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Decarboxylative sp^3 C–N Coupling via Dual Copper/Photoredox Catalysis

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Abstract

Over the last three decades, significant progress has been made in the development of methods to construct sp^2 C–N bonds using palladium, copper, or nickel catalysis[1,2]. However, the incorporation of alkyl substrates to form sp^3 C–N bonds remains one of the major challenges in the field of cross-coupling chemistry. Here, we demonstrate that the synergistic combination of copper catalysis and photoredox catalysis can provide a general platform to address this challenge. This cross-coupling system employs naturally abundant alkyl carboxylic acids and commercially available *N*-nucleophiles as coupling partners, and is applicable to a wide variety of primary, secondary, and tertiary alkyl carboxylic acids (via iodonium activation). At the same time, a vast array of *N*-nucleophiles, including *N*-heterocycles, amides, sulfonamides, and anilines, can undergo C–N coupling to provide *N*-alkyl products in good to excellent efficiency at room temperature and in short order (5 minutes to 1 hour). We have also demonstrated that this C–N coupling protocol can be applied to substrates bearing multiple amines with high regioselectivity, as well as complex drug molecules, enabling the rapid construction of molecular complexity and the late stage functionalization of bioactive pharmaceuticals.

Within the field of organic chemistry, the efficient construction of C–N bonds is important due to the prevalence of nitrogen-containing motifs in a wide array of natural products, pharmaceuticals, and functional materials[3–5]. There are several notable routes to form sp^2 C–N bonds, including the Buchwald–Hartwig reaction[1], Ullmann coupling[6], and Chan–Lam amination[7]. However, sp^3 C–N bond formation typically relies on classical methods, such as nucleophilic substitution reactions between *N*-nucleophiles and alkyl halides[8], Mitsunobu alkylations of alcohols using *N*-nucleophiles[9], reductive amination with carbonyls[10], or olefin hydroamination[11]. Recently, several research groups have reported transition metal-catalyzed variants of the alkylation reaction of *N*-nucleophiles with aliphatic halides[12,13]. In 1894, Curtius reported the rearrangement of acyl azides to form C–N containing aliphatic

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Author Contributions Y. L. and X. Z. performed and analyzed the experiments. Y. L., X. Z., and D.W.C.M. designed the experiments. Y. L., X. Z., and D.W.C.M. prepared this manuscript.

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substrates[14]. We questioned if it might be possible to expand this concept to complex, medicinally relevant *N*-bearing fragments thereby accelerating access to drug-like complexity in one step.

The synergistic merger of photoredox[15] and transition metal catalysis (termed metallaphotoredox catalysis) has resulted in the invention of many novel cross-coupling reactions that are now being widely adopted within the pharmaceutical sector[16]. The combination of nickel and photoredox catalysis has enabled the efficient construction of $C(sp^3)$–$C(sp^2)$ and $C(sp^3)$–$C(sp^3)$ bonds using abundant alkyl carboxylic acids[17] and alcohols[18]. Here we show that metallaphotoredox catalysis involving copper in lieu of nickel allows for alkyl sp^3 C–N bond formation in a generic sense without the use of alkyl halides or other prototypical electrophiles. More specifically, we hoped to merge i) the capacity of photoredox to form alkyl radicals from iodonium carboxylates (derived in situ from carboxylic acids) with ii) the long-established propensity of copper to participate in reductive elimination to form carbon–heteroatom bonds[2]. By taking advantage of the widely abundant nature of alkyl carboxylic acids and *N*-nucleophiles such as heteroaromatics, sulfonamides, amides, and anilines, we hoped to devise a new fragment coupling reaction that would be broadly useful yet mechanistically orthogonal to established alkylation reactions (Figure 1). Recently, two methods have been reported with this aim in mind[19,20], and these illustrate the capacity of copper to function in decarboxylative mechanisms.

A detailed mechanism for the proposed decarboxylative sp^3 C–*N*-nucleophile coupling is outlined in Figure 2a. Excitation of photocatalyst $Ir(F\text{-}Meppy)_2(dtbbpy)PF_6$ (**1**) [F-Meppy = 2-(4-fluorophenyl)-5-(methyl)pyridine, dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine] is known to generate the long-lived (τ = 1.1 μs)[21] triplet excited state $^*Ir^{III}$ complex **2**. At the same time, we hypothesized that coordination of the *N*-nucleophile **11** with a copper(I) pre-catalyst followed by deprotonation would readily form the copper(I)-amido species **3**. The excited state $^*Ir^{III}$ complex **2** ($E_{1/2}^{red}$ [$^*Ir^{III}/Ir^{II}$] = 0.94 V versus the standard calomel electrode (SCE) in CH_3CN)[21] should rapidly oxidize this copper(I) complex **3** ($E_{1/2}^{red}$ [$Cu^{II}(BPhen)_2/Cu^{I}(BPhen)_2$] = 0.08 V versus SCE in DMF, BPhen = 4,7-diphenyl-1,10-phenanthroline)[22] to generate the corresponding copper(II)-amido system **4** and the corresponding iridium(II) complex **5**. At this stage we envisaged that iodomesitylene dicarboxylate **8** (which is preformed via the mixing of carboxylic acid **6** and iodomesitylene diacetate **7** – see Supplementary Information) would be readily reduced by the newly formed iridium(II) species **5** ($E_{1/2}^{red}$ [Ir^{III}/Ir^{II}] = –1.50 V versus SCE in CH_3CN[21], E_p [**8**/**8**$^{\bullet-}$] = −1.14 V versus SCE in CH_3CN) to generate a carboxyl radical, which upon CO_2 extrusion[23,24] would produce desired alkyl radical **9**, while reconstituting the ground state photocatalyst **1**. At this stage, we anticipated that copper(II)-amido complex **4** would capture alkyl radical **9** to form copper(III) complex **10**, which upon reductive elimination[25] would forge the desired fragment-coupled sp^3 C–N bearing adduct **12** and regenerate copper(I) catalyst **3**.

