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Palladium-Catalyzed Cascade Cyclization of Alkene-Tethered Aryl Halides with *o*-Bromobenzoic Acids: Access to Diverse Fused Indolo[2,1-*a*]isoquinolines

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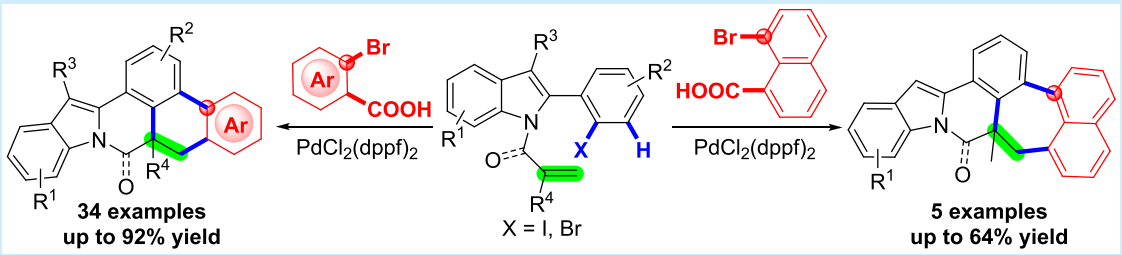
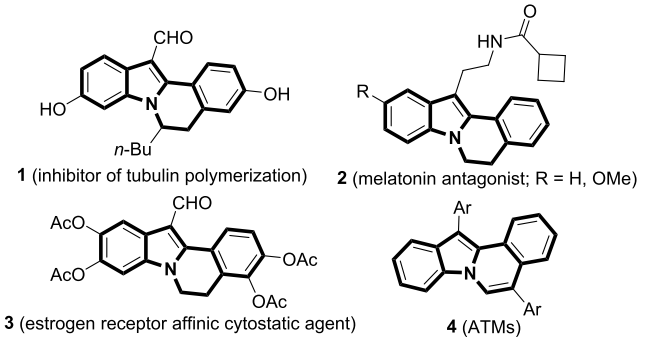
Supporting Information



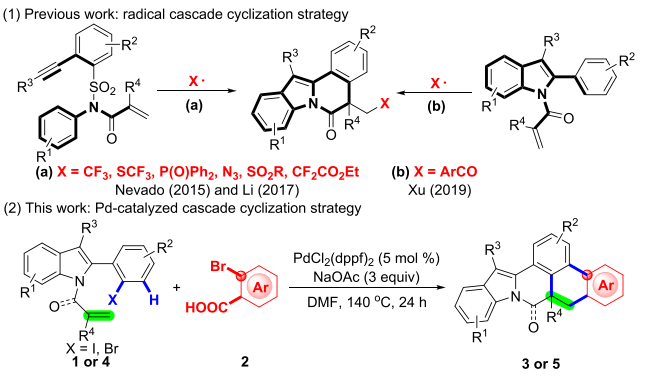
ABSTRACT: A novel palladium-catalyzed cascade cyclization of alkene-tethered aryl halides with *o*-bromobenzoic acids is described, which provides an efficient avenue for building various fused hexacyclic scaffolds containing indolo[2,1-*a*]isoquinoline in moderate to excellent yield. The method enables the construction of three C−C bonds through an intramolecular carbopalladation, C−H activation, and a decarboxylation sequence. Furthermore, dihydrocyclohepta[*de*]-naphthalene-fused indolo[2,1-*a*]isoquinolines can be synthesized in moderate yield by constructing a seven-membered ring.

Indolo[2,1-*a*]isoquinolines represent an important class of multifused N-heterocycles that is found in key structural frameworks of numerous pharmaceuticals, biologically active natural products, and functional materials.[1] For example, indolo[2,1-*a*]isoquinolines **1**−**4** have also received much attention because they can be used as an inhibitor of tubulin polymerization, a melatonin antagonist, an estrogen receptor affinic cytostatic agent, and hole-transporting materials (HTMs) in organic light-emitting diodes (Scheme 1). In the past several decades, considerable efforts have been devoted to construct indolo[2,1-*a*]isoquinoline derivatives.[2,3] In particular, an elegant radical cascade cyclization strategy has been developed by Nevado, Li, and Xu in recent years (Scheme 2 (1)).[3] However, on one hand, such methods for the synthesis of indolo[2,1-*a*]isoquinoline derivatives remain underdeveloped due to the complexity of polycyclic fused ring core scaffolds. On the other hand, the vast majority of the reported methods have focused on the assembly of polysubstituted indolo[2,1-*a*]isoquinolines, whereas this technology for the

