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Photoinduced Palladium-Catalyzed Intermolecular Radical Cascade Cyclization of *N*-Arylacrylamides with Unactivated Alkyl Bromides

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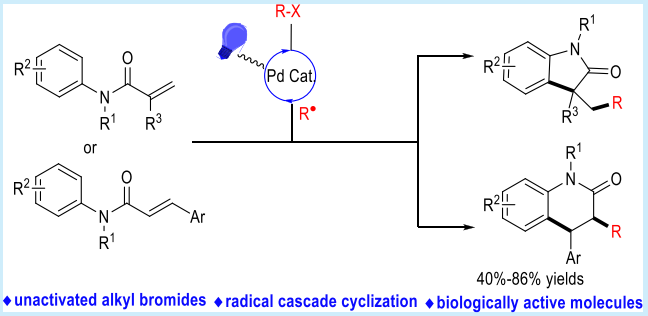
ABSTRACT: A mild visible-light-induced Pd-catalyzed intermolecular radical cascade reaction of *N*-arylacrylamides with unactivated alkyl bromides is disclosed. Photoexcited Pd complexes transfer a single electron in this protocol, and hybrid alkyl Pd-radical species are involved as the key reaction intermediates. Sophisticated bioactive oxindole derivatives bearing various substituents and substitution patterns can be efficiently afforded through this approach.



Palladium-catalyzed organic transformations are a significant part of organometallic chemistry.[1] They are not only efficiently used to construct carbon−carbon and carbon−heteroatom bonds but also play essential roles in many fields, such as pharmaceutical synthesis, materials application, and biological science.[2] However, in comparison to aryl/alkenyl halides, the application of alkyl halides is more challenging in palladium-catalyzed cross-coupling reactions, while this issue can be solved through palladium catalysis involving single-electron transfer (SET).[3] Traditionally, Pd-catalyzed radical reactions with alkyl halides usually require additional photosensitizers, oxidants, or high temperature (Scheme 1a).[3b,h,i,4] The use of simple Pd complexes as part of the photosensors instead of the classical photoredox catalysts for visible-light-induced organic transformations has recently received much attention.[3d−g,i]

In Pd-catalyzed photoredox reactions, the Pd catalysts are generally activated to their excited states by visible light and are also involved in the Pd-bonded covalent intermediates to participate in the catalytic cycles in the absence of traditional photoredox catalysts.[5] In 2016, Gevorgyan and co-workers disclosed a Pd-catalyzed 1,5-hydrogen atom transfer (HAT) process for a photoinduced intramolecular radical cyclization reaction.[6] The intramolecular C−H arylation of amides was realized by the same research group via a Pd-catalyzed photoredox C(sp^2)−O bond cleavage process under mild conditions.[7] Glorius and co-workers also envisioned the redox-neutral dicarbofunctionalization of olefins via a photoinduced C(sp^2)−Br bond cleavage/Baldwin-type cyclization/tertiary radical coupling cascade under the catalysis of a Pd complex (Scheme 1b).[8] In addition, the Yu[9a] and Liang[9b] groups have respectively reported the photoexcited Pd-catalyzed intramolecular alkylation of (hetero) aryl/alkene C(sp^2)−H bonds under mild reaction conditions (Scheme 1c). It worth noting that the Yu[10a] and Cheng[10b] groups have demonstrated multicomponent reactions of allylamines/anilines with CO_2. Despite the significant achievements obtained in the photoexcited Pd-catalyzed radical cyclization reactions, the intermolecular cascade cyclization of aromatic C(sp^2)−H bonds with unactivated alkyl halides remains unexplored.

Herein, we report a visible-light-induced Pd-catalyzed intermolecular cyclization of *N*-arylacrylamides. The alkyl halides are activated through this protocol to generate hybrid alkyl palladium radical intermediates, which can react with another substrate and then undergo an intramolecular radical cascade cyclization. The readily available, inexpensive Pd-$(PPh_3)_4$ was used as the sole reaction catalyst. Structurally significant oxindoles and 3,4-dihydroquinolinones with various substitution patterns are afforded in moderate to good yields.