We first examined the proposed sp^3 C–N coupling using three electronically disparate *N*-nucleophiles (indole **11a**, azaindole **11b**, and indazole **11c**, Figure 2b), along with cyclohexyl carboxylic acid **6** as the alkylating reagent, and a wide range of copper(I) and photoredox catalysts. Pleasingly, the desired decarboxylative sp^3 C–N coupling can be

achieved in good to excellent efficiency for all three substrates (60%, 76%, and 90% yield, respectively) using $Ir(F\text{-}Meppy)_2(dtbbpy)PF_6$ as the photocatalyst, CuTC (TC = thiophene-2-carboxylate) as the copper catalyst, BPhen or 4,7-dimethoxy-1,10-phenanthroline (dOMe-Phen) as the ligand, BTMG (BTMG = 2-*tert*-butyl-1,1,3,3-tetramethylguanidine) as the base, with exposure to 34 W blue LEDs. Intriguingly, a series of control experiments revealed that while the copper(I) catalyst is essential for the desired C–N bond formation in all cases, the absence of light and/or photocatalyst has a profound impact on reaction efficiency depending on the *N*-nucleophile employed. More specifically, the alkylation of indazole **11c** is successful with or without photocatalysis (90% versus 86% yield), while indole **11a** and azaindole **11b** achieve significantly improved yields and reaction times when light and the iridium photocatalyst are combined with copper (indole **11a**, 60% versus 7% yield; azaindole **11b**, 76% versus 47% yield). We speculate that a non-photonic mechanism is possible when copper(I)-amido species **3** is sufficiently electron-rich to undergo direct electron-transfer with the iodomesitylene dicarboxylate **8**, thereby removing the requirement for a redox catalyst to act as an electron shuttle. However, when copper(I)-amido species **3** is not sufficiently reducing, or is formed slowly, the presence of a photoexcited electron shuttle catalyst becomes essential to achieve useful efficiencies. Indeed, this latter case was found to be most common, with non-photonic conditions leading to useful yields with only a small subset of substrates (yields for non-photonic conditions are reported in parentheses/footnotes in Figure 3 and Figure 4). As such, the combination of copper/photoredox catalysts and light was identified as the superior protocol to evaluate a broad range of sp^3 C–N cross-coupling reactions.

Having established the preferred reaction conditions, we next examined the generality of this new C–N fragment coupling by exploring the scope of the carboxylic acid alkylation partner (Figure 3). Notably, a diverse range of alkyl carboxylic acids can be employed in this new protocol to deliver the *N*-alkyl heteroaryl derivatives in good to excellent efficiency. It is important to highlight that in all cases the reactions were complete at room temperature *within 1 hour*. Another feature of this protocol is that only one regioisomer of the product is produced for all cases shown in Figure 3, which offers a notable advantage when compared to traditional *N*-alkylation reactions. Indeed, a broad series of differentially-substituted primary alkyl acids can readily participate in this new C–N coupling (**13**–**21**, 50–82% yield). Moreover, these mild reaction conditions are compatible with a range of common functional groups, such as terminal olefins (**17**, 64% yield), terminal alkynes (**18**, 80% yield), nitro groups (**19**, 50% yield), esters (**21**, 80% yield) and protected amines (**16** and **20**, 63% and 82% yield, respectively). In contrast to many established alkylation reactions, steric encumbrance proximal to the acid group is also well-tolerated, as exemplified by the successful incorporation of a neopentyl system (**15**, 54% yield). Moreover, direct *N*-methylation (**13**, 65% yield) can also be realized by carrying out the C–N coupling protocol using commercial $MesI(OAc)_2$ **7**. Finally, we successfully applied this coupling technology to three complex natural products bearing alcohols, ketones, and internal alkenes. All were found to participate in decarboxylative *N*-alkylation with high efficiency (**22**–**24**, 54–76% yield).

We next sought to examine the scope of secondary alkyl carboxylic acids as alkylating agents. Importantly, a large array of ring-bearing carboxylates can be used to access *N*-cycloalkylation adducts in good to excellent efficiency (**26**–**31**, 40–85% yield). Moreover, this new transformation is not limited to cyclic systems, as exemplified by the rapid incorporation of acyclic secondary alkyl groups (**25**, 61% yield), a transformation that is not readily achieved using established alkylation protocols. An additional 6 examples using other secondary alkyl acids for this sp^3 C–N coupling are detailed in the Supplementary Information and Extended Data Figure 1.

A striking feature of this decarboxylative C–N coupling method is the number of tertiary carbon-bearing carboxylic acids that can be readily employed to forge heteroaryl *N*-tertiary alkyl derivatives with good to excellent efficiency (**32**–**36**, 53–80% yield). This is especially notable given that tertiary alkyl halide *N*-alkylation can often be elusive if not impossible using traditional technologies. Given the recent interest in the incorporation of rigid bicyclic structures into drug-like compounds, such as the bicyclo[1.1.1]pentane core (as shown in product **36**)[26], we expect this light-mediated *N*-alkylation protocol to be immediately applicable to a large range of medicinal chemistry programs. Indeed, the capacity to access these bridged bicyclic aryl isosteres in only one operation using commercial carboxylic acids/iodomesitylene diacetate (at room temperature in less than 1 hour) should allow for rapid adoption.

Next, we turned our attention to the scope of the *N*-nucleophile component in this new catalytic alkylation protocol (Figure 4). To our delight, almost every class of medicinally relevant *N*-heterocyclic ring, including, but not limited to, indazoles (**37** and **38**, 81% and 73% yield, respectively), azaindoles (**39** and **40**, 89% and 75% yield, respectively), indoles (**41** 58% yield), pyrazoles (**42** and **43**, 98% and 68% yield, respectively), pyrroles (**51**, 75% yield), imidazoles (**52**, 68% yield), triazoles (**53**, 90% yield), benzimidazoles (**54**, 67% yield), benzotriazoles (**55**, 80% yield), purines (**56**, 60% yield), and carbazoles (**57**, 46% yield), can be successfully employed to deliver *N*-alkyl products in good to excellent efficiency. Moreover, an additional 42 examples using other *N*-heterocycles are detailed in the Supplementary Information and Extended Data Figures 2 and 3. For nucleophiles that are equally or more acidic than pyrazoles (such as indazoles, triazoles, imidazoles, etc.), the addition of an exogenous base is not generally necessary. The carboxylate anion, which is generated upon the reduction of iodomesitylene dicarboxylate **8** (Figure 2a), can function as a weak base. One remarkable feature is that this heterocycle C–N forming mechanism exhibits excellent regioselectivity (Figure 4) with substrates that possess multiple *N*-alkylation sites (e.g., pyrazoles, imidazoles, triazoles, indazoles, benzimidazoles). At this stage, we presume that the significant steric bulk of the ligated copper complex, ensures that the sp^3 C–N coupling takes place at least hindered site of these heteroaromatic nucleophiles. This outcome is in sharp contrast to classical alkylation methods that typically lead to regioisomeric mixtures. A number of these *N*-heterocyclic substrates were also tested using our non-photonic conditions, and the corresponding yields are shown in parentheses. It is clear that while C–N formation can be achieved with these nucleophiles in the absence of light (**51**–**57**, 7–39% yield), the dual copper/photoredox protocol enables extensive scope

