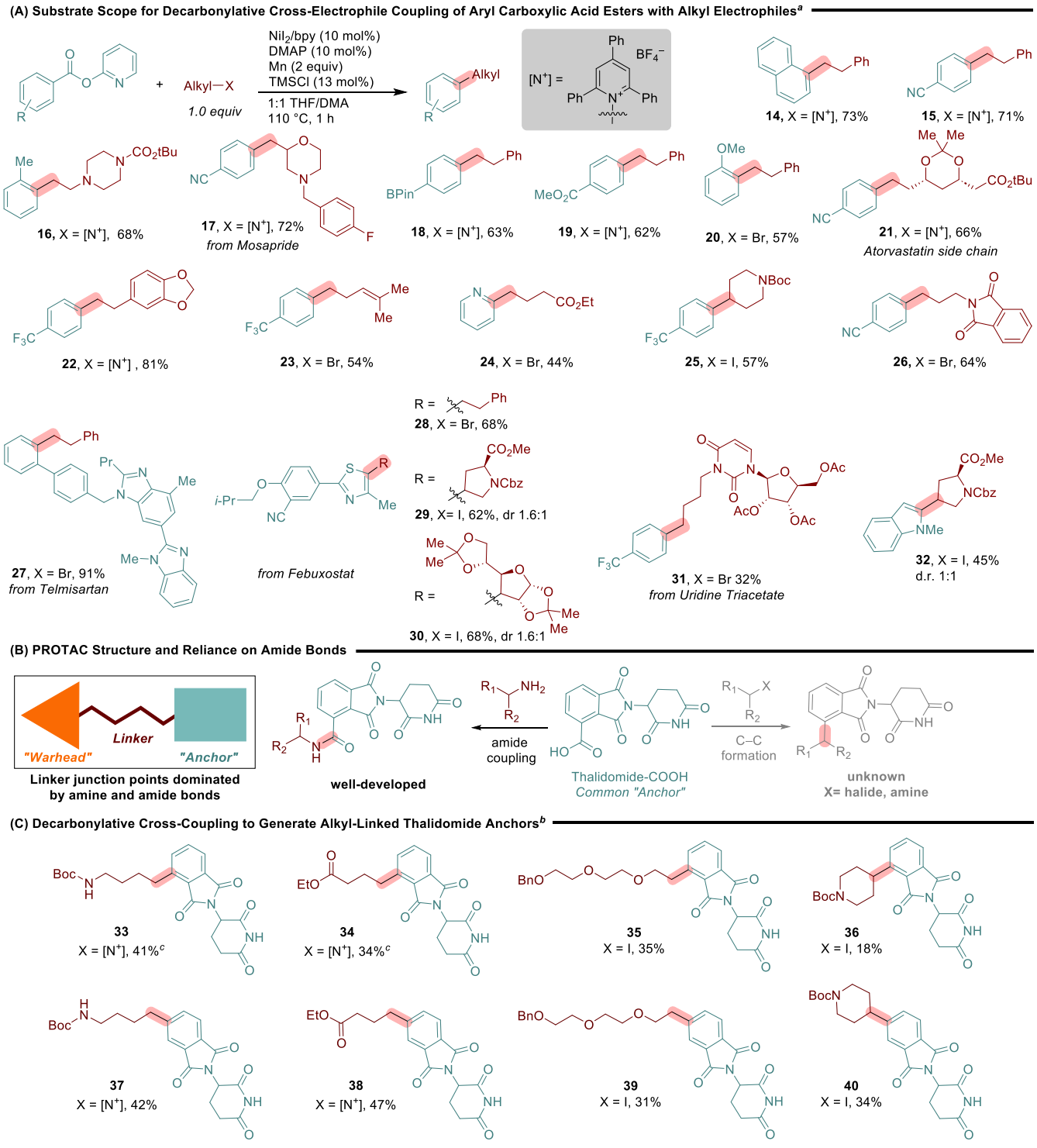
The substrate scope of the resulting reaction is broad (Scheme 3). Electron-rich (**16**, **20**, **28**-**30**, **32**), electron-poor (**15, 17, 19, 21**-**26**), and sterically hindered (**16**, **20, 27**) aryl and heteroaryl carboxylic acid esters worked similarly well. The coupling of aryl carboxylic 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 $N_{2(g)}$ and using a condenser to avoid solvent loss reduced the amount of ketone formed.[32]