Key results of the condition optimization are summarized in Table 1. The reaction was carried out with *N*-arylacrylamide (**1a**) and alkyl bromide (**2a**) used as the model substrates. To our delight, the oxindole product **3a** could be afforded in 81% yield in the presence of a stoichiometric amount of cesium carbonate in 1,4-dioxane (entry 1). Replacing the $Pd(PPh_3)_4$ catalyst with $PdCl_2$ or $Pd(OAc)_2$ led to little formation of the desired product **3a** (entry 2). The addition of frequently used phosphine ligands such as PPh_3, Xantphos, and BINAP did not further increase the reaction yields (entry 3). Decreasing the

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Scheme 1. Pd-Catalyzed Radical Cascade Cyclization

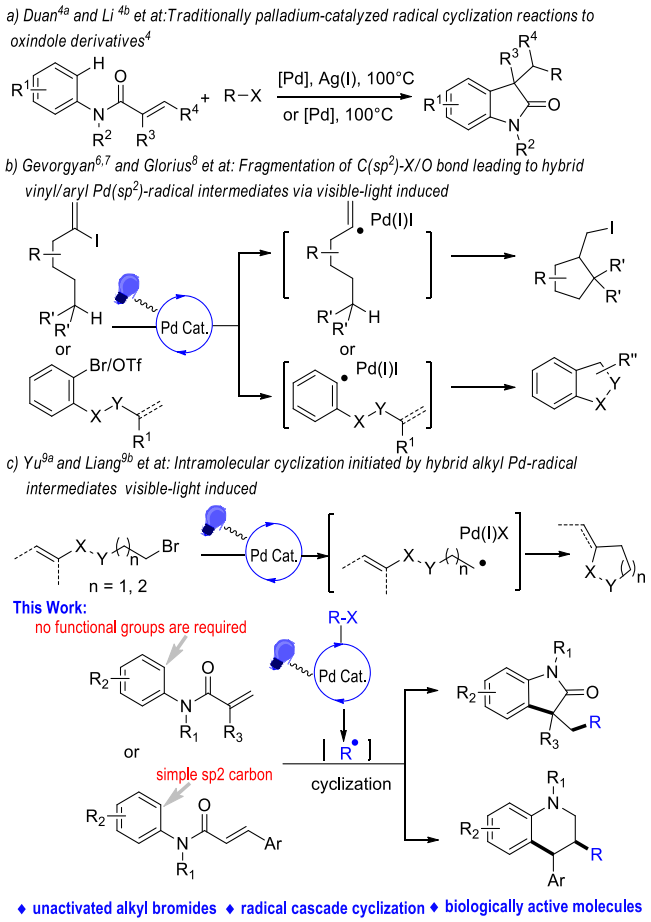
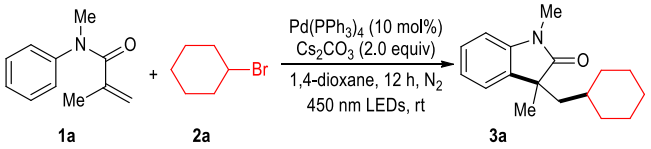


Table 1. Optimization of Conditions[a]



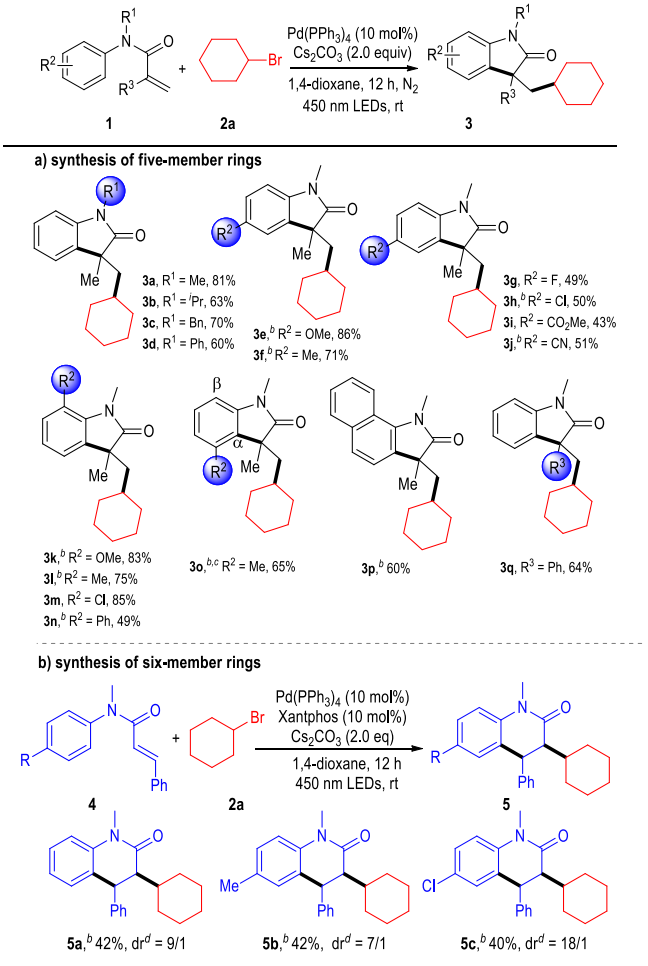
entry	variation from the standard conditions	yield (%)[b]
1	none	81
2	$PdCl_2$ or Pd $(OAc)_2$ as catalyst	trace
3	adding 10 mol % PPh_3/*rac*-BINAP/Xantphos	50/42/78
4	5 mol % $Pd(PPh_3)_4$	55
5	white light as light source	60
6	no light	0
7	no $Pd(PPh_3)_4$	0
8	no base	0
9	adding TEMPO (1.5 equiv)	0
10	cyclohexyl fluoride instead of **2a**	trace
11	cyclohexyl chloride instead of **2a**	19
12	cyclohexyl iodine instead of **2a**	58

