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Palladium-Catalyzed Sequential C−H Activation/Amination with Diaziridinone: An Approach to Indoles

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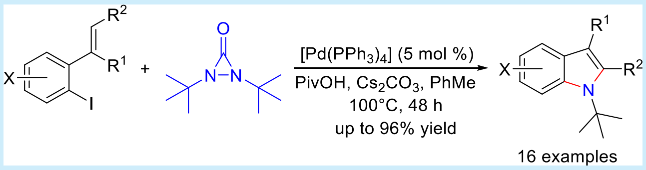
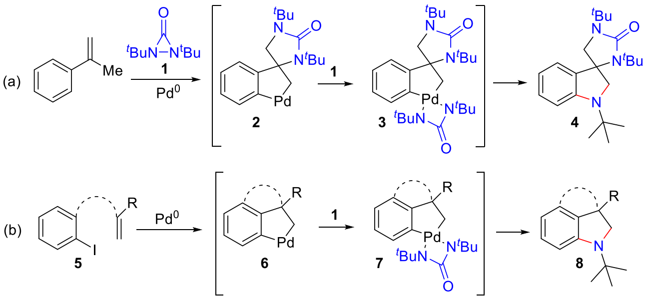
ABSTRACT: Indoles are an important class of molecules. This paper describes an efficient palladium-catalyzed synthesis of indoles from 2-iodostyrenes and di-*t*-butyldiaziridinone with a simultaneous installation of two C−N bonds. The reaction process likely proceeds through the oxidative insertion of Pd to aryl iodide and subsequent vinyl C−H activation to from a pallada(II)cycle intermediate, which is bisaminated by di-*t*-butyldiaziridinone to give the indole product.



Indoles are important moieties contained in various biologically active molecules, pharmaceuticals, materials, and fine chemicals.[1] While numerous methods have been developed,[2] the search for new reaction processes to this class of molecules is of constant interest. Metal-catalyzed direct C−H amination provides an attractive approach to indole synthesis and has received much attention.[3−5] In most cases, the reaction process usually involves the formation of one C−N bond with preexisting nitrogen in substrates.

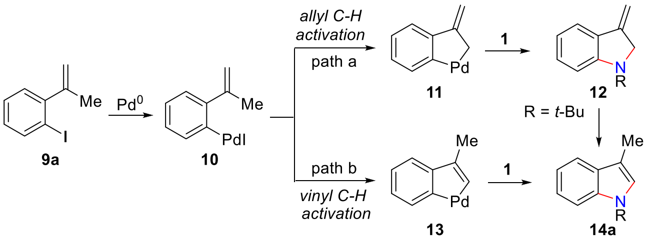
Previously we have found that α-methylstyrene can be converted to spiroindoline **4** with palladium catalyst and di-*t*-butyldiaziridinone (**1**) (Scheme 1, eq a).[6] The reaction likely involved a series of processes including allylic and aromatic C−H activation to form pallada(II)cycle **2**, which was intercepted by di-*t*-butyldiaziridinone (**1**) to generate spiroindoline **4** via pallada(IV)cycle **3**. Subsequently, we demonstrated that palladacycle **6** resulting from a Heck/aryl C−H activation process can be efficiently captured by di-*t*-butyldiaziridinone (**1**) to from indoline **8** (Scheme 1, eq b).[7−9] The bisamination process from a palladacycle allows the simultaneous formation of two C−N bonds and presents great potential for the synthesis of structurally diverse azacycles.

Scheme 1. Formation of Azacycles Via Palladacycles



To further exploit this process, we have been investigating a possible indole synthesis from 2-iodostyrenes such as **9a** (Scheme 2). We envisioned that palladium species **10** (generated from the oxidative addition of **9a**) could undergo an allyl C−H activation (path a)[10] to in situ form palladacycle **11**, which could react with di-*t*-butyldiaziridinone (**1**) to generate indoline **12**. In the end, indole **14a** could be formed from **12** upon aromatization. Alternatively, **10** could undergo a vinyl C−H activation (path b)[11] to give palladacycle **13**, which could be converted to indole **14a** via the bisamination with di-*t*-butyldiaziridinone (**1**). In principle, 2-iodostyrene **9a** could also undergo a series of transformations as described in Scheme 1 (eq a) to give a spiroindoline like **4** by an initiation of the reaction at the allylic position with a four-membered Pd(II) species resulting from the oxidative addition of Pd^0 to di-*t*-butyldiaziridinone (**1**).[6] The success for the desired indole

