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Domino C–N Bond Formation via a Palladacycle with Diaziridinone. An Approach to Indolo[3,2-*b*]indoles

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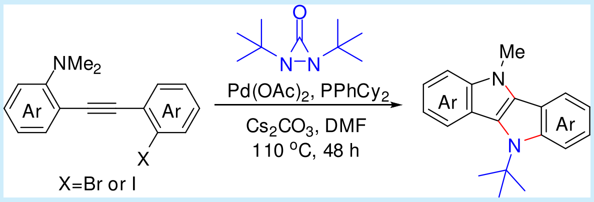
ABSTRACT: Palladium-catalyzed C–N bond formation is one of the widely used transformations for the synthesis of structurally diverse N-heterocycles. This work describes an efficient palladium-catalyzed multiple-C–N bond formation reaction for the synthesis of highly π-conjugated N-heterocycles, indolo[3,2-*b*]indoles with di-*tert*-butyldiaziridinone. The reaction likely proceeds through the initial formation of an indole-fused palladacycle by nucleophilic aminopalladation and subsequent bisamination to give indolo[3,2-*b*]indoles.



C–N bond formation is an important transformation in organic synthesis.[1] The palladium-catalyzed reaction process plays a crucial role in this field and has constantly received attention. In our own studies, we have found that di-*tert*-butyldiaziridinone (**1**) is a class of versatile reagent for amination. In addition to diamination of olefins (Scheme 1, eq a),[2] it can also effectively react with palladacycles **4** to generate azacycles **6** likely via a Pd(IV) intermediate **5** (Scheme 1, eq b).[3–5] In this bisamination process, two C–N bonds are simultaneously formed.

In general, most reported palladacycles are formed through C–H activation.[6] To expand the synthetic utility of our bisamination process, there has been search for different ways to generate palladacycles, which could be intercepted in situ by the diaziridione to form structurally diverse azacycles. Along this line, we have been investigating whether indole-fused palladacycle **9** could be formed via intramolecular nucleophilic aminopalladation of palladium species **8** and could be further intercepted by di-*tert*-butyldiaziridinone (**1**) to form the second indole moiety (Scheme 1, eq c). The indole synthesis from 2-alkynylanilines has been extensively studied.[7,8] For example, when 2-alkynylanilines are treated with ArPdX, an intermolecular nucleophilic aminopalladation leads to the formation of the 3-palladaindoles, which give 3-aryl-substituted indoles upon reductive elimination (Scheme 2).[7] However, an intramolecular version of this process (**8** to **9**) has been unexplored. The envisioned process as described in Scheme 1 (eq c) could lead to the overall formation of indolo[3,2-*b*]indoles **10**, an important class of molecules that may possess unique electronic properties and could be used for functional materials.[9,10] Herein, we report our preliminary studies of this subject.

In our initial studies, various nitrogen nucleophiles, including NH_2, $NHCOCF_3$, NHMs, NHTs, NMeMs, and NMeTs, were examined (Scheme 3). The results were somewhat disappointing, and no desired products were detected. To our delight, when substrate **7a** with NMe_2 as the nucleophile was subjected to the reaction conditions [di-*tert*-butyldiaziridinone (**1**) (1.5 equiv), $Pd(PPh_3)_4$ (5 mol %), and Cs_2CO_3 (1.5 equiv) in DMF at 110 °C for 48 h], the envisioned indolo[3,2-*b*]indole **10a** was formed in 62% NMR yield (Table 1, entry 1). Encouraged by this result, we subsequently screened various ligands with $Pd(OAc)_2$ as the catalyst (Table 1, entries 2–16). $PPhCy_2$ was found to be the best ligand, giving product **10a** in 95% isolated yield (Table 1, entry 11). With $PPhCy_2$ as the ligand, $Pd(OAc)_2$ appeared to be the choice of the catalyst (Table 1, entries 11 and 17–19). Other bases (Table 1, entries 20–22) and solvents (Table 1, entries 23–25) were found to be less effective for the reaction. The reaction temperature appeared to be important. A lower yield was obtained when the reaction was carried out at a lower (100 °C) or higher (130 °C) temperature (Table 1, entry 26 or 27, respectively).