[a]Unless otherwise specified, the reactions were carried out using **1a** (0.1 mmol), **2a** (0.15 mmol), Cs_2CO_3 (0.2 mmol), $Pd(PPh_3)_4$ (10 mol %), 450 nm LEDs and 1,4-dioxane (1.0 mL) at room temperature for 12 h under nitrogen.Abbreviations: LED, light-emitting diode; TEMPO, 2,2,6,6-tetramethylpiperidine-1-oxyl. [b]Isolated yield of **3a**.

catalyst loading of $Pd(PPh_3)_4$ resulted in a drop in the product yield (entry 4). Light played a significant role in this Pd-catalyzed alkylarylative reaction, since the product **3a** was afforded in a decreased yield when the light source was switched to white LEDs (entry 5). No desired product was obtained without the use of light, $Pd(Ph_3)_4$, or base (entries 6−8). It is worth noting that the addition of TEMPO completely inhibited the formation of the product **3a** (entry 9). When alkyl chloride or alkyl iodine was used instead of alkyl bromide as the substrate to participate in the reaction, the yields were significantly decreased (entries 11 and 12); alkyl fluoride was found to be an unsuccessful substrate (entry 10).

To examine the generality of our established method, we studied the substrate scope of *N*-arylacrylamide **1** and alkyl bromide **2** bearing various substituents and substitution patterns (Tables 2 and 3).

Table 2. Scope of the *N*-Arylacrylamides 1 and 4[a]



[a]Unless otherwise specified, the reactions were carried out using **1a** (0.1 mmol), **2a** (0.15 mmol), Cs_2CO_3 (0.2 mmol), $Pd(PPh_3)_4$ (10 mol %), 450 nm LEDs, and 1,4-dioxane (1.0 mL) at room temperature for 12 h under nitrogen. [b]Addition of 10 mol % Xantphos as ligand. [c]A mixture of two regioisomeric α/β isomers in a ratio of 2/1 determined by crude ^{1}H NMR analysis. [d]Diastereomeric ratio (dr) determined by crude ^{1}H NMR analysis.

First, the *N*-arylacrylamide substrates **1** possessing different N substituents (Me, ^{i}Pr, Ph, Bn) worked well in the reaction (Table 2, **3a−d**). Both electron-donating and electron-withdrawing substituents at the *para* position of the aniline moiety were well tolerated in this transformation (**3e−j**). However, only a trace amount of product was detected with *N*-

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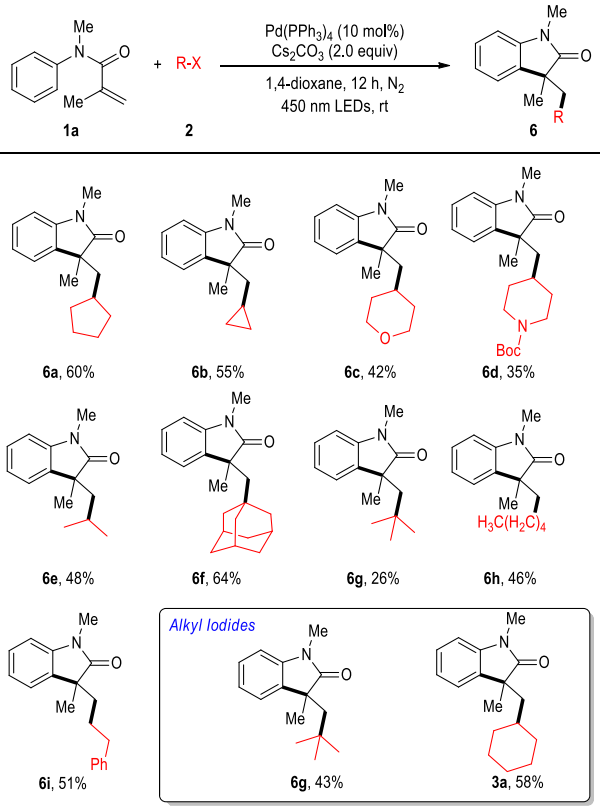
Table 3. Scope of the Unactivated Alkyl Bromides 2[a]



