LETTER

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Decarboxylative sp^3 C–N coupling via dual copper and photoredox catalysis

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Over the past three decades, considerable progress has been made in the development of methods to construct sp^2 carbon–nitrogen (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 from which to address this challenge. This cross-coupling system uses naturally abundant alkyl carboxylic acids and commercially available nitrogen nucleophiles as coupling partners. It is applicable to a wide variety of primary, secondary and tertiary alkyl carboxylic acids (through iodonium activation), as well as a vast array of nitrogen nucleophiles: nitrogen heterocycles, amides, sulfonamides and anilines can undergo C–N coupling to provide *N*-alkyl products in good to excellent efficiency, at room temperature and on short timescales (five minutes to one hour). We demonstrate that this C–N coupling protocol proceeds with high regioselectivity using substrates that contain several amine groups, and can also be applied to 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 owing 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 the formation of 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 nitrogen nucleophiles and alkyl halides[8], Mitsunobu alkylations of alcohols using nitrogen nucleophiles[9], reductive amination with carbonyls[10] or olefin hydroamination[11]. Recently, several research groups have reported transition-metal-catalysed variants of the alkylation reaction of nitrogen nucleophiles with aliphatic halides[12,13]. In 1894, Curtius reported the rearrangement of acyl azides to form C–N-containing aliphatic substrates[14]. We questioned whether it might be possible to expand this concept to complex, medicinally relevant nitrogen-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 development of many 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 place of nickel enables 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 the capacity of photoredox reactions to form alkyl radicals from iodonium carboxylates (derived in situ from carboxylic acids) with 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 nitrogen 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 (Fig. 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 coupling of sp^3 carbon with nitrogen nucleophiles is outlined in Fig. 2a. Excitation of photocatalyst Ir(F-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 triplet-excited-state *Ir^{III} complex **2** (with a lifetime, τ, of 1.1 μs)[21]. At the same time, we proposed that coordination of the nitrogen nucleophile **11** with a copper(I) precatalyst 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 considered 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 the 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 yield 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 nitrogen nucleophiles (indole **11a**, azaindole **11b** and indazole **11c**, Fig. 2b), along with cyclohexyl carboxylic acid **6** as the alkylating reagent, and a wide range of copper(I) and photoredox catalysts. 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-Meppy)$_2$(dtbbpy)PF$_6$ as the photocatalyst, CuTC (TC = thiophene-2-carboxylate) as the copper catalyst, BPhen or dOMe-Phen (dOMe-Phen = 4,7-dimethoxy-1,10-phenanthroline) as the ligand, BTMG (BTMG = 2-*tert*-butyl-1,1,3,3-tetramethylguanidine) as the base, with exposure to 34-W blue light-emitting diodes (LEDs). Notably, a series of control experiments revealed that although 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 effect on reaction efficiency depending on the nitrogen nucleophile used. More specifically, the alkylation of indazole **11c** is successful with or without photocatalysis (90% compared with 86% yield, respectively), whereas indole **11a** and azaindole **11b** achieve markedly improved yields and reaction times when light

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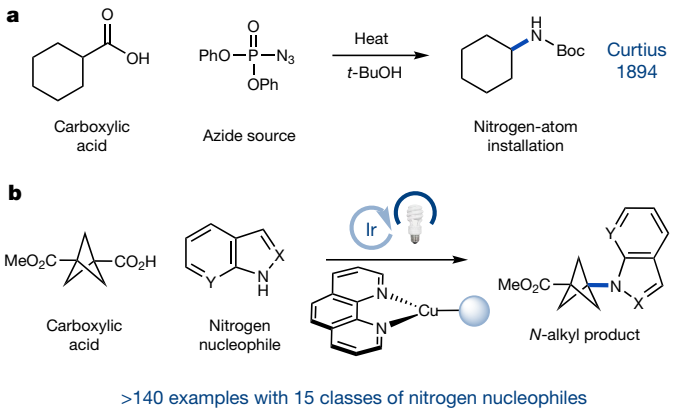
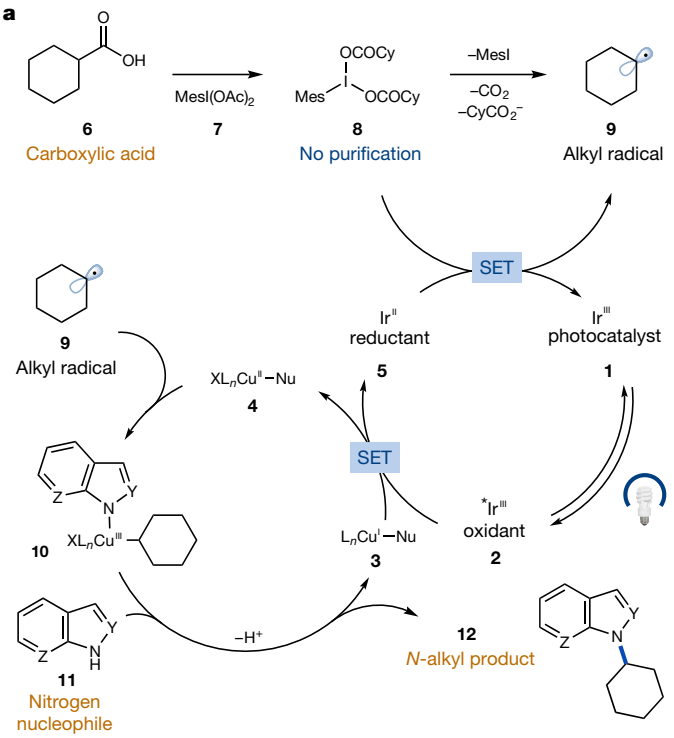


