Novel Synthesis of Fused Indoles by the Palladium-Catalyzed Cyclization of *N*-Cycloalkenyl-*o*-haloanilines

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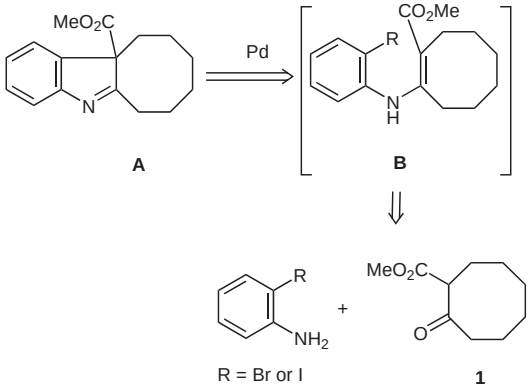
Abstract: A new palladium-catalyzed cyclization of *N*-alkenyl-*o*-haloanilines with selective isomerization of a double bond followed by 5-*endo* cyclization was developed and used to synthesize fused indoles.

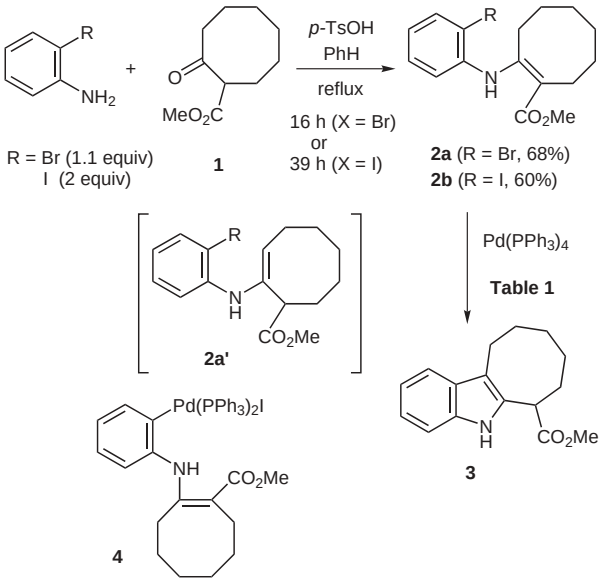
Key words: heterocycles, indole, palladium, synthesis

The intramolecular Heck reaction[1] is an important and powerful method for the construction of carbocyclic and heterocyclic compounds. The synthesis of indoles using this reaction has also been widely studied starting from the pioneering work by Mori and Ban.[2,3] However, the synthesis of fused indoles by palladium-catalyzed cyclization using *N*-cycloalkenyl-*o*-haloanilines, which are readily obtained from cyclic 1,3-diketones,[3d,e,g,i] has not been fully investigated, although the skeleton is involved in many important biologically active indole alkaloids. There has been no report on cyclization using enamine **B**, obtained from cyclic β-ketoesters, which can be expected to give fused indolenines **A** with a quaternary carbon center at C3 of indole (Scheme 1). In connection with our recent work on the synthesis of indole alkaloids, we were interested in the synthesis of fused indoles with medium-sized rings using the reaction shown in Scheme 1.



Scheme 1

Thus, *o*-bromo- or *o*-iodoaniline was heated in benzene with 2-methoxycarbonylcyclooctanone (**1**) in the presence of 1.1–2.0 equivalents of *p*-TsOH at reflux for 16–39 hours to give bromo- or iodophenylenamine (**2a** and **2b**), respectively. The resulting bromophenylenamine **2a** was reacted with $Pd(PPh_3)_4$ in the presence of Et_3N in CH_3CN at 80 °C for 22 hours, and gave fused indole **3** in 46% yield (Table 1). Considering the structure of **3**, cyclization might proceed via intermediate **2a′** (R = PdX), which would be generated from **2a** by selective isomerization of a double bond.



Scheme 2

Since **3** is also useful for indole alkaloid synthesis, the reaction in Scheme 2 was studied further. Reducing the amount of palladium(0) resulted in a low yield of **3** (run 2), and the reaction of iodophenylenamine (**2b**) was studied next. When iodophenylenamine **2b** was treated with 30 mol% of palladium(0), no desired **3** was obtained (run 3). However, the reaction of **2b** with an equimolar amount of palladium(0) gave Pd complex **4** as a crystalline solid in 86% yield. Its structure was unambiguously determined by X-ray crystallographic analysis (Figure 1) and shows that palladium metal is oxidatively inserted into the carbon-iodine bond without isomerization of a double bond. When the isolated palladium complex **4** was treated with Ag_3PO_4 (1 equiv)[4] in *N*,*N*-dimethylacetamide (DMA) at 100 °C for 35 hours, we were pleased to find that **3** was obtained in 25% yield. Therefore, the reaction of **2b** using 30 mol% of Pd(0) in the presence of Ag_3PO_4 was investigated in several solvents (runs 5–8).[5] Finally, the desired

