LETTER

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Metallaphotoredox-catalysed sp^3–sp^3 cross-coupling of carboxylic acids with alkyl halides

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In the past 50 years, cross-coupling reactions mediated by transition metals have changed the way in which complex organic molecules are synthesized. The predictable and chemoselective nature of these transformations has led to their widespread adoption across many areas of chemical research[1]. However, the construction of a bond between two sp^3-hybridized carbon atoms, a fundamental unit of organic chemistry, remains an important yet elusive objective for engineering cross-coupling reactions[2]. In comparison to related procedures with sp^2-hybridized species, the development of methods for sp^3–sp^3 bond formation via transition metal catalysis has been hampered historically by deleterious side-reactions, such as β-hydride elimination with palladium catalysis or the reluctance of alkyl halides to undergo oxidative addition[3,4]. To address this issue, nickel-catalysed cross-coupling processes can be used to form sp^3–sp^3 bonds that utilize organometallic nucleophiles and alkyl electrophiles[5–7]. In particular, the coupling of alkyl halides with pre-generated organozinc[8,9], Grignard[10] and organoborane[11] species has been used to furnish diverse molecular structures. However, the manipulations required to produce these activated structures is inefficient, leading to poor step- and atom-economies. Moreover, the operational difficulties associated with making and using these reactive coupling partners, and preserving them through a synthetic sequence, has hindered their widespread adoption. A generically useful sp^3–sp^3 coupling technology that uses bench-stable, native organic functional groups, without the need for pre-functionalization or substrate derivatization, would therefore be valuable. Here we demonstrate that the synergistic merger of photoredox and nickel catalysis enables the direct formation of sp^3–sp^3 bonds using only simple carboxylic acids and alkyl halides as the nucleophilic and electrophilic coupling partners, respectively. This metallaphotoredox protocol is suitable for many primary and secondary carboxylic acids. The merit of this coupling strategy is illustrated by the synthesis of the pharmaceutical tirofiban in four steps from commercially available starting materials.

Within the field of drug discovery, there is a demonstrated statistical correlation between clinical success and the molecular complexity of medicinal candidates with respect to the inherent ratio of sp^2–sp^3 to sp^3–sp^3 bond content[12]. Not surprisingly, these findings have created an emerging demand within medicinal chemistry for new reaction technologies that enable rapid access to drug-like molecules via the coupling of fragments that incorporate or build novel sp^3–sp^3 bonds. However, a major hurdle associated with achieving sp^3–sp^3 bond formation via transition metal catalysis is the limited availability of a diverse suite of nucleophilic coupling partners that are bench-stable, inexpensive, and easily procured. An attractive option would be to use simple carboxylic acids, an abundant native functional group that is chemically robust yet can be readily exploited as a latent leaving group after multistep synthetic sequences (Fig. 1).

The emergence of visible-light-mediated photoredox catalysis within the field of synthetic organic chemistry has enabled the discovery and invention of numerous unique and valuable transformations[13,14]. Indeed, the electronic duality of photocatalyst excited states (which are simultaneously strong oxidants and reductants) has prompted the exploitation of these polypyridyl transition metal complexes in unconventional bond disconnections[15] and facilitated the manipulation of oxidation states in organometallic complexes to enable previously elusive reactions[16–19]. For example, the synergistic merger of single-electron transfer (SET) based decarboxylation with nickel-activated electrophiles has promoted the formation of valuable sp^2–sp^3 bonds while broadening the field of cross-coupling chemistry via the use of non-conventional reaction substrates[20,21]. This work has further served as a foundation for several extensions of our decarboxylative nickel cross-coupling concept using preactivated phthalimido-derivatized acids[7,22]. Recently, we hypothesized that a straightforward and generic procedure might be developed to enable sp^3–sp^3 bond formation via the application of ubiquitous carboxylic acids in a decarboxylative cross-coupling with alkyl halides using photoredox catalysis. In developing a method for direct coupling of carboxylic acids with alkyl halides, we hoped to introduce a paradigm for carbon–carbon bond construction that would (i) provide rapid access to complex fragments via sp^3–sp^3 coupling, (ii) systematically streamline synthetic routes towards drug candidates, and (iii) enable alkyl–alkyl coupling using native functional groups and without substrate preactivation.