and substantially higher efficiencies across the board, providing a more general protocol for this new C–N heterocyclic coupling reaction.

As shown in Figure 4, this decarboxylative C–N coupling method is not limited to the cross-coupling of *N*-heterocycles. Under our optimized conditions, a large selection of electron-deficient (and also less acidic) *N*-nucleophiles, including anilines (**44** and **45**, 55% and 70%, respectively), aryl sulfonamides (**46**, 59% yield), alkyl sulfonamides (**47**, 51% yield), aryl amides (**48**, 79% yield), phthalimides (**49**, 61% yield), and cyclic carbamates (**50**, 71% yield), were found to participate readily in this sp^3 C–N coupling. Notably, functional groups including aryl iodides (**44**, 55% yield), aryl bromides (**46**, 59% yield), and ketones (**45**, 70% yield) were readily tolerated, a useful feature with respect to further synthetic manipulation.

A long-established problem for primary amine functionalization with alkyl halides is the formation of polyalkylation products, given that the initial secondary amine adduct is more nucleophilic than the starting amine. Remarkably, and as revealed in Figure 4, only mono-alkylated products are obtained when primary amides, sulfonamides and anilines are employed in this new copper-catalyzed protocol (**44–48**, also see Supplementary Information for additional examples using primary alkyl acids). Moreover, an additional 27 examples using other electron-deficient *N*-nucleophiles are detailed in the Supplementary Information and Extended Data Figure 3. As highlighted earlier, this coupling protocol does not appear to be negatively influenced by steric constraints, as *ortho*-substituted and *ortho-,ortho*-disubstituted anilines, sulfonamides, and amides are readily employed (**44**, **46**, and **48**, 55–79% yield).

To illustrate the utility of this new transformation with respect to drug discovery, we examined this decarboxylative sp^3 C–N coupling using six known pharmaceuticals (Celebrex, Axitinib, Zelboraf, Actos, Rilutek, and Skelaxin). Using three separate carboxylic acids, we were able to achieve decarboxylative alkylation in all cases in good to excellent yield (**58**–**63**, 44–90% yield). An additional 10 examples of pharmaceutical functionalization utilizing this technology are described in the Supplementary Information and Extended Data Figure 4.

For substrates bearing multiple nucleophilic sites, achieving regioselective mono-functionalization has been a long-standing challenge[27]. Therefore, we were delighted to find that this new alkylation technology can be applied sequentially to the same drug molecule to achieve selective alkylation at two discrete *N*-positions via the judicious choice of reaction conditions. As demonstrated in Figure 5a, heterocycle **64** incorporates both an indazole nitrogen and a primary amide; however, when the coupling protocol is performed *without* an exogenous base, regioselective *N*-alkylation of the indazole was observed in 80% yield. Moreover, we have executed the regioselective *N*-alkylation step on a 7.4 mmol scale to prepare 1.45 g of the *N*-cyclohexyl indazole derivative **65**. The origins of regioselectivity in this decarboxylative coupling arise from the relative acidity of the two N–H moities in substrate **64** (i.e., indazole versus amide). More specifically, when no exogenous base is used, the carboxylate anion (formed via reduction of the iodomesitylene dicarboxylate **8**) can function as a weak base and thereby selectively deprotonate the more acidic indazole

nitrogen [pK_a (indazole) < 19.8 in DMSO[28,29]; pK_a (phenyl acetamide) = 23.3 in DMSO[28]] upon coordination to the copper catalyst (which in turn leads to regioselective *N*-alkylation of the indazole N1 position). Perhaps most important, subsequent exposure of the resulting *N*-cyclohexyl indazole **65** to our coupling protocol with a second carboxylic acid *in the presence of a strong organic base*, BTTP [*tert*-butyliminotri(pyrrolidino)phosphorane] leads to a second *N*-alkylation on the remaining amide nitrogen (again in useful yield). We anticipate that the capacity to perform regioselective and sequential C–N coupling steps as a function of relative N–H acidities will have significant benefit with respect to the step economy of building complex molecules (i.e., removing the need to install and remove *N*-protecting groups).

Finally, to further showcase the utility of this new sp^3 C–N coupling method, we performed a series experiments to compare the decarboxylative protocol with traditional nucleophilic substitution reactions (Figure 5b). Under a variety of classical S_N2 and S_N1 alkylation conditions, tertiary alkyl bromide **67** and bromocyclopropane (**68**) failed to react with 3-chloroindazole to generate the desired *N*-alkyl products (consistent with a lack of literature precedent for using these alkyl bromides with indazole nucleophiles). In contrast, the desired *N*-alkyl products can be obtained in good yields and excellent regioselectivities via decarboxylative C–N couplings employing commercially available carboxylic acids **69** and **70** using our mild, catalytic protocol *within 30 minutes* at room temperature using an integrated photoreactor[30]. As such, we anticipate that this new decarboxylative coupling strategy will provide a useful, complementary new approach to sp^3 C–N alkylation.

Methods

Here we describe a typical procedure for the decarboxylative sp^3 C–N coupling reaction; a summary of general conditions is included in Supplementary Information (Figure S36) and further experimental details are also provided in the Supplementary Information.

