Heterocycles

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Palladium(0)-Catalyzed Heck Reaction/C–H Activation/Amination Sequence with Diaziridinone: A Facile Approach to Indolines**

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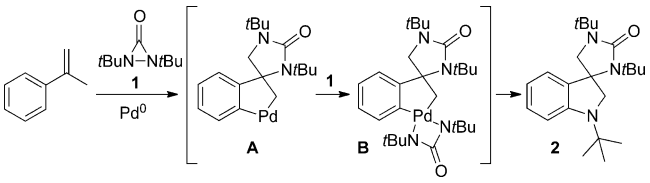
Abstract: *Indolines are important moieties present in various biologically significant molecules and have attracted considerable attention in synthetic chemistry. This paper describes a Heck reaction/C–H activation/amination sequence for forming indolines using di-tert-butyldiaziridinone. The reaction process likely proceeds via a pallada(II)cycle, which is converted into an indoline by oxidative addition to the diaziridinone and two subsequent C–N bond formations.*

Indolines are important moieties contained in various biologically and pharmaceutically active compounds,[1] and their syntheses have attracted considerable attention. The cyclization involving replacement of a leaving group by a nitrogen atom is among the widely used methods to synthesize indolines.[2,3] Direct C–H amination presents an attractive strategy for the construction of this class of molecules and has become an active area of research in recent years.[4–6]

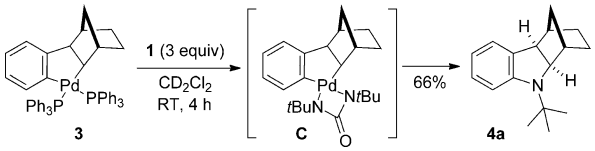
Recently, we reported that α-methylstyrene can be efficiently transformed into spirocyclic indolines by a palladium(0)-catalyzed sequential C–N bond formation involving allylic and aromatic C–H amination with di-*tert*-butyldiaziridinone (**1**; Scheme 1).[7] This reaction process likely proceeds



Scheme 1. The formation of spirocyclic indolines from α-methylstyrene.

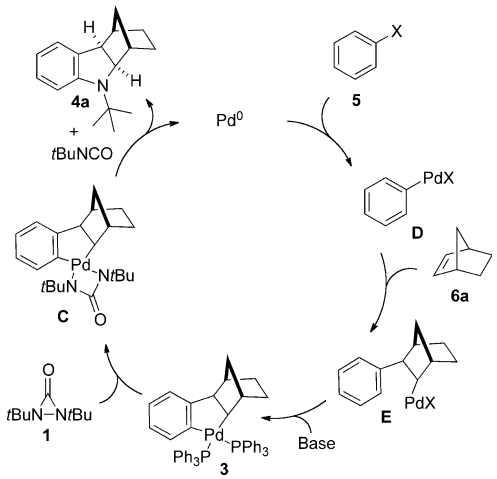
via the pallada(II)cycle **A**, which oxidatively inserts into the diaziridinone to form the pallada(IV)cycle **B**.[8] Upon release of *tert*-butyl isocyanate (*t*BuNCO), **B** is converted into the spirocyclic indoline **2** through two consecutive reductive eliminations.

Previously, we have shown that palladium(0) can readily insert into the N–N bond of **1**, and the resulting four-membered palladium(II) species reacts with dienes to form diamination products.[9] The oxidative insertion of a pallada(II)cycle into **1** is mechanistically interesting. To further probe this process, the known pallada(II)cycle **3**[10] was thus prepared[11] and reacted with **1** (Scheme 2). The palladacycle



Scheme 2. Synthesis of the indoline **4a** from the pallada(II)cycle **3**.

was indeed smoothly transformed into the indoline **4a** in 66% yield at room temperature.[12] This result prompted us to investigate if the indoline could be directly formed from an aryl halide (**5**), norbornene (**6a**), and **1** with catalytic amounts of palladium(0) by in situ formation of **3** by a Heck reaction and subsequent C–H activation (Scheme 3). The key issue for



Scheme 3. Proposed catalytic cycle.

such a transformation is whether the aryl halide can compete with the diaziridinone for the oxidative addition by the palladium(0) catalyst to initiate the catalytic cycle. Herein, we report our preliminary studies on this subject.