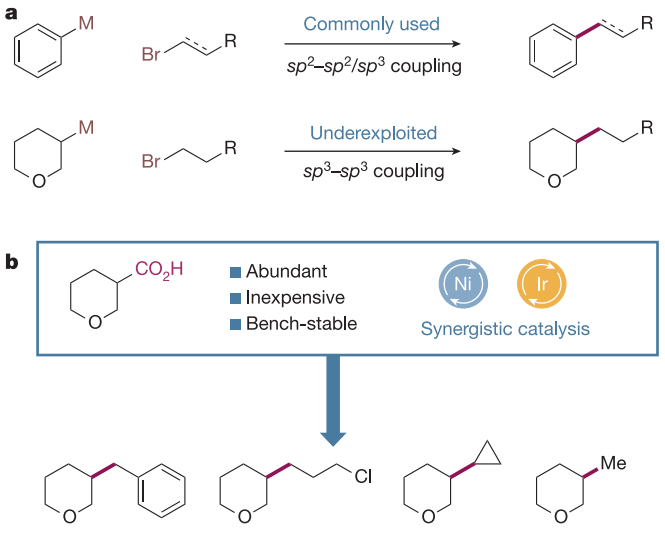

Figure 1 | Carboxylic acids as coupling partners in a metallaphotoredox-mediated process to form sp^3–sp^3 bonds. a, The majority of transition-metal-catalysed cross-couplings commonly use at least one sp^2-hydridized coupling partner (top). At present, sp^3–sp^3 cross-coupling is underexploited (bottom). **b**, The direct utilization of abundant, bench-stable, native functional groups such as carboxylic acids in combination with Ni and Ir synergistic catalysis under mild conditions (top) should encourage greater adoption of sp^3–sp^3 bond forming methods, leading to products such as those shown at the bottom. M, metal; R, organic functional group.

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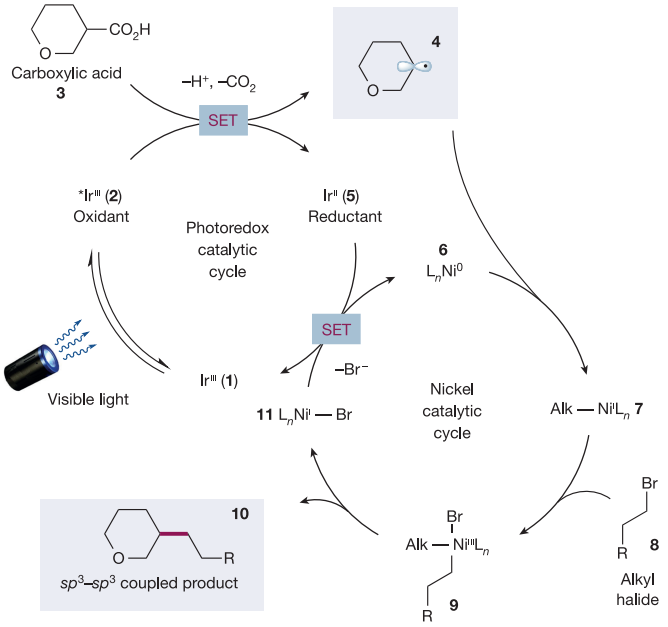

Figure 2 | Proposed mechanism for the metallaphotoredox-mediated cross-coupling of carboxylic acids to generate sp^3–sp^3 bonds. The photoredox catalytic cycle commences with excitation of Ir^{III} **1** to give the excited state **2**. Single electron oxidation of the carboxylate anion derived from acid **3** by oxidant **2** produces the alkyl radical **4** after CO_2-extrusion along with Ir^{II} **5**. The nickel catalytic cycle starts with Ni^0 catalyst **6** capturing the alkyl radical **4** (boxed at top) to form the Ni^I species **7**. Ensuing oxidative addition with alkyl halide **8** leads to nickel(III) intermediate **9**. Reductive elimination would then liberate the desired product **10** (boxed at bottom) and Ni^I **11**. Both catalytic cycles converge to complete a single turnover via a SET event that regenerates the photoredox and nickel catalysts.

