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Letter

Dual Catalytic Platform for Enabling sp^3 α C−H Arylation and Alkylation of Benzamides

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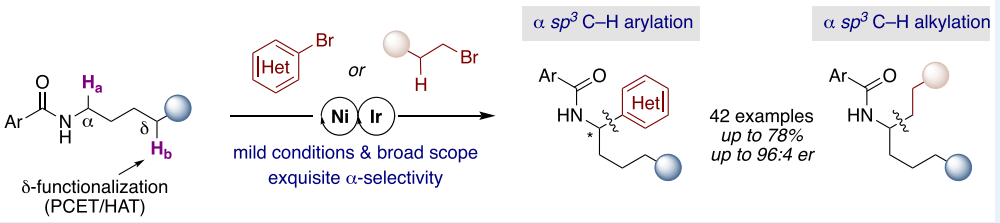


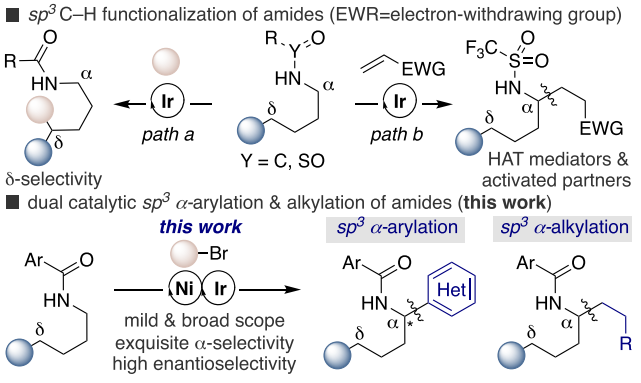
ABSTRACT: A dual catalytic sp^3 α C−H arylation and alkylation of benzamides with organic halides is described. This protocol exhibits an exquisite site selectivity, chemoselectivity, and enantioselectivity pattern, offering a complementary reactivity mode to existing sp^3 arylation or alkylations via transition metal catalysis or photoredox events.

KEYWORDS: *sp^3 C−H activation, photocatalysis, nickel, enantioselectivity, metallaphotoredox*

Catalytic C−H functionalization reactions have streamlined the synthesis of valuable molecules by avoiding functional group manipulations while offering a reliable solution to forge C−C bonds from simple precursors.[1] However, the ability to rationally and predictably switch the site-selectivity pattern in these endeavors still remains a problematic, yet highly rewarding, scenario.[2]

The prevalence of aliphatic amines in a myriad of molecules displaying biological activities[3] has prompted chemists to develop mild, noninvasive site-selective sp^3 C−H functionalizations as a platform for structural diversity.[4] In this vein, photoredox catalysis has recently offered new tactics for the α sp^3 C−H functionalization of aliphatic tertiary amines via single-electron transfer (SET) or hydrogen-atom transfer (HAT) pathways due to their favorable redox profile.[4,5] Although the higher reduction potential of tertiary amide congeners makes the functionalization of this substrate class more difficult, elegant solutions have been described with more oxidizing catalysts or conditions.[6] In contrast, the sp^3 C−H functionalization of aliphatic *secondary* amides has received much less attention. Independent work developed by Rovis[7] and Knowles[8] established a new rationale for enabling δ sp^3 C−H alkylation with activated Michael acceptors through 1,5-HAT processes via amidyl radical species (Scheme 1, path a).[9] Although a site-selectivity switch has recently been obtained with specific amide patterns (path b),[10] this technology remains confined to activated electron-deficient olefins and stoichiometric HAT-mediators.[6,11] In view of the foregoing, the design of a catalytic protocol aimed at expanding the boundaries of sp^3 α-functionalization of aliphatic *secondary* amides with broadly applicable counterparts might provide an opportunity to explore inaccessible chemical space while offering new strategic bond-forming reactions. Herein, we describe the successful realization of this goal via dual catalysis (Scheme 1, bottom).[12,13] Our protocol is distinguished by its mild reaction conditions, broad substrate scope and exquisite site-selective, chemoselective, and enantioselective pattern.

