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

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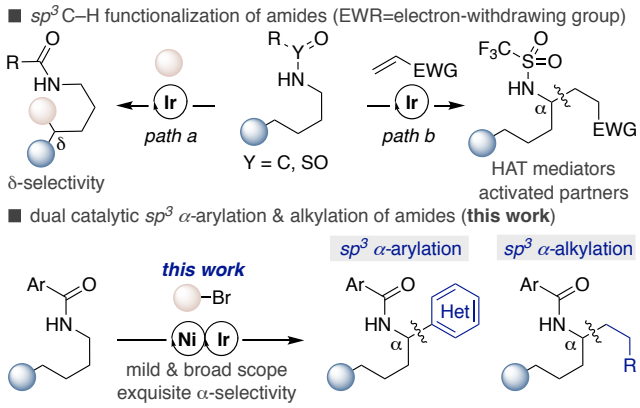
Supporting Information Placeholder

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

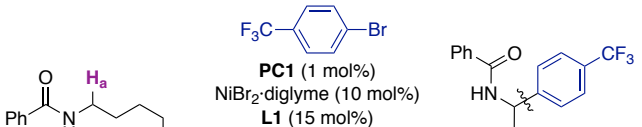
Transition metal-catalyzed cross-coupling reactions have streamlined the synthesis of valuable molecules from simple precursors while offering a reliable solution to selectively forge C–C bonds at prefunctionalized sites.[1] However, the ability to rationally and predictably switch the site-selectivity pattern of these endeavors still remains a problematic, yet highly rewarding, scenario.[2]

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

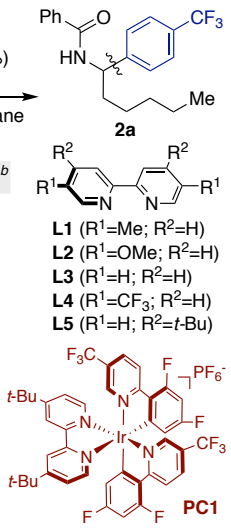


The prevalence of aliphatic amines in a myriad of molecules displaying biological activities[3] have prompted chemists to develop mild, non-invasive and site-selective sp^3 C–H functionalization techniques as a platform for structural diversity.[4] In this vein, photoredox catalysis has recently offered new tactics for the sp^3 C–H functionalization of aliphatic amines via single-electron transfer (SET) or hydrogen-atom transfer (HAT) pathways due to their favorable redox profile.[4,5] Although the lower oxidation potential of aliphatic amides might a priori preclude the implementation of related sp^3 C–C bond-formations, independent work by Rovis[6] and Knowles[7] established a new photochemical rationale for enabling δ sp^3 C–H alkylation of aliphatic *secondary* amides through [1,5]-HAT (Scheme 1, *path a*).[8] Recently, a site-selectivity switch could be obtained with particularly activated trifluoromethansulfonamides (*path b*);[9] however, this technology remains confined to activated electron-deficient olefins and stoichiometric HAT-mediators, reinforcing a change in strategy.[10,11] In view of the foregoing, a catalytic blueprint 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. As part of our interest in site-selective Ni catalysis,[12] we report herein the successful realization of this goal (Scheme 1, *bottom*). Our dual catalytic platform[13] is distinguished by its mild conditions, broad applicability and exquisite α-selectivity pattern, offering a complementary reactivity mode to existing sp^3 α-arylation and alkylation tactics.

Table 1. Optimization of the Reaction Conditions.[a]