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Table 1 Synthesis of **3** from **2** by Palladium-Catalyzed Cyclization

Entry	X	$Pd(PPh_3)_4$ (mol%)	Additive (equiv)	Solvent	Temp (°C)	Time (h)	Product (%)
1	Br (**2a**)	100	Et_3N (2.4)	MeCN	80	22	**3** (46)
2	Br (**2a**)	30	Et_3N (2.4)	MeCN	80	64	**3** (25)
3	I (**2b**)	30	Et_3N (2.4)	MeCN	80	24	**3** (0)[a]
4	I (**2b**)	100	Et_3N (2.4)	MeCN	80	32	**4** (86)
5	I (**2b**)	30	Ag_3PO_4 (2)	DMA	100	10	**3** (51)
6	I (**2b**)	30	Ag_3PO_4 (2)	DMF	100	16	**3** (65)
7	I (**2b**)	30	Ag_3PO_4 (1)	NMP	100	16	**3** (82)
8	I (**2b**)	10	Ag_3PO_4 (1)	DMSO	100	15	**3** (quant.)

[a] A mixture of **2b** and **4** (2:1) was obtained.

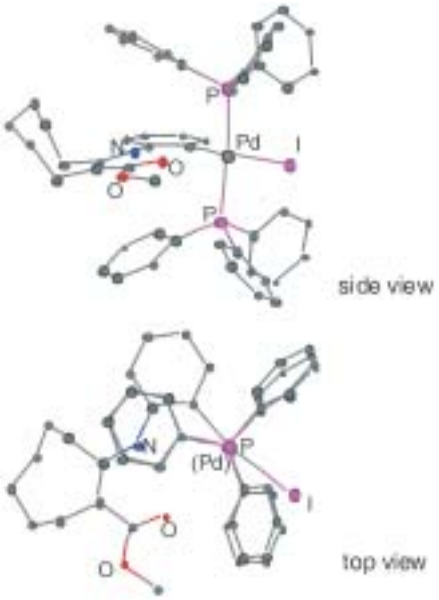


Figure 1 X-ray structure of Pd complex **4** (hydrogens are omitted for clarity. This crystal structure was deposited at the Cambridge Crystallographic Data Centre, CCDC231397)

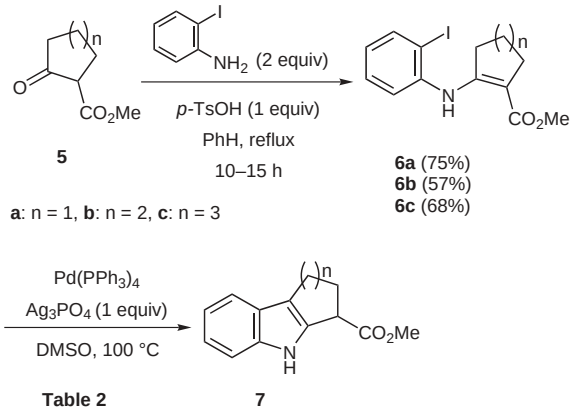
3 was obtained in quantitative yield by treatment of **2b** with 10 mol% of $Pd(PPh_3)_4$ and Ag_3PO_4 (1 equiv) in DMSO (entry 8).

Other fused indoles containing smaller rings were also prepared under similar conditions (Scheme 3 and Table 2).

Table 2 Palladium-Catalyzed Cyclization of **6**

Substrate	$Pd(PPh_3)_4$ (mol%)	Time (h)	Product (%)
6a	10	23	**7a** (39)
6b	30	16	**7b** (40)
6c	30	17	**7c** (59)

Kopsia alkaloids, lapidilectine A (**8**) and lapidilectam (**9**), have been isolated from the stem and bark of *Kopsia lapidelecta* (Figure 1).[6] Although their biological activities have not been fully investigated, some *Kopsia* plants are used in China to treat rheumatoid arthritis, dropsy and tonsillitis. These *Kopsia* alkaloids have a unique structure in which an indole skeleton is fused to azacyclooctane to form an azocino[5,4-*b*]indole skeleton. Due to this complex structure, *Kopsia* alkaloids have attracted the interest of synthetic chemists, and lapidilectine B (**10**) has recently been synthesized (Figure 2).[7]



