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COMMUNICATION

The Formal Cross-Coupling of Amines and Carboxylic Acids to Form sp^3–sp^3 Carbon–Carbon Bonds

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Abstract: We have developed a deaminative-decarboxylative protocol to form sp^3–sp^3 carbon–carbon bonds from activated amines and carboxylic acids. Amines and carboxylic acids are ubiquitous building blocks, available in broad chemical diversity and at lower cost than typical C–C coupling partners. To leverage amines and acids for C–C coupling, we developed a reductive nickel-catalyzed cross-coupling utilizing building block activation as pyridinium salts and redox active esters, respectively. Miniaturized high-throughput experimentation studies were critical to our reaction optimization, with subtle experimental changes such as order of reagent addition, composition of a binary solvent system, and ligand identity having a significant impact on reaction performance. The developed protocol is used in the late-stage diversification of pharmaceuticals while more than one thousand systematically captured and machine-readable reaction datapoints are reposited.

Carbon–carbon bond forming reactions are essential in the synthesis of natural and synthetic products and have been a focal point of reaction development for over a century. The formation of sp^3–sp^3 C–C bonds is particularly important and the availability of reactive building blocks has greatly expanded the available chemical space. The classic Suzuki[1] and Negishi[2] couplings to form sp^2–sp^2 C–C bonds have been augmented to include sp^3–sp^3 C–C cross couplings from alkyl halides and alkylboron[3-9] or alkylzinc[10-14] reagents, respectively. Carboxylic acids[15-34] and amines[18, 35-49] have advanced considerably as coupling partners and have been used, independently, in couplings with halides and organometallic reagents. Amines and carboxylic acids are available in the highest diversity[50, 51] and are typically less expensive than the corresponding organohalide or organometallic reagent.[50] For these reasons, a cross-coupling of amines and carboxylic acids to form sp^3–sp^3 C–C bonds would be an impactful addition to the synthetic chemistry toolbox (Figure 1). A C–C coupling of amines and carboxylic acids remains elusive with the amide coupling – one of the most prevalent reaction in organic synthesis[52-54] – being used nearly exclusively to unite these common building blocks. The groups of Watson and Weix have recently reported an amine-acid alkyl-acyl coupling.[44] We report herein the first deaminative-decarboxylative sp^3–sp^3 C–C cross-coupling of activated amines and carboxylic acids.

Our lab has been mapping the coupling of amines and acids to understand the link of reactions to physicochemical properties and to identify unknown but impactful reactions that expand the synthetic chemistry toolbox.[55] Our map of the amine–acid coupling system was motivated by the realization that the coupling of an amine and acid to form an amide bond is the single most frequently used synthetic transformation in pharmaceutical research,[53, 54, 56] but represents just one of many possible ways that an amine and acid can conceivably unite.

In our analysis, the formation of sp^3–sp^3 C–C bonds stood out as the single most impactful reaction to develop in amine-acid coupling space, due to the prevalence of this bond in DrugBank (Figure 1B).[57] Given the importance of this specific transformation, we sought to develop the amine-acid cross-coupling so that researchers could forge a C–C bond instead of an amide bond.

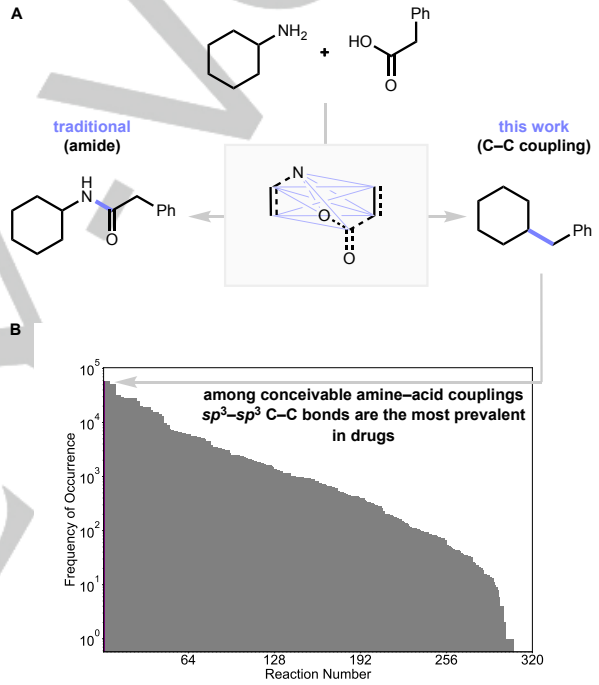


Figure 1. A. The cross-coupling of amines and carboxylic acids to form sp^3–sp^3 carbon–carbon bonds as a valuable complement to the venerable amide coupling. **B**. A substructure search of 320 possible ways to couple an amine and acid in the DrugBank database revealed the sp^3–sp^3 C–C cross-coupling as the most frequently occurring substructure in drugs.