Initial studies were carried out with *p*-iodoanisole (**5b**) as a test substrate under various reaction conditions. As shown in Table 1, the base had a significant effect on the reaction efficiency. No products were isolated with K_2CO_3, Na_2CO_3,

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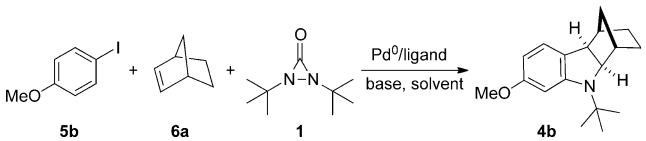
Table 1: Studies on the reaction conditions.[a]



5b 6a 1 4b

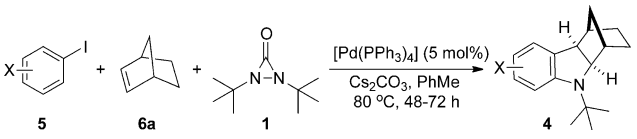
Entry	Solvent	Base	Catalyst	Ligand	Yield [%][b]
1	PhMe	K_2CO_3	$[Pd(PPh_3)_4]$	–	0
2	PhMe	Na_2CO_3	$[Pd(PPh_3)_4]$	–	0
3	PhMe	Et_3N	$[Pd(PPh_3)_4]$	–	0
4	PhMe	K_3PO_4	$[Pd(PPh_3)_4]$	–	79
5	PhMe	NaO*t*Bu	$[Pd(PPh_3)_4]$	–	82
6	PhMe	Cs_2CO_3	$[Pd(PPh_3)_4]$	–	90
7	DMF	Cs_2CO_3	$[Pd(PPh_3)_4]$	–	70
8	MeCN	Cs_2CO_3	$[Pd(PPh_3)_4]$	–	84
9	THF	Cs_2CO_3	$[Pd(PPh_3)_4]$	–	76
10	1,4-dioxane	Cs_2CO_3	$[Pd(PPh_3)_4]$	–	74
11[c]	PhMe	Cs_2CO_3	$[Pd(PPh_3)_4]$	–	89
12	PhMe	Cs_2CO_3	$[Pd_2(dba)_3]$	–	0
13	PhMe	Cs_2CO_3	$[Pd_2(dba)_3]$	PPh_3	84
14	PhMe	Cs_2CO_3	$[Pd_2(dba)_3]$	$P(p\text{-}MeOC_6H_5)_3$	81
15	PhMe	Cs_2CO_3	$[Pd_2(dba)_3]$	$P(p\text{-}CF_3C_6H_5)_3$	90
16	PhMe	Cs_2CO_3	$[Pd_2(dba)_3]$	binap	0

[a] All reactions were carried out with *p*-iodoanisole (**5b**; 0.30 mmol), norbornene (**6a**; 0.60 mmol), di-*tert*-butyldiaziridinone (**1**; 0.45 mmol), Pd (0.030 mmol; Pd/P = 1/4), base (0.60 mmol), and solvent (0.30 mL) at 80 °C under Ar for 36 h unless otherwise stated. For entry 4, the reaction time was 72 h. [b] Yield of isolated product. [c] The reaction was carried out with $[Pd(PPh_3)_4]$ (0.015 mmol) and **1** (0.35 mmol) at 80 °C for 48 h. binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, dba = dibenzylideneacetone, DMF = *N*,*N*-dimethylformamide, THF = tetrahydrofuran.

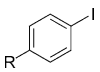
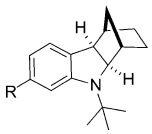
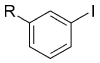
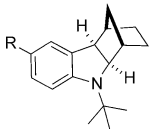
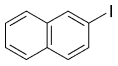
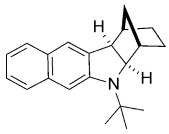
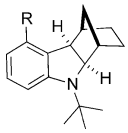
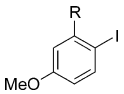
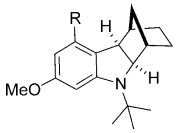
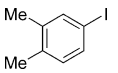
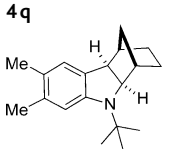
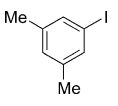
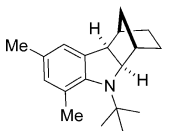
and Et_3N (entries 1–3). To our delight, the reaction proceeded efficiently with bases such as K_3PO_4, NaO*t*Bu, and Cs_2CO_3 (entries 4–6). For example, treating **5b** and **6a** with 1.5 equivalents of **1**, 10 mol% $[Pd(PPh_3)_4]$, and 2.0 equivalents of Cs_2CO_3 in toluene at 80 °C gave **4b** in 90% yield (entry 6). Polar solvents such as DMF, MeCN, THF, and 1,4-dioxane gave lower yields as compared to toluene (entries 7–10). A similar yield (89%) was obtained when the amount of $[Pd(PPh_3)_4]$ was reduced from 10 mol% to 5 mol% (entries 6 and 11). The effect of the ligand was also briefly investigated with $[Pd_2(dba)_3]$ as a catalyst (entries 12–16). No product was formed with $[Pd_2(dba)_3]$ alone (entry 12). PPh_3, $P(p\text{-}MeOC_6H_5)_3$, and $P(p\text{-}CF_3C_6H_5)_3$ were shown to be effective ligands for the reaction, thus giving **4b** in 81–90% yield (entries 13–15). However, no desired product was obtained with binap (entry 16).