Scheme 2. Formation of Indoles Via Palladacycles



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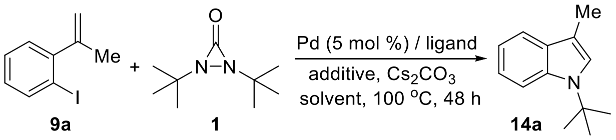
formation requires that aryl iodide can compete with di-*t*-butyldiaziridinone (**1**) for the oxidative addition by Pd^0 catalyst to start the envisioned reaction sequence as described in Scheme 2. Herein, we report our preliminary studies on this subject.

2-Iodostyrene **9a** was used as the substrate for our initial studies. To our delight, indole **14a** was isolated in 55% yield when **9a** was treated with 5 mol % $Pd(PPh_3)_4$, di-*t*-butyldiaziridinone (**1**) (1.5 equiv), and Cs_2CO_3 (2.0 equiv) in $PhCH_3$ at 100 °C for 48 h (Table 1, entry 1). Studies showed that the reaction outcome could be further influenced by additives (Table 1, entries 2 and 3). The reaction yield was dramatically increased to 91% with the addition of 5 mol % PivOH (Table 1, entry 3). The $PivO^-$ is likely bound to the Pd and facilitates the deprotonation of the C−H activation step.[12] Among the solvents examined (Table 1, entries 3−8), $PhCH_3$ gave the best result (Table 1, entry 3). The reaction process was further investigated with different Pd catalysts and ligands. Among Pd catalysts studied (Table 1, entries 9−13), $Pd(TFA)_2$ (TFA = trifluoroacetic acid) was found to be the most effective with PPh_3 as ligand (Table 1, entry 13). With $Pd(TFA)_2$ as the catalyst, various ligands were subsequently investigated for the reaction (Table 1, entries 14−27). The product yield varied with the ligand used. Good yields were obtained with some of the ligands. For example, indole **14a** was isolated in 83% yield with dppf [1,1′-bis(diphenylphosphino)ferrocene] (Table 1, entry 27). Overall, $Pd(PPh_3)_4$ was found to be the choice of the catalyst.

To gain some insights about the reaction mechanism, deuterium-labeling experiments with **9a′** and **9a″** were prepared and examined for the reaction process (Scheme 3).

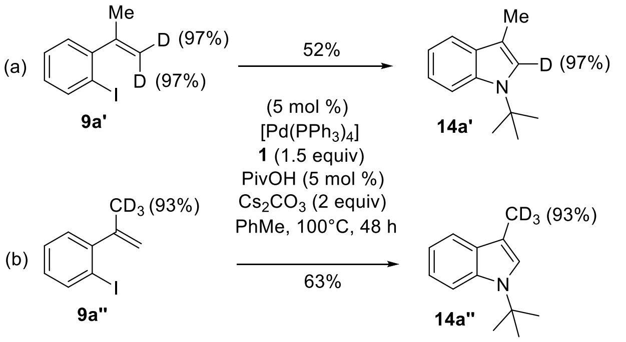
Table 1. Studies on Reaction Conditions[a]



