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Pd-Catalyzed Cascade Cyclization by Intramolecular Heck Insertion of an Allene−Allylic Amination Sequence: Application to the Synthesis of 3,4-Fused Tricyclic Indoles

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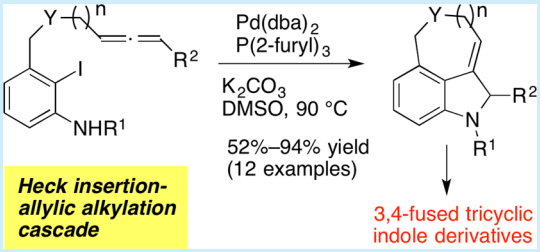
Supporting Information

ABSTRACT: A novel Pd-catalyzed cascade cyclization by intramolecular Heck insertion of an allene−allylic amination sequence was developed. Allenes tethered to *ortho*-iodoaniline derivatives at the *meta*-position were reacted with 5−10 mol % of Pd catalyst and 4 equiv of K_2CO_3 in DMSO at 90 °C, producing 3,4-fused tricyclic 3-alkylidene indoline derivatives in moderate to excellent yield. The reaction products were divergently transformed into three types of 3,4-fused tricyclic indole derivatives, successfully demonstrating the versatile properties of the reaction products.



3,4-Fused tricyclic indole skeletons are found in various bioactive natural products and pharmaceuticals. Most of these molecules possess a functionalized medium-size ring bridging the C3- and C4-positions of the indole (Figure 1). This class

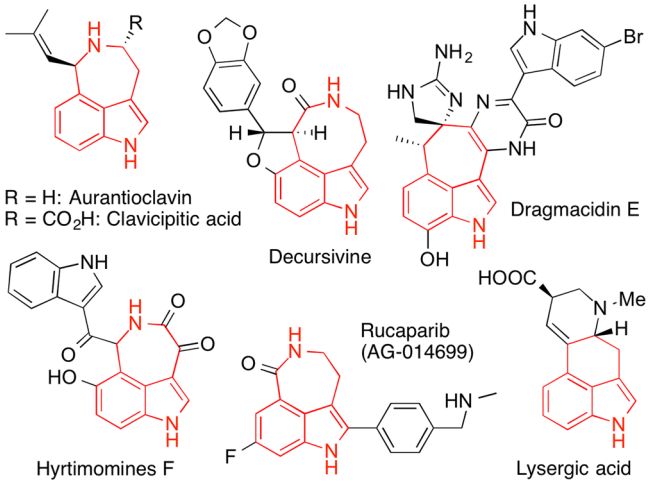


Figure 1. Selected examples of biologically active 3,4-fused tricyclic indoles.

of compounds is an attractive target in synthetic organic chemistry due to the ubiquity of the structural motif in bioactive molecules, as well as their characteristic structures. Considerable efforts have focused on the development of a synthetic method for this skeleton. The formation of the 3,4-fused tricyclic indole framework generally involves building the third ring onto a prefunctionalized indole substrate.[1−3] Direct functionalization of the indole C4-position, however, is difficult due to the low reactivity toward electrophiles. Expensive 4-haloindoles or their derivatives are therefore often utilized as starting materials for the preparation of such indole derivatives.[1,2b−h,3d] Recently, efficient construction of the target skeleton was achieved using simple linear substrates with an anilinic or aromatic ring moiety based on such processes as intramolecular Fischer indole synthesis,[4] intramolecular Larock indole synthesis,[5] Rh-catalyzed intramolecular dearomatizing [3 + 2] annulation of α-imino carbenoids,[6] and Rh-catalyzed C−H activation.[7]

Allenes generally react with an aryl halide in the presence of a Pd(0) catalyst to give the corresponding π-allylpalladium(II) species through a Heck insertion process.[8] Subsequent nucleophilic addition to the π-allylpalladium(II) species provides 2-aryl-3-substituted propene derivatives.[9] We hypothesized that treatment of allenes tethered to *ortho*-iodoaniline derivatives at the *meta*-position **I** with a Pd(0) catalyst in the presence of base would lead to the formation of bicyclic π-allylpalladium(II) intermediates **II** through an intramolecular Heck insertion process, which could be then transformed into 3,4-fused tricyclic 3-alkylidene indoline derivatives **III** via an intramolecular allylic amination (Scheme 1). Various isomerization protocols from 3-alkylidene indolines into functionalized indole derivatives have been reported,[10] indicating that several types of 3,4-fused indole derivatives are accessible using compound **III** as a common precursor. Herein, we report a novel Pd-catalyzed cascade cyclization by intramolecular Heck insertion of an allene−allylic amination sequence that produces 3,4-fused tricyclic 3-alkylidene indoline derivatives. The reaction products were successfully transformed into three types of 3,4-fused tricyclic indole derivatives.