PROTACs are a rapidly growing area of interest in biomedical research and drug development with at least 15 PROTACs entering clinical trials recently.[33,34] These heterobifunctional molecules are comprised of an E3 ligase anchor that recruits the human proteosome, 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,[6a] which can present issues with hydrolytic and enzymatic stability, such as in amide bonds.[6b] The introduction of $C(sp^2)$–$C(sp^3)$ bond linkages in PROTACs has been shown to improve their stability and protein degradation ability[35] but is less explored due to limited synthetic approaches to access this motif.[34] 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.[36] Notably, approximately 1% of published CRBN anchors contain a $C(sp^2)$–$C(sp^3)$ bound linker,[37] which are generally prepared through Songashira coupling, followed by reduction of the alkyne.[34] In a more direct approach, Novartis applied cross-electrophile coupling to lenalidomide-derived aryl bromides with alkyl tosylates,[7] but the analogous thalidomide scaffolds were not assessed.

We prepared the 4- and 5- carboxylic acid substituted thalidomide[6a,38] 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.[39] We anticipate that this new chemistry will expand the types of synthetically accessible linkages in PROTAC development, potentially leading to greater clinical success.

Scheme 3. Substrate Scope for the Cross-Coupling of 2-Pyridyl Aryl Carboxylic Acid Esters with Alkyl Radical Donors.



[a]Reaction conditions: X = Br, I: Ar-CO_2Py (0.5 mmol), Alk-X (0.5 mmol), NiI_2 (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+]: Alk-[N^+] (0.6 mmol, 1.2 equiv) was used in place of alkyl-Br/I; DMAP and TMSCl were omitted. [b]Reaction conditions: thalidomide-CO_2Py (125 μmol), Alk-I or Alk-[N^+] (1.5 equiv), NiI_2 (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. [c]NMR yield with CH_2Br_2 internal standard. Samples of analytically pure cross-product were obtained by reverse phase preparative HPLC.

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.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Additional tables of optimization data, full experimental procedures, characterization data, copies of NMR spectra. (PDF)

X-ray Crystallography Data (CIF)

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REFERENCES

(1) Boström, J.; Brown, D. G,; Young, R.; Keserü, G. M. Expanding the medicinal chemistry synthetic toolbox. *Nat. Rev. Drug Discov*. **2018**. *17*, 709–727.

(2) Cooper. T. W. J.; Campbell. I. B.; Macdonald. S. J. F. Factors Determining the Selection of Organic Reactions by Medicinal Chemists and the Use of These Reactions in Arrays (Small Focused Libraries). *Angew. Chem. Int. Ed*. **2010**, *49*, 8082-8091.

(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) 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

(5) Schneider. N.; Lowe. D. M.; Sayle. R. A.; Tarselli, M. A.; Landrum. G. A. Big Data from Pharmaceutical Patents: A Computational Analysis of Medicinal Chemists' Bread and Butter. *J. Med. Chem*. **2016**, *59*, 4385-4402.

(6) (a) Bricelj, A.; Steinebach, C.; Kuchta, R.; Gütschow, M.; Sosič, I. E3 Ligase Ligands in Successful PROTACs: An Overview of Syntheses and Linker Attachment Points. *Front. Chem*. **2021**, *9*, 707317. (b) Bricelj, A.; Dora Ng, Y. L.; Ferber, D.; Kuchta, R.; Müller, S.; Monschke, M.; Wagner, K. G.; Krönke, J.; Sosič, I.; Gütschow, M.; Steinebach, C. Influence of Linker Attachment Points on the Stability and Neosubstrate Degradation of Cereblon Ligands. *ACS Med. Chem. Lett*. **2021**, *12*, 1733–1738.