A detailed mechanism for the proposed decarboxylative sp^3–sp^3 coupling is delineated in Fig. 2. Initial visible-light excitation of the iridium(III) photocatalyst $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (**1**) would generate the long-lived (lifetime $\tau = 2.3\,\mu s$)[23] excited-state $*Ir^{III}$ complex **2** ($dF(CF_3)ppy$ = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine, dtbbpy = 4,4′-di-*tert*-butyl- 2,2′-bipyridine). Complex **2** is a strong single-electron oxidant (half-wave redox potential $E_{1/2}^{red}[*Ir^{III}/Ir^{II}] = +1.21$ V versus the standard calomel electrode, SCE, in CH_3CN)[23] and should undergo reduction by a carboxylate anion derived from deprotonation of the acid **3**. The resultant carboxyl radical is expected to rapidly extrude CO_2 to produce alkyl radical **4** and the reduced Ir^{II} catalyst **5**. Concurrently, the ligated nickel(0) complex **6** is generated *in situ* via two discrete SET reductions of $(dtbbpy)Ni(II)Cl_2$ by the iridium(II) state of the photocatalyst through sacrificial carboxylic acid consumption ($E_{1/2}^{red}[Ir^{III}/Ir^{II}] = -1.37$ V versus SCE in CH_3CN, $E_{1/2}^{red}[Ni^{II}/Ni^0] = -1.2$ V versus SCE in dimethylformamide, DMF)[23,24]. The Ni^0 complex **6** can intercept radical **4** to produce alkyl-Ni^I intermediate **7**[25]. Subsequent oxidative addition with alkyl halide **8** forms the putative organometallic Ni^{III} species **9**, which after reductive elimination forges the desired sp^3–sp^3 bond to furnish the coupled product **10** and Ni^I adduct **11**[26–28]. At this stage the two catalytic cycles would converge by reduction of nickel(I) intermediate **11** by the reduced form of the iridium photocatalyst to re-establish both the Ir^{III} complex **1** and the Ni^0 catalyst **6**[23]. At present, we cannot rule out the possibility of an alternative mechanism that involves Ni^0-mediated oxidative addition and trapping of the alkyl radical **4** by a Ni^{II} species[20,25].

Based on this approach, we began our primary investigations with consideration of the metallaphotoredox conditions previously developed within our group[20]. In these studies we used *N*-Boc proline (Boc, *t*-butyloxycarbonyl) and 1-bromo-3-phenylpropane as coupling partners. Unfortunately, owing to the basic reaction conditions in combination with the polar aprotic solvent DMF, exclusive ester formation was observed. Therefore, we recognized that judicious selection of solvent and base would be necessary to suppress this unwanted by-product formation without obstructing the desired photocatalytic oxidation reaction pathway. To accomplish this goal, a survey of solvents and inorganic bases was conducted in the presence of $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$, $NiCl_2$·glyme and dtbbpy with visible-light irradiation from blue-light-emitting diodes (LEDs). This revealed that the combination of acetonitrile and K_2CO_3 greatly reduced the rate of carboxylate alkylation and furnished the desired product in 68% yield. Further optimization improved conversion to product through switching to the more electron-rich ligand 4,4′-dOMe-bpy (4,4′-dimethoxy-2,2′-bipyridine). Finally, the addition of water, which decelerated ester formation, provided an additional enhancement and an isolated yield of 85%. A series of control experiments omitting each individual reaction component highlighted the importance of photocatalyst, nickel and light for promoting this decarboxylative sp^3–sp^3 bond-forming reaction (see Supplementary Information).