Scheme 1. Site-Selective sp^3 Functionalization of Amides



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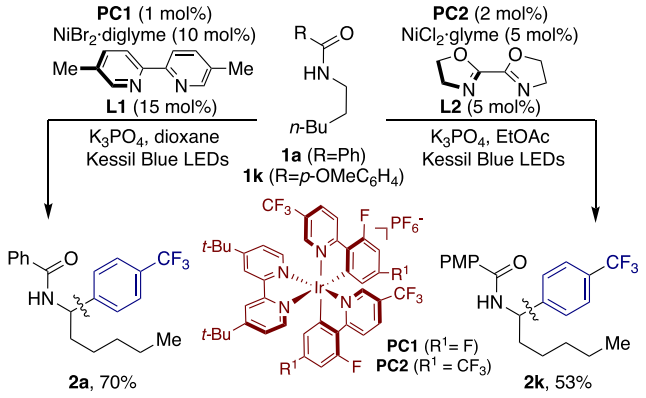
We started our investigations by studying the sp^3 α-arylation of **1a** and **1k** with 4-(trifluoromethyl)bromobenzene (Scheme 2). After systematic evaluation of all reaction parameters,[14] we

Scheme 2. sp^3 α C−H Arylation of Aliphatic Benzamides

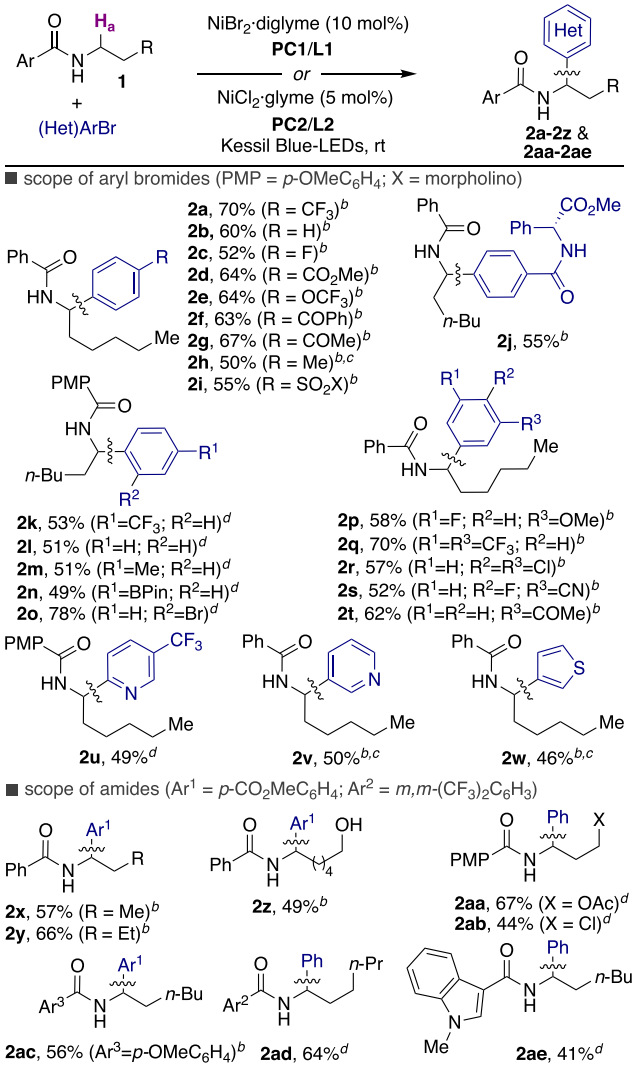


found that a protocol based on **PC1**/**L1** or **PC2**/**L2** provided the best results under Blue-LED irradiation, affording **2a** and **2k** in 70% and 53% yield. As expected, the nature of the ligand, nickel precatalyst, and photocatalyst had a non-negligible impact on reactivity. Equally important was the nature of the base and solvent; indeed, inferior results were found for K_2HPO_4 and Cs_2CO_3 or solvents other than dioxane and EtOAc, thus showing the subtleties of our protocol.[15,16]