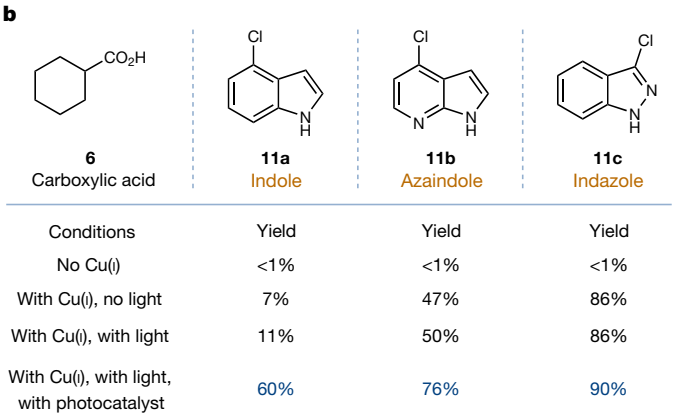
Fig. 1 | Decarboxylative nitrogen-nucleophile fragment coupling. **a**, An example of the Curtius[14] rearrangement of acyl azides to form C–N-containing aliphatic substrates. **b**, A general platform for decarboxylative sp^3 C–N coupling can be realized by the combination of copper catalysis and photoredox catalysis. A broad range of readily available carboxylic acids and nitrogen nucleophiles are used to generate various *N*-alkyl products. Boc, *tert*-butoxycarbonyl; Ph, phenyl; X and Y, carbon or nitrogen atom.

and the iridium photocatalyst are combined with copper (indole **11a**, 60% compared with 7% yield; azaindole **11b**, 76% compared with 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 the 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 in Figs. 3 and 4). As such, the combination of copper and photoredox catalysts with light was identified as the superior protocol with which 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 (Fig. 3). Notably, a diverse range of alkyl carboxylic acids can be used 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 h. Another feature of this protocol is that only one regioisomer of the product is produced for all cases shown in Fig. 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 that contain 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





Conditions	Yield	Yield	Yield
No Cu(I)	<1%	<1%	<1%
With Cu(I), no light	7%	47%	86%
With Cu(I), with light	11%	50%	86%
With Cu(I), with light, with photocatalyst	60%	76%	90%

Fig. 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 nitrogen nucleophile **11**. **b**, Control experiments were performed with three different nitrogen 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. Cy, cyclohexyl; L, ligand; Mes, mesityl; Nu, nucleophile; SET, single-electron transfer; X, anionic ligand, such as a carboxylate; Y and Z, carbon or nitrogen atoms.

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 six examples using other secondary alkyl acids for this sp^3 C–N coupling are detailed in Supplementary Information and Extended Data Fig. 1.