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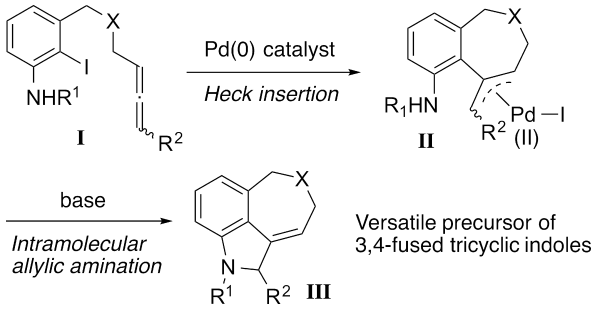
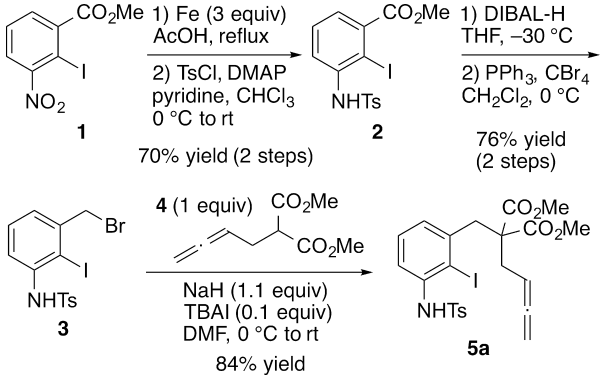
Scheme 1. Reaction Design



First, a model substrate for the target cascade cyclization was prepared using readily available compound **1**[11] as the starting material (Scheme 2). Reduction of the nitro group followed by protection of the resulting amine with a tosyl group afforded compound **2** in 70% yield (two steps). The ester moiety in **2** was transformed into a bromomethyl group by a two-step reaction sequence involving DIBAL-H reduction and bromination (76% yield, two steps). The obtained benzyl bromide derivative **3** was coupled with the known allenyl compound **4**[12] to give the model substrate **5a** in 84% yield.

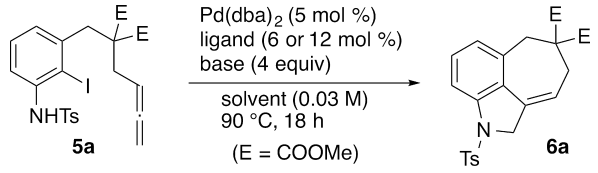
Scheme 2. Synthesis of Model Substrate 5a



The reaction conditions were optimized using 5 mol % of $Pd(dba)_2$ and 4 equiv of K_2CO_3 at 90 °C (Table 1). Solvent effect studies revealed that polar aprotic solvents were suitable for this transformation, and the desired product **6a** was obtained in 72% yield using DMSO as the solvent (entries 1–5). Reactions with other metal carbonates or other potassium bases produced less satisfactory results (entries 6–10). The yield was less satisfactory when the reaction concentration was increased (entry 11). The effect of phosphorus ligands was then investigated in DMSO using K_2CO_3 as a base (entries 12–17). Among the examined ligands, tri(2-furyl)phosphine was the most effective ligand for this cascade cyclization, and compound **6a** was obtained in 78% yield (entry 13).

