

Cross-Coupling

International Edition: DOI: 10.1002/anie.201511438
German Edition: DOI: 10.1002/ange.201511438Direct Acylation of C(sp³)–H Bonds Enabled by Nickel and Photoredox Catalysis

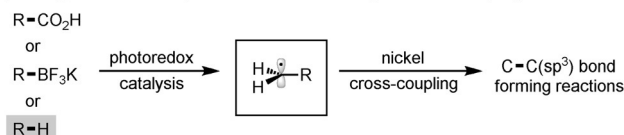
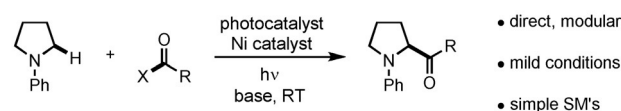
Candice L. Joe and Abigail G. Doyle*

Abstract: Using nickel and photoredox catalysis, the direct functionalization of C(sp³)–H bonds of *N*-aryl amines by acyl electrophiles is described. The method affords a diverse range of α -amino ketones at room temperature and is amenable to late-stage coupling of complex and biologically relevant groups. C(sp³)–H activation occurs by photoredox-mediated oxidation to generate α -amino radicals which are intercepted by nickel in catalytic C(sp³)–C coupling. The merger of these two modes of catalysis leverages nickel's unique properties in alkyl cross-coupling while avoiding limitations commonly associated with transition-metal-mediated C(sp³)–H activation, including requirements for chelating directing groups and high reaction temperatures.

Transition metal catalyzed functionalization of C–H bonds represents a transformative approach to the construction of C–C and C–heteroatom bonds.^[1] Its power originates in the ability to accomplish site-selective derivatization of otherwise inert arenes and alkanes without the need for prefunctionalized starting materials. While the direct functionalization of C(sp²)–H bonds is well-represented in the literature, functionalization of C(sp³)–H bonds remains a paramount challenge.^[2] Given the emerging value of nickel catalysis in achieving alkyl cross-coupling, its application in C(sp³)–H activation presents an exciting opportunity to develop new C(sp³)–C bond-forming reactions. Recently, transition metal catalyzed C(sp³)–H functionalization reactions with nickel have been reported.^[3] However, these methods require the use of coordinating directing groups and high reaction temperatures (>100°C) to accomplish the key C(sp³)–H activation step, thus limiting their breadth and impact in the context of complex molecule synthesis.

Our group, along with those of MacMillan and Molander, recently reported that the combination of visible-light-mediated photoredox catalysis and nickel catalysis can enable new C(sp³)–type cross-coupling reactions between aryl halides and either alkyl carboxylic acids or alkyl boronates.^[4] By using single-electron transfer (SET), the photocatalyst converts the C(sp³) reaction partner into an organic radical, which is intercepted by the nickel catalyst to forge a new C(sp³)–C bond (Figure 1 a). Photoredox catalysts can also generate organic radicals from C(sp³)–H bonds by

a) Photogeneration of alkyl radicals for nickel-catalyzed cross-coupling

b) This work: C(sp³)–H cross-coupling with acyl electrophiles

c) Proposed catalytic cycle for metallaphotoredox C–H acylation

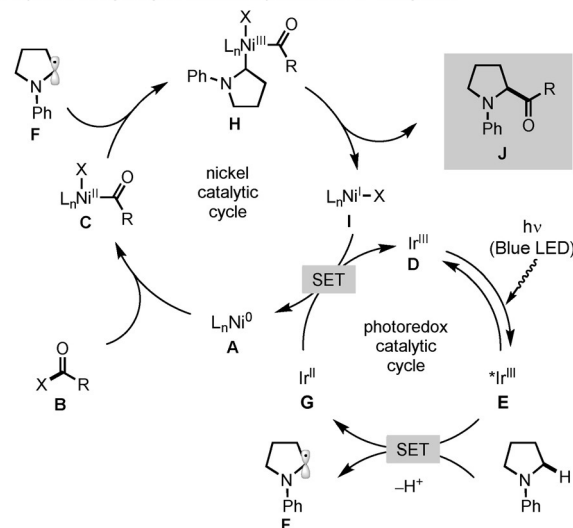


Figure 1. Metallaphotoredox C(sp³)–H cross-coupling with acyl electrophiles. SM = starting material.