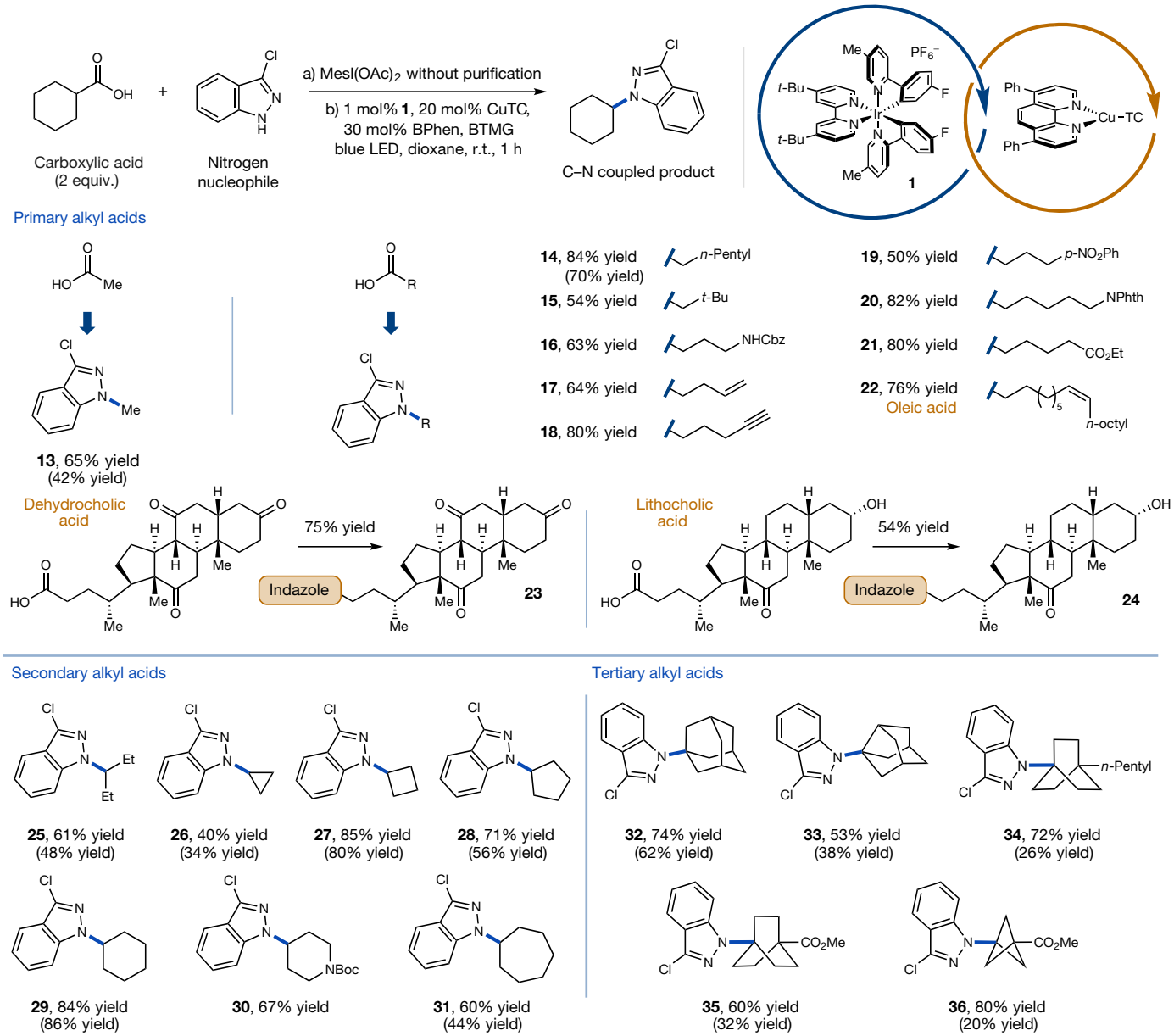


Fig. 3 | Decarboxylative C–N couplings of 3-chloroindazole with a range of alkyl carboxylic acids. A wide variety of alkyl carboxylic acids can be cross-coupled with 3-chloroindazole. The carboxylic acid is added as part of step a, and the nitrogen nucleophile as part of step b. The protocol provides the product as a single regioisomer in all cases. The yields shown first are isolated yields of reactions conducted according to our standard protocol; yields shown in parentheses are for reactions that were conducted in the absence of light and a photocatalyst and were determined by ^{1}H nuclear magnetic resonance (^{1}H NMR) spectroscopy with an internal standard. See Supplementary Information for full experimental details, and Extended Data Fig. 1 for additional examples. All reactions were replicated at least twice for consistency. Ac, acetyl; BTMG, 2-tert-butyl-1,1,3,3-tetramethylguanidine; Cbz, carboxybenzyl; Et, ethyl; Me, methyl; NPhth, phthalimide; TC, thiophene-2-carboxylate; r.t., room temperature.

A notable feature of this decarboxylative C–N coupling method is the number of tertiary-carbon-bearing carboxylic acids that can be readily used to prepare heteroaryl *N*-tertiary alkyl derivatives with good to excellent efficiency (**32**–**36**, 53%–80% yield). This is especially important given that the *N*-alkylation using tertiary alkyl halides 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 and iodomesitylene diacetate (at room temperature in less than 1 h) should enable the rapid adoption of this method.

Next, we turned our attention to the scope of the nitrogen-nucleophile component in this new catalytic alkylation protocol (Fig. 4). Almost every class of medicinally relevant nitrogen heterocycle, 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 used to deliver *N*-alkyl products in good to excellent efficiency. Moreover, an additional 42 examples using other nitrogen heterocycles are detailed in Supplementary Information and Extended Data Figs. 2 and 3. For nucleophiles that are as acidic as or more acidic than pyrazoles (such as indazoles, triazoles and imidazoles), the addition of an exogenous base is not generally necessary. The carboxylate anion, which is generated

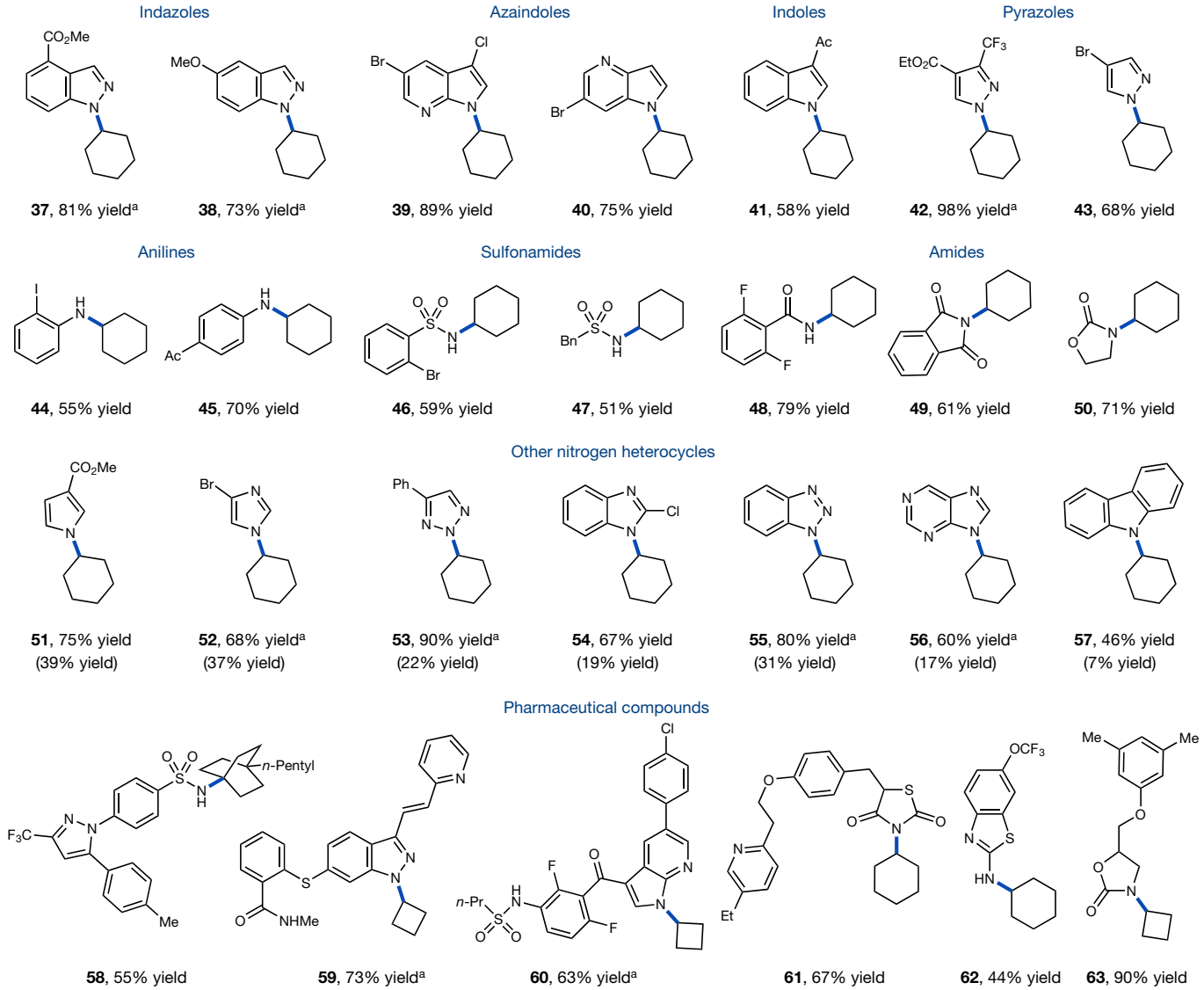


Fig. 4 | Decarboxylative C–N couplings of cyclohexyl carboxylic acid with various nitrogen nucleophiles. This new C–N bond-forming protocol shows a markedly broad scope with respect to the nitrogen nucleophiles. Almost every class of important nitrogen heterocycle can provide *N*-alkylated products in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