Next, we turned our attention to investigating the generality of our dual catalytic sp^3 α-arylation. As shown in Table 1, compounds bearing esters (**2d**, **2j**), nitriles (**2s**), sulfonamides (**2i**), ketones (**2f**, **2g**, **2t**), or amides (**2j**) could all be well-accommodated. Similar results were found independently whether substituents were located at the *ortho*, *meta*, or *para* position. Importantly, however, electron-deficient arenes generally provided better yields of the targeted sp^3 α-arylated products. The method shows a strong preference for aryl bromides, as the corresponding aryl chlorides (**2r**), aryl fluorides (**2c**, **2p**, **2s**), or boronic esters (**2n**) remained inert, thus providing ample room for further derivatization via conventional cross-coupling reactions. Albeit in slightly lower yields, the method was shown to be compatible with heteroaryl bromides (**2u**−**2w**). The exclusive formation of **2j** bearing two seemingly similar benzamides is particularly noteworthy; no traces of sp^3 C−H functionalization adjacent to the ester motif were found in the crude mixtures. Although tentative, this result is consistent with C−C bond-formation occurring at the more hydridic sp^3 C−H bond that is more susceptible to HAT by electrophilic radical species.[4,5] Notably, similar results were found for benzamides possessing different electronic environments (**2ac**, **2ad**) or with heteroaryl-substituted motifs (**2ae**) regardless of the length of the alkyl side-chain (**2x**, **2y**), even in the presence of free alcohols (**2z**), acetates (**2aa**), or alkyl chlorides (**2ab**).

Encouraged by these results, we wondered whether our method would be robust enough to forge related sp^3−sp^3 linkages by using *unactivated* alkyl halides as counterparts. The successful implementation of such a protocol, however, might not be particularly straightforward. Indeed, the available sp^3 α-alkylation portfolio of aliphatic *secondary* amides largely remains confined to the use of particularly activated α,β-unsaturated carbonyls as coupling partners,[9a] although some developments from MacMillan have described alkylations on

Table 1. sp^3 α-Arylation of Benzamides[a]



[a]Isolated yields, average of two independent runs. [b]**1** (0.40 mmol), (Het)ArBr (0.20 mmol), $NiBr_2$·diglyme (10 mol %), **L1** (15 mol %), **PC1** (1 mol %), K_3PO_4 (0.30 mmol), dioxane (1.0 mL) at rt for 20 h. [c]**1** (3 equiv) were used. [d]**1** (0.20 mmol), (Het)ArBr (1.50 mmol), $NiCl_2$·glyme (5 mol %), **L2** (5 mol %), **PC2** (2 mol %), K_3PO_4 (0.4 mmol), EtOAc (1.0 mL) at rt for 20 h.

substrate classes other than secondary aliphatic amides.[9b] In addition, β-hydride elimination and the low propensity for sp^3−sp^3 C−C reductive elimination represent important drawbacks to be overcome.[17] Therefore, at the outset of our investigations it was unclear whether it would be possible to promote a sp^3−sp^3 bond-formation adjacent to the amide function with *unactivated* alkyl halides. Gratifyingly, we found that the sp^3 α-alkylation was within reach by using a Ni/**L3** regime under otherwise identical reaction conditions to those shown in the sp^3 α-arylation event (Table 1). As shown in Table 2, a host of unactivated alkyl halides possessing β-hydrogens promoted the targeted transformation with similar ease. In addition, the presence of nitriles (**3d**), free alcohols (**3f**), alkyl chlorides (**3g**), amides (**3h**), and ketones or esters (**3i**) did not hinder the reaction.

A close inspection into the literature data reveals that an asymmetric sp^3 C−H arylation initiated via photoinduced HAT processes remains an elusive endeavor within the