Having identified a target reaction, we initiated the identification of initial reaction conditions using miniaturized high-throughput experimentation (HTE).[58-62] Using tools for reaction miniaturization in concert with our software phactor™,[63] we merged conditions for sp^3-deamination with conditions for sp^3-decarboxylation. Among the initial conditions surveyed, we were drawn to metallophotoredox catalysis.[64] A 96-reaction array of metallophotoredox reactions was executed (Figure 2), wherein half of the array contained *N*-Boc-proline as a free acid (**1**) and the other half of the array contained the corresponding redox active ester (**2**). *N*-benzyltriphenylpyridinium tetrafluoroborate (**3**) was used as an activated amine,[36, 65] and reactions were monitored for the formation of C–C coupled product **4**. The performance of 4 bases, 2 reductants, 2 nickel precatalysts, 2 bipyridyl ligands, and 4 photocatalysts was investigated. From

this experiment emerged an initial reaction "hit" wherein redox active ester **2**, with Ni(cod)$_2$ as precatalyst, di-*tert*-butylbipyridyl as ligand, Ir[dF(CF$_3$)ppy]$_2$(dtbpy) as photocatalyst, and 2-^{t}Bu-1,1,3,3,-tetranethylguanidine in acetonitrile produced **4** in 25% assay yield. This lead reaction was repeated on a 0.15 mmol reaction scale, from which desired product **4** was isolated in 22% yield (Figure 2B, entry 1).

Our initial lead reaction was next optimized using both high-throughput and traditional reaction development tools. All reactions were documented in a machine-readable format to provide valuable reaction data for the machine learning community.[66] During reaction optimization, an additional metallophotoredox survey interrogated the possibility of replacing **3** with benzyltrimethylammonium chloride, but the triphenylpyridinium salt (**3**) uniformly outperformed trimethylammonium as a C–N bond activating group in this reaction (see Supporting Information). Follow up studies (see Supporting Information) revealed that reactions performed similarly in the absence of photocatalyst and blue light irradiation so further studies omitted photoredox technology. Decarboxylation using silver salts in analogy to the Minisci reaction were also unproductive (see Supporting Information). A survey of 8 catalysts, 6 ligands, and 2 reductants led us to the observation that NiBr$_2$•glyme, dtbpy, and zinc in a 1:1 mixture of dioxane and acetonitrile as solvent at 60 °C produced **4** in 45% assay yield, which translated to a 41% isolated yield on 50 mg scale (Figure 2B, entry 2). A subsequent survey of 4 catalysts, 3 ligands, 2 reductants, 2 redox active esters and 2 triphenylpyridinium salts revealed a modest improvement in yield by using manganese instead of zinc as the reductant (48% versus 41% yield) (Figure 2B, entry 3). Further exploitive searching in this pocket of reaction space, by surveying 6 catalysts, 16 ligands revealed dCF$_3$bpy (**L1**) as a uniquely effective ligand, producing **4** in 65% assay yield in the screen, and 68% isolated yield upon repetition on 50 mg scale (Figure 2B, entry 4).

The strategic use of explorative and exploitative HTE in our reaction "hit" identification and optimization studies was essential. We observed multiple instances where apparently similar reaction conditions yielded distinct results. In fact, we performed 1,392 high-throughput reactions, documented in a machine-readable format (Figure 2C), over the course of our studies and the vast majority of these reactions gave 0% or just traces of the desired C–C coupling product, highlighting that the identification of winning reaction conditions is challenged by nearby local minima in reaction space where no product is formed. This is further highlighted by investigations into closely related reaction conditions. For instance, we subjected **2** and **3** to the reaction conditions recently reported by Watson and Weix[44] (10 mol% NiCl$_2$, 2,2′:6′,2″-terpyridine, Mn, NMP, 60 °C) for the synthesis of ketones from triphenylpyridinium salts acyl fluorides and did not observe any ketone or C–C coupled product (see Supporting Information).