(7) Beckwith, R. E. J.; Bonazzi, S.; Cernijenko, A.; Fazal, A.; Tichkule, R. B.; Visser, M. S. 3-(1-Oxoisoindolin-2-yl)piperidine-2,6-dione Derivatives and Uses Thereof. US2019062309A1, February 28, 2019.

(8) (a) Gooßen, L. J.; Deng, G.; Levy, L.M. Synthesis of Biaryls via Catalytic Decarboxylative Coupling. *Science* **2006**, *313*, 662-664. (b) Tang, J.; Biafora, A.; Goossen, L. J., Catalytic Decarboxylative Cross-Coupling of Aryl Chlorides and Benzoates without Activating ortho Substituents. *Angew. Chem., Int. Ed.* **2015**, *54*, 13130-13133.

(9) (a) LaBerge, N. A.; Love, J. A. Nickel-Catalyzed Decarbonylative Coupling of Aryl Esters and Arylboronic Acids. *Eur. J. Org. Chem.* **2015**, 5546–5553. (b) Muto, K.; Yamaguchi, J.; Musaev, D. G.; Itami, K. Decarbonylative Organoboron Cross-Coupling of Esters by Nickel Catalysis. *Nat. Commun*. **2015**, *6*, 7508-7515. (c) Shi, S.; Meng, G.; Szostak, M. Synthesis of Biaryls through Nickel-Catalyzed Suzuki–Miyaura Coupling of Amides by Carbon–Nitrogen Bond Cleavage. *Angew. Chem. Int. Ed*. **2016**, *55*, 6959-6963. (d) Malapit, C. A.; Bour, J. R.; Brigham, C. E.; Sanford, M. S. Base-free Nickel-Catalysed Decarbonylative Suzuki–Miyaura Coupling of Acid Fluorides. *Nature*. **2018**, *563*, 100–104. (e) Zhou, T.; Xie, P.; Ji, C.; Hong, X.; Szostak, M. Decarbonylative Suzuki–Miyaura Cross-Coupling of Aroyl Chlorides. *Org. Lett*. **2020**, *22*, 6434–6440. (f) Wang, Z.; Wang, X.; Nishihara, Y. Nickel or Palladium-Catalyzed Decarbonylative Transformations of Carboxylic Acid Derivatives. *Chem. Asian J*. **2020**, *15*, 1234-1247.

(10) Liu, X.; Jia, J.; Rueping, M. Nickel-Catalyzed C–O Bond-Cleaving Alkylation of Esters: Direct Replacement of the Ester Moiety by Functionalized Alkyl Chains. *ACS Catal*. **2017**, *7*, 4491–4496.

(11) Keaveney, S. T.; Schoenebeck, F. Palladium-Catalyzed Decarbonylative Trifluoromethylation of Acid Fluorides. *Angew. Chem., Int. Ed.* **2018**, *57*, 4073-4077.

(12) (a) Chatupheeraphat, A.; Liao, H.; Srimontree, W.; Guo, L.; Minenkov, Y.; Poater, A.; Cavallo, L.; Rueping, M. Ligand-Controlled Chemoselective C(acyl)–O Bond vs C(aryl)–C Bond Activation of Aromatic Esters in Nickel Catalyzed C(sp2)–C(sp3) Cross-Couplings. *J. Am. Chem. Soc*. **2018**, *140*, 3724–3735. (b) Masson-Makdissi, J.; Vandavasi, J. K.; Newman, S. G. Switchable Selectivity in the Pd-Catalyzed Alkylative Cross-Coupling of Esters. *Org. Lett*. **2018**, *20*, 4094–4098. (c) Fu, L.; Chen, Q.; Wang, Z.; Nishihara, Y. Palladium-Catalyzed Decarbonylative Alkylation of Acyl Fluorides. *Org. Lett*. **2020**, *22*, 2350–2353.