Under the optimal conditions, we examined the substrate scope of the developed process using 5 mol % of Pd catalyst (Scheme 3).[13] In addition to tosyl derivative **6a**, methanesulfonyl and 2,4,6-triisopropylbenzenesulfonyl derivatives **6b** and **6c** were obtained from the corresponding allenyl substrates **5a–c** in 67–78% yield. Although the yield was moderate, carboxybenzyl-protected substrate **5d** was also applicable to this reaction, and compound **6d** was obtained in 46% yield. The chemical yield improved to 57% when 10 mol % of Pd catalyst was used. The present cascade

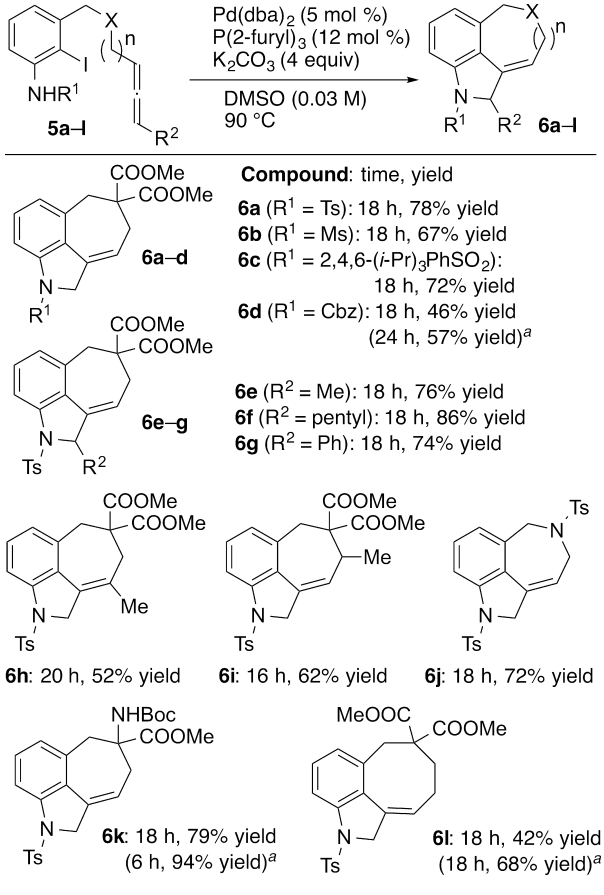
Table 1. Optimization of the Reaction Conditions



entry	solvent	base	ligand[a]	yield (%)
1	toluene	K_2CO_3	PPh_3	0
2	dioxane	K_2CO_3	PPh_3	0
3	CH_3CN	K_2CO_3	PPh_3	33
4	DMF	K_2CO_3	PPh_3	64
5	DMSO	K_2CO_3	PPh_3	72
6	DMSO	Li_2CO_3	PPh_3	31
7	DMSO	Cs_2CO_3	PPh_3	42
8	DMSO	Ag_2CO_3	PPh_3	0
9	DMSO	KOAc	PPh_3	42
10	DMSO	KO*t*-Bu	PPh_3	58
11[b]	DMSO	K_2CO_3	PPh_3	55
12	DMSO	K_2CO_3	$P(o\text{-tol})_3$	77
13	DMSO	K_2CO_3	$P(2\text{-furyl})_3$	78
14	DMSO	K_2CO_3	XPhos	45
15	DMSO	K_2CO_3	$AsPh_3$	59
16	DMSO	K_2CO_3	DPPE	63
17	DMSO	K_2CO_3	DPPF	75

[a]Monodentate ligands: 12 mol %, bidentate ligands: 6 mol %. [b]This reaction was performed in DMSO (0.05 M).

Scheme 3. Substrate Scope[a]



Compound: time, yield

6a (R^1 = Ts): 18 h, 78% yield
6b (R^1 = Ms): 18 h, 67% yield
6c (R^1 = 2,4,6-(i-Pr)$_3$PhSO$_2$): 18 h, 72% yield
6d (R^1 = Cbz): 18 h, 46% yield (24 h, 57% yield)[a]

6e (R^2 = Me): 18 h, 76% yield
6f (R^2 = pentyl): 18 h, 86% yield
6g (R^2 = Ph): 18 h, 74% yield

[a]Reactions were performed in DMSO (0.01 M) in the presence of 10 mol % of $Pd(dba)_2$ and 24 mol % of $P(2\text{-furyl})_3$.