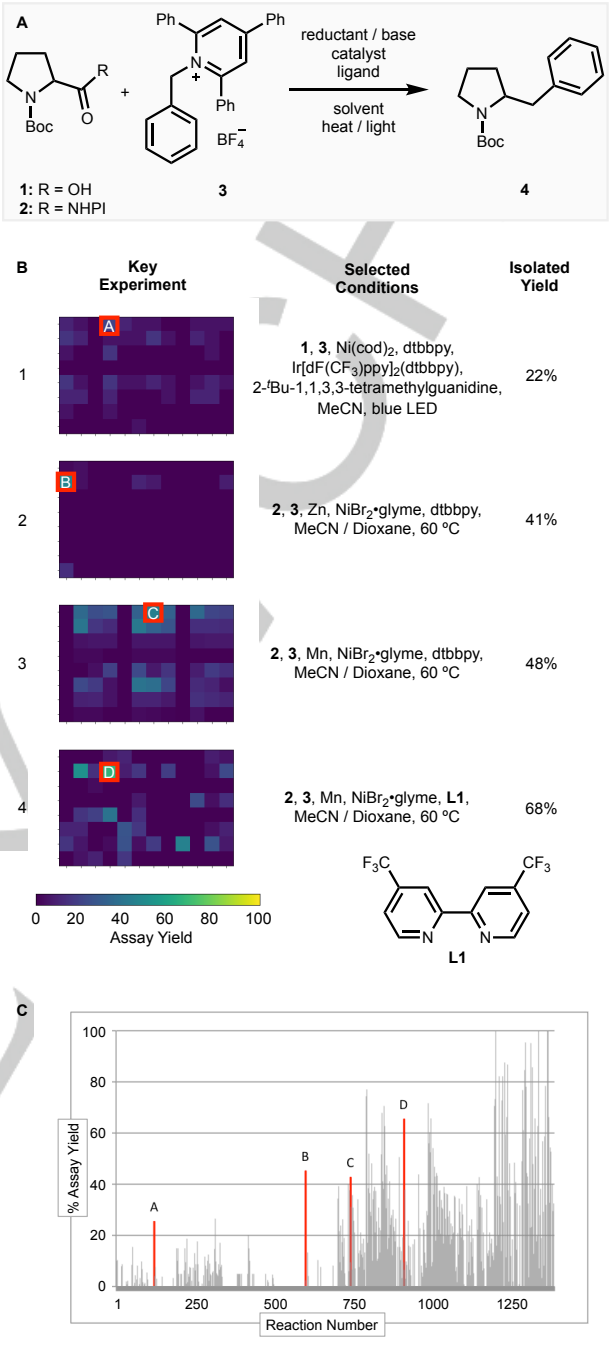
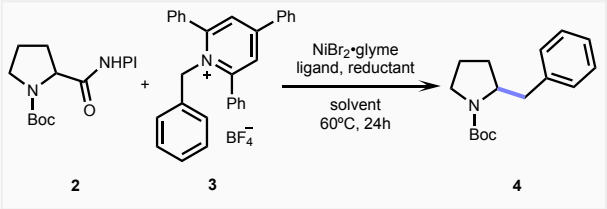


Figure 2. A. High-throughput reaction lead identification and optimization. **B.** Miniaturized reactions were analyzed by UPLC-MS, and lead reactions from each screen were repeated on larger scale to obtain isolated yields. **C.** Reaction optimization. NHPI: *N*-Hydroxyphthalimide.



Entry	Solvent	Order of Addition	Ratio of **4** and **2**	Conc.	(LC) Yield
1	MeCN	**2**, **3**, $NiBr_2$•glyme, dtbpy, Zn, *then* MeCN	1:1	0.10 M	(36%)
2	dioxane	**2**, **3**, $NiBr_2$•glyme, dtbpy, Zn, *then* dioxane	1:1	0.10 M	(25%)
3	1:1 MeCN:dioxane	**2**, **3**, $NiBr_2$•glyme, **L1**, *then* dioxane, *then* MeCN, Mn	1:1	0.10 M	(64%) 68%
4	1:1 MeCN:dioxane	$NiBr_2$•glyme, **L1**, *then* dioxane, *then* MeCN, Mn, *then* **2**, **3** in 1:1 MeCN:dioxane	1:1	0.10 M	(61%) 61%
5	1:1 MeCN:dioxane	As entry 3	1:2	0.10 M	48%
6	1:1 MeCN:dioxane	As entry 3	2:1	0.10 M	74%
7	1:1 MeCN:dioxane	As entry 3	1:1	0.050 M	75%
8	1:1 MeCN:dioxane	As entry 3	1:1	0.025 M	81%

Table 1. Optimization studies. NHPI: *N*-Hydroxyphthalimide.

