A Dual Catalytic Platform for Enabling sp^3 α C–H Arylation & Alkylation of Benzamides

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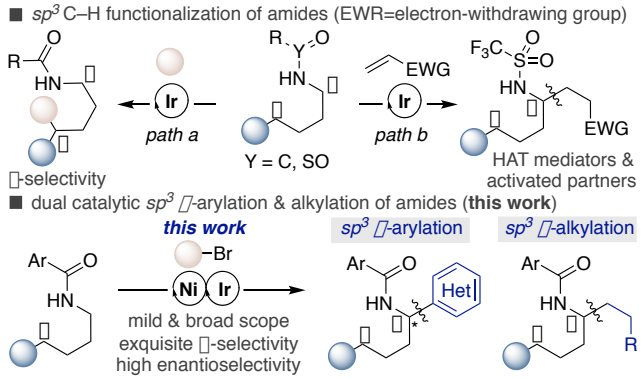
Supporting Information Placeholder

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

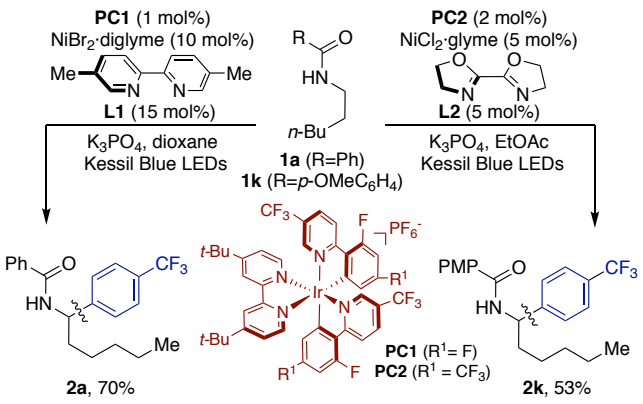
Catalytic C–H functionalization reactions have streamlined the synthesis of valuable molecules by avoiding functional group manipulations while offering a reliable solution to forge C–C bonds from simple precursors.[1] However, the ability to rationally and predictably switch the site-selectivity pattern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

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



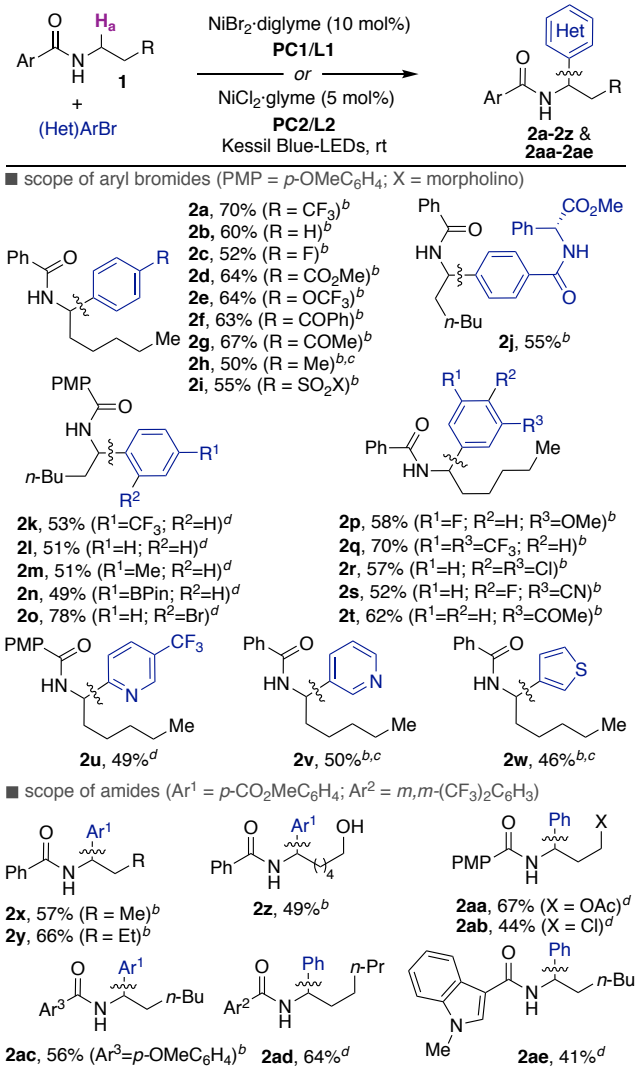
The prevalence of aliphatic amines in a myriad of molecules displaying biological activities[3] has prompted chemists to develop mild, non-invasive site-selective sp^3 C–H functionalizations as a platform for structural diversity.[4] In this vein, photoredox catalysis has recently offered new tactics 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 have 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-, chemo- and enantioselective pattern.