SET.^[5] We hypothesized that the combination of photoredox and nickel catalysis could be leveraged to develop novel C(sp³)–H functionalization reactions which take advantage of nickel's unique characteristics in C(sp³)–C bond formation while avoiding its limitations in the C–H activation step.^[6] A proof-of-concept study provided support for this idea, demonstrating that an iridium photocatalyst and nickel catalyst promote arylation of the α -C(sp³)–H bond of *N,N*-dimethylaniline at room temperature.^[4b] Unfortunately, amines bearing β -hydrogen atoms were not competent reaction partners. Given the mildness of these reaction conditions, we sought to demonstrate the value of this approach as a platform for the discovery of novel C(sp³)–H functionalization reactions of broad scope.^[7] Herein we report a photoredox and nickel-catalyzed C(sp³)–H coupling of acyl donors with *N*-aryl amines, including those containing β -hydrogen atoms, a trans-

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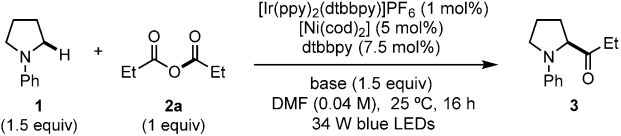
formation currently not possible using either mode of catalysis alone (Figure 1 b).

This α -amine functionalization reaction^[8] generates α -amino ketones in a single step from simple and inexpensive starting materials. Classic approaches to the synthesis of this valuable motif require multistep processes and prefunctionalized reagents.^[9,10] An α -amino C(sp³)-H carbonylation has been previously reported by Murai and co-workers utilizing a rhodium catalyst, CO, and ethylene. However, this reaction requires a 2-pyridyl directing group on the amine substrate, temperatures exceeding 100 °C, and only generates ethyl ketones.^[11] The metallaphotoredox strategy described herein utilizes instead an *N*-aryl moiety for the photoredox potential-gated mechanism of C(sp³)-H activation. This key mechanistic feature allows the reaction to take place under exceptionally mild reaction conditions compared to most transition metal catalyzed C(sp³)-H functionalization reactions, thus enabling late-stage coupling of complex and biologically relevant partners.

For the C(sp³)-H acylation reaction, we envisioned a catalytic cycle (Figure 1 c) initiated by oxidative insertion of the nickel(0) catalyst **A** into the acyl-X **B** to afford the nickel(II)-acyl oxidative adduct **C**.^[12] Concurrently, irradiation of the iridium photocatalyst, [Ir(ppy)₂(dtbbpy)]PF₆ (**D**) (ppy = 2-phenylpyridine, dtbbpy = 4,4'-di-*tert*-butyl-2,2'-dipyridyl), produces the long-lived excited state complex **E** (τ = 557 ns).^[13] The complex **E** ($E_{1/2}^{\text{red}}[*\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}] = +0.70$ V vs. SCE in MeCN)^[13] can undergo SET with *N*-phenylpyrrolidine (**1**; $E_{1/2}^{\text{red}} = +0.70$ V),^[14] which, upon deprotonation, generates the α -amino radical **F** and reduced iridium(II) species **G**. Interception of **F** by **C** likely affords the nickel(III) complex **H**. Subsequent reductive elimination forges the C-C bond, thus providing **J** with concomitant generation of the nickel(I) intermediate **I**. We expect that both catalytic cycles are closed by SET from the highly reducing **G** ($E_{1/2}^{\text{red}}[\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}] = -1.5$ V vs. SCE in MeCN)^[13] to **I** ($E_{1/2}^{\text{red}}[\text{Ni}^{\text{II}}/\text{Ni}^0] = -1.2$ V vs. SCE in DMF),^[15] thereby reconstituting the nickel(0) catalyst and the iridium(III) photocatalyst.^[16]