Moreover, replacing **3** with benzyl bromide[67] did not lead to any C–C coupling product under our conditions instead giving significant amounts of the dimer of **3**: 1,2-diphenylethane (see Supporting Information). The nuanced complexities of reaction development are further exemplified in Table 1. For instance, the discovery of the mixed dioxane-acetonitrile solvent system was critical to the development of our reaction (Table 1, entries 1–3). Order of reagent addition was also critical, for instance, admixing **2**, **3**, $NiBr_2$•glyme and **L1**, with addition first of acetonitrile and then dioxane with Mn added last was the optimal order of addition (entries 3–4 and Supporting Information) providing a 68% isolated yield of **4**. Further studies revealed improved performance by running the reaction at 0.025 M (entries 7–8) and we moved forward with the use of a 1.3:1 stoichiometric ratio of **2** to **3** as a balance of performance and atom economy (entries 5–6).

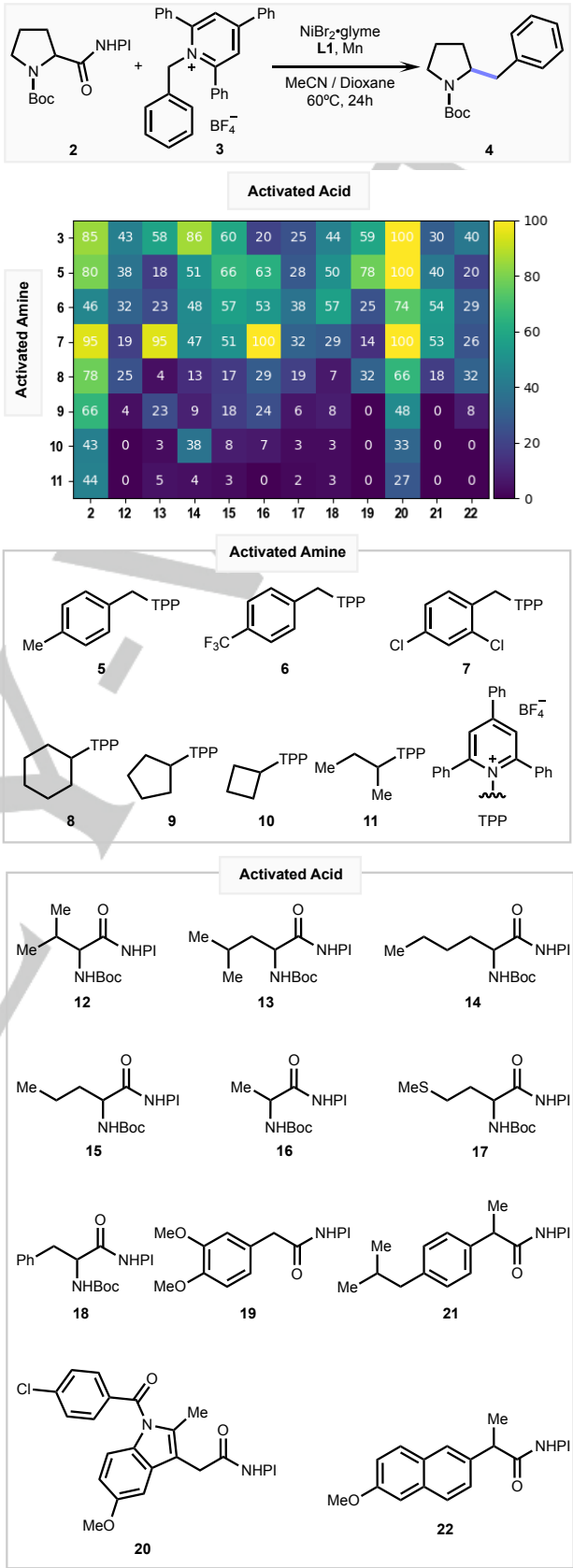


Figure 3. Substrate scope. 8 Katritzky salts were allowed to reaction with 12 diverse redox active esters under influence of 20 mol% $NiBr_2$•glyme, 20 mol% L1, and manganese in a 1:1 mixture of acetonitrile and dioxane at 60 °C. NHPI: *N*-Hydroxyphthalimide.

