

## Photochemistry

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## Visible-Light-Driven Palladium-Catalyzed Radical Alkylation of C–H Bonds with Unactivated Alkyl Bromides

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**Abstract:** Reported herein is a novel visible-light photoredox system with Pd(PPh<sub>3</sub>)<sub>4</sub> as the sole catalyst for the realization of the first direct cross-coupling of C(sp<sup>3</sup>)–H bonds in N-aryl tetrahydroisoquinolines with unactivated alkyl bromides. Moreover, intra- and intermolecular alkylations of heteroarenes were also developed under mild reaction conditions. A variety of tertiary, secondary, and primary alkyl bromides undergo reaction to generate C(sp<sup>3</sup>)–C(sp<sup>3</sup>) and C(sp<sup>2</sup>)–C(sp<sup>3</sup>) bonds in moderate to excellent yields. These redox-neutral reactions feature broad substrate scope (> 60 examples), good functional-group tolerance, and facile generation of quaternary centers. Mechanistic studies indicate that the simple palladium complex acts as the visible-light photocatalyst and radicals are involved in the process.

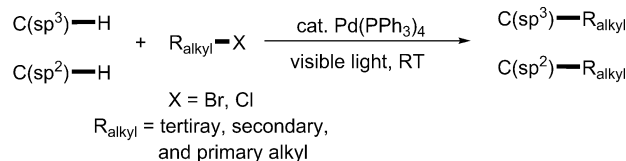
Over the past decades, visible-light photoredox catalysis has emerged as a useful method for realizing novel organic transformations under mild reaction conditions.<sup>[1]</sup> Besides organic dyes,<sup>[2]</sup> ruthenium and iridium complexes, chemists have applied many other transition-metal complexes as photocatalysts in organic synthesis (Scheme 1 A).<sup>[3,4]</sup> Although palladium catalysts have been widely used in cross-coupling reactions,<sup>[5]</sup> and its limited photophysical properties have been studied,<sup>[6]</sup> the use of a simple and commercially available palladium complex, without any exogenous photosensitizer, in a visible-light photoredox procedure has been less investigated.<sup>[7,8]</sup>

Palladium-catalyzed direct transformations of C–H bonds are highly useful and attractive methods in organic chemistry.<sup>[9]</sup> Although significant progress has been achieved, palladium-catalyzed C–H functionalization with unactivated alkyl halides, especially tertiary ones, lags behind because of the challenges associated with sluggish oxidative addition and reductive elimination, as well as the competitive side reactions such as β-H elimination and protonation of the resulting alkylpalladium intermediates.<sup>[10]</sup> Recently, a breakthrough has been independently realized by the groups of Fu, Zhou,

A) Visible-light photocatalysts in organic synthesis developed:<sup>[1,2]</sup> developing:<sup>[3,4,7]</sup>



B) Simple Pd-complex as the catalyst in photoredox process (this work)



**Scheme 1.** Visible-light photocatalysis.

and Alexanian for the palladium-catalyzed radical alkylation of (hetero)arenes with unactivated alkyl halides.<sup>[11,12]</sup> Palladium-catalyzed alkylation of C(sp<sup>3</sup>)–H bonds with unactivated tertiary and secondary alkyl halides, however, remains unexplored. We wondered whether it was possible to resolve such challenges by introducing visible light as an energy source to activate the palladium-catalyst and facilitate the radical cross-couplings. As a continuation of our interest in visible-light-driven transition-metal catalysis,<sup>[11,13]</sup> herein, we report the discovery of a unique visible-light photoredox system with Pd(PPh<sub>3</sub>)<sub>4</sub> as the sole catalyst to realize the first general cross-coupling of C(sp<sup>3</sup>)–H bonds in N-aryl tetrahydroisoquinolines with unactivated alkyl halides (Scheme 1 B). Moreover, alkylation of (hetero)aryl C(sp<sup>2</sup>)–H bonds was also realized under mild reaction conditions.

