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Auxiliary-Directed C(sp^3)-H Arylation by Synergistic Photoredox and Palladium Catalysis

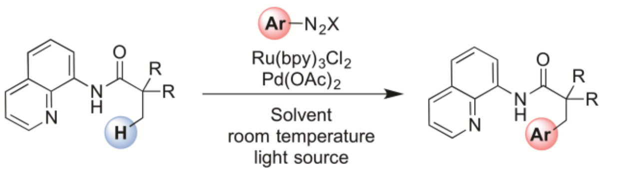
Milena L. Czyz,[a] David W. Lupton[b] and Anastasios Polyzos[a,c]*

This manuscript is dedicated to Professor Steven V. Ley.

Abstract: Herein we describe the auxiliary-directed arylation of unactivated C(sp^3)-H bonds with aryldiazonium salts, which proceeds under synergistic photoredox and palladium catalysis. The site-selective arylation of aliphatic amides with α-quaternary centers is achieved with high selectivity for β-methyl C(sp^3)-H bonds. This operationally simple method is compatible with carbocyclic amides, a range of aryldiazonium salts and proceeds at ambient conditions.

The direct, chemoselective functionalization of unactivated aliphatic C-H bonds is a strategic transformation, which enables the straightforward diversification of simple organic molecules to complex molecular architectures. The broad application of C-H activation reactions has been impeded by the lack of methods with acceptable regio- and chemo-selectivity. Over the last decade, transition metal-catalyzed activation of distal C(sp^2)-H bonds with auxiliary-directing group assistance has developed into a useful synthetic method.[1-3]

In contrast, extension of this stratagem to less reactive aliphatic C-H bonds remains scarce.[4] Despite ongoing progress, transition metal-catalysed activation of distal C(sp^3)-H centers via directing auxiliaries remains a noteworthy challenge and available methods usually mandate high temperatures, stoichiometric additives and extended reaction times to be viable.[5] Recently, synergistic photoredox and transition metal catalysis, also known as metallaphotoredox catalysis, has emerged to address the associated limitations of traditional cross-coupling chemistry.[6, 7] The method harnesses a visible light photoredox catalytic cycle to generate carbon-centred radicals under mild conditions, which then engage in single electron oxidative addition[8-12] or transmetallation[13-15] steps. In a pioneering study, Sanford and co-workers applied synergistic catalysis to develop an auxiliary-directed arylation of C(sp^2)-H bonds.[8] However, the development of auxiliary-directed functionalizatio of unactivated C(sp^3)-H bonds under metallaphotoredox conditions remains largely unexplored. Herein we report the direct and selective β-arylation of C(sp^3)-H bonds in quaternary aliphatic amides through the application of synergistic photoredox and palladium catalysis (Scheme 1).



Scheme 1: **This work**: Auxiliary-directed arylation of C(sp^3)-H bonds by synergistic photoredox and palladium catalysis

Given the effectiveness of the 8-aminoquinoline auxiliary in Pd catalyzed activation of C-H bonds,[16-23] we hypothesized that palladacycle **II** would be a suitable intermediate for a one electron oxidative addition step (Figure 1). The reaction design requires irradiation of a photocatalyst, **PC^n**, to produce the excited state complex ***PC^n**, which undergoes exergonic single electron transfer (SET) with aryl radical precursor. This SET process generates an aryl radical that intercepts palladacycle **II** to afford the Pd(III) intermediate **III**. We proposed that the oxidized **PC^{n+1}** subsequently oxidizes the Pd(III) intermediate **III**, to re-generate the photocatalyst **PC^n** in an overall redox-neutral process. Reductive elimination from Pd(IV) complex **IV** releases the product and closes the Pd cycle. Reductive elimination from **III** followed by oxidation of the resulting Pd(I) species cannot be excluded.[24] We reasoned that the proposed synergistic catalytic cycle reduces the kinetic barrier to direct C(sp^3)-H arylation, leading to milder reaction conditions, without the need for a range of additives typical in C-H activation methodologies.[25]