Control studies showed that no reaction occurred in the absence of nickel precatalyst or ligand, suggesting that catalysis is involved in the reaction rather than a coupling of two free radicals. Admixing $NiBr_2$•glyme, **L1**, and Mn with **3** in the absence of the redox active ester led to formation of 1,2-diphenylethane. Based on these observations we favor a mechanism that requires both Ni and Mn to break the C–N bond of **3**. In the absence of Katritzky salt we observed low conversion to an apparent dimer of the redox active ester.[68] The formation of **4** from **2** and **3** was completely inhibited by the addition of TEMPO although an *O*-benzylated adduct of TEMPO was isolated, suggesting involvement of single-electron species. The yield was effectively unchanged whether the reaction was performed in the dark or in the presence of ambient light. A mechanistic proposal based on our preliminary studies is shown in the Supporting Information.

Having optimized reaction conditions for the sp^3–sp^3 amine–acid cross-coupling, we explored the substrate scope using a miniaturized reaction array (Figure 3). For this study, our optimized protocol was used with 8 Katritzky salts derived from diverse alkyl amines (**3, 5**–**11**), alongside 12 redox active esters (**2, 12**–**22**) derived from amino acids or carboxylic acid containing pharmaceuticals such as indomethacin (**20**), ibuprofen (**21**) and naproxen (**22**). For the 96 reactions interrogated, the desired C–C coupling product was observed in >10% conversion (UPLC-MS) for 68 of the 96 substrate pairs. An average conversion of 37% was observed across the entire reaction plate. A variety of benzylamines performed exceptionally well, while sterically congested amines such as *sec*-butylamine only coupled with select redox active esters such as those derived from *N*-Boc-proline (**2**) and indomethacin (**20**).