Scheme 1. Examples of Important Indolo[2,1-*a*]isoquinolines



Scheme 2. Synthesis of Indolo[2,1-*a*]isoquinoline Derivatives via Two Different Strategies



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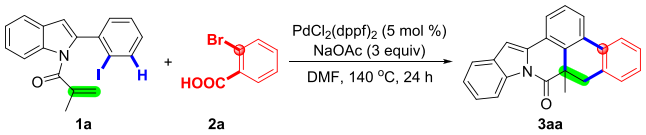
synthesis of fused indolo[2,1-*a*]isoquinolines[2b] continues to be an arduous challenge. Consequently, the development of new efficient strategies that provide straightforward access to fused indolo[2,1-*a*]isoquinolines is of significant importance in consideration of the above.

Cascade (otherwise termed domino) reactions have attracted considerable attention because they provide an efficient and step-economical process to simultaneously achieve the construction of multiple bonds in a single operation.[4] In addition, transition-metal-catalyzed C−H functionalization reactions are interesting to scientific researchers due to their high atom economy without prefunctionalization of the starting materials.[5] Accordingly, the introduction of the C−H bond activation strategy in the domino process is extremely appealing.[6,7] In the field, considerable progress has been made in the palladium-catalyzed cascade cyclization of aryl halides bearing a tethered alkene.[7−11] This protocol, reported initially by the group of Grigg,[8h,i] undergoes intramolecular carbopalladation, followed by C−H bond activation to form the key intermediate palladacycle, which can furnish structurally diversified heteropolycycles by three different types of transformations, including reductive elimination,[8] a [1,4]-Pd shift,[9] and a reaction with various coupling partners.[10,11] Recently, significant breakthroughs in this field have been reported[10,11] through migratory insertion or oxidative addition of coupling partners, such as aryl iodides, diaziridinones, arynes, and activated alkynes, α-diazocarbonyl compounds, and dibromomethane, to palladacycles generated by regioselective C−H activation, in particular, the *ortho*-C−H bond activation of aryl halides,[11] thus leading to the synthesis of fused and spiro-heteropolycycles. However, such examples for the synthesis of fused heteropolycycles are quite rare. Inspired by these reasons and our research interests in the tandem reactions involving palladacycles,[10a,12a−e] herein, we reported a new palladium-catalyzed cascade cyclization of alkene-tethered aryl halides for accessing fused hexacyclic scaffolds containing indolo[2,1-*a*]isoquinoline by the use of *o*-bromobenzoic acids as a suitable coupling partner (Scheme 2 (2)).

Our initial investigation focused on the cascade reaction of 1-(2-(2-iodophenyl)-1*H*-indol-1-yl)-2-methylprop-2-en-1-one (**1a**) with *o*-bromobenzoic acid (**2a**) (Table 1). After an extensive screening of the reaction parameters, we were pleased to find that the treatment of **1a** with **2a**, $PdCl_2(dppf)_2$ (5 mol %), NaOAc (3 equiv), and DMF (2 mL) at 140 °C under a N_2 atmosphere for 24 h could afford the desired product **3aa** in 88% yield (entry 1). Other palladium catalysts, such as $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$, and $Pd(PPh_3)_4$, proved to be less efficient than $PdCl_2(dppf)_2$ in terms of yield (entries 2−4). Control experiments revealed that ligands had a negative effect for this cascade reaction because performing the reaction with ligands, including PPh_3, P*t*-Bu_3, and $P(3,5\text{-}(CF_3)_2C_6H_3)_3$, resulted in a lower yield (entries 5−7). The examination of other bases, including K_2CO_3, K_3PO_4, Cs_2CO_3, and Na_2CO_3, indicated that all of them were inferior to NaOAc (entries 8−10). Furthermore, the nature of solvents was found to be crucial for the reaction: Using DMSO or DMA as a medium led to a slightly diminished yield (entries 11 and 12), yet the reaction was completely suppressed by replacing DMF with MeCN or toluene as the solvent (entry 13). A lower or higher temperature showed worse efficiency than the results at 140 °C (entries 14 and 14). Finally, the addition of TBAB afforded an almost the identical yield (entry 16). Gratifyingly, the reaction