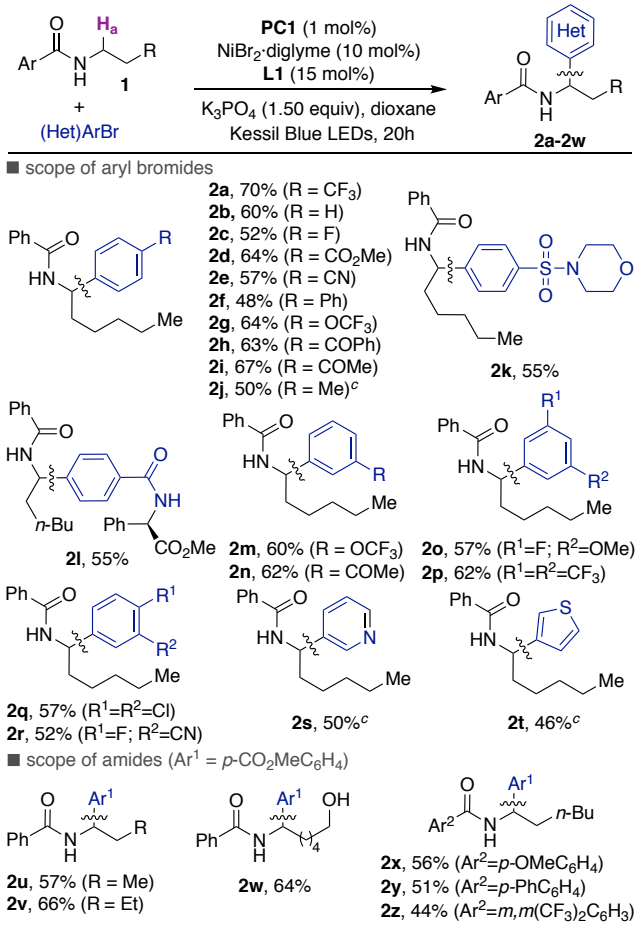
entry	deviation standard conditions	2a (%)[b]
1	***none***	*70*[c]
2	**L2** instead of **L1**	66
3	**L3** instead of **L1**	62
4	**L4** instead of **L1**	0
5	**L5** instead of **L1**	16
6	$Ni(cod)_2$ instead of $NiBr_2$·diglyme	28
7	*fac*-$Ir(ppy)_3PF_6$ instead of **PC1**	0
8	$Ir(ppy)_2(dtbpy)PF_6$ instead of **PC1**	0
9	DME(THF) as solvent	18(0)
10	K_2HPO_4 instead of K_3PO_4	18
11	Cs_2CO_3 instead of K_3PO_4	57
12	no **L1**, Ni, K_3PO_4, **PC1** or light	0



[a] **1a** (0.20 mmol), *p*-$CF_3C_6H_4Br$ (0.10 mmol), $NiBr_2$·diglyme (10 mol%), **L1** (15 mol%), **PC1** (1 mol%), K_3PO_4 (0.15 mmol), dioxane (0.50 mL) at rt. [b] NMR yields using mesitylene as internal standard. [c] Isolated yield.

We started our investigations by studying the sp^3 α-arylation of **1a** with 4-trifluoromethyl bromobenzene (Table 1). After systematic evaluation of all reaction parameters,[14] a regime based on $NiBr_2$·diglyme (10 mol%), **L1** (15 mol%), **PC1** (1 mol%), K_3PO_4 in dioxane under Blue-LED irradiation provided the best results, affording **2a** in 70% yield with an exquisite α-selectivity pattern. As expected, the nature of the ligand had a non-negligible impact on reactivity (entries 2-5). Indeed, a seemingly trivial modification at 4,4'- or 5,5'-position had a deleterious effect (entries 4-5). Similarly, $Ni(COD)_2$ provided lower conversions to **2a**, suggesting that COD might compete with **L1** for binding at the Ni center (entry 6). Notably, stronger reducing photocatalysts such as *fac*-$Ir(ppy)_3PF_6$ or related $Ir(ppy)_2(dtbpy)PF_6$ did not afford even traces of **2a** (entries 7 and 8).[15] Equally important was the nature of the base and solvent; indeed, inferior results were found for K_2HPO_4 and Cs_2CO_3 or ethereal solvents other than dioxane (entries 9-11), thus showing the subtleties of our protocol.[16] As expected, control experiments revealed that all variables were critical for success (entry 12).[17]