upon the reduction of iodomesitylene dicarboxylate **8** (Fig. 2a), can function as a weak base. One notable feature is that this heterocycle C–N forming mechanism exhibits excellent regioselectivity (Fig. 4) with substrates that possess several *N*-alkylation sites (for example, pyrazoles, imidazoles, triazoles, indazoles and benzimidazoles). At this stage, we presume that the considerable steric bulk of the ligated copper complex ensures that the sp^3 C–N coupling takes place at the least hindered site of these heteroaromatic nucleophiles. This outcome is in sharp contrast to classical alkylation methods that typically lead to regioisomeric mixtures. Several of these nitrogen heterocycles were also tested using our non-photonic conditions, and the corresponding yields are shown in parentheses in Fig. 4. It is clear that although C–N formation can be achieved with these nucleophiles in the absence of light (**51**–**57**, 7–39% yield), the dual copper and photoredox protocol enables a more 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 Fig. 4, this decarboxylative C–N coupling method is not limited to the cross-coupling of nitrogen heterocycles. Under our optimized conditions, a large selection of electron-deficient (and also less acidic) nitrogen 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 in the functionalization of primary amines with alkyl halides is the formation of polyalkylation products, given that the initial secondary amine adduct is more nucleophilic than the starting amine. Notably, as shown in Fig. 4, only monoalkylated products are obtained when primary amides, sulfonamides and anilines are used in this new copper-catalysed protocol (**44**–**48**, also see Supplementary Information for additional examples using primary alkyl acids). Moreover, an additional 27 examples using other electron-deficient nitrogen nucleophiles are detailed in Supplementary Information and Extended Data Fig. 3. As already highlighted, this

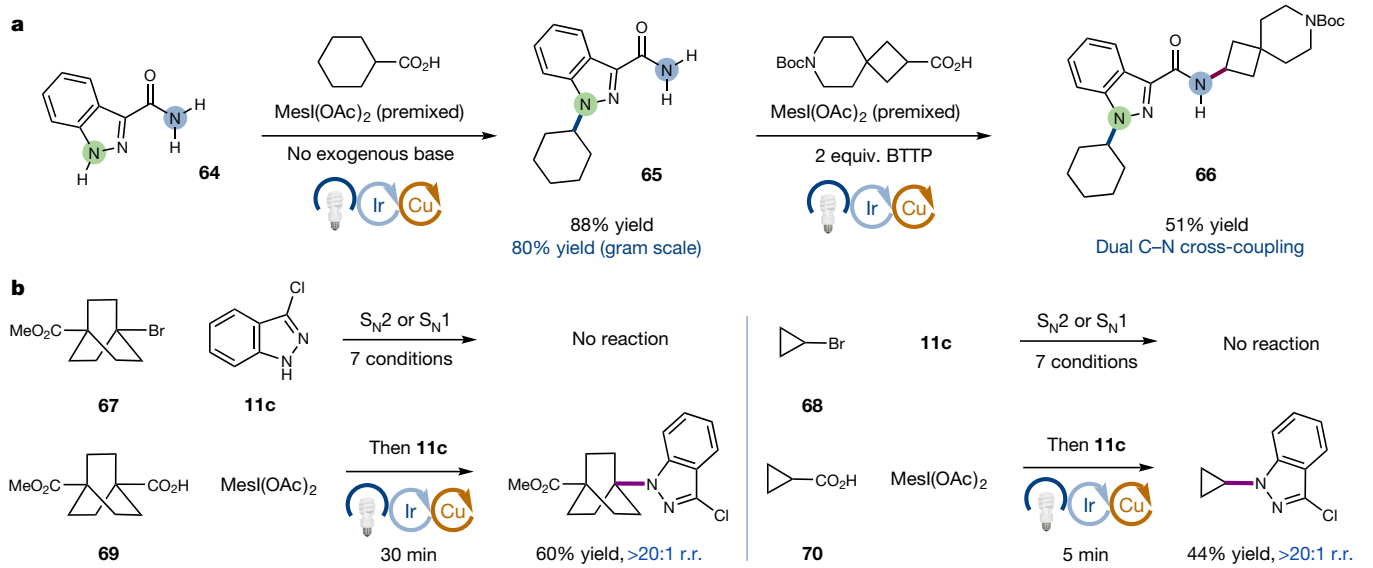


Fig. 5 | Sequential C–N couplings and comparisons with nucleophilic substitutions. a, Sequential decarboxylative C–N couplings can be realized using indazole derivative **64** that contains two nucleophilic sites, demonstrating the construction of molecular complexity. The *N*,*N*′-dialkylated product, which contains two different alkyl groups, can be easily generated through two C–N coupling reactions using 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.

coupling protocol does not appear to be negatively influenced by steric constraints, as *ortho*-substituted and *ortho*-,*ortho*-disubstituted anilines, sulfonamides and amides can be used readily (**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 yields (**58**–**63**, 44%–90% yield). An additional ten examples of pharmaceutical functionalization using this technology are described in Supplementary Information and Extended Data Fig. 4.

For substrates with several nucleophilic sites, achieving regioselective monofunctionalization has been a long-standing challenge[27]. Therefore, we were pleased to find that this new alkylation technology can be applied sequentially to the same drug molecule to achieve selective alkylation at two discrete nitrogen positions through the judicious choice of reaction conditions. As demonstrated in Fig. 5a, heterocycle **64** contains 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 carried out this 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 moieties in substrate **64** (that is, indazole and amide). More specifically, when no exogenous base is used, the carboxylate anion (formed by 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 (BTTP = *tert*-butyliminotri(pyrrolidino) phosphorane) leads to a second *N*-alkylation on the remaining amide nitrogen, again with a 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 substantial benefit with respect to the step economy of building complex molecules, by removing the need to install and remove nitrogen protecting groups.

Finally, to further showcase the utility of this new sp^3 C–N coupling method, we performed a series of experiments to compare the decarboxylative protocol with traditional nucleophilic substitution reactions (Fig. 5b). Under various 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, which is consistent with a lack of literature precedent for using these alkyl bromides with indazole nucleophiles. By contrast, through decarboxylative C–N couplings using commercially available carboxylic acids **69** and **70** and our mild catalytic protocol, the desired *N*-alkyl products can be obtained in good yields and excellent regioselectivities within 30 min 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.