With optimal metallaphotoredox conditions in hand, we probed the generality of this process with respect to the aliphatic halide electrophile. As representative nucleophilic coupling partners, *N*-Boc- and *N*-Cbz proline (Cbz, carboxybenzyl) were used interchangeably for this purpose (Fig. 3). Simple unfunctionalized primary alkyl halides such as 1-bromo-3-phenylpropane were examined, and these underwent efficient cross-coupling (**12**, 85% yield). Functionality vicinal to the bromide was also tolerated, with benzyl 2-bromoethyl ether coupling in good yield (**13**, 65% yield). A substrate bearing a terminal olefin performed favourably under the reaction conditions to deliver the desired product (**14**, 84% yield). As this protocol is conducted at near ambient temperature, hydrolysis of an ethyl ester does not occur under the optimized basic reaction conditions, and the corresponding carbamate-protected amine was isolated in good yield (**15**, 64% yield). In addition, perfect chemoselective functionalization of an alkyl bromide in the presence of a primary chloroalkane was observed (**16**, 96% yield). A deprotection-cyclization sequence with this material would provide rapid access to the bicyclic tertiary amine core of the naturally occurring pyrrolizidine alkaloids. The presence of free hydroxyl groups is fully compatible with the iridium photocatalyst and the nickel complex (**17**, 86% yield). Moreover, reactive Lewis basic functionalities, such as epoxides and aldehydes, are well tolerated in this cross-coupling procedure and provide numerous opportunities for further derivatization (**18** and **19**, 83% and 62% yield, respectively).

The influence of substitution on the alkyl halide was also investigated to probe the steric limits of the electrophilic coupling partner. No detrimental effects to the efficiency of this process were observed when a β,β-disubstituted bromoalkane was used, and neopentyl bromide coupled in modest yield (**20** and **21**, 75% and 52% yield, respectively). The higher propensity for activated electrophiles to promote esterification led to the utilization of benzyl chloride, as opposed to benzyl bromide, which generated a homobenzylic amine in good yield (**22**, 84% yield). Notably, bromomethane was a competent coupling partner in this protocol which formally affords the product of a fully reduced carboxylic acid moiety in a single step (**23**, 62% yield).

Expanding the substrate scope to encompass secondary alkyl halides permitted us to forge sp^3–sp^3 bonds with adjacent tertiary carbon centres. For example, five- and six-membered cyclic bromoalkanes smoothly reacted to form the desired alkylated products in good to excellent yields (**24**–**26**, 57–91% yield). Smaller ring systems, including cyclopropane and oxetane, were also introduced via this metallaphotoredox procedure (**27** and **28**, 50% and 79% yield, respectively). These motifs have found application in drug discovery programmes as chemically and metabolically stable bioisosteres[29]. Lastly, an acyclic secondary alkyl bromide was also successfully cross-coupled to generate the desired Cbz-protected amine (**29**, 69% yield).

We subsequently examined the scope of the nucleophilic component and found that an assortment of readily available carboxylic acids were viable for this transformation. For instance,