With this hypothesis in mind, we started to investigate the reaction of 2-phenyl-1,2,3,4-tetrahydroisoquinoline (**1**)<sup>[14]</sup> and *tert*-butylbromide (**2**), in which the catalytic formation of new quaternary centers<sup>[15]</sup> would be achieved. After screening several parameters (see the Supporting Information for more details), we were happy to obtain the desired product **3** in 90% yield, upon isolation, with Pd(PPh<sub>3</sub>)<sub>4</sub> as the catalyst and in the absence of any extra photoinitiators (Table 1, entry 1). Control experiments demonstrated that the phosphorus ligand, palladium catalyst, and visible-light irradiation were necessary for the reaction (entries 2–8; for more details see Table S2 and Figure S14 in the Supporting Information). Importantly, the thermal reaction, without light, delivered no product (entry 9).

On the basis of these observations, we evaluated the generality of this reaction with a range of unactivated tertiary alkyl bromides (Table 2, section A). A variety of other sterically hindered *tert*-alkyl bromides were conveniently converted into the desired products in good to excellent yields, thus indicating the high versatility of this catalytic system. Notably, these congested quaternary centers were

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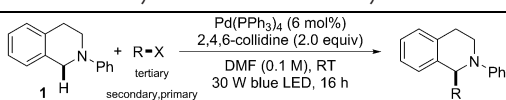
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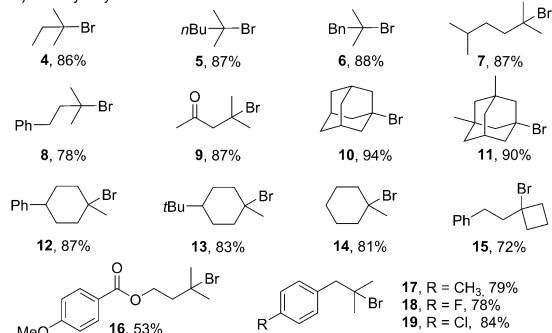
**Table 1:** Screening the reaction conditions.<sup>[a]</sup>

Entry	Variation from the standard conditions	Yield [%] <sup>[b]</sup>
1	None	98 (90)
2	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> as catalyst	89
3	PdBr <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> as catalyst	94 (87)
4	Pd(OAc) <sub>2</sub> as catalyst	trace
5	Pd <sub>2</sub> (dba) <sub>3</sub> as catalyst	n.d.
6	Pd <sub>2</sub> (dba) <sub>3</sub> , 10 mol% PPh <sub>3</sub>	62
7	no light	n.d.
8	no Pd(PPh <sub>3</sub> ) <sub>4</sub>	n.d.
9	110 °C, without light	n.d.

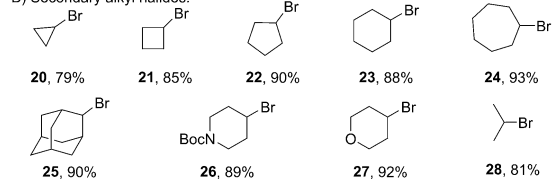
[a] **1** (0.2 mmol), **2** (0.3 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (6 mol%), 2,4,6-collidine (0.4 mmol) in *N,N*-dimethyl formamide (DMF) (2 mL) at room temperature (20 °C) for 24 h under irradiation with 30 W blue LED. [b] Yields determined by GC analysis. The yield of the isolated product is given within parentheses. LED = light-emitting diode, n.d. = not detected.