Online content

Any Methods, including any statements of data availability and Nature Research reporting summaries, along with any additional references and Source Data files, are available in the online version of the paper at https://doi.org/10.1038/s41586-018-0234-8.

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1. Ruiz-Castillo, P. & Buchwald, S. L. Applications of palladium-catalyzed C–N cross-coupling reactions. *Chem. Rev.* **116**, 12564–12649 (2016).
2. Bhunia, S., Pawar, G. G., Kumar, S. V., Jiang, Y. & Ma, D. Selected copper-based reactions for C–N, C–O, C–S, and C–C bond formation. *Angew. Chem. Int. Ed.* **56**, 16136–16179 (2017).
3. Knölker, H.-J. (ed.) *The Alkaloids: Chemistry and Biology* Vol. 70 (Elsevier, San Diego, 2011).
4. Vitaku, E., Smith, D. T. & Njardarson, J. T. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. *J. Med. Chem.* **57**, 10257–10274 (2014).
5. Ćirić-Marjanović, G. Recent advances in polyaniline research: polymerization mechanisms, structural aspects, properties and applications. *Synth. Met.* **177**, 1–47 (2013).

6. Sambiagio, C., Marsden, S. P., Blacker, A. J. & McGowan, P. C. Copper catalysed Ullmann type chemistry: from mechanistic aspects to modern development. *Chem. Soc. Rev.* **43**, 3525–3550 (2014).
7. Qiao, J. X. & Lam, P. Y. S. Copper-promoted carbon–heteroatom bond cross-coupling with boronic acids and derivatives. *Synthesis* **2011**, 829–856 (2011).
8. Salvatore, R. N., Yoon, C. H. & Jung, K. W. Synthesis of secondary amines. *Tetrahedron* **57**, 7785–7811 (2001).
9. Swamy, K. C. K., Kumar, N. N. B., Balaraman, E. & Kumar, K. V. P. P. Mitsunobu and related reactions: advances and applications. *Chem. Rev.* **109**, 2551–2651 (2009).
10. Abdel-Magid, A. F. & Mehrman, S. J. A review on the use of sodium triacetoxyborohydride in the reductive amination of ketones and aldehydes. *Org. Process Res. Dev.* **10**, 971–1031 (2006).
11. Huang, L., Arndt, M., Gooßen, K., Heydt, H. & Gooßen, L. J. Late transition metal-catalyzed hydroamination and hydroamidation. *Chem. Rev.* **115**, 2596–2697 (2015).
12. Matier, C. D., Schwaben, J., Peters, J. C. & Fu, G. C. Copper-catalyzed alkylation of aliphatic amines induced by visible light. *J. Am. Chem. Soc.* **139**, 17707–17710 (2017).
13. Peacock, D. M., Roos, C. B. & Hartwig, J. F. Palladium-catalyzed cross coupling of secondary and tertiary alkyl bromides with a nitrogen nucleophile. *ACS Cent. Sci.* **2**, 647–652 (2016).
14. Curtius, T. 20. Hydrazide und azide organischer säuren I. Abhandlung. *J. Prakt. Chem.* **50**, 275–294 (1894).
15. Shaw, M. H., Twilton, J. & MacMillan, D. W. C. Photoredox catalysis in organic chemistry. *J. Org. Chem.* **81**, 6898–6926 (2016).
16. Twilton, J., Le, C., Zhang, P., Shaw, M. H., Evans, R. W. & MacMillan, D. W. C. The merger of transition metal and photocatalysis. *Nat. Rev. Chem.* **1**, 0052 (2017).
17. Zuo, Z. et al. Merging photoredox with nickel catalysis: coupling of α-carboxyl sp^3-carbons with aryl halides. *Science* **345**, 437–440 (2014).
18. Zhang, X. & MacMillan, D. W. C. Alcohols as latent coupling fragments for metallaphotoredox catalysis: sp^3–sp^2 cross-coupling of oxalates with aryl halides. *J. Am. Chem. Soc.* **138**, 13862–13865 (2016).
19. Zhao, W., Wurz, R. P., Peters, J. C. & Fu, G. C. Photoinduced, copper-catalyzed decarboxylative C–N coupling to generate protected amines: an alternative to the Curtius rearrangement. *J. Am. Chem. Soc.* **139**, 12153–12156 (2017).
20. Mao, R., Frey, A., Balon, J. & Hu, X. Decarboxylative C(sp^3)–N cross-coupling via synergistic photoredox and copper catalysis. *Nat. Catal.* **1**, 120–126 (2018).
21. Lowry, M. S. et al. Single-layer electroluminescent devices and photoinduced hydrogen production from an ionic iridium(III) complex. *Chem. Mater.* **17**, 5712–5719 (2005).
22. Sanna, G., Pilo, M. I., Zoroddu, M. A. & Seeber, R. Electrochemical and spectroelectrochemical study of copper complexes with 1,10-phenanthrolines. *Inorg. Chim. Acta* **208**, 153–158 (1993).
23. He, Z., Bae, M., Wu, J. & Jamison, T. F. Synthesis of highly functionalized polycyclic quinoxaline derivatives using visible-light photoredox catalysis. *Angew. Chem. Int. Ed.* **53**, 14451–14455 (2014).
24. Minisci, F., Vismara, E., Fontana, F. & Barbosa, M. C. N. A new general method of homolytic alkylation of protonated heteroaromatic bases by carboxylic acids and iodosobenzene diacetate. *Tetrahedr. Lett.* **30**, 4569–4572 (1989).
25. Tran, B. L., Li, B., Driess, M. & Hartwig, J. F. Copper-catalyzed intermolecular amidation and imidation of unactivated alkanes. *J. Am. Chem. Soc.* **136**, 2555–2563 (2014).
26. Stepan, A. F. et al. Application of the bicyclo[1.1.1]pentane motif as a nonclassical phenyl ring bioisostere in the design of a potent and orally active γ-secretase inhibitor. *J. Med. Chem.* **55**, 3414–3424 (2012).
27. Afagh, N. A. & Yudin, A. K. Chemoselectivity and the curious reactivity preferences of functional groups. *Angew. Chem. Int. Ed.* **49**, 262–310 (2010).
28. Bordwell, F. G. Equilibrium acidities in dimethyl sulfoxide solution. *Acc. Chem. Res.* **21**, 456–463 (1988).
29. Lõkov, M. et al. On the basicity of conjugated nitrogen heterocycles in different media. *Eur. J. Org. Chem.* 4475–4489 (2017).
30. Le, C. C. et al. A general small-scale reactor to enable standardization and acceleration of photocatalytic reactions. *ACS Cent. Sci.* **3**, 647–653 (2017).