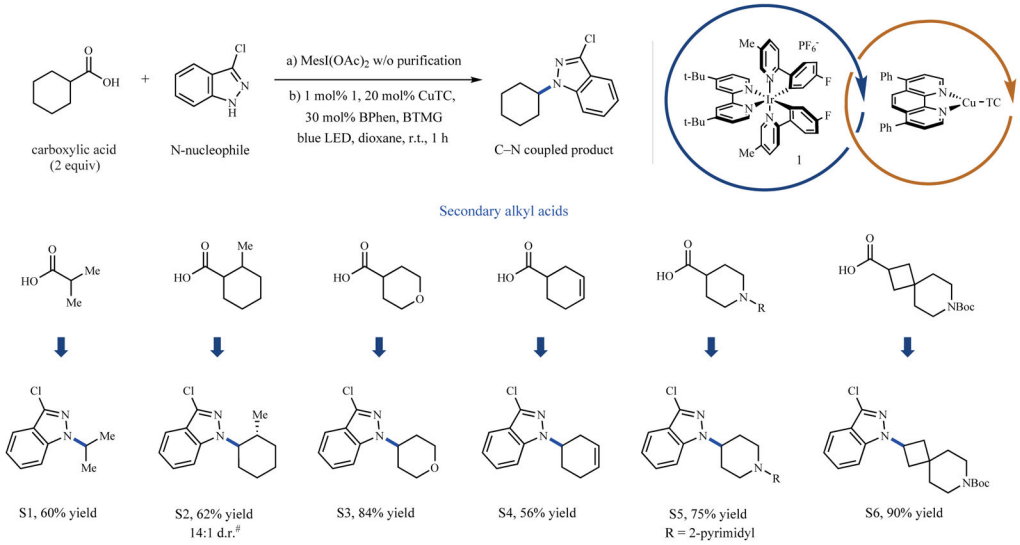
Procedure for decarboxylative sp^3 C–N couplings

To a 20 mL or 40 mL vial equipped with a stir bar was added photocatalyst, *N*-nucleophile, iodomesitylene dicarboxylate, copper salt, and ligand. Dioxane was added followed by the addition of the base. The solution was sonicated for 1–3 min until it became homogeneous. Next, the solution was degassed by sparging with nitrogen for 5–10 minutes before sealing with parafilm. The reaction was stirred and irradiated using two 34 W blue LED lamps (3 cm away, with cooling fan to keep the reaction at room temperature) for 1 hour. The reaction mixture was removed from the light, cooled to ambient temperature, diluted with water (15 mL) and EtOAc (25 mL), and the aqueous layer was extracted with three portions of EtOAc (25 mL each time). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel to afford the desired decarboxylative C–N coupling product. For aniline substrates, a solution of these *N*-nucleophiles in dioxane was used. Also, if the iodomesitylene dicarboxylate is a liquid, its solution in dioxane was used.

Data Availability

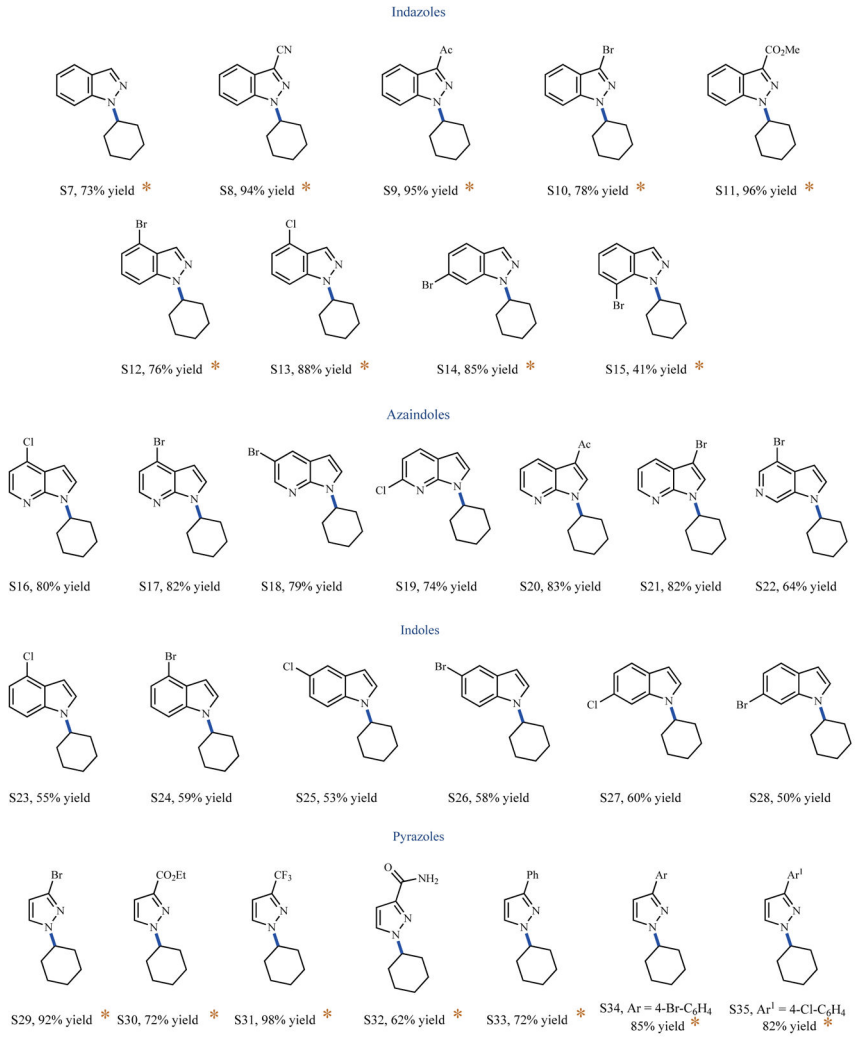
The authors declare that findings of this study are available within the paper and its Supplementary Information.