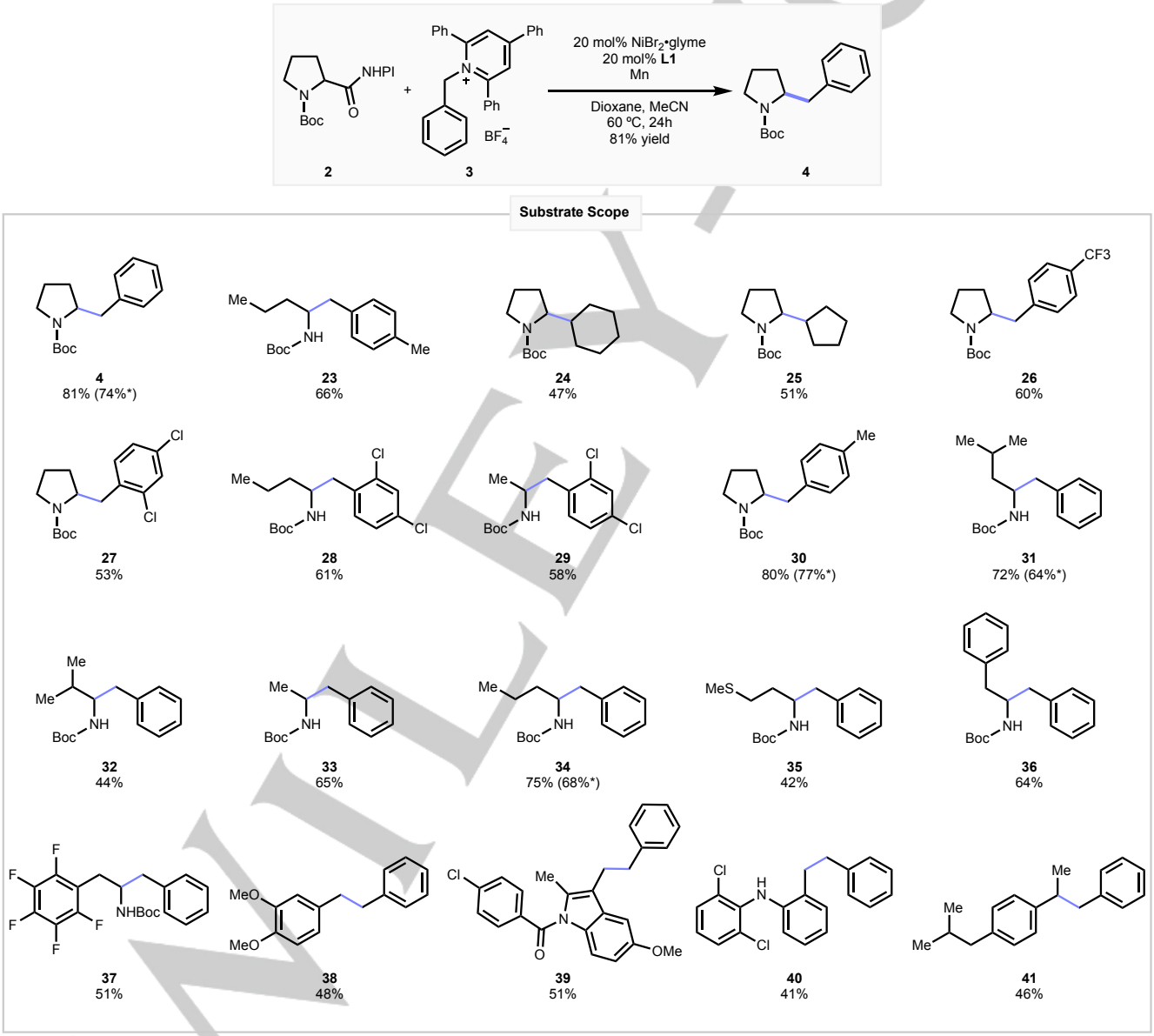


Figure 4. Substrate scope. Reactions were performed on 0.15 mmol reaction scale and isolated yields are shown. *Reactions were run at 10% Ni catalyst loading. NHPI: *N*-Hydroxyphthalimide.

Additional substrate scope studies gave diverse products in 41%–81% yield following purification (Figure 4). Protected α-amino acids and benzylic acids provided satisfying results. Small alkyl groups, such as cyclohexyl and cyclopentyl performed well giving **24** and **25**, respectively. The reaction was tolerant to a variety of functionalities, such as *tert*-butyl carbamates (**23**–**37**), aryl chlorides (**27**–**29**, **39**, **40**), aryl fluoride (**37**), indole (**39**) and thioether (**35**) groups, which are broadly represented in pharmaceuticals. Indeed, a variety of medicinally relevant molecules, such as **39**–**41** derived from indomethacin, diclofenac and ibuprofen, were successful candidates for late-stage diversification using our amine–acid C–C coupling.

In conclusion, we have developed the first deaminative-decarboxylative coupling of amines to carboxylic acids. This reaction class expands the available coupling space beyond halide–boronate and related couplings as a tool for sp^3–sp^3 carbon–carbon bond formation. Beyond the report of the reaction itself, we pursued a reaction development strategy that mimics contemporary pharmaceutical development in the use of informatics to mine for a specific target reaction, followed by high-throughput tactics to identify initial reaction leads, which were subjected to a lead optimization phase using both HTE and traditional reaction development studies. Meanwhile, we observed that many of the >1,000 reactions performed led to traces or no C–C coupling product at all, highlighting the necessity to uncover subtle experimental details. The experimental tactics we used facilitated the systematic execution and reporting of both positive and negative reaction outcomes and their documentation in a machine-readable format. As such, we have been able to reposit 1,392 systematically captured reaction datapoints from our studies as a comma separated value file. We anticipate this dataset will serve as a viable data source for machine learning studies.

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Conflict of Interest

T.C. is a co-founder and equity holder of Entos, Inc. and equity holder of Scorpion Therapeutics. The Cernak Lab receives research funding from MilliporeSigma, Janssen Therapeutics, Relay Therapeutics, and Entos, Inc. as well as gifts from Merck & Co., Inc. and SPT Labtech.

keywords: amines • carboxylic acids • C–C bonds • nickel catalysis • high-throughput experimentation

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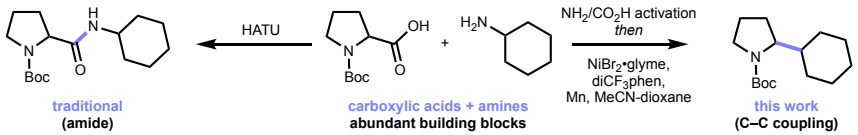

Carbon–carbon bonds are the most prevalent bonds in pharmaceuticals. Meanwhile, amines and carboxylic acids are abundant as feedstocks for chemical synthesis. An amine-acid C–C coupling would be a valuable addition to the synthetic toolbox. Using miniaturized high-throughput experimentation, we have developed the first sp^3–sp^3 amine-acid cross-coupling to form C–C bonds based on preactivation of the building blocks and nickel catalysis.