entry	catalyst	ligand	additive	solvent	yield[b] (%)
1	$Pd(PPh_3)_4$			PhMe	55
2	$Pd(PPh_3)_4$		PivOK	PhMe	61
3	$Pd(PPh_3)_4$		PivOH	PhMe	91
4	$Pd(PPh_3)_4$		PivOH	mesitylene	83
5	$Pd(PPh_3)_4$		PivOH	1,4-dioxane	73
6	$Pd(PPh_3)_4$		PivOH	DCE	39
7	$Pd(PPh_3)_4$		PivOH	MeCN	34
8	$Pd(PPh_3)_4$		PivOH	DMF	31
9	$Pd(dba)_2$	PPh_3	PivOH	PhMe	58
10	$Pd(OAc)_2$	PPh_3	PivOH	PhMe	66
11	$PdCl_2$	PPh_3	PivOH	PhMe	62
12	$Pd(NO_3)_2$	PPh_3	PivOH	PhMe	30
13	$Pd(TFA)_2$	PPh_3	PivOH	PhMe	80
14	$Pd(TFA)_2$	P(*o*-tolyl)$_3$	PivOH	PhMe	44
15	$Pd(TFA)_2$	P(*p*-tolyl)$_3$	PivOH	PhMe	67
16	$Pd(TFA)_2$	P(*p*-MeOPh)$_3$	PivOH	PhMe	78
17	$Pd(TFA)_2$	P(*p*-FPh)$_3$	PivOH	PhMe	48
18	$Pd(TFA)_2$	P(*p*-ClPh)$_3$	PivOH	PhMe	26
19	$Pd(TFA)_2$	P(*p*-CF$_3$Ph)$_3$	PivOH	PhMe	51
20	$Pd(TFA)_2$	P(2-furyl)$_3$	PivOH	PhMe	5
21	$Pd(TFA)_2$	$CyPPh_2$	PivOH	PhMe	65
22	$Pd(TFA)_2$	Cy_2PPh	PivOH	PhMe	75
23	$Pd(TFA)_2$	Cy_3P	PivOH	PhMe	79
24	$Pd(TFA)_2$	dppe	PivOH	PhMe	45
25	$Pd(TFA)_2$	dppp	PivOH	PhMe	41
26	$Pd(TFA)_2$	dppb	PivOH	PhMe	56
27	$Pd(TFA)_2$	dppf	PivOH	PhMe	83

[a] All reactions were performed with substrate **9a** (0.30 mmol), di-*t*-butyldiaziridinone **1** (0.45 mmol), Pd (0.015 mmol; Pd/P = 1/4), additive (0.015 mmol), Cs_2CO_3 (0.60 mmol), and solvent (0.30 mL) under Ar at 100 °C for 48 h unless otherwise noted. [b] Isolated yield.

Scheme 3. Deuterium-Labeling Experiments



Subjecting **9a′** to the reaction conditions gave **14a′** in 52% yield with 97% D at the 2-position of the indole. With **9a″** as the substrate, indole **14a″** was obtained in 63% yield with 93% D at the methyl group. These results suggest that the reaction selectively proceeded through the oxidative addition of the Pd to aryl iodide and subsequent vinyl C−H activation (Scheme 2, path b).

The efficient formation of indole **14a** from **9a** prompted us to further explore the reaction substrate scope. As shown in Table 2, the bisamination process can be extended to various 2-iodostyrenes (Table 2, entries 1−17). For disubstituted terminal olefins, indoles **14a**−**14d** were obtained in 61−90% yields with Me, Et, Bu, and Ph substituents on the olefins (Table 2, entries 1−4). Various substituents on the phenyl groups, including Me, F, Cl, CF_3, can be tolerated, giving the corresponding substituted indoles (**14e**−**14j**) in 60−80% yields. When a substituent such as an Me group was introduced to the *o*-position of iodide, a low yield (25%) was obtained for the indole product, possibly due to the steric congestion (Table 2, entry 11). The reaction process can also apply to trisubstituted olefins. Both an electron-donating group like OMe and electron-withdrawing groups like CO_2Et and CN were compatible with the reaction, giving the corresponding 2,3-disubstituted indoles (**14l**−**14n**) in 76−96% yields (Table 2, entries 12−14). Cyclic olefin **9o** was also effective for the reaction, giving six-membered ring-fused indole **14o** in 90% yield (Table 2, entry 15). Under the reaction conditions, carbazole **14p** was obtained with 90% yield when the olefin was replaced with a phenyl group (Table 2, entry 16).[8a] Thiophene fused indole **14q** was obtained in 58% yield from 3-(2-iodophenyl)thiophene **9q** (Table 2, entry 17). However, no reaction was observed when the thiophene was replaced with a furan group.