Extended Data



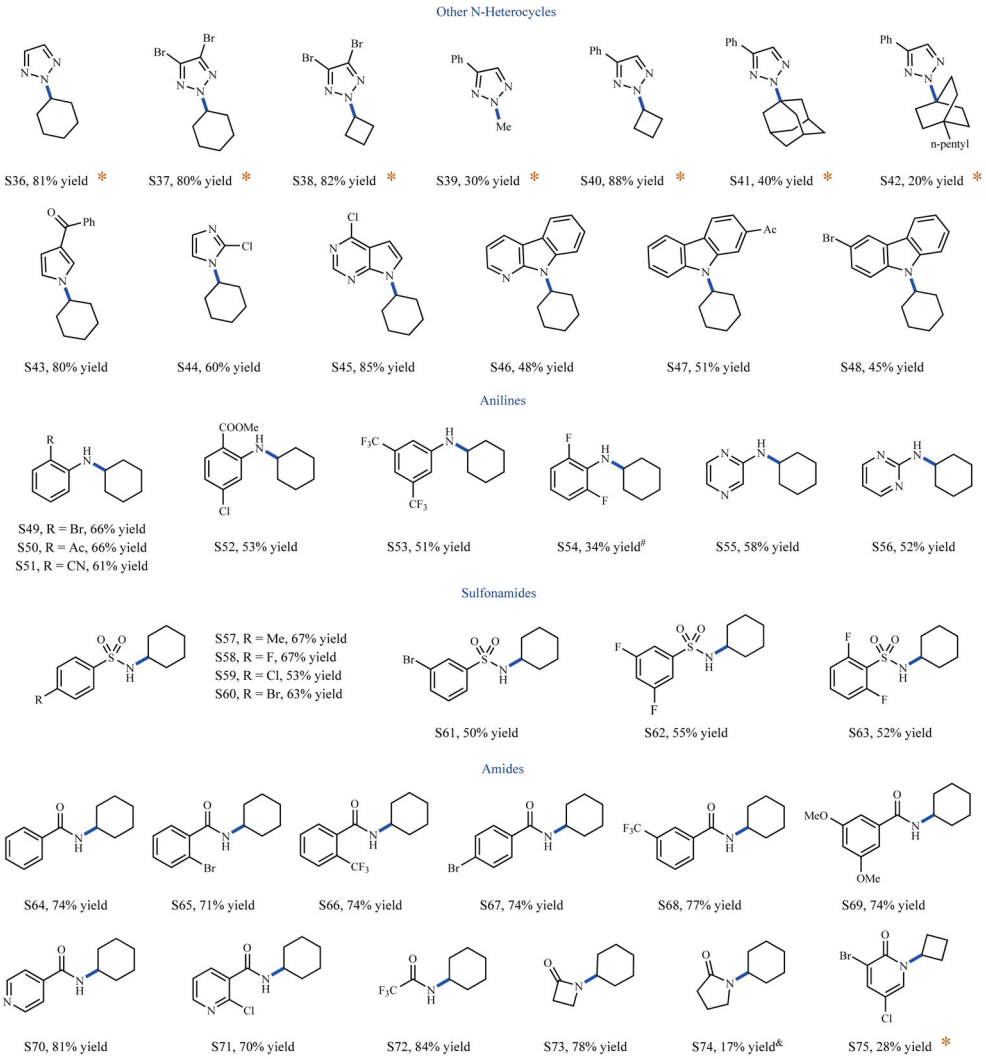
Extended Data Figure 1. Decarboxylative *sp*^{3} C–N couplings with a series of secondary alkyl acids

An array of secondary alkyl carboxylic acids can be cross-coupled with 3-chloroindazole. The protocol provides the product as a single regioisomer for all cases. All yields are isolated. See Supplementary Information for full experimental details. d.r., diastereomeric ratio. #d.r. was determined by ^{1}H NMR.



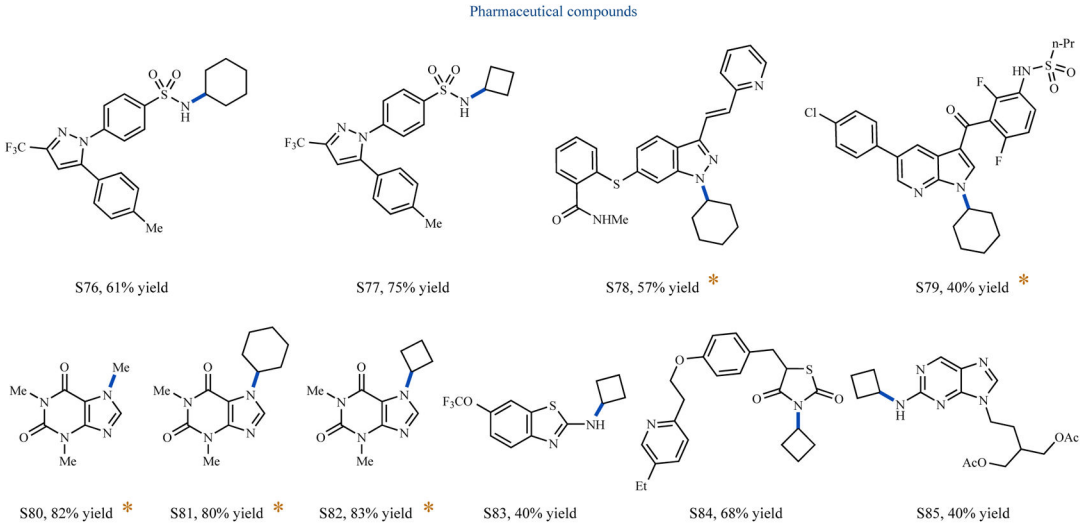
Extended Data Figure 2. Decarboxylative sp^3 C–N couplings with a series of *N*-heterocycles

A variety of *N*-heterocycles, including indazoles, azaindoles, indoles, and pyrazoles, can cross-couple with carboxylic acids in good efficiency. All yields are isolated. See Supplementary Information for full experimental details. *Single regioisomer.



Extended Data Figure 3. Decarboxylative sp^3 C–N couplings with a series of *N*-nucleophiles

A variety of *N*-nucleophiles, including *N*-heterocycles, anilines, sulfonamides, and amides, can cross-couple with carboxylic acids in good efficiency. All yields are isolated unless otherwise noted. See Supplementary Information for full experimental details. #Yield was determined by ^{19}F NMR with an internal standard. &Yield was determined by gas chromatography analysis with an internal standard. *Single regioisomer.