(13) For representative examples of bromo- and iododecarboxylation/decarbonylation of aryl carboxylic acids and aryl esters, see: (a) Barton, D. H. R.; Lacher, B.; Zard, S. Z. Radical Decarboxylative Bromination of Aromatic Acids. *Tetrahedron Lett*. **1985**, *26*, 5939–5942. (b) Fu, Z.; Li, Z.; Song, Y.; Yang, R.; Liu, Y.; Cai, H. Decarboxylative Halogenation and Cyanation of Electron-Deficient Aryl Carboxylic Acids via Cu Mediator as Well as Electron-Rich Ones through Pd Catalyst under Aerobic Conditions. *J. Org. Chem*. **2016**, *81*, 2794–2803. (c) Perry, G. J. P.; Quibell, J. M.; Panigrahi, A.; Larrosa, I. Transition-Metal-Free Decarboxylative Iodination: New Routes for Decarboxylative Oxidative Cross-Couplings. *J. Am. Chem. Soc*. **2017**, *139*, 11527–11536. (d) Quibell, J. M.; Perry, G. J. P.; Cannas, D. M.; Larrosa, I. Transition-Metal-Free Decarboxylative Bromination of Aromatic Carboxylic Acids. *Chem. Sci*. **2018**, *9*, 3860–3865. (e) Boehm, P.; Martini, T.; Lee, Y, H.; Cacherat, B.; Morandi, B. Palladium-Catalyzed Decarbonylative Iodination of Aryl Carboxylic Acids Enabled by Ligand-Assisted Halide Exchange. *Angew. Chem. Int. Ed*. **2021**, *60*, 17211-17217. (f) Chen, T. Q.; Pedersen, P. S.; Dow, N. W.; Fayad, R.; Hauke, C. E.; Rosko, M. C.; Danilov, E. O.; Blakemore, D. C.; Dechert-Schmitt, A.-M.; Knauber, T.; Castellano, F. N.; MacMillan, D. W. C. A Unified Approach to Decarboxylative Halogenation of (Hetero)Aryl Carboxylic Acids. *J. Am. Chem. Soc*. **2022**, *144*, 8296–8305.

(14)(a) Pu, X.; Hu, J.; Zhao, Y.; Shi, Z. Nickel-Catalyzed Decarbonylative Borylation and Silylation of Esters. *ACS Catal*. **2016**, *6*, 6692–6698. (b) Guo, L.; Rueping, M. Functional Group Interconversion: Decarbonylative Borylation of Esters for the Synthesis of Organoboronates. *Chem. Eur. J*. **2016**, *22*, 16787–16790. (c) Candish, L.; Teders, M.; Glorius, F. Transition-Metal-Free, Visible-Light-Enabled Decarboxylative Borylation of Aryl N-Hydroxyphthalimide Esters. *J. Am. Chem. Soc*. **2017**, *139*, 7440–7443. (d) Liu, C.; Ji, C.-L.; Hong, X.; Szostak, M. Palladium-Catalyzed Decarbonylative Borylation of Carboxylic Acids: Tuning Reaction Selectivity by Computation. *Angew. Chem., Int. Ed*. **2018**, *57*, 16721–16726. (e) Wang, Z.; Wang, X.; Nishihara, Y. Nickel-Catalysed Decarbonylative Borylation of Aroyl Fluorides. *Chem. Commun*. **2018**, *54*, 13969-13972. (f) Malapit, C. A.; Bour, J. R.; Laursen, S. R.; Sanford, M. S. Mechanism and Scope of Nickel-Catalyzed Decarbonylative Borylation of Carboxylic Acid Fluorides. *J. Am. Chem. Soc*. **2019**, *141*, 17322–17330. (g) Kubosaki, S.; Takeuchi, H.; Iwata, Y.; Tanaka, Y.; Osaka, K.; Yamawaki, M.; Morita, T.; Yoshimi, Y. Visible- and UV-Light-Induced Decarboxylative Radical Reactions of Benzoic Acids Using Organic Photoredox Catalysts. *J. Org. Chem*. **2020**, *85*, 5362–5369. (h) Deng, X.; Guo, J.; Zhang, X.; Wang, X.; Su, W. Activation of Aryl Carboxylic Acids by Diboron Reagents towards Nickel-Catalyzed Direct Decarbonylative Borylation. *Angew. Chem. Int. Ed*. **2021**, *60*, 24510-24518. (i) Dow, N. W.; Pedersen, P. S.; Chen, T. Q.; Blakemore, D. C.; Dechert-Schmitt, A.-M.; Knauber, T.; MacMillan, D. W. C. Decarboxylative Borylation and Cross-Coupling of (Hetero)aryl Acids Enabled by Copper Charge Transfer Catalysis. *J. Am. Chem. Soc*. **2022**, *144*, 6163–6172.