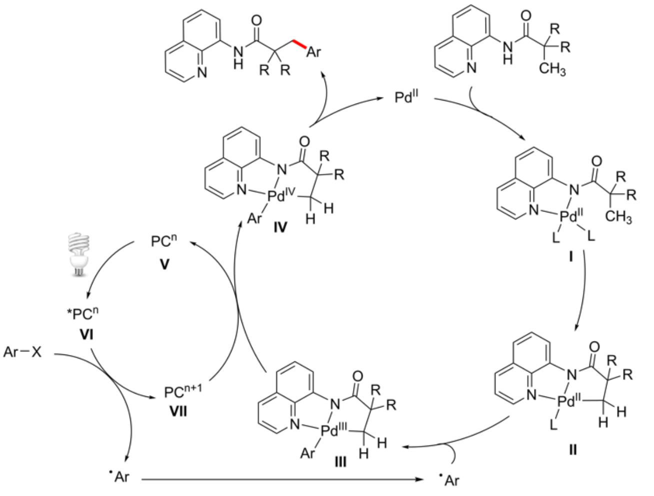


Figure 1: Reaction design for C(sp^3)-H arylation by synergistic photoredox and palladium catalysis

Studies commenced by examining stoichiometric formation of

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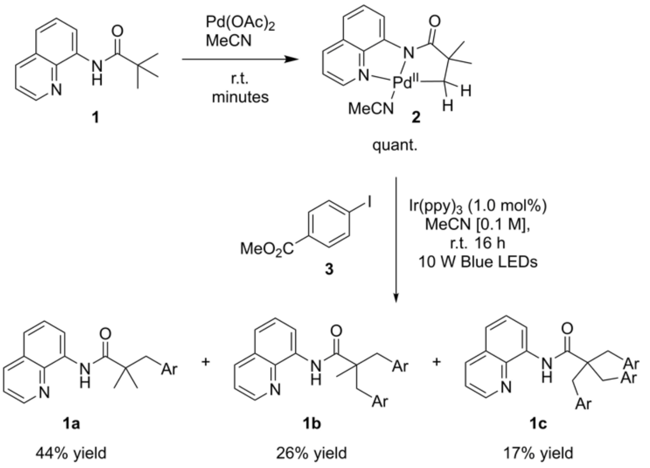
Supporting information for this article is given via a link at the end of the document palladacycle **2** at ambient temperature (Scheme 2). Reaction of amide **1** with one equivalent of $Pd(OAc)_2$ in MeCN at 23 °C afforded palladacycle **2** quantitatively.

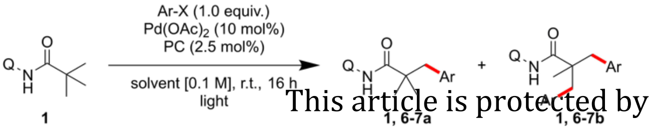


Scheme 2: Formation and reactivity of palladacycle **2** under photoredox conditions

We next evaluated the propensity of palladacycle **2** to intercept a radical generated under photoredox conditions and subsequently undergo a single electron transfer with the oxidized $\mathbf{PC^{n+1}}$. Methyl-4-iodobenzoate (**3**) ($E_{1/2}^{red} \cong -1.3$ V vs SCE)[26] served as a radical precursor with *fac*-$Ir(ppy)_3$ ($E_{1/2}^{red}[{}^*Ir^{III}/Ir^{IV}] = -1.76$ V vs SCE). Reaction of palladacycle **2** with 2 equivalents of **3** and 1.0 mol % of *fac*-$Ir(ppy)_3$ in MeCN produced a mixture of mono- di- and triarylated products **1 a-c** in a combined, isolated yield of 87 % (Scheme 2). Encouraged by these preliminary results, we proceeded with the development of a catalytic reaction with respect to Pd(II) and photocatalyst. With the addition of 10 mol% of $Pd(OAc)_2$, monoarylated (**1a**) and diarylated (**1b**) products were detected by ^1H NMR analysis, albeit in 8% yield (Table 1, entry 1). Further investigation revealed a dependence of reaction yield on $Pd(OAc)_2$ loading, implying that Pd(II) turnover was not occurring (see Supporting Information). Substantial formation of Pd black was generated in each reaction suggesting that the catalytic reaction may not be operating due to the undesired electron transfer from $^*Ir^{III}(ppy)_3$ to Pd(II) or Pd(I), resulting in Pd(0) and effectively shutting down the reaction.