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Author contributions Y.L. and X.Z. performed and analysed the experiments. Y.L., X.Z. and D.W.C.M. designed the experiments. Y.L., X.Z. and D.W.C.M. prepared the manuscript.

Competing interests The authors declare no competing interests.

Additional information
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Supplementary information is available for this paper at https://doi.org/10.1038/s41586-018-0234-8.

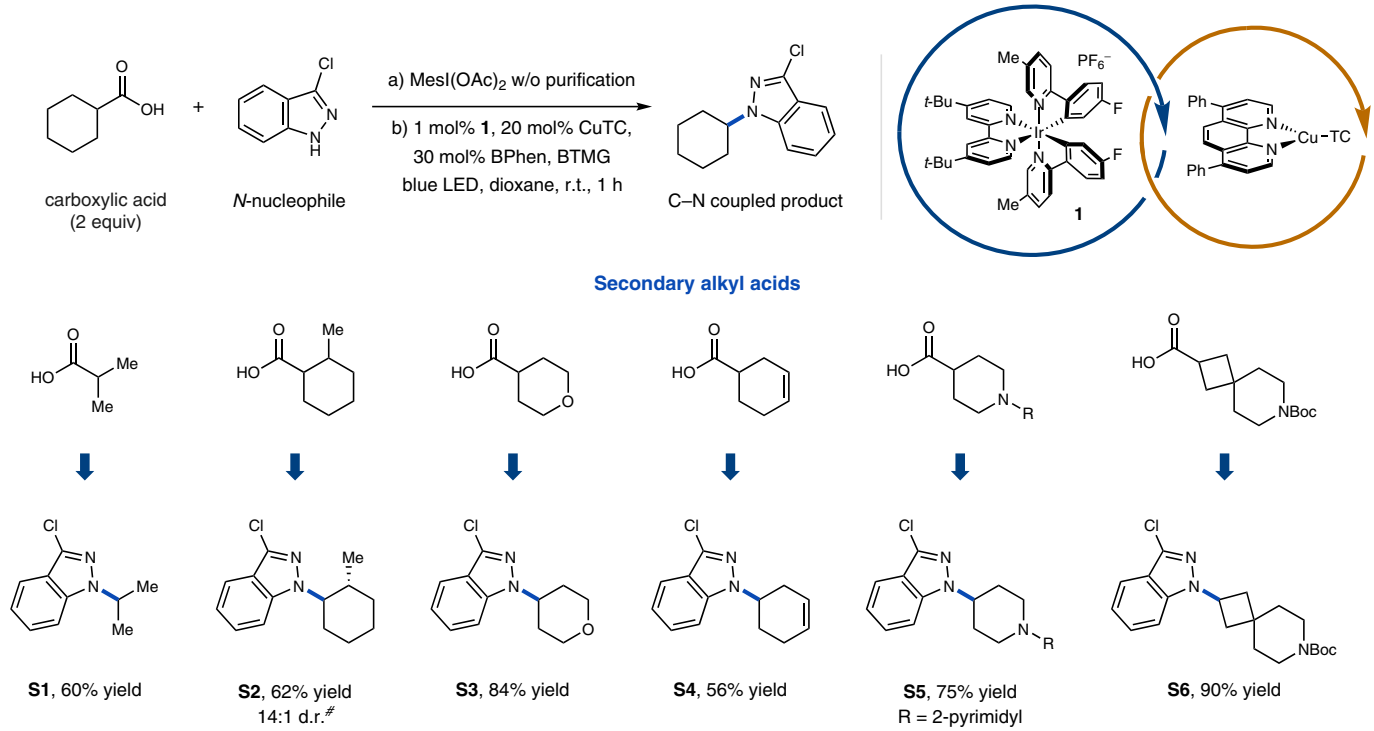
Correspondence and requests for materials should be addressed to D.W.C.M.

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 (Supplementary Fig. 36) and further experimental details are also provided in Supplementary Information.

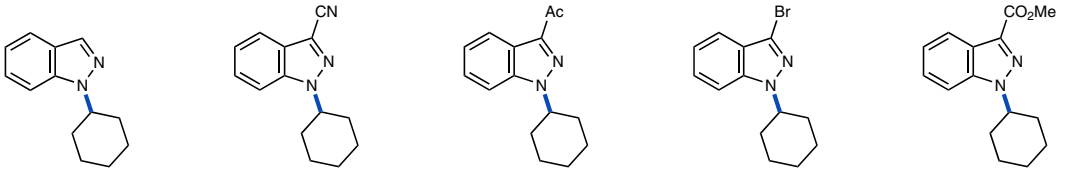
Procedure for decarboxylative sp^3 C–N couplings. To a 20 ml or 40 ml vial equipped with a stir bar was added photocatalyst, nitrogen nucleophile, iodomesitylene dicarboxylate, copper salt, and ligand. Dioxane was added followed by addition of the base. The solution was sonicated for 1–3 min until it became homogeneous. Next, the solution was degassed by sparging with nitrogen for 5–10 min 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 h. The reaction mixture was removed from the light, cooled to ambient temperature, diluted with water (15 ml) and ethyl acetate (25 ml), and the aqueous layer was extracted with ethyl acetate (3×25 ml). 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 nitrogen nucleophiles in dioxane was used; additionally, if the iodomesitylene dicarboxylate is a liquid, its solution in dioxane was used.