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



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 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]

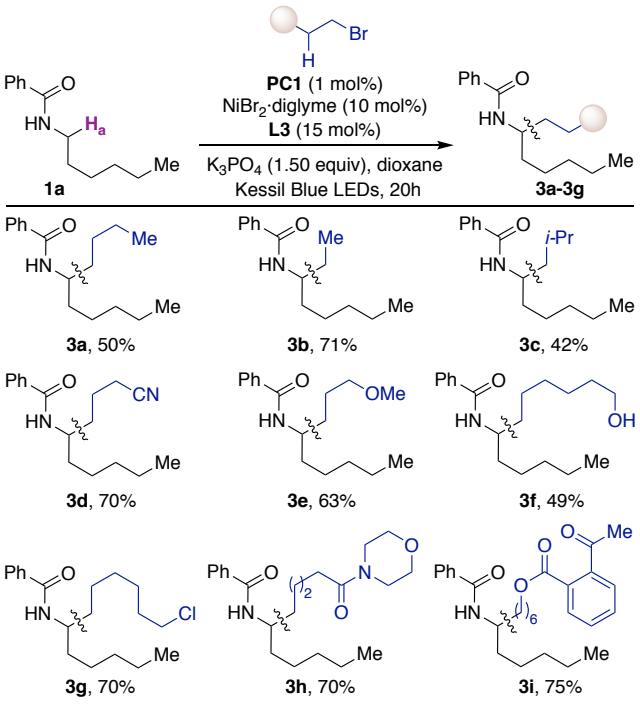
Table 1. ***sp*^{3} α-Arylation of Benzamides.**[a]



[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.

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**).

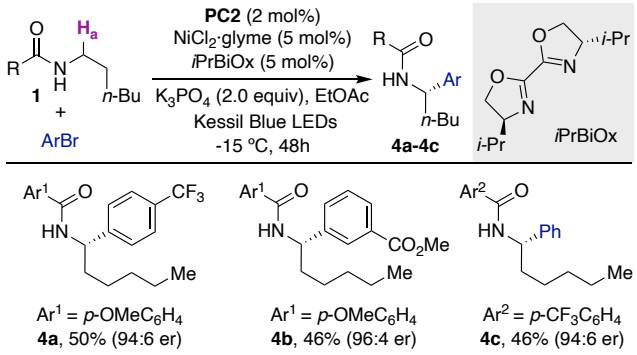
Table 2. ***sp*^{3} α-Alkylation of Benzamides.**[a,b]



[a] **1** (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.

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 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 2). As shown in Table 3, 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**), ketones or esters (**3i**) did not hinder the reaction.

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

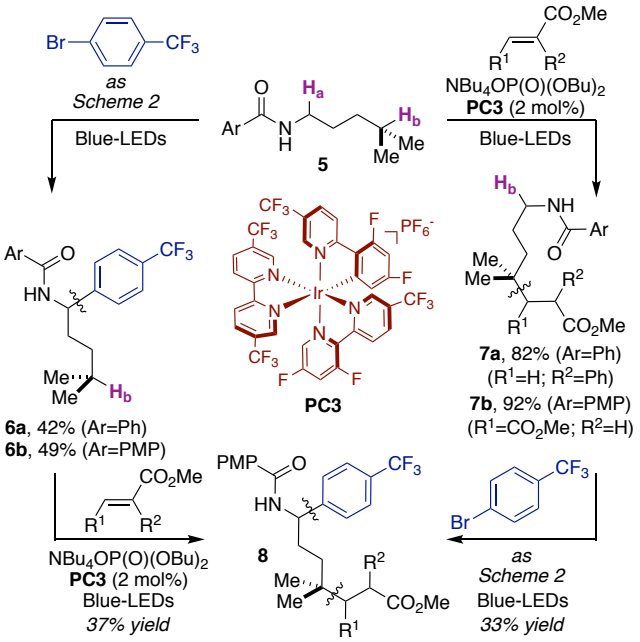


[a] **1** (0.20 mmol), ArBr (1.50 mmol), $NiCl_2$·glyme (5 mol%), ^{i}PrBiOx (5 mol%), **PC1** (2 mol%), K_3PO_4 (0.40 mmol), EtOAc (1.0 mL) at –15 °C. [b] Isolated yields.