Extended Data Figure 4. Decarboxylative *sp*^{3} C–N couplings with a series of pharmaceutical compounds

A number of drug molecules can cross-couple with carboxylic acids in good efficiency. All yields are isolated. See Supplementary Information for full experimental details. *Single regioisomer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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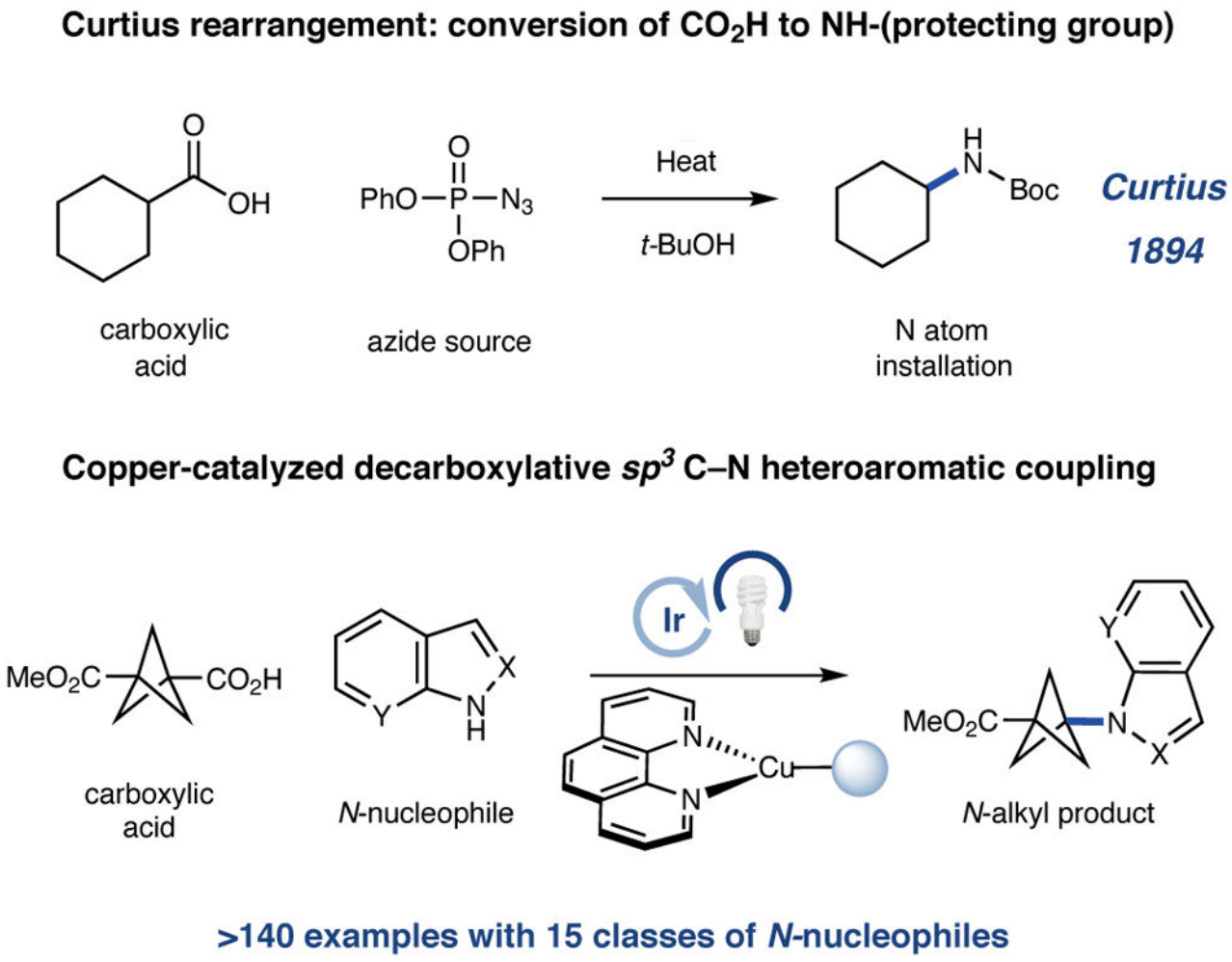

Figure 1. Decarboxylative *N*-nucleophile fragment coupling

A general platform for decarboxylative sp^3 C–N coupling can be realized by the combination of copper catalysis and photoredox catalysis. A broad range of readily available carboxylic acids and *N*-nucleophiles are employed to generate a variety of *N*-alkyl products. Ph, phenyl; Boc, *tert*-butoxycarbonyl; X and Y, carbon or nitrogen atom.