The reaction can also be performed on a relatively large scale. For example, 1.61 g of indole **14a** was obtained in 86% yield (Scheme 4). As illustrated in the case of **14a**, the *t*-butyl group can be removed with CF_3SO_3H/cyclohexane, giving deprotected indole in 70% yield (Scheme 5).

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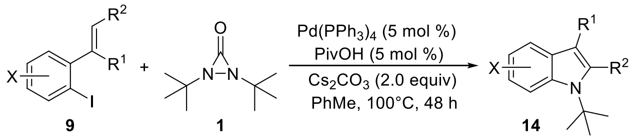
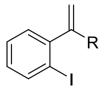
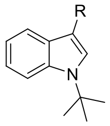
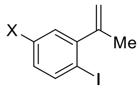
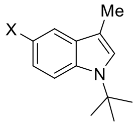
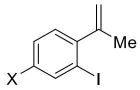
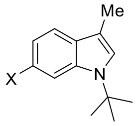
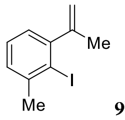
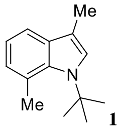
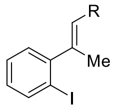
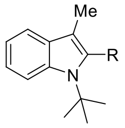
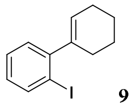
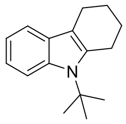
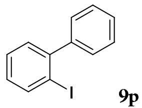
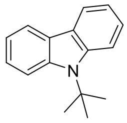
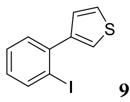
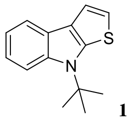
Table 2. Substrate Scope[a]



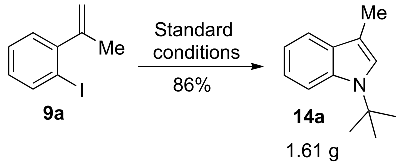
entry	substrate	product	yield (%)[b]
			
1	R = Me, **9a**	**14a**	90
2	R = Et, **9b**	**14b**	78
3	R = ^{n}Bu, **9c**	**14c**	75
4	R = Ph, **9d**	**14d**	61
			
5	X = Me, **9e**	**14e**	66
6	X = F, **9f**	**14f**	71
7	X = Cl, **9g**	**14g** (X-ray)	80
8	X = CF$_3$, **9h**	**14h**	70
			
9	X = Me, **9i**	**14i**	70
10	X = F, **9j**	**14j**	60
11	 **9k**	 **14k**	25
			
12	R = OMe, **9l**	**14l**	80
13	R = CO$_2$Et, **9m**	**14m**	76
14	R = CN, **9n**	**14n**	96
15	 **9o**	 **14o**	90
16	 **9p**	 **14p**	90
17	 **9q**	 **14q**	58

[a] All reactions were performed with 2-iodostyrene **9** (0.60 mmol), di-*t*-butyldiaziridinone **1** (0.90 mmol), Pd(PPh$_3$)$_4$ (0.030 mmol), PivOH (0.030 mmol), and Cs$_2$CO$_3$ (1.20 mmol) in PhCH$_3$ (0.60 mL) under Ar at 100 °C for 48 h. [b] Isolated yield.

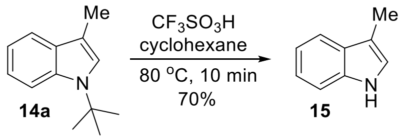
A precise reaction mechanism awaits further investigation. On the basis of previous studies,[6,7] a plausible catalytic cycle exemplified with substrate **9a** is outlined in Scheme 6. The reaction started with the oxidative addition of Pd to the aryl iodide to give aryl Pd(II) species **16**, which underwent an intramolecular vinyl C−H activation[11,13] to generate pallada(II)cycle **17**.[14] The oxidative addition of **17** to the N−N bond of di-*t*-butyldiaziridinone (**1**) formed pallada(IV)cycle **18**, which was converted to Pd(IV)-nitrene **19** upon the release of *t*-butyl isocyanate. Two consecutive reductive eliminations of **19** led to the formation of indole **14a** with the regeneration of Pd catalyst (path a). Alternatively, eight-membered pallada(II)cycle **20** could be formed from pallada(IV)cycle **18** via a reductive elimination. Indole **14a** was formed upon the release of *t*-butyl isocyanate from **20** and a subsequent reductive elimination (Path b).