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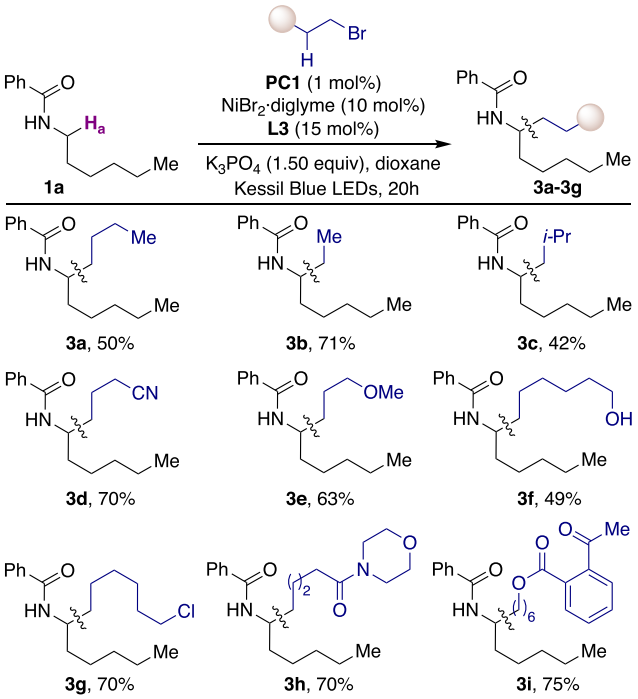
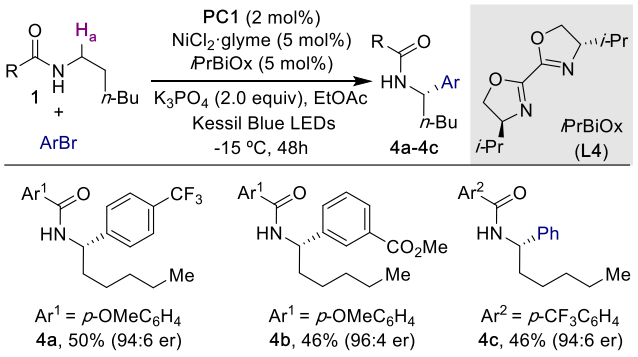
Table 2. sp^3 α-Alkylation of Benzamides[a,b]



[a]**1a** (0.60 mmol), (Het)ArBr (0.20 mmol), $NiBr_2$·diglyme (10 mol %), **L3** (bipyridine; 15 mol %), **PC1** (1 mol %), K_3PO_4 (0.30 mmol), dioxane (1.0 mL) at rt. [b]Isolated yields, average of at least two independent runs.

metallaphotoredox arena.[13,18] To address this gap, we focused on developing an enantioselective sp^3 α C−H functionalization of aliphatic secondary amides with aryl halides. Gratifyingly, we found that a protocol based on *i*PrBiOx (**L4**) was particularly suited for our purposes (Table 3). Although preliminary, the

Table 3. Enantioselective sp^3 α-Arylation of Benzamides[a,b]

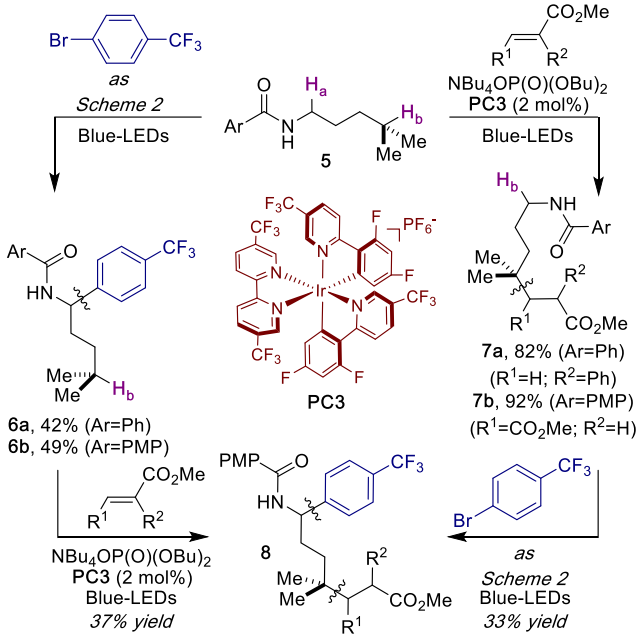


[a]**1** (0.20 mmol), ArBr (1.50 mmol), $NiCl_2$·glyme (5 mol %), *i*PrBiOx (5 mol %), **PC1** (2 mol %), K_3PO_4 (0.40 mmol), EtOAc (1.0 mL) at −15 °C. [b]Isolated yields.

corresponding α-arylated products could be obtained in high levels of enantioselectivity with comparable yields to those shown in Table 1 regardless of the substitution pattern at both the aryl halide and the aliphatic amide backbone (**4a**−**4c**), thus constituting a complementary, yet powerful, platform to elegant protocols recently described by Doyle and Yu.[18,19]