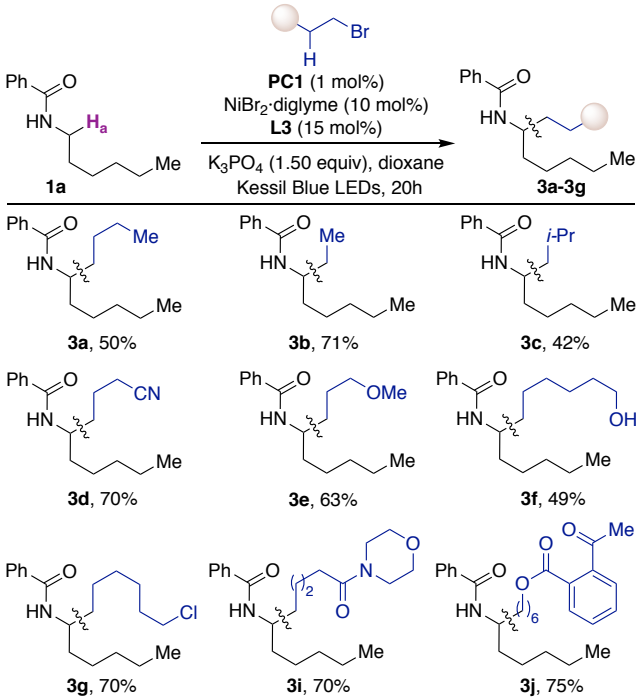
Table 2. sp^3 α-Arylation of Benzamides.[a,b]



[a] As Table 1 (entry 1), 0.20 mmol scale. [b] Isolated yields, average of two independent runs. [b] 3 equiv of **1** were used.

Next, we turned our attention to investigating the generality of our dual catalytic sp^3 α-arylation. As shown in Table 2, compounds bearing esters (**2d, 2l**), nitriles (**2e**), sulfonamides (**2k**), ketones (**2h**, **2i, 2n**) or amides (**2l**) could all be well-accommodated. Similar results were found independently whether substituents were located at either *meta* or *para* position. Note, however, that electron-deficient arenes generally provided better yields of the targeted sp^3 α-arylated products. The method showed a strong preference for aryl bromides, as the corresponding aryl chlorides (**2q**) or aryl fluorides (**2c**, **2o**, **2r**) 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 (**2s**, **2t**). The exclusive formation of **2l** bearing two seemingly similar benzamides is particularly noteworthy; indeed, not even 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 electron-rich or electron-deficient arenes (**2x-2z**) regardless of the length of the alkyl side-chain (**2u-2w**).

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

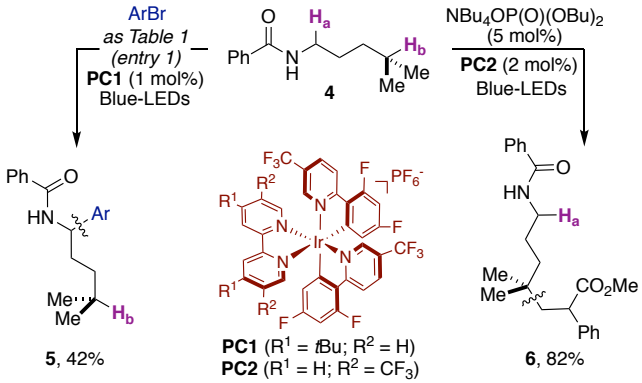


[a] As Table 1 (entry 1), 0.20 mmol scale, using **L3**. [b] Isolated yields, average of two independent runs. [c] dr = 1.5:1.

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. A close inspection into the literature data, however, indicated that such a protocol might not be particularly straightforward, as the available sp^3 α-alkylation portfolio of aliphatic *secondary* amides remains confined to the use of particularly activated α,β-unsaturated carbonyls as coupling partners.[9] In addition, parasitic β-hydride elimination and the low propensity for sp^3–sp^3 C–C reductive elimination represent important drawbacks to be overcome.[18] 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 halide counterparts. Gratifyingly, we found that the targeted 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 (**3i**), ketones or esters (**3j**) did not hinder the reaction.