The comparative studies were performed with (*E*)-trisubstituted olefin **9m** and (*Z*)-trisubstituted **9r** (Scheme 7). The corresponding indole **14m** was obtained from **9m** in 76% yield (Table 2, entry 13). In contrast, no product was formed from **9r**. These results support that the indole formation involves an intramolecular vinyl C−H activation. Further studies show the olefin substituents are also important for the reaction process. For example, the yield dropped dramatically from 90% to less than 5% when the methyl group of *α*-methylstyrene was removed (**9a** vs **9s**) (Scheme 8). However, significant amounts of the indole were formed when

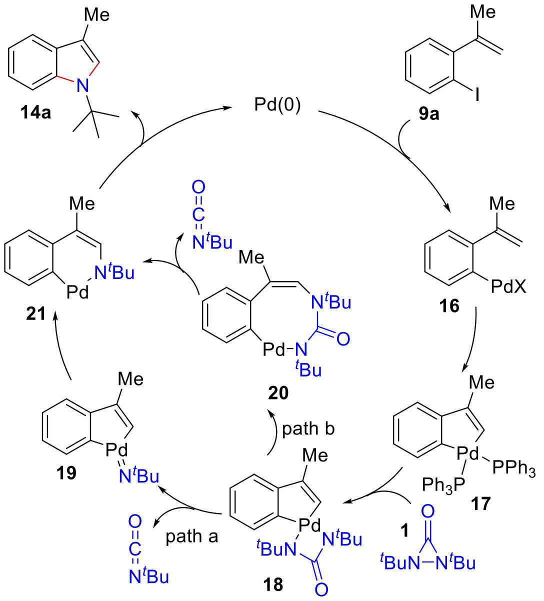
Scheme 4. Gram-Scale Reaction



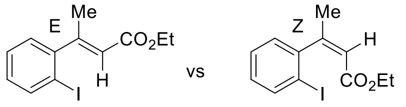
Scheme 5. Removal of the *t*-Butyl Group of Indole 14a



Scheme 6. Proposed Mechanism



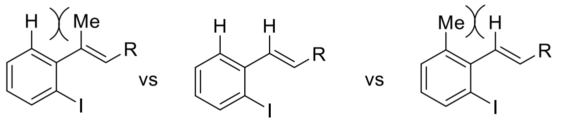
Scheme 7. Effect of Olefin Geometry on Indole Formation



9m (76%)
Table 2, entry 13

9r (0%)

Scheme 8. Substitution Effect on Indole Formation



R = H, **9a** (90%)
Table 2, entry 1

R = CO$_2$Et, **9m** (76%)
Table 2, entry 13

R = H, **9s** (trace)

R = CO$_2$Et, **9t** (trace)

R = H, **9u** (33%)

R = CO$_2$Et, **9v** (73%)

the methyl group was introduced ortho to the vinyl group (**9u** vs **9s**). The same trend was also observed with **9m**, **9t**, and **9v**. These results suggest that the steric repulsion between the vinyl group and phenyl group could facilitate the C−H activation. A better understanding of this issue requires further studies.

In summary, we have developed an efficient palladium-catalyzed sequential C−H activation/amination process with 2-iodostyrenes and di-*t*-butyldiaziridinone (**1**), providing a variety of substituted indoles in good yields. The reaction likely proceeded through the oxidative addition of Pd to the aryl iodide and subsequent vinyl C−H activation to give a pallada(II)cycle, which was converted to the indole via a bisamination with di-*t*-butyldiaziridinone (**1**). This work further illustrates the versatile reactivity and synthetic utility of di-*t*-butyldiaziridinone (**1**). The development of more reaction processes with this class of reagent is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01043.

Experimental procedures, characterization data, and NMR spectra (PDF)

Accession Codes

CCDC 2052689 contain 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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