The two-electron reduction potential of Pd(II) to Pd(0) ($E_{1/2}^{red} \cong +0.951$ V vs NHE)[27] is sufficiently low for Pd(II) reduction to occur. Furthermore, oxidation potential of the Pd(III) intermediate may not be sufficient to promote electron transfer to $Ir^{IV}(ppy)_3$ ($E_{1/2}^{red}[Ir^{IV}/Ir^{III}] = +0.77$ V vs SCE) and regenerate $Ir^{III}(ppy)_3$ under catalytic conditions. Attention shifted to the phenyl iodonium salt **4** in conjunction with $[Ir(ppy)_2(dtbpy)]PF_6$ ($E_{1/2}^{red}[{}^*Ir^{III}/Ir^{IV}] = -0.96$ V vs SCE) and these gave traces of the desired products **6a** and **6b**. Conversely, the use of aryldiazonium salt **5** and $[Ru(bpy)_3]Cl_2$ ($E_{1/2}^{red}[{}^*Ru^{II}/Ru^{III}] = -0.81$ V vs SCE) produced a mixture of mono- and diarylated products **7a** and **7b** in an overall 15% yield, without formation of Pd black precipitate. Thus, diazonium salts were chosen for further optimization.

Table 1. Screening of aryl radical precursors[a]

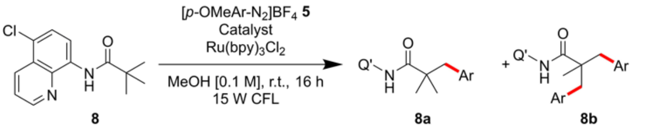


Entry	Ar-X	Solvent	Photocatalyst	Total yield [%][d]
1[b]	Ar-I (**3**)	MeCN	$Ir(ppy)_3$	8
2[b]	$[Ph_2I]BF_4$ (**4**)	MeOH	$Ir(ppy)_2(dtbpy)$ PF_6	trace
3[c]	[*p*OMeArN$_2$] BF_4 (**5**)	MeOH	$Ru(bpy)_3Cl_2$	15

[a] General conditions: Ar-X (1.0 equiv.), $Pd(OAc)_2$ (10 mol%), PC (2.5 mol%), solvent (0.1 M in substrate), r.t., 16 h, light source. [b] reaction irradiated with 10 W Blue LEDs [c] reaction irradiated with 15 W CFL [d] Yield determined by ^1H NMR spectroscopy using sulfolene as an internal standard. Q = quinoline

Chatani[28] and Rao[29] reported that substitution at the 5-position of the 8-aminoquinoline ring improved C-H activation. Accordingly, a series of modified C-5-substituted 8-aminoquinolines, were prepared and examined in our system (See Supporting Information). It was found that the 5-chloro-8-aminoquinoline derivative **8** resulted in improved yields of mono- and diarylated products **8a**, and **8b** to 25%. Consequently, the 5-chloro-8-aminoquinoline auxiliary (Q') was selected for further optimization of catalyst loading and concentration of aryldiazonium salt (Table 2). We initially turned our attention to photocatalyst stoichiometry. A loading of 5 mol% of $Ru(bpy)_3Cl_2$ significantly increased yield of mono- and diarylated products **8a**, and **8b** (Table 2, entry 2).

Table 2. Screening of palladium catalysts and aryldiazonium salt stoichiometry[a]