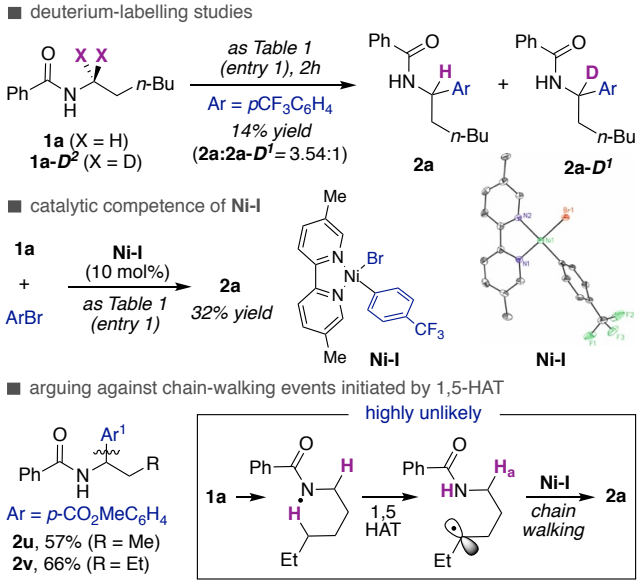
Scheme 2. Orthogonality with 1,5-HAT processes.[a]



Prompted by the seminal work of Rovis[6,8] and Knowles[7] on the δ sp^3 C–H alkylation of aliphatic *secondary* amides with electron-deficient alkenes triggered by a photochemical proton-couple electron transfer (PCET) regime,[19] we wondered whether our results might serve as an orthogonal gateway to forge sp^3 C–C bonds at the α-position with otherwise identical precursors. As shown in Scheme 2, this turned out to be the case and a regiodivergent C–C bond-forming scenario could be within reach by using **4** as substrate. As expected, δ-alkylation with an activated α,β-unsaturated compound was obtained by subjecting **4** to **PC-2** and $NBu_4OP(O)(OBu)_2$ under Blue-LED irradiation,[7] whereas exclusive sp^3 α-arylation was obtained under our optimized reaction conditions based on the Ni(**L1**)/**PC-1** couple. Taken together, the results in Tables 2-3 and Scheme 2 clearly illustrates 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-labelling (Scheme 3, *top*). As shown, a primary kinetic isotope effect (KIE) was observed by exposing a 1:1 mixture of **1a** and **1a-*D*^{2}** under our optimized reaction conditions, suggesting that sp^3 C–H bond-cleavage might be involved in the rate-determining step of the reaction. 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. 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 stunning absorption in the visible light region.[20] In addition, the successful preparation of **2u** and **2v** is particularly illustrative, arguing against a scenario based on 1,5-HAT followed by recombination with **Ni-I** followed by a chain-walking manifold prior to C–C bond-formation at the α-position (*bottom*).[21] 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.[22,23]

Scheme 3. Preliminary Mechanistic Experiments.[a]



In summary, we have documented a dual catalytic strategy that enables a sp^3 α-arylation and sp^3 α-alkylation of benzamides. The protocol is characterized by its mild conditions, wide substrate scope and exquisite site-selectivity, forging the targeted C–C bonds adjacent to the amide function. This new platform offers a complementary activation mode to existing sp^3–arylation and sp^3–alkylation in the transition metal-catalyzed or metallaphotore-

dox arena. 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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No competing financial interests have been declared.

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REFERENCES

(1) Diederich, F.; de Meijere, A., Eds. *Metal-Catalyzed Cross-Coupling Reactions;* Wiley-VCH: Weinheim, 2004

(2) For selected reviews: (a) Yamaguchi, M.; Manabe, K. Ligand-controlled site-selective cross-coupling. *Top. Curr. Chem.* **2016**, *372*, 1. (b) Mahatthananchai, J.; Dumas, A. M.; Bode, J. W. Catalytic selective synthesis. *Angew. Chem., Int. Ed*. **2012**, *51*, 10954. (c) Afagh, N. A.; Yudin, A. K. Chemoselectivity and the curious reactivity preferences of functional groups. *Angew. Chem., Int. Ed.* **2010**, *49*, 262. (d) Trost, B. M. Selectivity: a key to synthetic efficiency. *Science* **1983**, *219*, 245.