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3aa

entry	variation from the standard conditions	yield (%)[b]
1	none	88
2	$Pd(OAc)_2$ instead of $PdCl_2(dppf)_2$	72
3	$PdCl_2(PPh_3)_2$ instead of $PdCl_2(dppf)_2$	86
4	$Pd(PPh_3)_4$ instead of $PdCl_2(dppf)_2$	63
5	PPh_3 (10 mol %) was added	69
6	P*t*-Bu_3 (10 mol %) was added	82
7	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (10 mol %) was added	71
8	K_2CO_3 or K_3PO_4 instead of NaOAc	70
9	Cs_2CO_3 instead of NaOAc	62
10	Na_2CO_3 instead of NaOAc	81
11	DMSO instead of DMF	78
12	DMA instead of DMF	85
13	MeCN or toluene instead of DMF	0
14	at 130 °C	81
15	at 150 °C	76
16	TBAB (0.5 equiv) was added	90 (83)[c]

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (1.2 equiv), $PdCl_2(dppf)_2$ (5 mol %), NaOAc (3 equiv), and DMF (2 mL) at 140 °C under N_2 for 24 h. [b]Isolated yield. [c]**1a** (1 mmol) and DMF (8 mL) were used.

is applicable to scale up to 1 mmol of **1a**, thus giving the product **3aa** in 83% yield (entry 16).

With the optimal reaction conditions in hand, we set out to evaluate the generality of this protocol with respect to alkene-tethered aryl halides (I and Br) **1** and *o*-bromobenzoic acids **2** (Scheme 3). Initially, a range of substrates **1b−l** with substituents on the indole ring or the iodo-bearing benzene ring were investigated by employing *o*-bromobenzoic acid as the coupling reagent. To our delight, various substituents, including Me, OMe, F, Cl, Br, and CF_3, were well tolerated, and the desired products **3ba−la** were afforded in 42−85% yield. Importantly, substrate **1m** bearing a phenyl group on the alkene could smoothly undergo the cascade reaction to furnish the target product **3ma** in 80% yield. Subsequently, the optimal reaction conditions were applicable to an array of *o*-bromobenzoic acids **2b−l**. Monosubstituted *o*-bromobenzoic acids **2b−g** containing Me, OMe, NH_2, F, and Cl groups afforded the products **3ab−ag** in 31−85% yield. The structure of **3ad** was unambiguously confirmed by single-crystal X-ray crystallography. (See the Supporting Information (SI).) Disubstituted (OMe and F) and fused *o*-bromobenzoic acids could successfully be converted into the target products **3ah−aj** in 74, 54, and 84% yield, respectively. 3-Bromothiophene-2-carboxylic acid and 4-bromonicotinic acid also exhibited high reactivity, and the desired products **3ak** and **3al** were obtained in 80 and 70% yield, respectively. It was noteworthy that *o*-chlorobenzoic acid was also a competent substrate, albeit providing a diminished yield in comparison with *o*-bromobenzoic acid **1a**. Finally, we unexpectedly found that the extra addition of TBAB (0.5 equiv) had a positive effect on the reaction because the vast majority of substrates **1** and **2** were transformed into the products **3** in higher yield (the yields in parentheses with superscript *b*). We speculated that TBAB could activate and stabilize palladium complexes in the catalytic cycle.[10d,13] (See the SI.)