(15) *N*-alkyl pyridinium salts have been utilized extensively in nickel-catalyzed cross-coupling and cross-electrophile coupling to form aryl–alkyl bonds. (a) Basch, C. H.; Liao, J.; Xu, J.; Piane, J. J.; Watson, M. P. Harnessing Alkyl Amines as Electrophiles for Nickel-Catalyzed Cross Couplings via C–N Bond Activation. *J. Am. Chem. Soc*. **2017**, *139*, 5313-5316. (b) Liao, J.; Basch, C. H.; Hoerrner, M. E.; Talley, M. R.; Boscoe, B. P.; Tucker, J. W.; Garnsey, M. R.; Watson, M. P., Deaminative Reductive Cross-Electrophile Couplings of Alkylpyridinium Salts and Aryl Bromides. *Org. Lett*. **2019**, *21*, 2941-2946. (c) Martin-Montero, R.; Yatham, V. R.; Yin, H.; Davies, J.; Martin, R., Ni-Catalyzed Reductive Deaminative Arylation at sp3 Carbon Centers. *Org. Lett*. **2019**, *21*, 2947-2951. (d) Yi, J.; Badir, S. O.; Kammer, L. M.; Ribagorda, M.; Molander, G. A., Deaminative Reductive Arylation Enabled by Nickel/Photoredox Dual Catalysis. *Org. Lett*. **2019**, *21*, 3346-3351. (e) Yue, H.; Zhu, C.; Shen, L.; Geng, Q.; Hock, K. J.; Yuan, T.; Cavallo, L.; Rueping, M. Nickel-Catalyzed C–N bond activation: Activated Primary Amines as Alkylating Reagents in Reductive Cross-Coupling. *Chem. Sci*. **2019**, *10*, 4430-4435. (f) Ni, S.; Li, C.-X.; Mao, Y.; Han, J.; Wang, Y.; Yan, H.; Pan, Y., Ni-Catalyzed Deaminative Cross-Electrophile Coupling of Katritzky Salts with Halides via C—N Bond Activation. *Sci. Adv*. **2019**, *5*, eaaw9516. (g) Rössler, S. L., Jelier, B. J., Magnier, E., Dagousset, G., Carreira, E. M., Togni, A. Pyridinium Salts as Redox-Active Functional Group Transfer Reagents. *Angew. Chem. Int. Ed*. **2020**, *59*, 9264-9280. (h) Berger, K. J., Levin, M. D. Reframing Primary Alkyl Amines as Aliphatic Building Blocks. *Org. Biomol. Chem*. **2021**, *19*, 11-36. (i) Zhang, Z., Cernak, T. The Formal Cross-Coupling of Amines and Carboxylic Acids to Form sp3–sp3 Carbon–Carbon bonds. *Angew. Chem. Int. Ed*. **2021**, *60*, 27293-27298.

(16) For an alternate method to couple aryl carboxylic acids and amines via an amide coupling and elimination of isocyanate, see: Shimazumi, R.; Tanimoto, R.; Kodama, T.; Tobisu, M. Palladium-Catalyzed Unimolecular Fragment Coupling of N -Allylamides via Elimination of Isocyanate. *J. Am. Chem. Soc*. **2022**, *144*, 11033–11043.