As shown in Table 2, the reaction process can be extended to various *para*-, *meta*-, *ortho*-, and disubstituted iodobenzenes, thus giving the corresponding indoline products in 67–97% yield (entries 1–19). The Heck reaction occurred from the *exo* face of norbornene as indicated by the X-ray structure of **4g** (see the Supporting Information). For the bromo-substituted iodobenzenes **5d** and **5n**, the reaction selectively occurred at iodide to give the indolines **4d** and **4n**, respectively, in good yields (entries 4 and 14). For *meta*-substituted iodobenzenes (entries 9–12 and entry 18), the C–H amination regioselectively occurred at the sterically less hindered position. Good yields (72–96%) were also obtained for the

Table 2: Substrate scope.[a]



5 6a 1 4

Entry	5	4	Yield [%][b]
			
1	**5a**, R = H	**4a**	90
2	**5b**, R = OMe	**4b**	89
3	**5c**, R = *n*Bu	**4c**	91
4	**5d**, R = Br	**4d**	68
5	**5e**, R = F	**4e**	72
6	**5f**, R = CF_3	**4f**	78
7	**5g**, R = CO_2Me	**4g** (X-ray)	93
8	**5h**, R = NO_2	**4h**	84
			
9	**5i**, R = OMe	**4i**	82
10	**5j**, R = CH_2OTBS	**4j**	97
11	**5k**, R = CO_2Me	**4k**	85
12			
	5l	**4l**	84
			
13	**5m**, R = OMe	**4m**	90[c]
14	**5n**, R = Br	**4n**	81[c]
15	**5o**, R = NO_2	**4o**	88[c]
			
16	**5p**, R = OMe	**4p**	94[c]
17	**5q**, R = NO_2	**4q**	80[c]
18			
	5r	**4r**	93
19			
	5s	**4s**	67

[a] All reactions were carried out with the iodobenzene **5** (0.30 mmol), norbornene (**6a**; 0.60 mmol), di-*tert*-butyldiaziridinone (**1**; 0.35 mmol), $[Pd(PPh_3)_4]$ (0.015 mmol), Cs_2CO_3 (0.60 mmol), and toluene (0.30 mL) at 80 °C under Ar for 48 h unless otherwise stated. [b] Yield of isolated product based on **5**. [c] Reaction time, 72 h. TBS = *tert*-butyldimethylsilyl.

corresponding indolines (**7–9**)[13] when **6b** and the bridged olefins **6c**,**d** were used (Figure 1).[14] For the indoline **7b**, the reaction process is amenable to gram scale. The indoline **7b** can be converted into the *N*-*tert*-butyl indole **10** in 79% yield

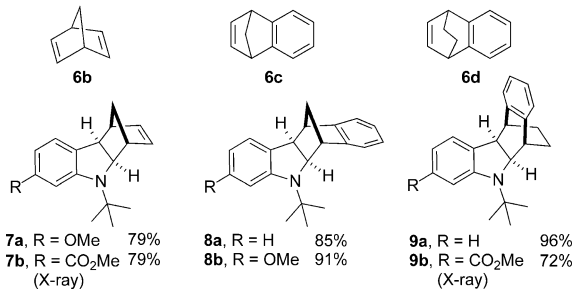
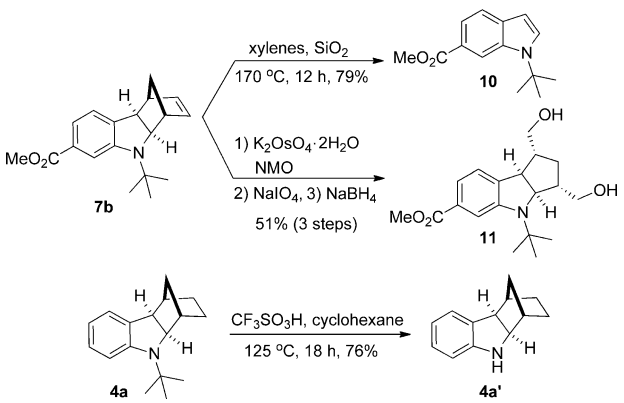


Figure 1. Indolines from other bridged olefins.

with SiO_2 in xylenes by a retro-Diels–Alder reaction, and into the tricyclic indoline **11** in 51% yield over three steps involving dihydroxylation, oxidative diol cleavage, and reduction (Scheme 4).[15] As shown in the case of **4a**, the removal of the *tert*-butyl group was accomplished with CF_3SO_3H/cyclohexane, thus giving the deprotected indoline **4a′** in 76% yield (Scheme 4).