Data availability. The findings of this study are available within the paper and its Supplementary Information.

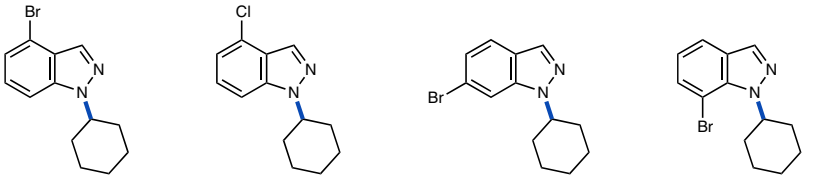


Extended Data Fig. 1 | Decarboxylative sp^3 C–N couplings with a series of secondary alkyl acids. An array of secondary alkyl carboxylic acids can be cross-coupled with 3-chloroindazole. The protocol provides the product as a single regioisomer in all cases. All yields are isolated. All reactions were replicated at least twice for consistency. See Supplementary Information for full experimental details. d.r., diastereomeric ratio. #d.r. was determined by ^{1}H NMR.

Indazoles

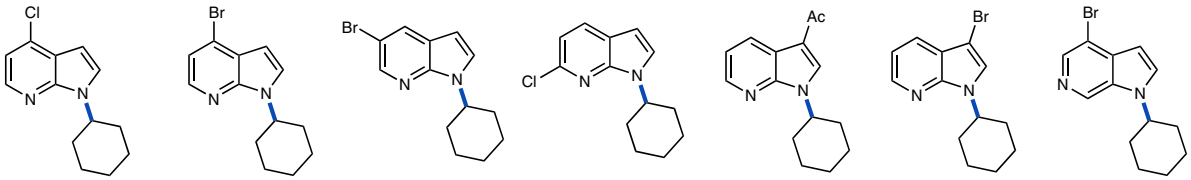


S7, 73% yield* **S8**, 94% yield* **S9**, 95% yield* **S10**, 78% yield* **S11**, 96% yield*



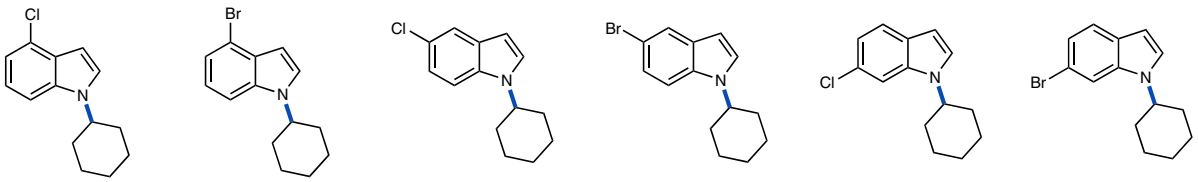
S12, 76% yield* **S13**, 88% yield* **S14**, 85% yield* **S15**, 41% yield*

Azaindoles



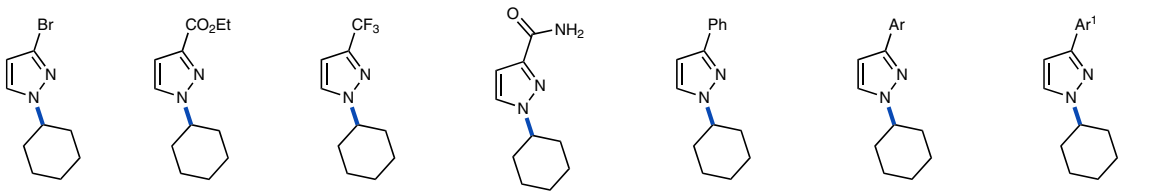
S16, 80% yield **S17**, 82% yield **S18**, 79% yield **S19**, 74% yield **S20**, 83% yield **S21**, 82% yield **S22**, 64% yield

Indoles



S23, 55% yield **S24**, 59% yield **S25**, 53% yield **S26**, 58% yield **S27**, 60% yield **S28**, 50% yield

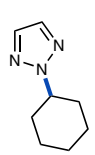
Pyrazoles



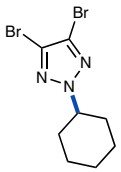
S29, 92% yield* **S30**, 72% yield * **S31**, 98% yield* **S32**, 62% yield* **S33**, 72% yield* **S34**, Ar = 4-Br-C_6H_4 85% yield* **S35**, Ar^1 = 4-Cl-C_6H_4 82% yield *

Extended Data Fig. 2 | Decarboxylative sp^3 C–N couplings with a series of nitrogen heterocycles. Various nitrogen heterocycles, including indazoles, azaindoles, indoles and pyrazoles, can cross-couple with carboxylic acids with good efficiency. All yields are isolated. All reactions were replicated at least twice for consistency. See Supplementary Information for full experimental details. *Single regioisomer.

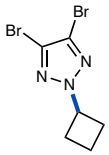
Other N-Heterocycles



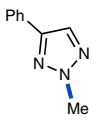
S36, 81% yield*



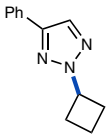
S37, 80% yield*



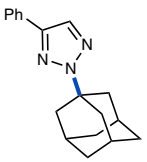
S38, 82% yield*



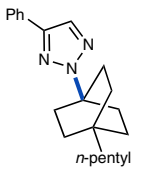
S39, 30% yield*



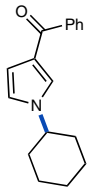
S40, 88% yield*



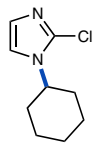
S41, 40% yield*



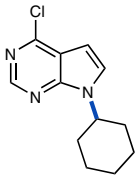
S42, 20% yield*



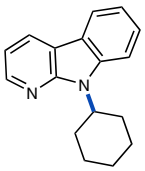
S43, 80% yield



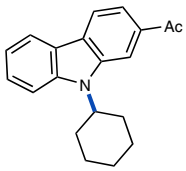
S44, 60% yield



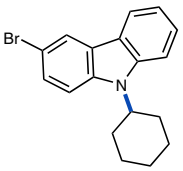
S45, 85% yield



S46, 48% yield

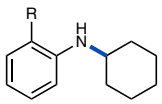


S47, 51% yield

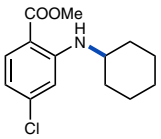


S48, 45% yield

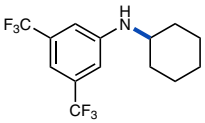
Anilines



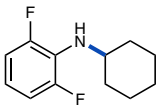
S49, R = Br, 66% yield
S50, R = Ac, 66% yield
S51, R = CN, 61% yield