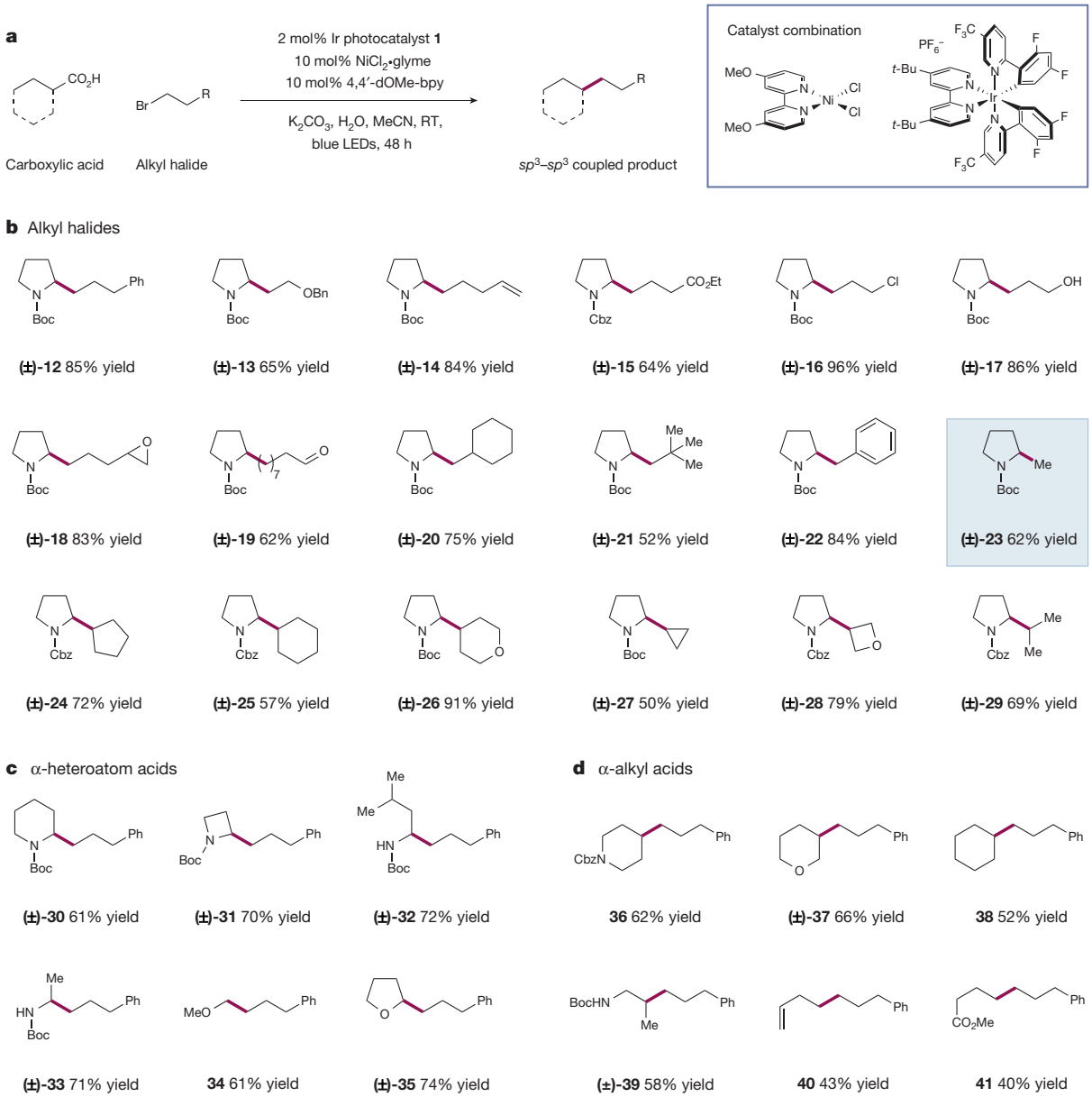

Figure 3 | Carboxylic acid and alkyl halide scope in the dual nickel-photoredox catalysed sp^3–sp^3 coupling reaction. A broad array of alkyl halides and carboxylic acids are amenable coupling partners in this transformation. **a**, Generalized reaction; **b**–**d**, substrate scope. Optimal catalysts shown in the top right box (some substrates require minor modification; see Supplementary Information). Primary and secondary electrophiles were coupled efficiently with proline derivatives. Alternative α-heteroatom substituted carboxylic acids could also be used to form functionalized amines and ethers. Challenging substrates lacking apparent radical stabilization could also be used successfully. Isolated yields are reported below each entry. See Supplementary Information for full experimental details. For product (±)-**23** shown in shaded box at right in **b**, a yield of 55% was obtained when the reaction was run in flow (GC yield); see Supplementary Information. For product **40** at bottom right in **d**, cyclopropylacetic acid was used.

Boc-protected pipecolic acid and an azetidine derivative both underwent decarboxylative coupling to furnish alkylated products in good yields (**30** and **31**, 61% and 70% yield, respectively). Naturally occurring amino acids, which are inexpensive and obtainable from ample biomass feedstocks, can also be exploited to form α-functionalized amines with excellent efficiency (**32** and **33**, 72% and 71% yield, respectively). Similarly, *O*-methylated glycolic acid functions well to provide access to linear ethers in a straightforward manner (**34**, 61% yield). The cyclic substrate tetrahydrofuran-2-carboxylic acid was also coupled with 1-bromo-3-phenylpropane under these dual nickel-photoredox conditions to afford the ethereal product in very good yield (**35**, 74% yield). Although beneficial, the inclusion of an α-heteroatom on the acid fragment is not a prerequisite for this sp^3–sp^3 bond forming process. For example, Cbz-protected isonipecotic acid and a tetrahydro-2*H*-pyran derivative were cleanly converted to the corresponding coupled products in an effective fashion (**36** and **37**, 62% and 66% yield, respectively). Simple alkyl precursors lacking heteroatoms can also be used, with cyclohexanecarboxylic acid reacting in reasonable yield (**38**, 52% yield). An acyclic β-amino acid that would generate a secondary radical upon decarboxylation exhibited respectable efficiency and offers the opportunity to synthesize β-functionalized amines with ease (**39**, 58% yield).