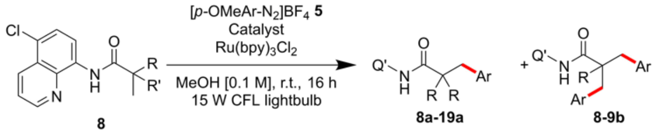


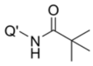
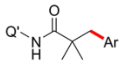
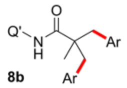
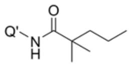
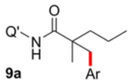
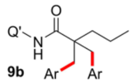
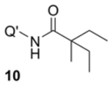
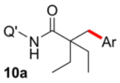
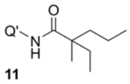
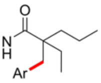
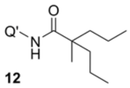
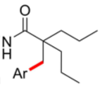
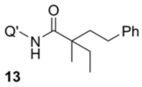
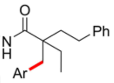
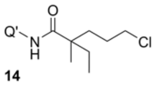
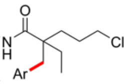
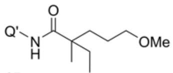
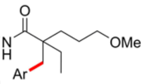
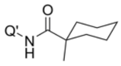
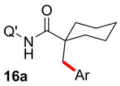
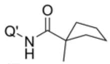
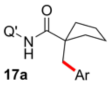
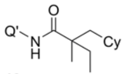
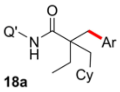
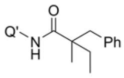
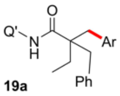
Entry	[Ru] [mol%]	Cat.	Cat. [mol%]	[Ar–N$_2$] BF$_4$ (equiv.)	Total Yield [%]
1	2.5	$Pd(OAc)_2$	10	1	25
2	5	$Pd(OAc)_2$	10	1	42
3	5	$Pd(OPiv)_2$	10	1	12
4	5	$Pd(TFA)_2$	10	1	31
5	5	$Pd(OAc)_2$	15	1	48
6	5	$Pd(OAc)_2$	20	1	39
7	**5**	$\mathbf{Pd(OAc)_2}$	**15**	**1.5**	**55 (52)**[c]
8	5	$Pd(OAc)_2$	15	2	38
9	0	$Pd(OAc)_2$	15	1.5	N.D.
10	5	$Pd(OAc)_2$	0	1.5	N.D.
11	5[d]	$Pd(OAc)_2$	15	1.5	N.D.

[a] General conditions: MeOH (0.1 M in substrate), r.t., 16 h, 15 W CFL. [b] Yield determined by 1H NMR spectroscopy using sulfolene as an internal standard. [c] Isolated yield in parentheses. [d] General conditions, without light irradiation. Q' = 5-chloroquinoline.

Replacing $Pd(OAc)_2$ with $Pd(TFA)_2$ or $Pd(OPiv)_2$ resulted in a lower yield of arylated products (Table 2, entries 3-4) and we reverted to screening additional reaction conditions with $Pd(OAc)_2$.An observable dependence on equivalents of Pd(II) was evidenced (Table 2 entries 2, 5-6). With an affiliated increase of diazonium tetrafluoroborate **5** to 1.5 equivalents, mono- and diarylated products were formed in an overall yield of 55% (Table 2, entry 7).

Table 3. The arylation of aliphatic amides under synergistic photoredox and palladium catalysis[a]



Entry	Substrate	Products		Yield [%][b]
1	 8	 8a	 8b	52 **8a** = 26 **8b** = 26
2	 9	 9a	 9b	54 **9a** = 40 **9b** = 14
3	 10	 10a		52
4	 11	 11a		57
5	 12	 12a		50
6	 13	 13a		61
7	 14	 14a		57
8	 15	 15a		54
9	 16	 16a		47
10	 17	 17a		28
11	 18	 18a		40
12	 19	 19a		21

[a] General conditions: [p-OMePh-N2]BF4 5 (1.5 equiv.) Pd(OAc)2 (15 mol%), Ru(bpy)3Cl2 (5 mol%) MeOH (0.1 M in substrate), r.t., 16 h, 15 W CFL. [b] Isolated yields. Q' = 5-chloroquinoline.

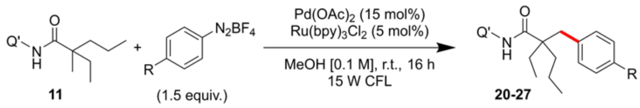
Furthermore, control experiments (Table 2, entries 9-11) demonstrate that Pd(II), Ru(bpy)$_3$Cl$_2$ and light are essential for the transformation.

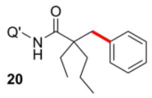
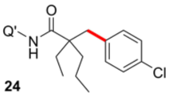
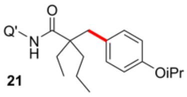
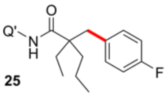
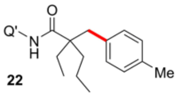
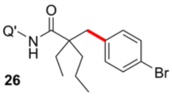
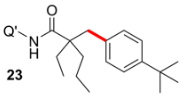
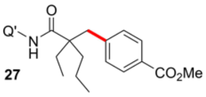
With the establishment of the optimized conditions, we then turned attention to the amide scope and a series of aliphatic amides derived from carboxylic acids with α-quaternary centers were examined (Table 3). There are two reported examples of direct C-H arylation of a quaternary aliphatic amide, highlighting the challenging nature of this transformation.[30, 31] Selectivity for monoarylation over diarylation was higher for sterically congested substrates (entries 1 and 2).