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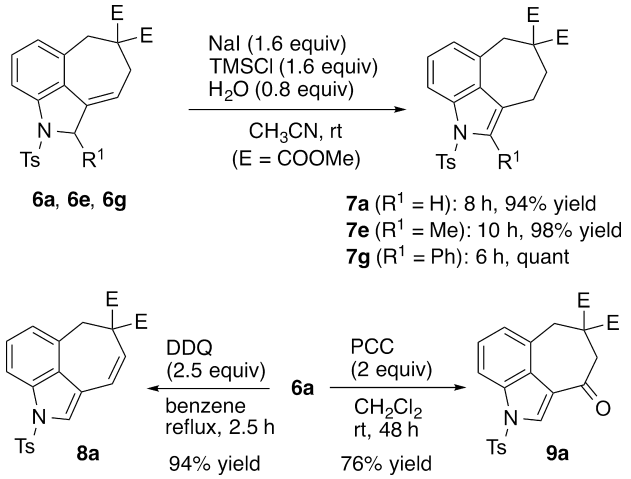
cyclization also proceeded using 1,3-disubstituted allenes **5e**–**g** as substrates, affording 2-substituted 3,4-fused tricyclic 3-alkylidene indoline derivatives **6e**–**g** in 74–86% yield. When 1,1-disubstituted allene derivative **5h** and α-branched allene derivative **5i** were used, the corresponding products **6h** and **6i** were obtained in moderate yield. The reaction using *N*-tosyl-tethered-type substrate **5j** and quaternary α-amino acid derivative **5k** proceeded under the same reaction conditions, providing compounds **6j** and **6k** in 72 and 79% yield, respectively. The yield of **6k** improved to 94% yield using 10 mol % of Pd catalyst. Moreover, the reaction of **5l**, bearing a CH_2-unit-longer tether than that in **5a**, gave the corresponding eight-membered ring-fused tricyclic 3-alkylidene indoline derivative **6l** in 68% yield when using 10 mol % of Pd catalyst.

Transformations of the reaction products into 3,4-fused tricyclic indole derivatives were further examined (Scheme 4).

Scheme 4. Transformations of the Reaction Products into 3,4-Fused Tricyclic Indole Derivatives



Olefin isomerization of compounds **6a**, 2-methyl-substituted product **6e**, and 2-phenyl-substituted product **6g** occurred smoothly following treatment with in situ-generated HI in CH_3CN at room temperature,[10b] affording the corresponding 3,4-fused tricyclic indole derivatives **7a**, **7e**, and **7g** in excellent yield. In addition, oxidation of **6a** using DDQ afforded double-bond-conjugated 3,4-fused tricyclic indole derivative **8a** in 94% yield.[10h] Furthermore, oxidation of **6a** with PCC in CH_2Cl_2 at room temperature provided ketone derivative **9a** in 76% yield.[10c] These results clearly demonstrate that 3,4-fused tricyclic 3-alkylidene indoline derivatives are versatile precursors for the synthesis of functionalized 3,4-fused tricylic indole derivatives.

In conclusion, we developed a novel Pd-catalyzed cascade cyclization to produce 3,4-fused tricyclic 3-alkylidene indoline derivatives. Using allenes tethered to *ortho*-iodoaniline derivatives at the *meta*-position as substrates, an intramolecular Heck insertion of the aryl iodide into the allene, followed by an intramolecular allylic amination, proceeded sequentially in the presence of 5–10 mol % of Pd catalyst, producing 3,4-fused tricyclic 3-alkylidene indoline derivatives in moderate to excellent yield. The reaction adducts were divergently transformed into three types of functionalized 3,4-fused tricyclic indole derivatives, successfully demonstrating the synthetic utility of the developed cascade process. Further studies on the application of this process to natural product synthesis, as well as mechanistic investigation into the reaction pathway,[14] are in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure, compound characterization, and NMR charts. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b00973.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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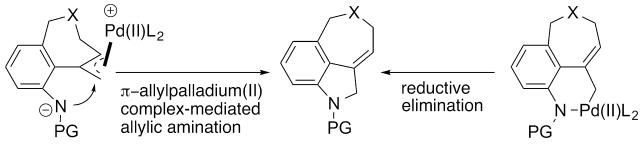
(13) For the preparation of allenyl substrates, see Supporting Information.
(14) There are two possible reaction pathways for the allylic amination step as shown below. At the present stage, it is unclear which reaction pathway is operative. Computational and experimental elucidation of this issue is the focus of further investigations and will be reported in due course.



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