(17) For selected reviews on cross-electrophile couplings of aryl halides with various alkyl electrophiles, see: (a) Weix, D. J. Methods and Mechanisms for Cross-Electrophile Coupling of Csp2 Halides with Alkyl Electrophiles. *Acc. Chem. Res*. **2015**, *48*, 1767-1775. (b) Liu, J.; Ye, Y.; Sesslerm J. L. Gong, H. Cross-Electrophile Couplings of Activated and Sterically Hindered Halides and Alcohol Derivatives. *Acc. Chem. Res*. **2020**, *53*, 1833–1845. (c) Goldfogel, M. J.; Huang, L.; Weix, D. J.Cross-Electrophile Coupling: Principles and New Reactions. In Nickel Catalysis in Organic Synthesis; Ogoshi, S., Ed.; *Wiley-VCH: Weinheim*, **2020**; pp 183–222.

(18) For selected aryl alkyl ketone synthesis using aryl carboxylic acid esters under cross-electrophile coupling conditions, see: (a) Onaka, M.; Matsuoka, Y.; Mukaiyama, T. A Convenient Method for the Direct Preparation of Ketones from 2-(6-(2- Methoxyethyl)pyridyl)carboxylates and Alkyl Iodides by Use of Zinc Dust and a Catalytic Amount of Nickel Dichloride. *Chem. Lett.* **1981**, *10*, 531–534. (b) Wu, F.; Lu, W.; Qian, Q.; Ren, Q.; Gong, H. Ketone Formation via Mild Nickel-Catalyzed Reductive Coupling of Alkyl Halides with Aryl Acid Chlorides. *Org. Lett.* **2012**, *14*, 3044–3047. (c) Lu, W.; Liang, Z.; Zhang, Y.; Wu, F.; Qian, Q.; Gong, H. Gram-Scale Ketone Synthesis by Direct Reductive Coupling of Alkyl Iodides with Acid Chlorides. *Synthesis*. **2013**, *45*, 2234–2240. (d) Ni, S.; Padial, N. M.; Kingston, C.; Vantourout, J. C.; Schmitt, D. C.; Edwards, J. T.; Kruszyk, M. M.; Merchant, R. R.; Mykhailiuk, P. K.; Sanchez, B. B.; Yang, S.; Perry, M. A.; Gallego, G. M.; Mousseau, J. J.; Collins, M. R.; Cherney, R. J.; Lebed, P. S.; Chen, J. S.; Qin, T.; Baran, P. S. A Radical Approach to Anionic Chemistry: Synthesis of Ketones, Alcohols, and Amines. *J. Am. Chem. Soc.* **2019**, *141*, 6726-6739. (e) Wang, J.; Cary, B. P.; Beyer, P.; Gellman, S. H.; Weix, D. J. Ketones from Nickel-Catalyzed Decarboxylative, Non-Symmetric Cross-Electrophile Coupling of Carboxylic Acid Esters. *Angew. Chem. Int. Ed*. **2019**, *58*, 12081-12085. (f) Yang, F.; Ding, D.; Wang, C. Nickel-Catalyzed Directed Cross-Electrophile Coupling of Phenolic Esters with Alkyl Bromides. *Org. Lett.* **2020**, *22*, 9203–9209. (g) Yu, C.; Matsuo, Y. Nickel-Catalyzed Deaminative Acylation of Activated Aliphatic Amines with Aromatic Amides via C–N Bond Activation. *Org. Lett.* **2020**, *22*, 950–955.

(19) Rieke reported the decarbonylative coupling of pentafluorophenylcarbonyl chloride with benzyl chloride to give $C_6F_5CH_2C_6H_5$ in 51% yield using 1.25 equiv of metallic nickel. Inaba, S.; Rieke, R. Metallic nickel-mediated synthesis of ketones by the reaction of benzylic, allylic, vinylic, and pentafluorophenyl halides with acid halides. *J. Org. Chem.* **1985**, *50*, 1373-1381.

(20) Pre-prints of this study and a concurrent study by Cernak and co-workers were posted to ChemRxiv on Nov 1, 2022. (a) Wang, J.; Ehehalt, L.; Huang, Z.; Beleh, O.; Guzei, I.; Weix, D. *ChemRxiv* **2022**. https://doi.org/10.26434/chemrxiv-2022-ms1hb. (b) Douthwaite, J. L.; Zhao, R.; Shim, E.; Mahjour, B.; Zimmerman, P.; Cernak, T. *ChemRxiv* **2022**. https://doi.org/10.26434/chemrxiv-2022-mtlwb.