We then investigated selectivity for substrates containing β-methyl C(sp^3)-H bonds and β-methylene C(sp^3)-H bonds (substrates 10-12). Arylation of the β-methyl C(sp^3)-H bonds was exclusively observed, demonstrating high selectivity for β-methyl C(sp^3)-H bonds (entries 3-5).[32] This selectivity was also observed for the benzylic substrate (**19**) (entry 12). Carbocyclic rings were compatible with the arylation reaction and longer alkyl chains, methoxy, chloride, and phenyl groups were tolerated. It should be noted that substrates **8–15** have not been previously studied with C-H arylation chemistry, probably due to competitive intramolecular C-N amidation.[33-37]

The scope of para-substituted aryldiazonium salts was examined (Table 4). Electron donating and electron withdrawing substituents were compatible with reaction conditions. The presence of ester and halogen functionalities was also well tolerated. Although aryl bromides have been reported to engage in Pd(II)-catalyzed arylation of unactivated C(sp^3)-H bonds at 120 °C,[23] excellent chemoselectivity was noted for the brominated derivative **26** under our conditions (Table 4, entry 7).

Table 4. Scope for the aryldiazonium salts[a]



Entry	Product	Yield [%][b]	Entry	Product	Yield [%][b]
1	 20	52	5	 24	78
2	 21	54	6	 25	64
3	 22	60	7	 26	58
4	 23	55	8	 27	45

[a] General conditions: [Ar-N$_2$]BF$_4$ (1.5 equiv.) Pd(OAc)$_2$ (15 mol%), Ru(bpy)$_3$Cl$_2$ (5 mol%), MeOH (0.1 M in substrate), r.t., 16 h, 15 W CFL [b] Isolated yields. Q' = 5-chloroquinoline.

Likewise, aryl bromides ($E^{1/2}_{red}$ = -1.76 V vs SCE) which may be redox active under the reaction conditions, did not interfere with the photoredox catalytic cycle. Interestingly, electron poor diazonium salts tended to give slightly higher yields than electron rich analogs, which contrasts with transition-metal catalyzed C(sp^3)-H arylation with aryl iodides.[18, 31, 38]

In summary, we have developed a new, mild C(sp^3)-H arylation reaction through the combination of Pd-catalyzed C-H activation with photoredox chemistry. The method enables the straightforward arylation of aliphatic amides with α-quaternary centers, with high selectivity for β-methyl C(sp^3)-H bonds.

Studies have commenced in our laboratory to extend this approach to the direct alkylation of unactivated C(sp^3)-H bonds.

Experimental Section

See Supporting Information

Keywords: C-H Activation • Metallaphotoredox • Photoredox • Arylation • Palladium

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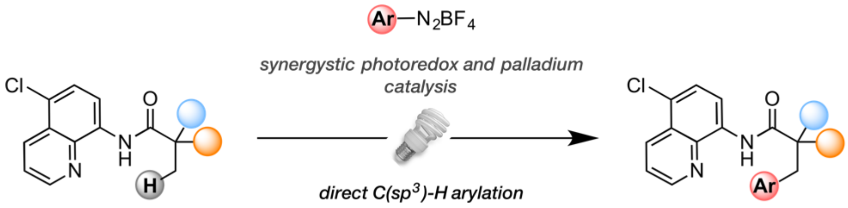
COMMUNICATION



Of Earth and Light: An auxiliary-directed arylation of unactivated C(sp^3)-H bonds with synergistic photoredox and palladium catalysis is reported. This approach enables the site-selective arylation of aliphatic amides with α-quaternary centers and high selectivity for β-methyl C(sp^3)-H bonds. The operationally simple method is compatible with a range of amides, aryldiazonium salts and proceeds at room temperature.

*Milena L. Czyz, David W. Lupton and Anastasios Polyzos**

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Auxiliary-Directed C(sp^3)-H Arylation by Synergistic Photoredox and Palladium Catalysis