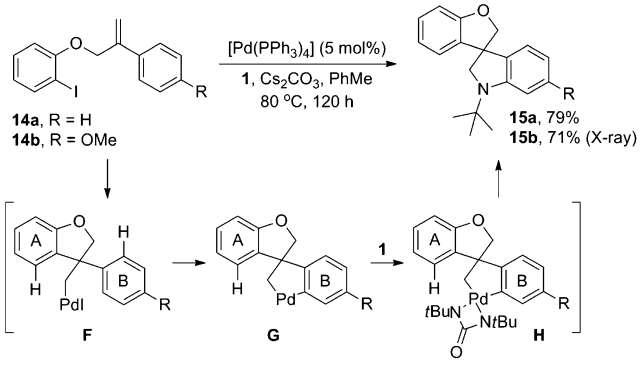
Scheme 4. Synthetic transformations of **7b** and **4a**. NMO = *N*-methylmorpholine *N*-oxide.

The intramolecular reaction process was also found to be feasible with alkene-tethered iodobenzenes.[16] As shown in Table 3, polycyclic fused indolines (**13a–e**)[13] were readily obtained in 62–93% yield (entries 1–5). Iodobenzenes bearing nonbridged 1,1-disubstituted olefins were also effective substrates for the reaction (entries 2–5). When *o*-iodophenyl allyl ethers (**14**) with phenyl substituents on the olefins were subjected to the reaction conditions, the polycyclic spiroindolines **15** were obtained in 71–79% yield (Scheme 5). In these cases, the C–H activation occurred selectively at the phenyl group **B** rather than phenyl group **A** to reduce the ring strain. The pentacyclic indoline **17** was obtained in 90% yield when the iodobenzene **16**, containing an exocyclic olefin, was used as substrate (Scheme 6).[17]

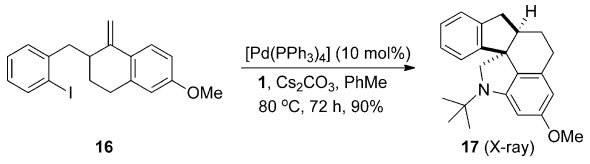
Table 3: Intramolecular process.[a]

Entry	12	13	Yield [%][b]
1	**12a**	**13a**	93
2	**12b**	**13b**	75
3	**12c**	**13c** (X-ray)	65[c,d]
4	**12d**	**13d**	81[c]
5	**12e**	**13e** (X-ray)	62[c]

[a] All reactions were carried out with the iodobenzene **12** (0.30 mmol), di-*tert*-butyldiaziridine (**1**; 0.35 mmol), $[Pd(PPh_3)_4]$ (0.015 mmol), Cs_2CO_3 (0.60 mmol), and toluene (0.30 mL) at 80 °C under Ar for 72 h unless otherwise stated. [b] Yield of the isolated product based on **12**. [c] Used 0.030 mmol of $[Pd(PPh_3)_4]$. [d] Reaction time, 120 h.



Scheme 5. Synthesis of the polycyclic spiroindoline **15**.



Scheme 6. Synthesis of the pentacyclic indoline **17**.

In summary, we have developed a novel palladium(0)-catalyzed Heck reaction/C–H activation/amination sequence with iodobenzenes, olefins, and di-*tert*-butyldiaziridinone (**1**), thus providing a variety of polycyclic indolines in good yields. The reaction process likely proceeds via a pallada(II)cycle, which is intercepted by the diaziridinone through oxidative addition (Scheme 3). The resulting pallada(IV)cycle is transformed into the indoline product after release of *tert*-butyl isocyanate and subsequent reductive elimination. The current work not only provides a new approach to indolines, which are contained in various biologically important molecules, but also further illustrates the versatile reactivity and synthetic utility of diaziridinone, and may open up new opportunities for the development of other reaction processes.

Experimental Section

Representative procedure for intermolecular process (Table 2, entry 1): Iodobenzene (**5a**; 0.0612 g, 0.30 mmol), norbornene (**6a**; 0.0564 g, 0.60 mmol), di-*tert*-butyldiaziridinone (**1**; 0.0595 g, 0.35 mmol), $[Pd(PPh_3)_4]$ (0.0173 g, 0.015 mmol), Cs_2CO_3 (0.1956 g, 0.60 mmol), and toluene (0.30 mL, distilled from sodium) were added to a 1.5 mL vial equipped with a magnetic stir bar. The vial was flushed with argon for 20 s, sealed, and then immersed into an oil bath (80 °C). The reaction mixture was vigorously stirred at 80 °C for 48 h, cooled to room temperature, and purified by flash chromatography on silica gel (hexanes/ethyl acetate = 100:1) to give the indoline **4a** (0.065 g, 90 %).

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Keywords: C–H activation · cyclization · heterocycles · palladium · synthetic methods

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