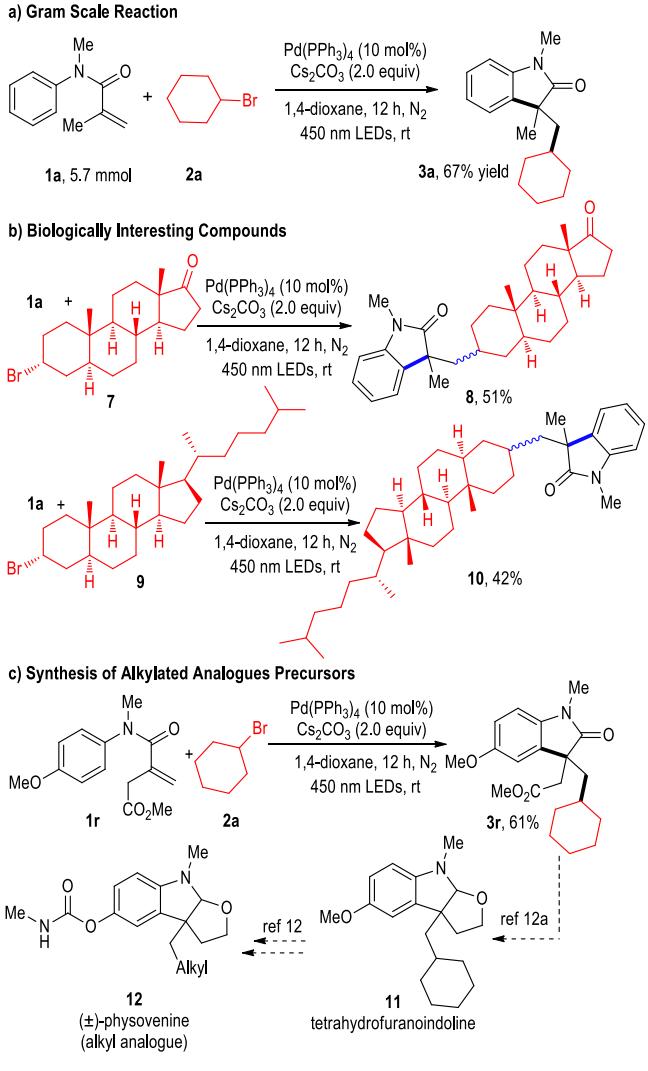
[a]Unless otherwise specified, the reactions were carried out using **1a** (0.1 mmol), **2a** (0.15 mmol), Cs_2CO_3 (0.2 mmol), $Pd(PPh_3)_4$ (10 mol %), 450 nm LEDs, and 1,4-dioxane (1.0 mL) at room temperature for 12 h under nitrogen.

arylacrylamides bearing Br/I at the *para* position. The possible reason is that the aryl radicals could be generated from aryl iodide/bromide under photoinduced Pd catalysis,[6b,8a] which resulted in more complicated reactions. In addition, the steric effect of *ortho* substituents had little influence on this reaction, with the corresponding products being afforded in 49−85% yields (**3k−n**). The *N*-arylacrylamide **1** bearing a *m*-CH_3 group on its aryl ring could also give the desired product **3o** in a satisfactory yield. Switching the phenyl ring on **1a** into a naphthyl ring led to product **3p** in a moderate yield. Replacing the CH_3 on the α-position of the acrylamide moiety of **1a** with a Ph group resulted in a drop of the product yield (**3q**). When the R^3 group of *N*-arylacrylamides **1** was a hydrogen atom, none of the desired product was observed. Finally, molecules containing internal C═C double bonds were evaluated under the typical reaction conditions (Table 2b). *N*-Methyl-*N*-arylcinnamamides (**4a−c**) were found to be effective substrates, and the corresponding six-membered-ring products **5a−c** were smoothly afforded (Table 2) in acceptable yields and with good dr values.