(3) (a) Mayol-Llinas, J.; Nelson, A.; Farnaby, W.; Ayscough, A. Assessing molecular scaffolds for CNS drug discovery. D*rug Discovery Today* **2017**, *22*, 965. (b) Marciano, D. P.; Chang, M. R.; Corzo, C. A.; Lam, V. Q.; Pascal, B. D.; Griffin, P. R. The therapeutic potential of nuclear receptor modulators for the treatment of metabolic disorders: PPARγ, RORs and Reverbs. *Cell Metab.* **2014**, *19*, 193. (c) McGrath, N. A.; Brichacek, M.; Njardarson, J. T. A graphical journey of innovative organic architectures that have improved our lives. *J. Chem. Educ.* **2010**, *87*, 1348.

(4) For selected reviews: (a) Chu, J. C. K.; Rovis, T. Complementary strategies for directed *sp*^{3} C–H functionalization: A comparison of transition metal-catalyzed activation, hydrogen atom transfer and carbene/nitrene transfer. *Angew. Chem., Int. Ed.* **2018**, *57*, 62. (b) He, J.; Hamann, J. G.; Davies, H. M. L.; Beckwith, R. E. J. Late-stage C-H functionalization of complex alkaloids and drug molecules via intermolecular rhodium-carbenoid insertion. *Nature Commun.* **2015**, *6*, 5943. (c) Seidel, D. The azomethine ylide route to amine C-H functionalization: redox-version of classic reactions and a pathway to new transformations. *Acc. Chem. Res*. **2015**, *48*, 317. (d) Li, H.; Li, B.-J.; Shi, Z. –J. Challenge and progress: palladium-catalyzed sp^3 C-H activation. *Catal. Sci. Technol.* **2011, *1*,** 191. (e) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreuter, J.; Baudoin, O. Functionalization of organic molecules by transition metal-catalyzed C(sp^3)-H activation. *Chem. –Eur. J.* **2010**, *16*, 2654. (f) Campos, K. R. Direct *sp*^{3} C–H bond activation adjacent to nitrogen in heterocycles. *Chem. Soc. Rev.* **2007**, *36*, 1069.

(5) For an excellent review on the topic: He, C.; Whitehurst, W. G.; Gaunt, M. J. Palladium-catalyzed C(sp^3)–H bond functionalization of aliphatic amines. *Chem* **2019**, *5*, 1031.

(6) Chu, J. C. K.; Rovis, T. Amide-directed photoredox-catalysed C–C bond formation at unactivated sp^3 C–H bonds. *Nature* **2016**, *539*, 272.

(7) Choi, G. J.; Zhu, Q.; Miller, D. C.; Gu, C. J.; Knowles, R. R. Catalytic alkylation of remote C–H bonds enabled by proton-coupled electron transfer. *Nature* **2016**, *539*, 268.

(8) Recently, an elegant δ-alkylation has been designed using a similar photochemical PCET-type approach, see: Thullen, S. M.; Treacy, S. M.; Rovis, T. Regioselective alkylative cross-coupling of remote unactivated C(sp^3)–H bonds. *J. Am. Chem. Soc.* **2019**, *141*, 36.

(9) (a) Ashley, M. A.; Yamauchi, C.; Chu, J. C. K.; Otsuka, S.; Yorimitsu, H.; Rovis, T. Photoredox-catalyzed site-selective α-C(sp^3)–H alkylation of primary amine derivatives. *Angew. Chem. Int., Ed.* **2019**, *58*, 4002. (b) Ye, J.; Kalvet, I.; Schoenebeck, F.; Rovis, T. *Nat. Chem.* **2018**, *10*, 1037.