(21) While this manuscript was in review a related study using aroyl fluorides and alkyl bromides was published. Chen, Q.; You, J.; Tian, T.; Li, Z.; Kashihara, M.; Mori, H.; Nishihara, Y. Nickel-Catalyzed Decarbonylative Reductive Alkylation of Aroyl Fluorides with Alkyl Bromides. *Org. Lett.* **2022**, *24*, 9259-9263.

(22) CCDC 2192589 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

(23) Wotal, A. C.; Ribson, R. D.; Weix, D. J. Stoichiometric Reactions of Acylnickel(II) Complexes with Electrophiles and the Catalytic Synthesis of Ketones. *Organometallics* **2014**, *33*, 5874-5881.

(24) (a) Kerackian, T.; Reina, A.; Bouyssi, D.; Monteiro, N.; Amgoune, A. Silyl Radical Mediated Cross-Electrophile Coupling of N-acyl-imides with Alkyl Bromides under Photoredox/Nickel Dual Catalysis. *Org. Lett.* **2020**, *22*, 2240– 2245. (b) Wang, Z.; Wang, X.; Ura, Y.; Nishihara, Y. Nickel-Catalyzed Decarbonylative Cyanation of Acyl Chlorides. *Org. Lett.* **2019**, *21*, 6779– 6784. (c) Kerackian, T.; Reina, A.; Krachko, T.; Boddaert, H.; Bouyssi, D.; Monteiro, N.; Amgoune, A., C(sp3)–H Bond Acylation with N-Acyl Imides under Photoredox/ Nickel Dual Catalysis. *Synlett* **2021**, *32*, 1531-1536.

(25) Safety note: $Ni(CO)_4$ is a flammable, volatile, and toxic compound. As it may be formed in small amounts in these experiments, these reactions should be conducted in an efficient fume hood. See SI for further details.

(26) Yamamoto *et al* reported a similar equilibrium that favored nickel carbonyl at very low temperatures. See: Yamamoto, T.; Kohara, T.; Yamamoto, A. Insertion of Carbon Monoxide into Nickel-Alkyl Bonds of Monoalkyl-and Dialkylnickel(II) Complexes, NiR(Y)L2 and NiR2L2. Preparation of Ni(COR)(Y)L2 from NiR(Y)L2 and Selective Formation of Ketone, Diketone, and Aldehyde from NiR2L2. *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 $(L)Ni^0(CO)_2$ and even $Ni^0(CO)_4$ 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.

(28) Zhong, H.; Egger, D.; Gasser, V.; Finkelstein, P.; Keim, L.; Seidel, M.; Trapp, N.; Morandi, B. *ChemRxiv* **2023**. https://doi.org/10.26434/chemrxiv-2023-4mw5f.

(29) Sanford also noted that larger vessel headspace could help favor decarbonylation to avoid ketone formation (See reference 9d.) See Figure S1 for reaction equipment setup and Figures S6-S10 for reaction setup photos. Under our conditions, both CO removal from solution and thermal acceleration of CO dissociation appear to be important. See SI Section 4.1 for more information.

(30) Phthalimide ligands have been demonstrated to be highly stabilizing to organonickel(II) complexes. See: (a) Yamamoto, T.; Kohara, T.; Yamamoto, A. Preparation and Properties of Monoalkylnickel(II) Complexes NiR(NR1R2)L2 Having Imido, Imidazolato, or Methyl Phenylcarbamato-N Ligand. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1720-1726. (b) 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*, 532-539.

(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, S. B.; Dang, H.; Ispizua-Rodriguez, X.; Mathew, T.; Prakash, G. K. S. Direct Access to Acyl Fluorides from Carboxylic Acids Using a Phosphine/Fluoride Deoxyfluorination Reagent System. *Org. Lett*, **2019**, *21*, 1659-1663.