Subsequently, the scope of alkyl halides with **1a** was evaluated (Table 3). Secondary alkyl bromides, including cyclic and acyclic species, all reacted effectively (**6a−e**). *tert*-Alkyl bromides were conveniently converted into the desired products in 26−64% yields (**6f,g**). Replacing 1-bromoadamantane with 2-bromo-2-methylpropane led to a dramatic decrease in the corresponding product yields. Moreover, primary alkyl bromides also worked well (**6h,i**). Notably, alkyl iodides were also tolerated in this reaction (**6g**, **3a**).

3,3-Disubstituted oxindoles are valuable structure motifs that widely exist in biologically active natural products, alkaloids, and pharmaceutical agents.[11] The multicyclic oxindole products (**3** and **6**) obtained from our reactions are readily available in synthetic transformations to give sophisticated functional molecules. Note that the photoexcited Pd catalytic transformation can be carried out on a gram scale without obvious erosions of the product yields (Scheme 2a). Further

Scheme 2. Applications of the Synthetic Methodology



synthetic applications of photoinduced tandem reactions with the complicated functional molecules **7** and **9** were tested. It was found that the radicals underwent cascade reactions to afford the desired oxindoles **8** and **10**, respectively (Scheme 2b). The synthetic utility of this protocol was also used in the preparation of alkyl-substituted oxindole derivative **3r** in 61% yield, which could be readily converted into alkyl analogues of naturally existing (±)-physovenine (Scheme 2c).[12] This family of alkaloids exhibits inhibitory activity against acetylcholinesterase and tutyrylcholinesterase.[13]

To gain insights into this alkylation reaction, several control experiments were conducted. The radical scavenger TEMPO was introduced into the reaction system of *N*-arylacrylamide **1a**

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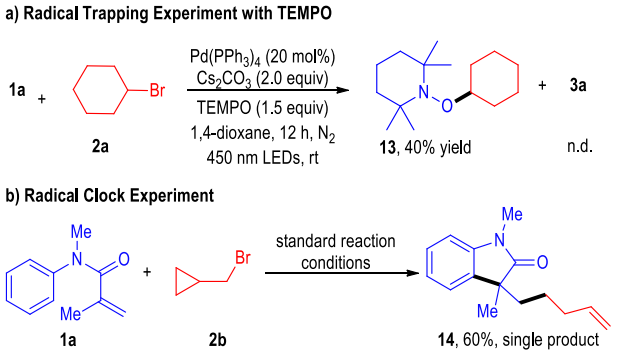
with alkyl bromide **2a**. No alkylated oxindole was detected. In addition, the radical trapping product 1-(cyclohexyloxy)-2,2,6,6-tetramethylpiperidine (**13**) was observed in 40% yield (Scheme 3a). Convincing evidence could be obtained through

Scheme 3. Control Experiments for Mechanistic Investigations



a radical-clock experiment to support the radical-mediated reaction mechanism. The radical-mediated ring-opening product **14** could be afforded in 60% yield from the Pd-catalyzed alkylarylation reaction when the (bromomethyl)-cyclopropane **2b** was used as the reaction substrate (Scheme 3b). All of these radical probe experiments indicated that this reaction proceeded through a radical-type mechanism. In addition, the Gevorgyan group proved that Pd species undergoes a Pd(0)/Pd(I) catalytic cycle, not a traditional Pd(0)/Pd(II) catalytic cycle, from the results of isotope labeling studies in visible-light-induced Pd-catalyzed reactions.[6b] On the basis of the above results and previous reports,[9a,14] we propose a plausible catalytic cycle involving radical mechanism (see the Supporting Information for more details). It starts from a SET from the excited Pd(0) complex to an alkyl bromide (**2**); thus, the corresponding hybrid alkyl Pd-radical species was obtained. Then, the alkyl radical adds to the alkene of substrates **1**, followed by cyclization, with subsequent deprotonation and rearomatization to obtain the final product **3**, as well as regeneration of the Pd(0) catalyst, which supported the next cycle.

In conclusion, we have developed an efficient radical cascade cyclization reaction of *N*-arylacrylamides and unactivated alkyl bromides via visible-light-induced Pd-catalysis under mild reaction conditions. A variety of unactivated tertiary, secondary, and primary alkyl bromides have been applied in this reaction to give valuable 3,3-dialkyl-substituted oxindoles and alkylated 3,4-dihydroquinolin-2(1*H*)-ones in moderate to good yields. This methodology features good functional-group tolerance, commercially available $Pd(PPh_3)_4$ as the sole photocatalyst, and simple and mild conditions and provides great potential for the practical synthesis of bioactive oxindole derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01698.

Experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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