Our initial investigations began with the coupling of *N*-phenylpyrrolidine (**1**) and commercially available propionic anhydride (**2a**; Table 1). Using [Ni(cod)₂], dtbbpy, and [Ir(ppy)₂(dtbbpy)]PF₆, it was discovered that the identity of the base was crucial for obtaining high yield of the α -amino ketone product **3**.^[17] In the absence of exogenous base, **3** was obtained in 65 % yield (entry 1). Addition of sodium propionate afforded the desired ketone product in an improved 82 % yield (entry 3). However, employing a carboxylate base that was not matched to the anhydride, such as sodium acetate, provided a mixture of methyl and ethyl ketone products, presumably due to the in situ generation of a mixed anhydride. Given the impracticality of using unique carboxylate bases for each anhydride partner, we sought a solution that could be universally applicable. Our attention turned to amine bases. While **3** was obtained in modest yield using DABCO and DBU (entries 4 and 5), switching to quinuclidine provided the coupled product in 83 % yield (entry 6).^[18] The reaction performs with marginally lower efficiency using NiCl₂·glyme, an air-stable nickel precatalyst (entry 7). Notably, control reactions in the absence of a photocatalyst

Table 1: Reaction optimization.^[a]



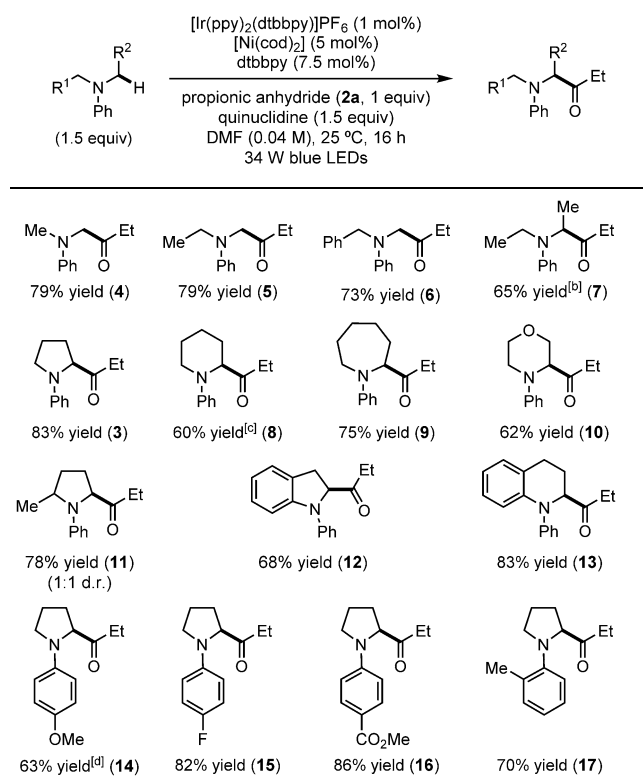
Entry ^[a]	Reaction conditions	Base	Yield [%] ^[a]
1	as shown	no base	65
2	as shown	Cs ₂ CO ₃	30
3	as shown	NaOC(O)Et	82
4	as shown	DABCO	37
5	as shown	DBU	57
6	as shown	quinuclidine	83
7	NiCl ₂ ·glyme as Ni catalyst	quinuclidine	70
8	no photocatalyst	quinuclidine	0
9	no Ni catalyst	quinuclidine	0
10	no light	quinuclidine	0

[a] Yield determined by ¹H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an external standard. DABCO = 1,4-diazabicyclo[2.2.2]octane, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMF = *N,N*-dimethylformamide, dtbbpy = 4,4'-di-*tert*-butyl-2,2'-dipyridyl, cod = 1,5-cyclooctadiene, ppy = 2-phenylpyridine.