With an optimized protocol in hand, the substrate scope was subsequently investigated. Bromide **7a′** was also shown to be an effective substrate, while a slightly lower yield was obtained compared to that of iodide **7a** (Table 2, entry 1). The bromides were used as substrates in cases in which the corresponding iodides were less accessible. As shown in Table 2, the reaction process can be extended to various substituted iodides and bromides, giving a variety of substituted indolo[3,2-*b*]indoles in 52–93% yields. Substrates bearing substituents such as Me, Cl, and CF_3 groups on the phenyl rings containing the halogen (Br or I) were effective under the

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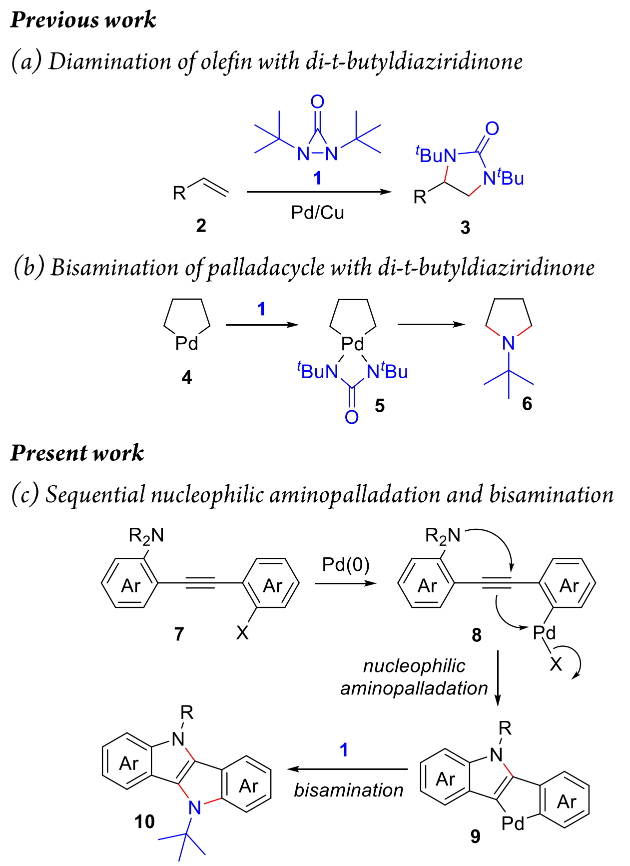
Scheme 1. Diamination and Bisamination with Di-*tert*-butyldiaziridinone



Scheme 3. Initial Studies of Nitrogen Nucleophiles

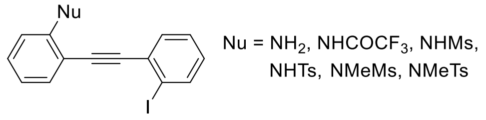
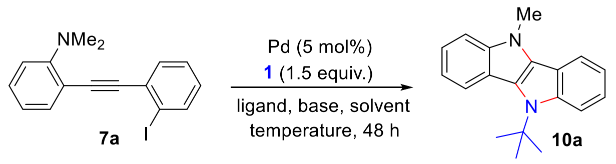


Table 1. Studies of the Reaction Conditions[a]



entry	Pd catalyst	ligand	yield (%)[b]
1	$Pd(PPh_3)_4$	–	62
2	$Pd(OAc)_2$	PPh_3	36
3	$Pd(OAc)_2$	P(*p*-tolyl)$_3$	33
4	$Pd(OAc)_2$	P(*o*-tolyl)$_3$	6
5	$Pd(OAc)_2$	P(*p*-FPh)$_3$	46
6	$Pd(OAc)_2$	P(*p*-MeOPh)$_3$	41
7	$Pd(OAc)_2$	$P(C_6F_5)_3$	–
8	$Pd(OAc)_2$	P(*p*-CF$_3$Ph)$_3$	41
9	$Pd(OAc)_2$	P(*o*-furyl)$_3$	12
10	$Pd(OAc)_2$	PCy_3	31
11	$Pd(OAc)_2$	$PPhCy_2$	99 (95)[c]
12	$Pd(OAc)_2$	PPh_2Cy	60
13	$Pd(OAc)_2$	dppe	18
14	$Pd(OAc)_2$	dppb	43
15	$Pd(OAc)_2$	dppf	25
16	$Pd(OAc)_2$	BINAP	11
17	$Pd(TFA)_2$	$PPhCy_2$	44
18	$PdCl_2$	$PPhCy_2$	53
19	$Pd_2(dba)_3$	$PPhCy_2$	47
20[d]	$Pd(OAc)_2$	$PPhCy_2$	57
21[e]	$Pd(OAc)_2$	$PPhCy_2$	37
22[f]	$Pd(OAc)_2$	$PPhCy_2$	–
23[g]	$Pd(OAc)_2$	$PPhCy_2$	44
24[h]	$Pd(OAc)_2$	$PPhCy_2$	23
25[i]	$Pd(OAc)_2$	$PPhCy_2$	32
26[j]	$Pd(OAc)_2$	$PPhCy_2$	50
27[k]	$Pd(OAc)_2$	$PPhCy_2$	65