Prompted by the PCET work of Rovis[7,9] and Knowles[7] on the δ sp^3 C−H alkylation of aliphatic *secondary* amides with electron-deficient olefins,[20] we anticipated that our protocol might serve as an orthogonal gateway to forge sp^3 C−C bonds in aliphatic amides at either α- or δ-positions. As shown in Scheme 3, this turned out to be the case and regiodivergent

Scheme 3. Orthogonality with 1,5-HAT Processes



C−C bond-formation could be accessed by using **5** as the substrate. As expected, δ-alkylation with an activated α,β-unsaturated compound was obtained by subjecting **5** to **PC3** and $NBu_4OP(O)(OBu)_2$ under Blue-LED irradiation,[7] whereas exclusive sp^3 α-arylation (**6a**, **6b**) was obtained under the Ni(**L1**)/**PC1** or Ni(**L2**)/**PC2** couple. Notably, **8** could be prepared from **6b** and **7b** following the same rationale, demonstrating the orthogonality of our sp^3 C−H functionalization approach for forging C−C bonds at either α- or δ-positions. At present, we do not have an explanation for the low yields obtained. Taken together, the results in Tables 1−3 and Scheme 3 illustrate the prospective impact of our dual catalytic platform for forging sp^3 C−C linkages adjacent to benzamide motifs in a site-selective manner.

Next, we decided to gather indirect evidence about the mechanism by deuterium-labeling (Scheme 4, top). As shown, a primary kinetic isotope effect (KIE) was observed by exposing a 1:1 mixture of **1a** and **1a**-d_2 under a **PC1**/**L1** regime, suggesting that sp^3 C−H bond-cleavage might be involved in the rate-determining step of the reaction. Similar results were found using a 1:1 ratio of **1k**:**1k**-d_2 with **PC2**/**L2**. Aimed at shedding light on the subsequent C−C bond-forming event, we turned our attention to study the reactivity of the putative oxidative addition species **Ni**−**I**, readily obtained by reacting 4-trifluoromethyl bromobenzene to Ni(COD)$_2$ and **L1** in THF (*middle*).[14] As expected, **Ni**−**I** was found to be catalytically competent, affording **2a** in 32% yield.[21] Although speculative, the lower yields of **2a** employing **Ni**−**I** when compared to an in situ protocol based on $NiBr_2$·diglyme/**L1** can tentatively be ascribed to its inherent instability in the absence of aryl bromide and its strong absorption in the visible light region.[22] In addition, the preparation of **2x**, **2y**, **2aa**, and **2ab** is particularly illustrative, arguing against a scenario based

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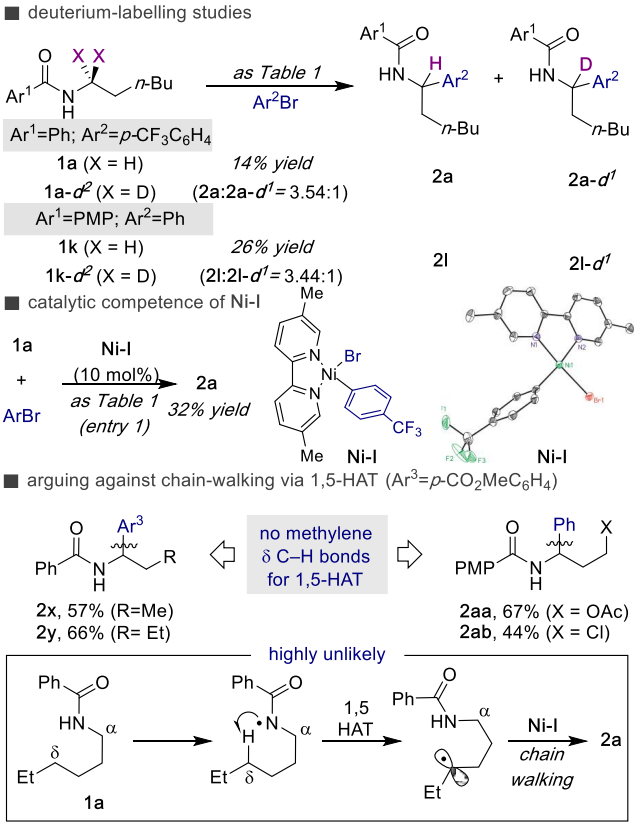
Scheme 4. Preliminary Mechanistic Experiments



on 1,5-HAT followed by recombination with **Ni–I** and a chain-walking manifold prior to C–C bond-formation at the α-position (*bottom*).[23] Whether the key transient radical species adjacent to the amide function are obtained via intermolecular HAT processes or invoke other mechanistic considerations is the subject of ongoing studies.[24]