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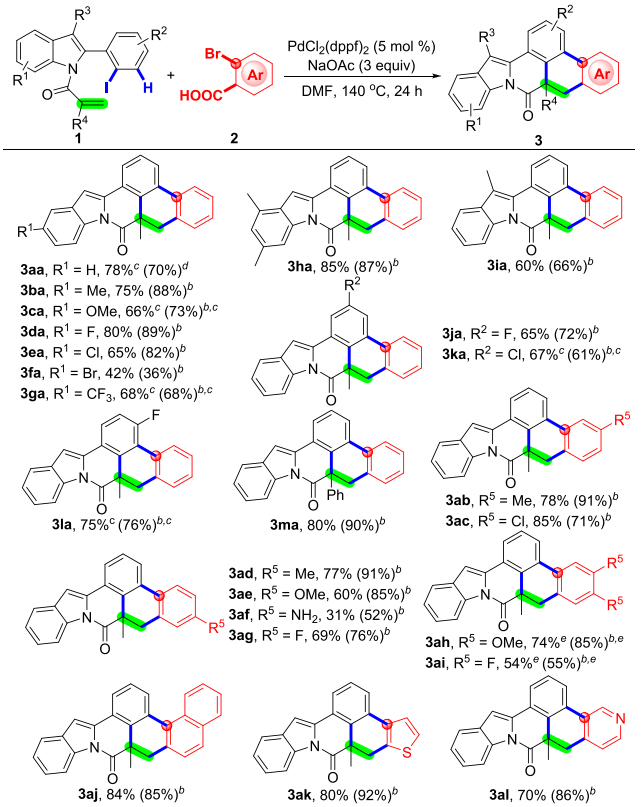
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Synthesis of Dihydronaphthalene-Fused Indolo[2,1-*a*]isoquinolinones[a]



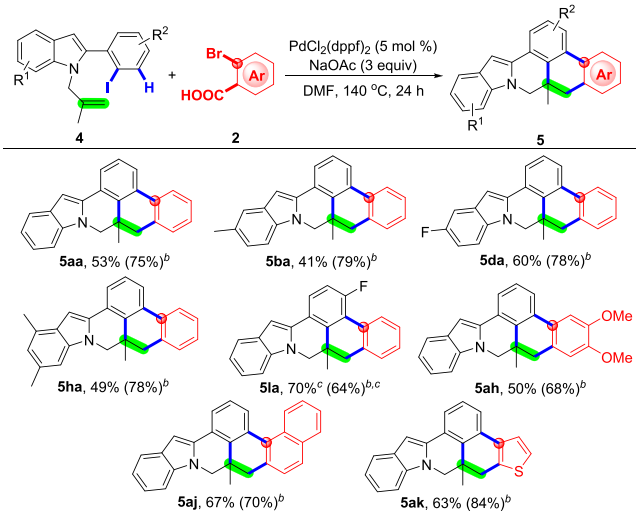
[a]Reaction conditions: **1** (0.2 mmol), **2** (1.2 equiv), $PdCl_2(dppf)_2$ (5 mol %), NaOAc (3 equiv), and DMF (2 mL) at 140 °C under N_2 for 24 h. [b]TBAB (0.5 equiv) was added. [c]Alkene-tethered aryl bromides instead of alkene-tethered aryl iodides. [d]*o*-Chlorobenzoic acid instead of *o*-bromobenzoic acid. [e]38 h.

We next turned our attention to exploring the feasibility of the reaction of 2-(2-iodophenyl)-1-(2-methylallyl)-1*H*-indole **4a** with *o*-bromobenzoic acid **2a** (Scheme 4). Gratifyingly, dihydronaphthalene-fused indolo[2,1-*a*]isoquinoline **5aa** was formed in 75% yield in the presence of TBAB, whereas the yield of **5aa** decreased to 53% without TBAB. Subsequently, several 2-(2-iodophenyl)-1-(2-methylallyl)-1*H*-indoles and *o*-bromobenzoic acids were examined in the presence or absence of TBAB. For example, substrates **4b**, **4d**, **4h**, and **4l** were subjected to the cascade cyclization with *o*-bromobenzoic acid to provide the desired products in 64−79% yield. The reaction of *o*-bromobenzoic acids (**2h**, **2j**, and **2k**) with **4a** proceeded favorably, and the corresponding products were afforded in 68−84% yield. Expectedly, for most of substrates, lower yields of the products **5** were obtained by the removal of TBAB.

To highlight the applicability of this strategy, we attempted to perform the reaction of **1a** with 8-bromo-1-naphthoic acid **2m** (Scheme 5). Fortunately, the corresponding products could be obtained in 60% yield by constructing a seven-membered ring. Inspired by these results, substrates **1c**, **1e**, **1g**, and **4a** were also investigated, and all of them underwent this reaction to afford the target products in moderate yield.