Finally, two primary substrates were evaluated in this system to fully exemplify the power of this new sp^3–sp^3 coupling paradigm. The rearrangement of a cyclopropyl system under the reaction conditions presents the opportunity to produce alkylated homoallylic products in a single step (**40**, 43% yield). Moreover, the monomethyl ester of glutaric acid was subjected to the optimized metallaphotoredox procedure and provided an encouraging quantity of the desired product (**41**, 40% yield).

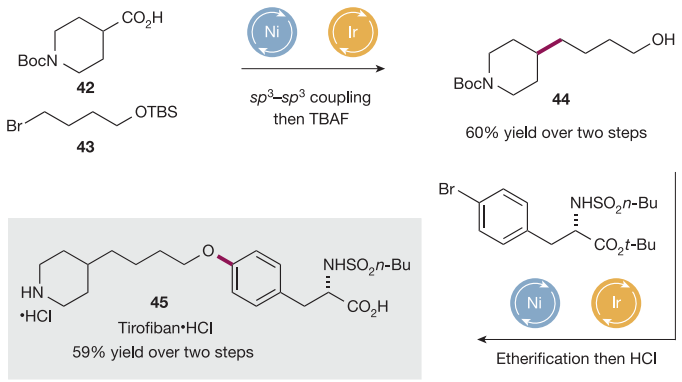

Figure 4 | Application of two metallaphotoredox strategies to the synthesis of tirofiban. The cross-coupling of acid **42** and alkyl halide **43** (top left) using Ni and Ir catalysis generates a new sp^3–sp^3 bond, and subsequent tetrabutylammonium fluoride (TBAF) deprotection provides alcohol **44** (top right). Tirofiban **45** (bottom left) is then synthesized in two further steps in good yield via a Ni/Ir-mediated etherification reaction and acidic deprotection; 34% of the bromide starting material was recovered.

This substrate highlights the potential for downstream modification of latent carboxylates since hydrolysis of the methyl ester would unlock the potential for further sp^3–sp^3 bond formation. Thus, molecules that contain multiple carboxylic acids can function as linch-pin reagents for the rapid assembly of complex molecular architectures. It should be noted that when tertiary acids were applied, the coupled products could be obtained in only limited efficiencies (about 5%–10%). Attempts to improve the yields to synthetically useful levels are continuing.

To further demonstrate the synthetic utility of this decarboxylative coupling protocol, we applied it to the synthesis of the antiplatelet drug tirofiban[30]. As shown in Fig. 4, Boc-isonipecotic acid **42** and alkyl bromide **43** (protected to avoid cyclization to tetrahydrofuran, THF) were exposed to the optimized metallaphotoredox conditions to afford alcohol **44** in good yield, following deprotection of the silyl ether. Thereafter, utilization of the previously established dual photoredox–nickel catalytic etherification reaction enabled direct formation of the desired C–O bond[16]. Following acidic deprotection, tirofiban **45** was synthesized in 59% yield over the final two steps.

We have established a robust strategy for the direct formation of sp^3–sp^3 bonds from abundant carboxylic acids and alkyl halides. This new platform for carbon–carbon bond construction is enabled by the catalytic activation of both coupling partners through the synergistic merger of photoredox and nickel catalysis. The benign nature of the reaction conditions has been exemplified by the breadth of functional groups tolerated in this transformation. We believe that the generality of this methodology and the ready availability of the starting materials used will aid the uptake of sp^3–sp^3 cross-coupling across several fields of synthetic organic chemistry.

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Supplementary Information is available in the online version of the paper.

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