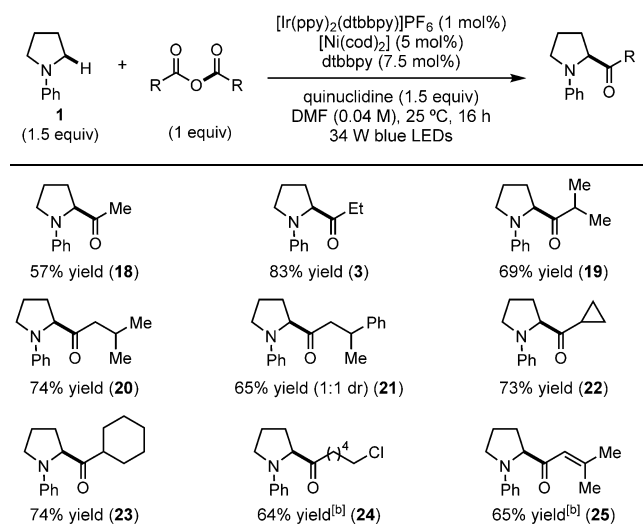
(entry 8), a nickel catalyst (entry 9), and light (entry 10) result in no conversion to product.

With optimized reaction conditions in hand, we investigated the scope with respect to the amine coupling partner (Table 2). A variety of symmetric (**4,7**) and nonsymmetric (**5,6**) acyclic *N*-aryl amines are tolerated, with ketone formation occurring selectively at the less hindered C-H bond. Five-, six-, and seven-membered cyclic amine substrates afford α -amino ketone products in high yields (**3, 8–9**). Consistent with a sterically driven deprotonation, the generation of the quaternary ketone product is not observed with 2-methyl-*N*-phenylpyrrolidine. Instead, the tertiary ketone product **11** is formed in 78 % yield as a 1:1 mixture of diastereomers. We were pleased to find that the acylation of pharmacologically important heterocycles, such as indolines (**12**), tetrahydroquinolines (**13**), and morpholines (**10**) occurs smoothly. Furthermore, examination of the substituents on the *N*-aryl group revealed that a *para*-methoxyphenyl (PMP) group (**14**), which can be removed under oxidative conditions to unmask the free amine, is competent under slightly modified reaction conditions. Additionally, electron-withdrawing (**15, 16**), and *ortho*-substituents (**17**) are well tolerated.

We next investigated the scope with respect to the symmetric anhydride electrophile (Table 3). While acetic anhydride provides the methyl ketone **18** in only moderate yield, the reaction performs well with linear, α -branched (**19**), and β -branched (**20,21**) alkyl substituents.^[19] Cyclopropyl (**22**) and cyclohexyl (**23**) ketones are also synthesized in high yields. The C(sp³)-H acylation is sufficiently mild that a primary alkyl chloride (**24**) remains unaltered. In addition, an anhydride containing a trisubstituted double bond furnishes the corresponding α,β -unsaturated ketone **25** in good yield.^[20]

Table 2: Amine scope.^[a]

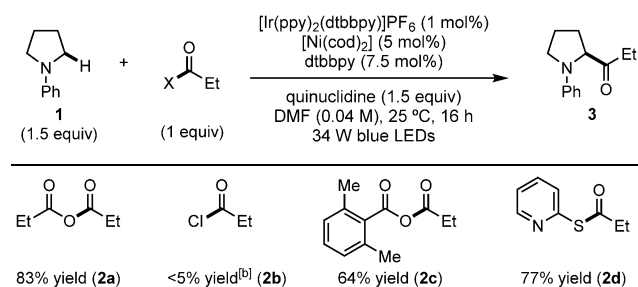
[a] Yield of isolated product is the average of two runs (0.50 mmol).
 [b] Contains 10% inseparable diethylaniline. [c] Used 3.0 equiv of amine.
 [d] [Ru(bpy)₃](PF₆)₂ (1 mol%), [Ni(cod)₂] (10 mol%), and dtbbpy (15 mol%).