**Table 2:** Direct  $\alpha$ -alkylation of amines with alkyl halides.<sup>[a]</sup>

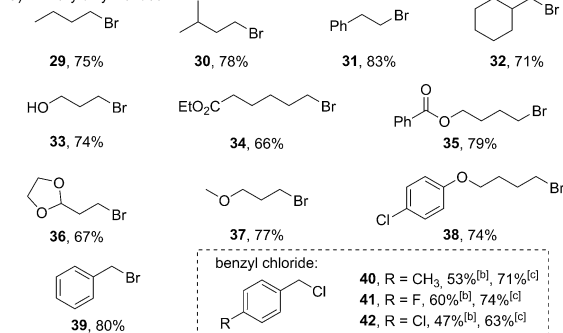
## A) Tertiary alkyl halides:



## B) Secondary alkyl halides:



## C) Primary alkyl halides:

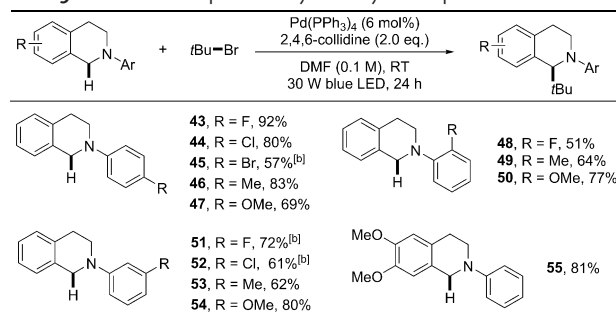


[a] The standard reaction conditions (Table 1, entry 1). Yields of the isolated products are reported. [b] 48 h. [c] LiBr (1.5 equiv) was added, 48 h.

generated efficiently with no detection of isomerization products by this photoredox strategy. Moreover, carbonyl-containing functional groups (**9** and **16**) survived the reaction conditions without complications.

In addition to tertiary alkyl bromides, various unactivated secondary and primary alkyl bromides were also examined (Table 2, sections B and C). For example, the secondary alkyl bromides (**20–28**), including cyclic and acyclic ones, all reacted smoothly. Moreover, a variety of unactivated primary alkyl bromides also worked well (**29–42**). Notably, LiBr was helpful for promoting the reactions of benzyl chlorides, thus indicating that benzyl bromides are key players in this reaction (**40–42**). This reaction tolerated many kinds of functional groups, including alcohol (**33**), ester (**34** and **35**), ether (**36** and **37**), chloro (**38** and **42**), and fluoro (**41**) moieties, all of which may be beneficial for subsequent transformations.

The catalytic system appears to be general with a variety of *N*-aryl tetrahydroisoquinolines (Table 3). The benzene

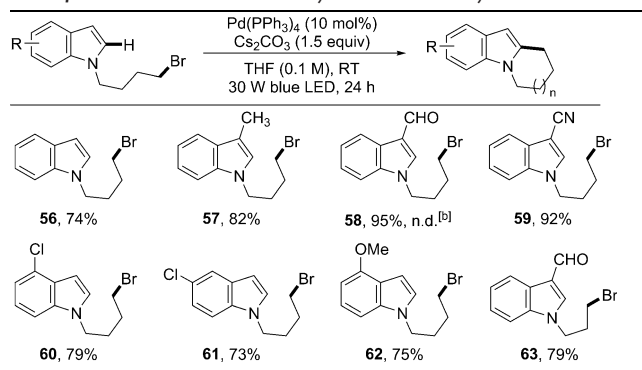
**Table 3:** Substrate scope of *N*-aryl tetrahydroisoquinolines.<sup>[a]</sup>

[a] The standard reaction conditions (Table 1, entry 1). Yields of isolated products are reported. [b] 48 h.

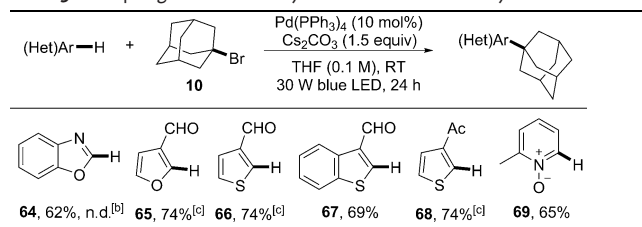
rings, bearing a fluoro, chloro, and bromo, as well as methoxy group at the *ortho*, *meta*, and *para* positions, on the nitrogen atom can successfully give the corresponding alkylation products (**43–54**) in moderate to excellent yields. The substituent on the benzene ring of tetrahydroisoquinoline can also be varied, as demonstrated by the selective *tert*-butylation of **55** in 81% yield. However, alternative benzyl amines show no reactivity in this transformation (please see more details in the Supporting Information).