(10) For related C–C bond-forming strategies using *tertiary* rather than *secondary* aliphatic amides or carbamates, see: (a) McManus, J. B.; Onuska, N. P. R.; Nicewitz, D. A. Generation and alkylation of α-carbamyl radicals via organic photoredox catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 9056. (b) Dai, C.; Meschini, F.; Narayanam, J. M. R.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 4425. (c) Tahara, Y. -K.; Michino, M.; Ito, M.; Kanyiva, K. S.; Shibata, T. *Chem. Commun.* **2015**, *51*, 16660. (d) Yan, H.; Lu, L.; Rong, G.; Liu, D.; Zheng, Y.; Chen, J.; Mao, J. Functionalization of amides via copper-catalyzed oxyalkylation of vinylarenes and decarboxylative alkenylation of sp^3 C–H. *J. Org. Chem.* **2014**, *79*, 7103. (e) Yang, X. -H.; Wei, W. -T.; Li, H. -B.; Song, R. -J.; Li, J.-H. Oxidative coupling of alkenes with amides using peroxides: selective amide C(sp^3)–H versus C(sp^2)-H functionalization. *Chem. Commun*. **2014**, *50*, 12867. (f) Shaw, M. H.; Shurtleff, V. W.; Terrett, J. A.; Cuthberson, J. D.; MacMillan, D. W. C. *Science* **2016**, *352*, 1304. (g) Rohe, S.; Morris, A. O.; McCallum, T.; Barriault, L. Hydrogen atom transfer reactions via photoredox catalyzed chlorine atom generation. *Angew. Chem., Int. Ed.* **2018**, *57*, 15664. (h) Capaldo, L.; Merli, D.; Fagnoni, M.; Ravelli, D. Visible light Uranyl Photocatalysis: Direct C–H to C–C bond conversion. *ACS Catal*. **2019**, *9*, 3054.

(11) For an elegant silylation technique requiring stoichiometric amounts of organometallic reagents, see: Liu, P.; Tang, J.; Zeng, X. Site-selective silylation of aliphatic C–H bonds mediated by [1,5]-hydrogen transfer: synthesis of α-sila benzamides. *Org. Lett.* **2016**, *18*, 5536.

(12) For selected recent references, see: (a) Sun, S. Z.; Borjesson, M.; Martin-Montero, R.; Martin, R. Site-selective Ni-catalyzed reductive coupling of alpha-haloboranes with unactivated olefins. *J. Am. Chem. Soc*. **2018**, *140*, 12765. (b) Shen, Y.; Gu, Y.; Martin, R. *sp*^{3} C–H arylation and alkylation enabled by the synergy of triplet excited ketones and nickel catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 12200. (b) Tortajada, A.; Ninokata, R.; Martin, R. Ni-catalyzed site-selective decarboxylation of 1,3-dienes with CO_2. *J. Am. Chem. Soc.* **2018**, *140*, 2050. (d) van Gemmeren, M.; Börjesson, M.; Tortajada, A.; Sun, S. -Z.; Okura, K.; Martin, R. Switchable site-selective catalytic carboxylation of allylic alcohols with

CO_2. *Angew. Chem. Int., Ed.* **2017**, *56*, 6558. (e) Juliá-Hernández, F.; Moragas, T.; Cornella, J.; Martin, R. Remote carboxylation of halogenated aliphatic hydrocarbons with carbon dioxide. *Nature* **2017**, *545*, 84. (f) Moragas, T.; Cornella, J.; Martin, R. Ligand-controlled regiodivergent Ni-catalyzed reductive carboxylation of allyl esters with CO_2. *J. Am. Chem. Soc.* **2014**, *136*, 17702, and references therein.

(13) For reviews on dual catalytic in photochemical events: (a) 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*. **2017**, *1*, 0052. (b) Kärkäs, M. D.; Porco, J. A.; Stephenson, C. R. J. Photochemical approaches to complex chemotypes: applications in natural product synthesis. *Chem. Rev*. **2016,** *116,* 9683. (c) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible light photoredox catalysis with transition metal complexes: applications in organic synthesis. *Chem. Rev*. **2013**, *113*, 5322. (d) Levin, M. D.; Kim, S.; Toste, F. D. Photoredox catalysis unlocks single-electron elementary steps in transition metal catalyzed cross-coupling. *ACS Cent. Sci*. **2016**, *2*, 293. (c) Skubi, K. L.; Blum, T. R.; Yoon, T. P. Dual catalysis strategies in photochemical synthesis. *Chem. Rev*. **2016**, *116*, 10035

(14) For details, see Supporting information.