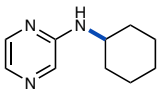
S52, 53% yield



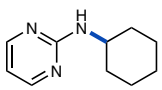
S53, 51% yield



S54, 34% yield#

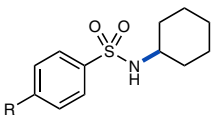


S55, 58% yield

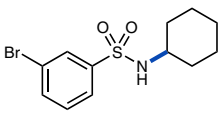


S56, 52% yield

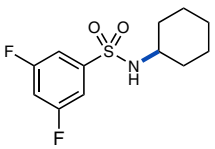
Sulfonamides



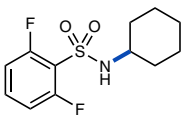
S57, R = Me, 67% yield
S58, R = F, 67% yield
S59, R = Cl, 53% yield
S60, R = Br, 63% yield



S61, 50% yield

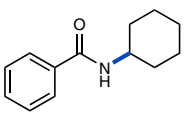


S62, 55% yield

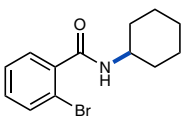


S63, 52% yield

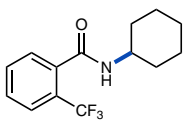
Amides



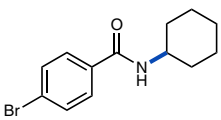
S64, 74% yield



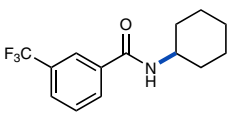
S65, 71% yield



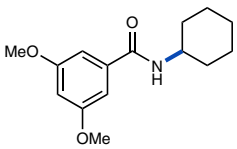
S66, 74% yield



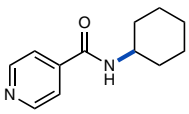
S67, 74% yield



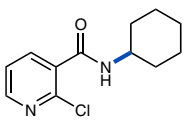
S68, 77% yield



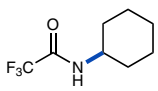
S69, 74% yield



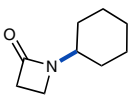
S70, 81% yield



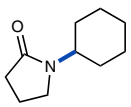
S71, 70% yield



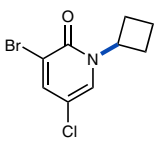
S72, 84% yield



S73, 78% yield

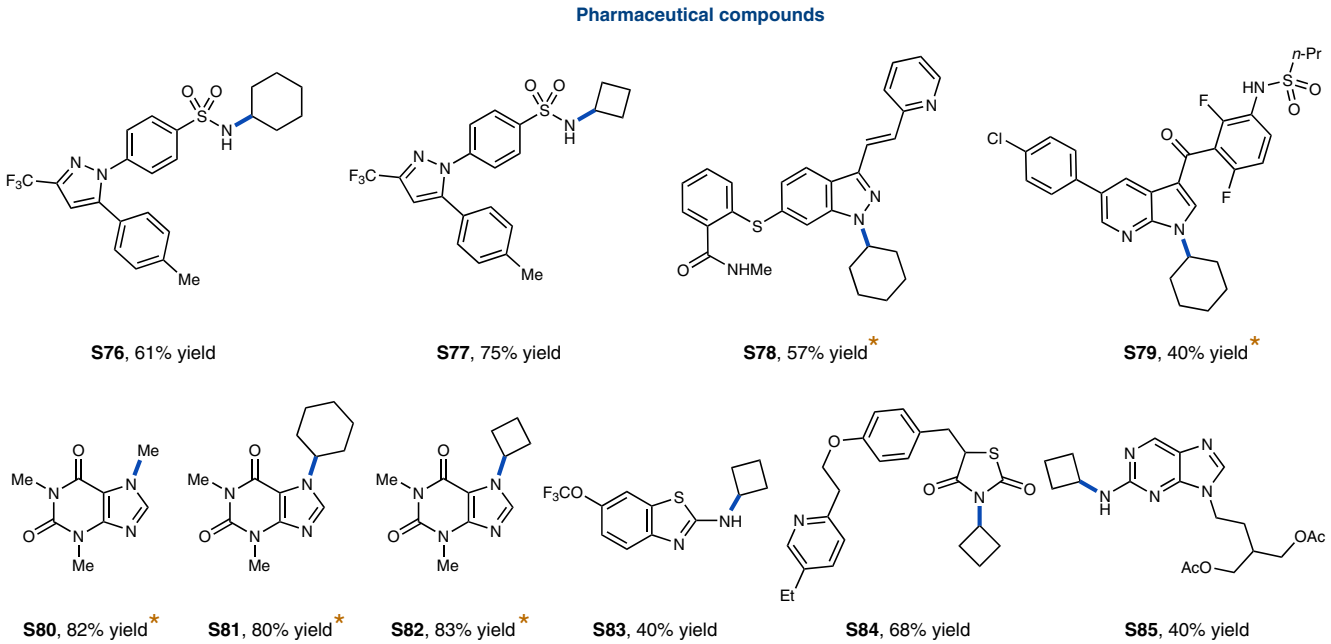


S74, 17% yield&



S75, 28% yield*

Extended Data Fig. 3 | Decarboxylative sp^3 C–N couplings with a series of nitrogen nucleophiles. Various nitrogen nucleophiles, including nitrogen heterocycles, anilines, sulfonamides and amides, can cross-couple with carboxylic acids with good efficiency. All yields are isolated unless otherwise noted. All reactions were replicated at least twice for consistency. 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 Fig. 4 | Decarboxylative sp^3 C–N couplings with a series of pharmaceutical compounds. Several drug molecules can cross-couple with carboxylic acids with good efficiency. All yields are isolated. All reactions were replicated at least twice for consistency. See Supplementary Information for full experimental details. *Single regioisomer.