Considering the high importance of functionalization of heteroarenes, we further applied this catalytic system toward the intramolecular alkylation of indoles under mild reaction conditions. With minor alterations of base and solvent, such cyclization proceeded efficiently to generate the desired products in good to excellent yields (Table 4). The electronic nature of the substituents on the indole ring has little effect on the transformation with a slight preference for electron-withdrawing groups at C3 (**57–63**). This method offers a mild and safe alternative to indole functionalization by avoiding the use of either organostannanes or ultraviolet light.<sup>[16]</sup>

Moreover, this photoredox protocol can also be applied to the intermolecular C–H alkylation of heteroarenes (Table 5). Benzoxazole (**64**), furan (**65**), thiophenes (**66–68**), and 2-methyl-pyridine *N*-oxide (**69**) all can be alkylated well with

**Table 4:** Indole functionalization by intramolecular cyclization.<sup>[a]</sup>

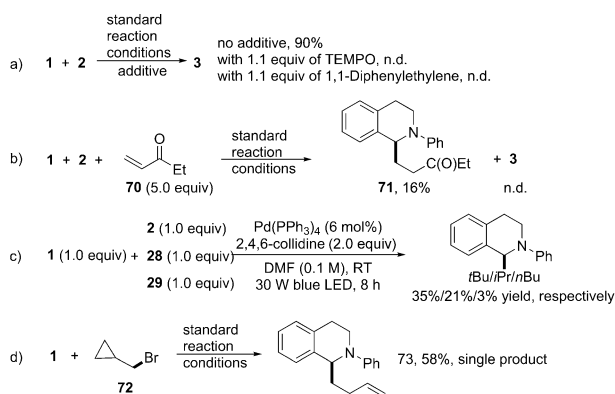
[a] N-alkylindole (0.2 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (10 mol %), and Cs<sub>2</sub>CO<sub>3</sub> (0.3 mmol) in THF (2 mL) at room temperature (20 °C) for 24 h under irradiation with 30 W blue LED. Yields of isolated products are reported. [b] Without light or without Pd(PPh<sub>3</sub>)<sub>4</sub>. THF = tetrahydrofuran.

**Table 5:** Coupling of 1-adamantyl bromide and heterocycles.<sup>[a]</sup>

[a] Heterocycles (0.4 mmol), **10** (0.2 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (10 mol %), Cs<sub>2</sub>CO<sub>3</sub> (0.3 mmol) in THF (2 mL) at room temperature (20 °C) for 24 h under irradiation with 30 W blue LED, unless otherwise noted. Yields of the isolated products are reported. [b] Without light or without Pd(PPh<sub>3</sub>)<sub>4</sub>. [c] 48 h.

**10**, thus delivering the desired products containing otherwise difficult to obtain quaternary centers. In all of these cases, C2-selective alkylated products were obtained. Notably, electron-withdrawing functional groups were important for the reactivity and regioselectivity.