A close inspection into the literature data reveals that an asymmetric sp^3 C–H arylation initiated via photoinduced HAT processes remains an elusive endeavour within the 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 (**L3**) was particularly suited for our purposes (Table 3). Although preliminary, the corresponding α-arylated products could be obtained in high levels of enantioselectivity with comparable yields to those shown in Table 2 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[6,8] 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 C–C bond-formation could be accessed by using **5** as substrate. As expected, δ-alkylation with an activated α,β-unsaturated compound was obtained by subjecting **5** to **PC-3** and $NBu_4OP(O)(OBu)_2$ under Blue-LED irradiation,[7] whereas exclusive sp^3 α-arylation (**7a**, **7b**) 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 don´t 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.

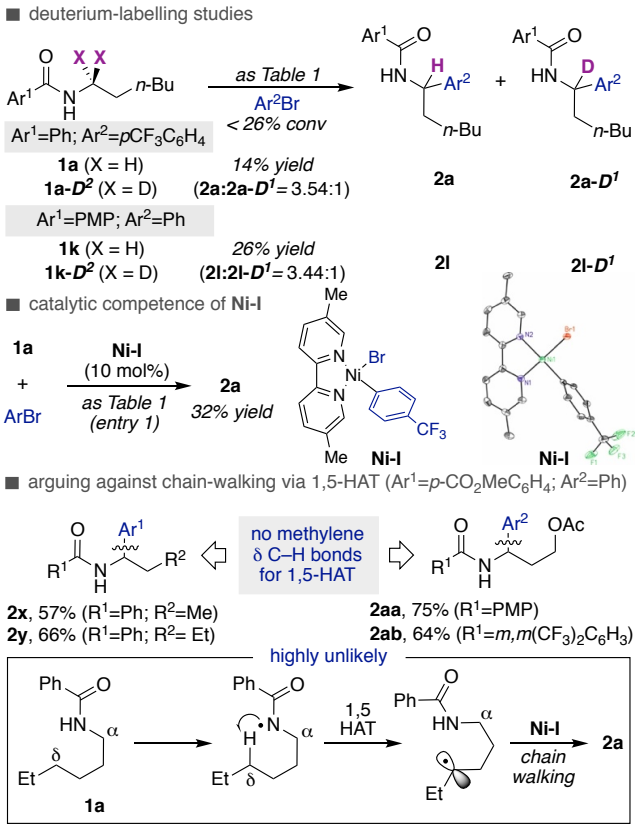
Scheme 3. Orthogonality with 1,5-HAT processes.[a]



Next, we decided to gather indirect evidence about the mechanism by deuterium-labelling (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 at-

tention 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 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]

Scheme 4. Preliminary Mechanistic Experiments.[a]



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-, chemo- 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. Experimental procedures, crystallographic data and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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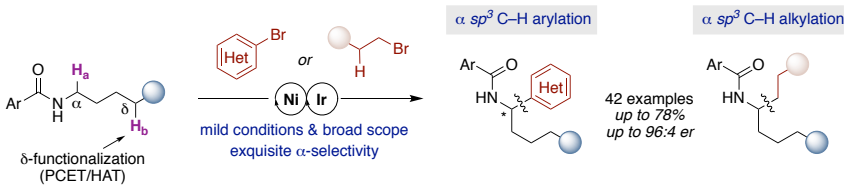
(24) Based on our available data, several possibilities might come into play for the generation of the key α-carbon radical intermediates. If we take **PC1** into consideration, we could consider the following: (a) triplet-triplet energy transfer occurring from **PC1*** to **Ni-I** (see ref. 21) followed 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 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;(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. *J. Am. Chem. Soc.* **2019**, *141*, 13253 and Wakaki, T.; Sakai, K.; Enomoto, T.; Kondo, M.; Masaoka, S.; Oisaki, K.; Kanai, M. *Chem. –Eur. J.* **2018**, *24*, 8051 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. *J. Am. Chem. Soc.* **2018**, *140*, 4213).


δ-functionalization
(PCET/HAT)
Het
Br
or
Br
H
Ni
Ir
mild conditions & broad scope
exquisite α-selectivity
α sp3 C–H arylation
α sp3 C–H alkylation
42 examples
up to 78%
up to 96:4 er