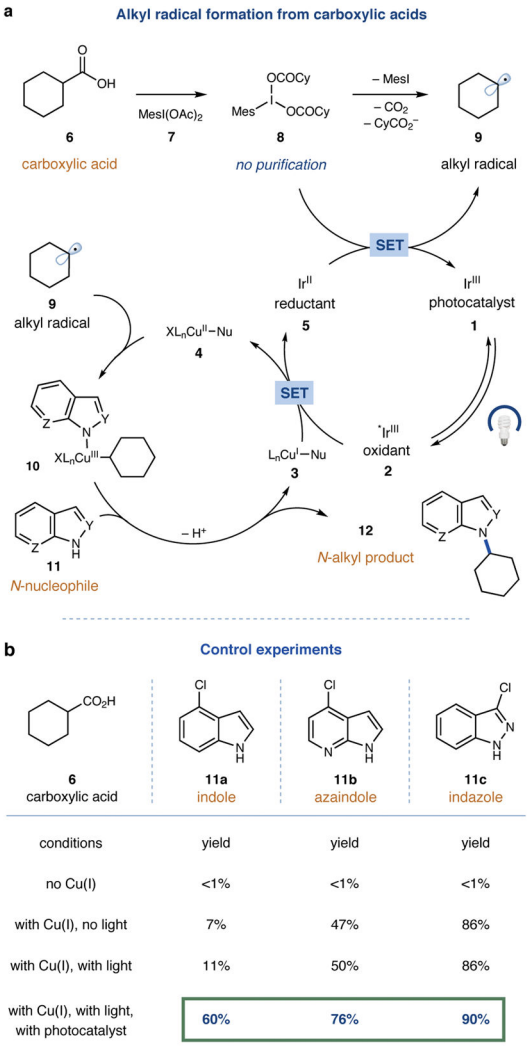

Figure 2. Catalytic cycles and control experiments

a, A proposed mechanism is outlined. Photocatalyst **1** is excited by visible light to produce a long-lived triplet excited state (**2**), which can readily oxidize copper(I) catalyst **3** to yield copper(II) species **4**. The reduced iridium(II) complex **5** can then be oxidized by iodomesitylene dicarboxylate **8**, which is derived from the reaction of carboxylic acid **6** and iodomesitylene diacetate **7**, to release alkyl radical **9** and photocatalyst **1**. Concurrently in the copper catalytic cycle, copper(II)-amido complex **4** can capture alkyl radical **9** to form the highly unstable copper(III) complex **10**. Reductive elimination from complex **10** provides the desired sp^3 C–N coupled product and regenerates the copper(I) catalyst **3** after coordination with the *N*-nucleophile **11. b,** Control experiments were performed with three different *N*-nucleophiles. In all cases, the presence of both the copper(I) catalyst and the photoredox catalyst under light irradiation conditions is crucial to achieve the best efficiency for the C–N coupling reactions. SET, single-electron transfer; Mes, mesityl; L, ligand; Cy, cyclohexyl; Nu, nucleophile; X, anionic ligand, such as a carboxylate; Y and Z, carbon or nitrogen atom.

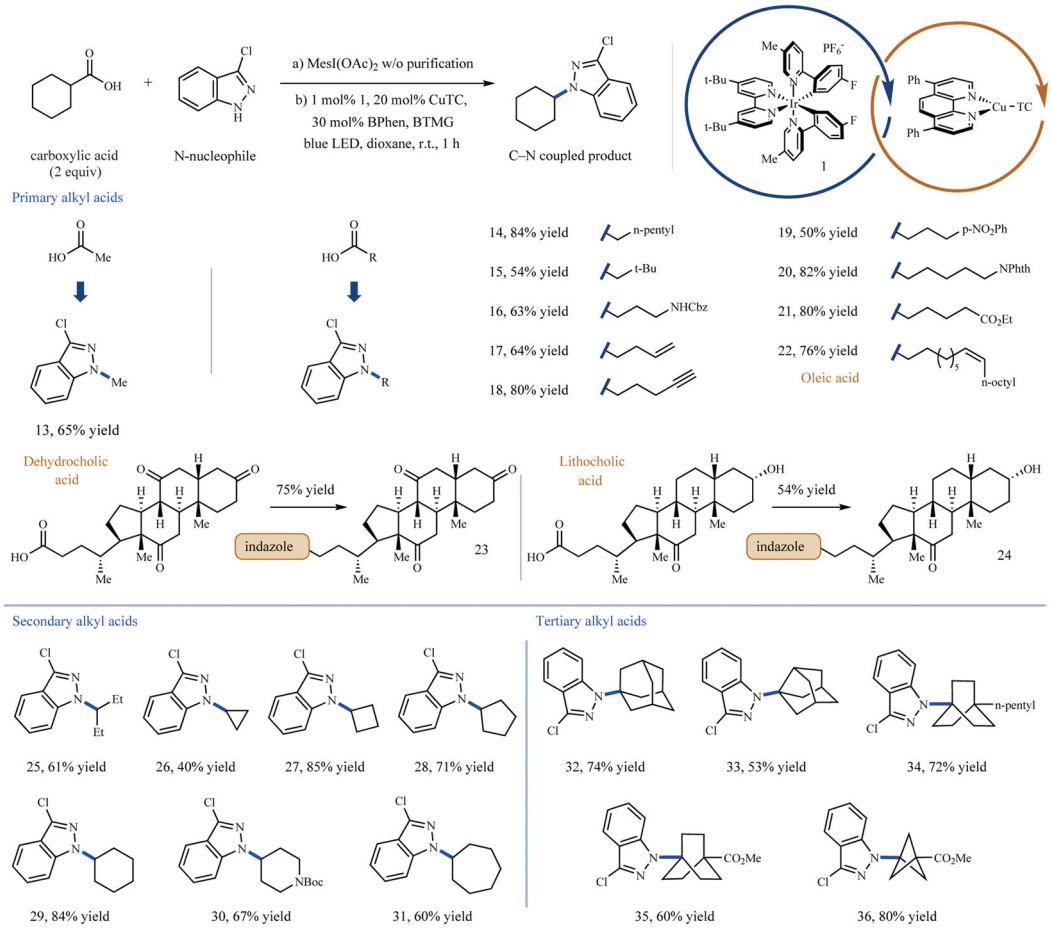

Figure 3. Decarboxylative C–N couplings of 3-chloroindazole with a range of alkyl carboxylic acids

A wide variety of alkyl carboxylic acids can be cross-coupled with 3-chloroindazole. The carboxylic acid is added in (a) and the *N*-nucleophile in (b). The protocol provides the product as a single regioisomer for all cases. All yields are isolated. In the absence of light and the photocatalyst, the yields of these compounds are: **13**, 42% yield; **14**, 70% yield; **25**, 48% yield; **26**, 34% yield; **27**, 80% yield; **28**, 56% yield; **29**, 86% yield; **31**, 44% yield; **32**, 62% yield; **33**, 38% yield; **34**, 26% yield; **35**, 32% yield; **36**, 20% yield. These yields were determined by ^{1}H nuclear magnetic resonance (^{1}H NMR) spectroscopy with an internal standard. See Supplementary Information for full experimental details. See Extended Data Figure 1 for additional examples. TC, thiophene-2-carboxylate; Me, methyl; Ac, acetyl; Et, ethyl; Cbz, carboxybenzyl; NPhth, phthalimide.