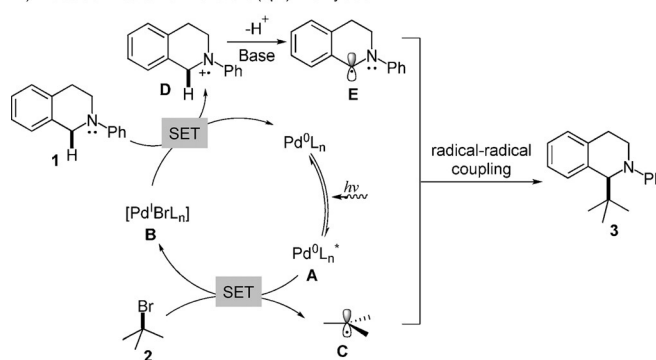
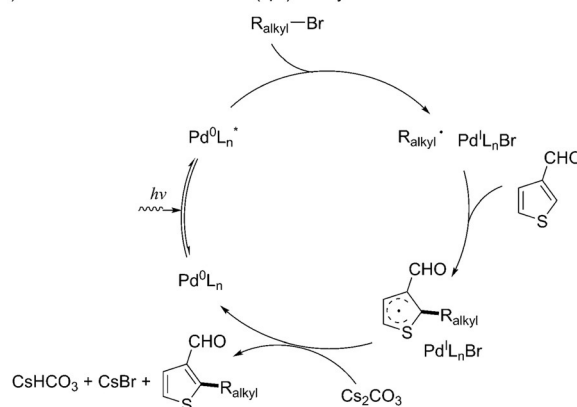
To gain more insight into this alkylation reaction, mechanistic studies were conducted with radical trapping experiments, competing reactions, and radical-clock reactions (Scheme 2; see the Supporting Information for details), which

**Scheme 2.** Selected mechanistic studies.

all indicated that this reaction proceeded through a radical-type mechanism.

To verify that the palladium(0) catalyst is the photo-absorbing species, photophysical behaviors including absorption and emission spectra were performed (see the Supporting Information for more details). As shown in Figures S5–S10, fluorescence quenching experiments and Stern–Volmer studies indicate that the alkyl bromide quenches the excited state of Pd(PPh<sub>3</sub>)<sub>4</sub>, where it presumably engages in single-electron transfer (SET) with the excited palladium(0) complex.<sup>[7]</sup>

Based on the obtained results and previous reports,<sup>[11,12]</sup> we propose the following mechanism with **1** and **2** as the substrates (Scheme 3A). Under visible-light irradiation, the

**A)** Plausible mechanism for the C(sp<sup>3</sup>)-H alkylation**B)** Plausible mechanism for the C(sp<sup>2</sup>)-H alkylation**Scheme 3.** Possible mechanism.

active palladium(0) complex **A** undergoes an SET process with **2** to provide the *tert*-butyl radical **C** and palladium complex **B**, which reacts with **1** to afford the radical cation **D** and regenerates the palladium(0) complex.<sup>[17]</sup> The resulting **D** undergoes deprotonation in the presence of a base to give the  $\alpha$ -amino radical **E**, which undergoes radical–radical coupling with **C** to afford the desired product **3**.<sup>[8c]</sup> At this stage, we could not exclude other pathways for this catalysis.

Based on previous reports,<sup>[11,12]</sup> our mechanistic hypothesis for the alkylation of heterocycles is shown in Scheme 3B. It starts from the SET from the excited Pd<sup>0</sup>L<sub>n</sub>\* to the alkyl halide, thus forming an alkyl radical and Pd<sup>I</sup>L<sub>n</sub>Br complex.<sup>[7]</sup> The carbon-centered radical then adds to the heteroarene to

generate an cyclic alkyl radical intermediate, with subsequent SET, deprotonation, and rearomatization to give the alkylated heteroarene, as well as regeneration of the palladium(0) catalyst. Further mechanistic studies and applications of such palladium complexes in visible-light photocatalysis are underway in our laboratory.

In conclusion, we have developed a unique visible-light-driven palladium-catalyzed process to realize the efficient radical alkylation of C–H bonds with alkyl halides under mild reaction conditions. A variety of unactivated alkyl bromides, including tertiary, secondary, and primary ones, undergo such reactions to selectively generate C(sp<sup>3</sup>)–C(sp<sup>3</sup>) and C(sp<sup>2</sup>)–C(sp<sup>3</sup>) bonds in moderate to excellent yields. These redox-neutral reactions feature broad substrate scope (> 60 examples), good functional-group tolerance, as well as facile construction of quaternary centers. Key for the success of this photochemistry is the use of the simple and commercially available Pd(PPh<sub>3</sub>)<sub>4</sub> as the sole catalyst.

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### Conflict of interest

The authors declare no conflict of interest.

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