Scheme 3

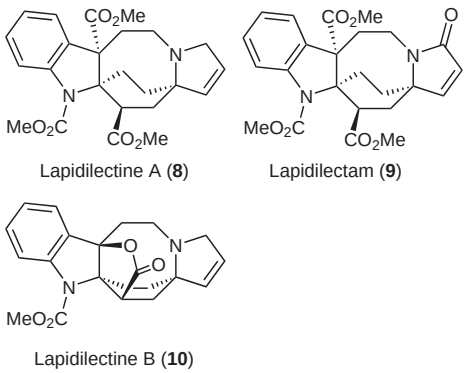
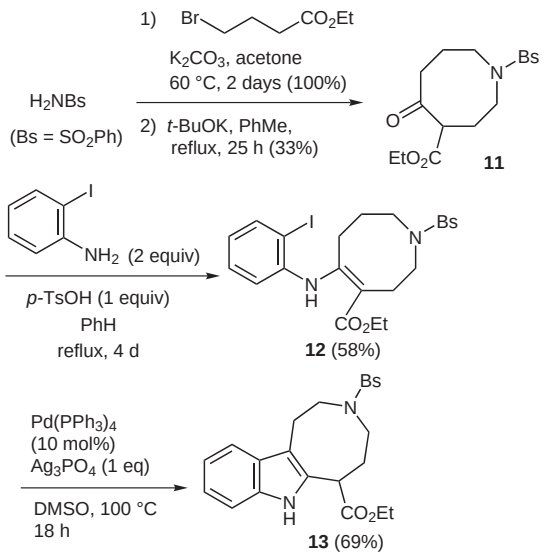


Figure 2 *Kopsia* lapidilecta alkaloids



Scheme 4

We were also interested in the synthesis of these alkaloids and applied our new cyclization to synthesize the azocinoindole skeleton **13** (Scheme 4). Thus, azocine derivative **11**,[8] which was prepared from benzenesulfonamide in two steps, was condensed with *o*-iodoaniline to give enamine **12** in 58% yield. Enamine **12** was converted to azocinoindole **13**[9] in 69% yield under the optimized conditions described above.

In conclusion, we have developed a new type of palladium-catalyzed cyclization, which proceeds via selective isomerization of a double bond in the enamine structure followed by 5-*endo* cyclization. This reaction is useful for synthesizing fused indoles.

Acknowledgment

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(5) While other silver salts, such as Ag_2CO_3, $AgPF_6$, AgOTf, and $AgBF_4$, also promoted this reaction, they were less effective.

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(9) **Experimental Procedure for the Synthesis of 13**: A mixture of enamine **12** (0.15 g, 0.28 mmol), Ag_3PO_4 (0.12 g, 0.28 mmol), and $Pd(PPh_3)_4$ (32 mg, 28 μmol) was heated (18 h) with stirring in DMSO (1.0 mL) at 100 °C under Ar. The mixture was diluted with Et_2O at r.t., and filtered through a celite pad. The filtrate was concentrated and the residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:5) to give **13** as a colorless oil (79 mg, 69%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.35 (t, *J* = 7.1 Hz, 3 H), 1.87 (td, *J* = 2.8, 12.9 Hz, 1 H), 2.18 (ddd, *J* = 3.9, 12.6, 14.8 Hz, 1 H), 2.56 (t, *J* = 12.1 Hz, 1 H), 2.66 (tt, *J* = 5.0, 12.9 Hz, 1 H), 2.94 (ddd, *J* = 3.0, 12.1, 15.1 Hz, 1 H), 3.13 (ddd, *J* = 1.4, 3.6, 15.1 Hz, 1 H), 3.48 (dd, *J* = 4.1, 15.1 Hz, 1 H), 4.12 (dt, *J* = 3.9, 13.2 Hz, 1 H), 4.24–4.32 (m, 2 H), 4.37 (dd, *J* = 5.2, 12.7 Hz, 1 H), 7.06 (td, *J* = 1.1, 7.1 Hz, 1 H), 7.13 (td, *J* = 1.1, 8.0 Hz, 1 H), 7.33 (d, *J* = 8.0 Hz, 1 H), 7.42 (d, *J* = 8.0 Hz, 1 H), 7.47 (td, *J* = 1.4, 7.7 Hz, 2 H), 7.54 (tt, *J* = 1.4, 7.2 Hz, 1 H), 7.78–7.80 (m, 2 H), 9.11 (s, 1 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.3, 25.8, 36.5, 39.4, 48.5, 53.7, 61.6, 111.2, 111.3, 117.6, 119.5, 121.9, 127.0, 129.2, 130.9, 132.7, 135.5, 139.1, 174.8.