In summary, we have documented a dual catalytic strategy that enables an sp^3 α-arylation and sp^3 α-alkylation of benzamides, offering a complementary activation mode to existing metal-catalyzed or photoinduced processes. The protocol is characterized by its mild conditions, wide scope and exquisite site selectivity, chemoselectivity, and enantioselectivity. Further studies to unravel the mechanistic intricacies of the reaction and the extension to other C–C bond-forming scenarios are currently ongoing.

■ ASSOCIATED CONTENT

Supporting Information

. The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c01318.

Crystal data for **Ni–I** (CIF)

Experimental procedures, crystallographic data, bond lengths and angles, and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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(12) This work was conducted independently at ICIQ and University of Michigan, and the contributions were deposited in ChemRxiv (10.26434/chemrxiv.10003277.v1 and 10.26434/chemrxiv.9978824.v1) and are now merged into a joint publication

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(14) For more details, see the Supporting Information.

(15) Significant amounts of sp^3 C−H arylation of THF (27%), DME (26%), and DMA (75%) were observed in the crude mixtures, suggesting competitive intermolecular HAT to the solvent. This is consistent with the lower bond-dissociation energies of the corresponding methylene sp^3 C−H bonds adjacent to the oxygen atom in THF and DME or nitrogen atom in DMA when compared to sp^3 C−H bonds in dioxane: Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res.* **2003**, *36*, 255−263.

(16) The mass balance accounts for recovered starting material, homocoupling/reduction of the aryl bromide and trace amounts of sp^3 C−H arylation of the solvent employed.

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(21) An otherwise similar result was obtained with PhBr.

(22) Unfortunately, the inherent instability of **Ni-I** prevented fluorescence quenching studies from being performed.

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(24) On the basis of our available data, several possibilities might come into play for the generation of the key α-carbon radical intermediates. If we take **PC1** into consideration, we could consider the following: (a) triplet−triplet energy transfer occurring from **PC1*** to **Ni-I** (see ref 21) followed by arylNi(II)−Br homolysis, generating bromine radicals that enable an intermolecular HAT at the α sp^3 C−H bond (a close look at the triplet energies of **PC-1** (61.8 kcal/mol) *vs fac*-$Ir(ppy)_3PF_6$ (58.1 kcal/mol) or $Ir(ppy)_2(dtbpy)PF_6$ (49.2 kcal/mol) is particularly illustrative (see he Supporting information for details)). For a leading reference, see: Shields, B.; Doyle, A. G. Direct $C(sp^3)$−H cross coupling enabled by catalytic generation of chlorine radicals. *J. Am. Chem. Soc.* **2016**, *138*, 12719−12722. (b) PCET followed by [1,2]-HAT assisted by the K_3PO_4 (see: Morton, C. M.; Zhu, Q.; Ripberger, H.; Troian-Gautier, Z. S.; Toa, D.; Knowles, R. R.; Alexanian, E. J. C−H Alkylation via Multisite-Proton-Coupled Electron Transfer of an Aliphatic C−H Bond. *J. Am. Chem. Soc.* **2019**, *141*, 13253−13260. and Wakaki, T.; Sakai, K.; Enomoto, T.; Kondo, M.; Masaoka, S.; Oisaki, K.; Kanai, M. C(sp3)−H Cyanation Promoted by Visible-Light Photoredox/Phosphate Hybrid Catalysis. *Chem. - Eur. J.* **2018**, *24*, 8051−8055. or (c) SET oxidation of **PC1*** to K_3PO_4 followed by intermolecular HAT (see Margrey, K. A.; Czaplyski, W. L.; Nicewicz, D. A.; Alexanian, E. J. A General Strategy for Aliphatic C−H Functionalization Enabled by Organic Photoredox Catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 4213−4217.)

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