(15) *fac*-Ir(ppy)$_3$PF$_6$ (E_{red} [Ir_{III}/Ir_{II}] = –2.19 V vs SCE in MeCN); Ir(ppy)$_2$(dtbpy)PF$_6$ (E_{red} [Ir_{III}/Ir_{II}] = –1.51 V vs SCE in MeCN; **PC1** (E_{red} [Ir_{III}/Ir_{II}] = –1.37 V vs SCE in MeCN).

(16) Significant amounts of sp^3 C–H arylation of THF (27%) and DME (26%) were observed in the crude mixtures, suggesting competitive intermolecular HAT to the ethereal 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 when compared to sp^3 C–H bonds in dioxane. For C−H bond dissociation energies of different organic molecules: Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res*. **2003**, *36*, 255.

(17) The mass balance accounts for <7% sp^3 C–H arylation of dioxane, and homocoupling/reduction of the aryl bromide.

(18) For selected reviews on cross-coupling reactions of sp^3 hybridized electrophiles, see: (a) Molander, G.; Milligan, J. A.; Phelan, J. P.; Badir, S. O. Recent advances in alkyl carbon-carbon bond formation by Nickel/Photoredox crosscoupling. *Angew. Chem., Int. Ed*. **2019**, *58*, 6152. (b) Choi, F.; Fu, G. C.; *Science* **2017**, *356*, 152. (c) Kambe, N.; Iwasaki, T.; Terao, J. Pd-catalyzed cross-coupling reactions of alkyl halides. *Chem. Soc. Rev.* **2011**, *40*, 4937. (d) Jana, R.; Pathak, T. P.; Sigman, M. S. Advances in transition metal (Pd,Ni,Fe)-catalyzed cross-coupling reaction using alkyl-organometallics as reaction patterns. *Chem. Rev*. **2011**, *111*, 1417. (e) Hu, X. Nickel-catalyzed cross-coupling of non-activated alkyl halides: a mechanistic perspective. *Chem. Sci*. **2011**, *2*, 1867.

(19) Gentry, E. C.; Knowles, R. R. Synthetic applications of proton-coupled electron transfer. *Acc. Chem. Res.* **2016**, *49*, 1546.

(20) Unfortunately, the inherent instability of **Ni-I** prevented fluorescence quenching studies to be performed.

(21) For selected reviews on chain-walking reactions: (a) Janssen-Müller, D.; Sahoo, B.; Sun, S.-Z.; Martin, R. Tackling remote sp$_3$ C−H functionalization via Ni-catalyzed "chain-walking" reactions. Isr. J. Chem. 2019, DOI: 10.1002/ijch.201900072. (b) Sommer, H.; Julia-Hernandez, F.; Martin, R.; Marek, I. Walking metals for remote functionalization. *ACS Cent. Sci.* **2018**, *4*, 153. (c) Vasseur, A.; Bruffaerts, J.; Marek, I. Remote functionalization through alkene isomerization. *Nat. Chem.* **2016**, *8*, 209. (d) Larionov, E.; Li, H.; Mazet, C. Well-defined transition metal hydrides in catalytic isomerizations. *Chem. Commun*. **2014**, *50*, 9816.

(22) Based on our available data, several possibilities might come into play for the generation of the key α-carbon radical intermediates: (a) triplet-triplet energy transfer occurring from **PC1*** to **Ni-I** (see ref. 20) followed by arylNi(II)–Br homolysis, thus 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)$_3$PF$_6$ (Table 1 (entry 7), 58.1 kcal/mol) or Ir(ppy)$_2$(dtbpy)PF$_6$ (Table 1 (entry 8), 49.2 kcal/mol) is particularly illustrative; (b) PCET followed by [1,2]-HAT assisted by the K$_3$PO$_4$ (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 or (c) SET oxidation of **PC1*** to K$_3$PO$_4$ followed by intermolecular HAT (see Margrey, K. A.; Czaplyski, W. L.; Nicewitz, D. A.; Alexanian, E. J. *J. Am. Chem. Soc*. **2018**, *140*, 4213).

(23) Control experiments revealed that no reaction occurred with *N*-methylated **1a**, thus revealing that the presence of a free N–H bond on the amide backbone was critical for success.