(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_2.

(33) For selected reviews on targeted protein degradation and the development of PROTACs see: (a) Pettersson, M.; Crews, C. M. PROteolysis TArgeting Chimeras (PROTACs) - Past, present and future. *Drug Discov. Today Technol.* **2019**, *31*, 15–27. (b) Hanzl, A.; Winter, G. E. Targeted Protein Degradation: Current and Future Challenges. *Curr. Opin. Chem. Biol.* **2020**, *56*, 35–41. (c) Verma, R.; Mohl, D.; Deshaies, R. J. Harnessing the Power of Proteolysis for Targeted Protein Inactivation. *Mol. Cell.* **2020**, *77*, 446–460. (d) Faust, T. B.; Donovan, K. A.; Yue, H.; Chamberlain, P. P.; Fischer, E. S. Small-Molecule Approaches to Targeted Protein Degradation. *Ann. Rev. Canc. Bio.* **2021**, *5*, 181–201. (e) Li, K.; Crews, C. M. PROTACs: past, present, and future. *Chem. Soc. Rev.* **2022**, *51*, 5214–5236. (f) Békés, M.; Langley, D. R.; Crews, C. M. PROTAC Targeted Protein Degraders: The Past is Prologue. *Nat. Rev. Drug Discovery* **2022**, *21*, 181–200.

(34) For a review on synthetic approaches to prepare PROTACs see: Sosic, I.; Bricelj, A.; Steinebach, C. E3 Ligase Ligand Chemistries: From Building Blocks to Protein Degraders. *Chem. Soc. Rev.* **2022**, *51*, 3487–3534.

(35) (a) Zhou, B.; Hu, J.; Xu, F.; Chen, Z.; Bai, L.; Fernandez-Salas, E.; Lin, M.; Liu, L.; Yang, C. Y.; Zhao, Y.; McEachern, D.; Przybranowski, S.; Wen, B.; Sun, D.; Wang, S. Discovery of a Small-Molecule Degrader of Bromodomain and Extra-Terminal (BET) Proteins with Picomolar Cellular Potencies and Capable of Achieving Tumor Regression. *J. Med. Chem.* **2018**, *61*, 462–481. (b) Steiner, A.; Krieger, J.; Jones, R.; Böse, R.; Wang, Y.; Eggenweiler, H.-M.; Williams, J. D.; Kappe, C. O. Photoredox Csp3–Csp2 Reductive Cross-Couplings of Cereblon Ligands for PROTAC Linker Exploration in Batch and Flow. *ChemCatChem.* **2022**, *14*, e202201184

(36) Wang, C.; Zhang, Y.; Wu, Y.; Xing, D. Developments of CRBN-Based PROTACs as Potential Therapeutic Agents. *Eur. J. Med. Chem.* **2021**, *225*, 113749.

(37) The Hou Group maintains an online database of all published PROTACS (over 3200, as of October 2022). Accessible at http://cadd.zju.edu.cn/protacdb/#

(38) (a) Burslem, G. M.; Ottis, P.; Jaime-Figueroa, S.; Morgan, A.; Cromm, P. M.; Toure, M.; Crews, C. M. Efficient Synthesis of Immunomodulatory Drug Analogues Enables Exploration of Structure-Degradation Relationships. *ChemMedChem.* **2018**, *13*, 1508–1512. (b) Steinebach, C.; Lindner, S.; Udeshi, N. D.; Mani, D. C.; Kehm, H.; Kopff, S.; Carr, S. A.; Gutschow, M.; Kronke, J. Homo-PROTACs for the Chemical Knockdown of Cereblon. *ACS Chem. Biol.* **2018**, *13*, 2771–2782.

(39) Steinebach, C.; Sosic, I.; Lindner, S.; Bricelj, A.; Kohl, F.; Ng, Y. L. D.; Monschke, M.; Wagner, K. G.; Kronke, J.; Gutschow, M. A MedChem Toolbox for Cereblon-Directed PROTACs. *MedChemComm.* **2019**, *10*, 1037–1041.

TOC Graphic