Table 3: Symmetric anhydride scope.^[a]

[a] Yield of the isolated product is the average of two runs (0.50 mmol).
 [b] 0.30 mmol scale.

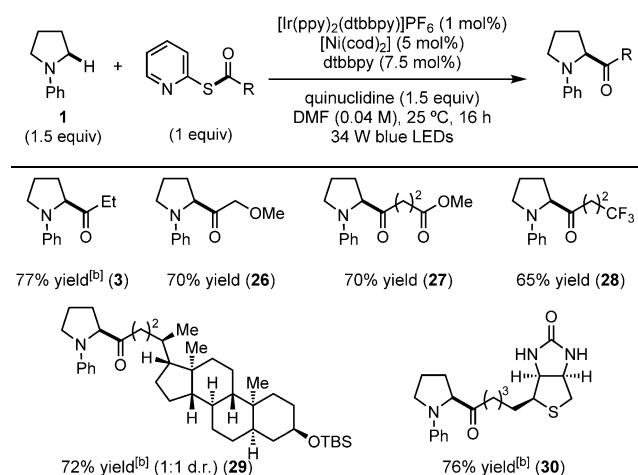
We recognized that in the event that one desires to couple larger or more complex acyl groups, the synthetic utility and atom economy associated with the use of symmetric anhydrides would be diminished. With this consideration in mind,

we sought a more general approach using acyl-X reagents, where X serves as a low-molecular-weight and universal leaving group which is amenable to oxidative addition with nickel(0) (Table 4). While only trace product was observed using propionyl chloride (**2b**), the mixed anhydride **2c** (X = 2,6-dimethylbenzoate)^[21] afforded the desired ketone product in only slightly attenuated yield compared to that obtained with **2a**. Gratifyingly, the 2-pyridylthioester^[22] (**2d**) provided **3** in a yield similar to that obtained with **2a**. Thioester substrates offer the benefit over anhydrides of being stable to both aqueous workup and chromatographic purification on silica gel.

Table 4: Acyl cross-coupling partners.^[a]

[a] Yield of the isolated product is the average of two runs (0.50 mmol).
 [b] Determined by ¹H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an external standard.

With this strategy in hand, we synthesized an array of thioesters to further showcase the functional-group tolerance of the transformation and its amenability to late-stage functionalization (Table 5). Thioester substrates bearing alkyl, ether, ester, and trifluoromethyl substituents provide the ketone products **3** and **26–28** in good yields. The use of a symmetric anhydride substrate containing a steroidal residue, such as TBS-lithocholic acid, would be highly impractical. Using this modified strategy, the thioester derived from

Table 5: Thioester scope.^[a]

[a] Yield of isolated product is the average of two runs (0.50 mmol).
 [b] 0.30 mmol scale. TBS = *tert*-butyldimethylsilyl.

TBS-lithocholic acid delivers the steroidal ketone **29** in 72 % yield. To our delight, *N*-phenylpyrrolidine can also be directly biotinylated to afford **30** in excellent yield without the need for protecting groups, thus highlighting the utility of this dual catalysis platform.

In summary, we have developed a novel method for C(sp³)-H acylation mediated by nickel and photoredox catalysis.^[23] This protocol enables the direct synthesis of α -amino-ketones from simple *N*-aryl amines and acyl donors. Importantly, this method can be extended to late-stage coupling of complex and biologically relevant partners. More generally, this work demonstrates that metallaphotoredox catalysis can afford a strategic alternative for C(sp³)-H functionalization and precludes the need for traditional metal-coordinating directing groups on the C-H partner, and features uncommonly mild reaction conditions.

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