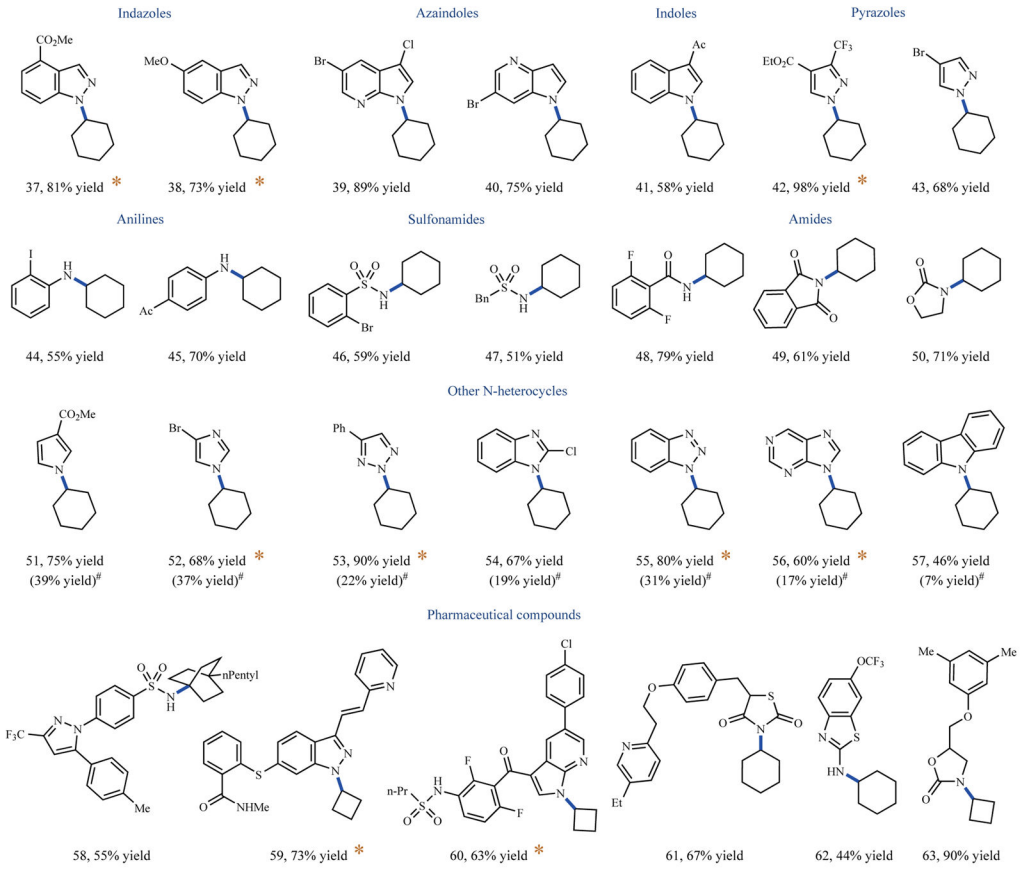

Figure 4. Decarboxylative C–N couplings of cyclohexyl carboxylic acid with a variety of *N*-nucleophiles

This new C–N bond-forming protocol shows a strikingly broad scope with respect to the *N*-nucleophiles. Almost every single class of important *N*-heterocycles can provide *N*-alkylated products in good yields and excellent regioselectivity. Less nucleophilic substrates and complex drug molecules are all viable coupling partners. All yields are isolated yields for the decarboxylative C–N coupling step.*Single regioisomer. #The yields of reactions that were conducted in the absence of light and a photocatalyst are shown in the parentheses and determined by ^{1}H NMR with an internal standard. See Supplementary Information for full experimental details. See Extended Data Figures 2–4 for additional examples. Pr, propyl; Bn, benzyl.

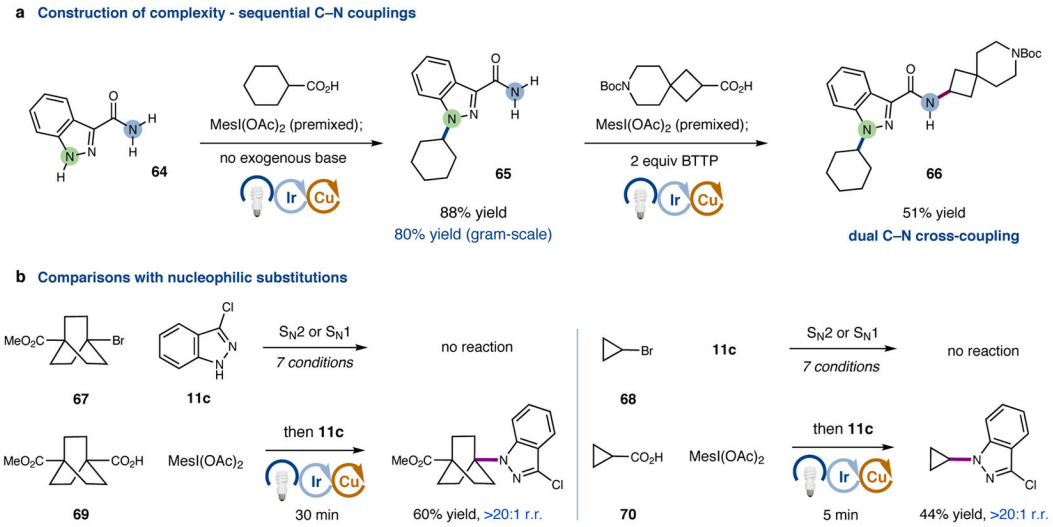

Figure 5. Sequential C–N couplings and comparisons with nucleophillic substitutions

a, Sequential decarboxylative C–N couplings can be realized using indazole derivative **64** bearing two nucleophilic sites. The *N*,*N*′-dialkylated product bearing two different alkyl groups can be easily generated via two C–N coupling reactions employing different alkyl acids under different reaction conditions. All yields in this section are isolated yields for the decarboxylative C–N coupling step. **b**, Comparing the current decarboxylative C–N coupling protocol with classical nucleophilic substitution methods using two alkyl electrophiles demonstrates the complementary nature of this new method. All yields in this section were determined by ^{1}H NMR studies with an internal standard. See Supplementary Information for full experimental details and additional examples. BTTP, *tert*-butylimino-tri(pyrrolidino)phosphorane; r.r., regiomeric ratio.