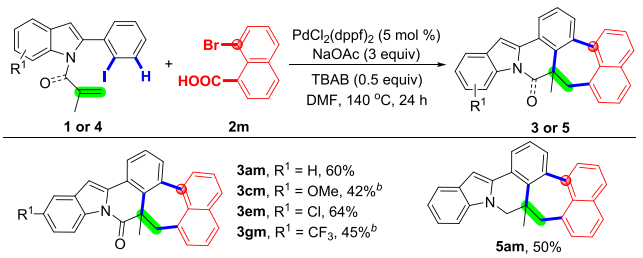
As shown in Scheme 6, the isotope experiment was performed by adding 3 equiv of D_2O under the standard conditions. The results revealed that the reaction mechanism involved the formation of palladacycle **C**. On the basis of our experimental results and previous work,[10,11,12e−g] a possible

Scheme 4. Synthesis of Dihydronaphthalene-Fused Indolo[2,1-*a*]isoquinolines[a]



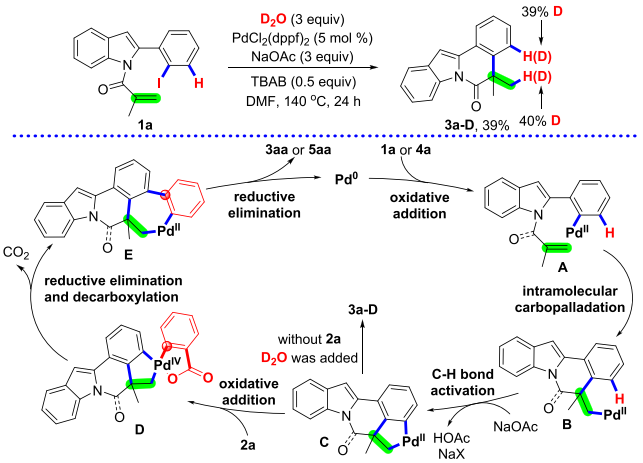
[a]Reaction conditions: **4** (0.2 mmol), **2** (1.2 equiv), $PdCl_2(dppf)_2$ (5 mol %), NaOAc (3 equiv), and DMF (2 mL) at 140 °C under N_2 for 24 h. [b]TBAB (0.5 equiv) was added. [c]Alkene-tethered aryl bromides were used.

Scheme 5. Synthesis of Dihydrocyclohepta[*de*]naphthalene-Fused Indolo[2,1-*a*]isoquinolines[a]



[a]Reaction conditions: **1** or **4a** (0.2 mmol), **2m** (1.2 equiv), $PdCl_2(dppf)_2$ (5 mol %), NaOAc (3 equiv), TBAB (0.5 equiv), and DMF (2 mL) at 140 °C under N_2 for 24 h. [b]Alkene-tethered aryl bromides were used.

Scheme 6. Control Experiment and Possible Reaction Mechanism



mechanism for this transformation was proposed (Scheme 6). Initially, the catalytic cycle starts with the oxidative addition of

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Org. Lett. XXXX, XXX, XXX−XXX

Pd(0) to the C−I bond to form aryl−Pd(II) intermediate **A**, which undergoes an intramolecular Heck reaction and a C−H bond activation sequence to generate palladacycle **C**. Subsequently, the oxidative addition of palladacycle **C** to the C−Br bond of *o*-bromobenzoic acid affords Pd(IV) intermediate **D**, which provides seven-membered palladacycle **E** by a reductive elimination and decarboxylation sequence. Finally, the reductive elimination of palladacycle **E** furnishes the desired product **3aa** or **5aa** and regenerates Pd(0), which continues to participate in the next cycle.

In conclusion, we have developed a novel palladium-catalyzed intermolecular cascade reaction for the synthesis of fused indolo[2,1-*a*]isoquinoline derivatives in which three C−C bonds are formed via an intramolecular Heck reaction, C−H activation, and decarboxylation sequence. The reaction employs readily available reagents, including alkene-tethered aryl halides and *o*-bromobenzoic acids, to construct interesting fused hexacyclic scaffolds in moderate to excellent yield with a broad substrate scope and good functional group tolerance. Importantly, 8-bromo-1-naphthoic acid as a coupling partner can be applicable to this approach, thus affording dihydrocyclohepta[*de*]naphthalene-fused indolo[2,1-*a*]-isoquinolines. This protocol opens up a new perspective to access fused indolo[2,1-*a*]isoquinoline derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02541.

Experimental procedures, full characterization of products, and nuclear magnetic resonance (NMR) spectra (PDF)

Accession Codes

CCDC 1941547 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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