[a] All reactions were carried out with **7a** (0.15 mmol), Pd (0.0075 mmol), ligand (0.015−0.030 mmol; 1:4 Pd:P), di-*tert*-butyldiaziridinone **1** (0.225 mmol), and Cs_2CO_3 (0.225 mmol) in DMF (2 mL) at 110 °C under N_2 for 48 h unless otherwise stated. [b] The yields were determined by ^{1}H NMR analysis of the crude reaction mixture using $PhCH_2OCH_3$ as the internal standard. [c] Isolated yield. [d] With K_2CO_3. [e] With Na_2CO_3. [f] With KOAc. [g] In MeCN. [h] In 1,4-dioxane. [i] In $PhCH_3$. [j] At 100 °C. [k] At 130 °C.

reaction conditions, affording the corresponding products **10b−e** in 70−91% yields (Table 2, entries 2−5, respectively). Substituents like Me, Ph, F, Cl, CN, CO_2Me, and NO_2 groups on the phenyl rings containing the NMe_2 were found to be compatible with the reaction, generating the corresponding indolo[3,2-*b*]indoles **10f−l** in 52−85% yields (Table 2, entries 6−12, respectively). Substrate **7m** with *N*,*N*-dimethylnaphthalen-1-amine also underwent the reaction smoothly to give product **10m** in 77% yield (Table 2, entry 13). The reaction can also effectively apply to substrates bearing different substituents in both phenyl rings, providing various substituted indolo[3,2-*b*]indoles **10n−u** in 69−93% yields (Table 2, entries 14−21, respectively). A substrate with a diethylamine group (**7v**) was also effective for the reaction, giving product **10v** in 78% yield (Table 2, entry 22).

As exemplified with **7a**, the reaction can be carried out on a gram scale (Scheme 4). The removal of a *tert*-butyl group for **10a** was achieved with trifluoroacetic acid (TFA) and *n*-hexane, affording indolo[3,2-*b*]indole **10a′** in 86% yield (Scheme 5). Gratifyingly, highly conjugated bisindolo[3,2-*b*]indole **10w** was achieved from **7w** via double-reaction processes (Scheme 6).

Scheme 2. Palladium-Catalyzed Indole Formation from 2-Alkynylanilines

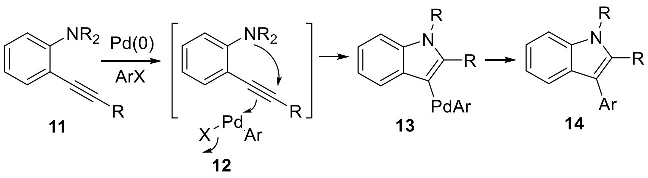
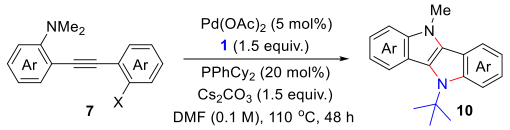
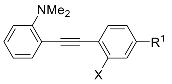
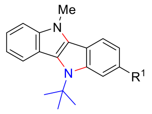
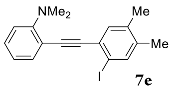
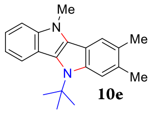
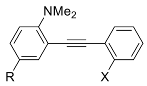
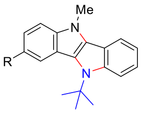
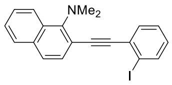
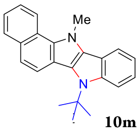
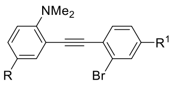
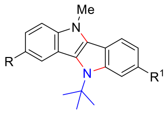
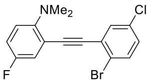
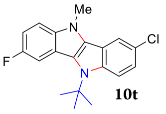
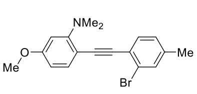
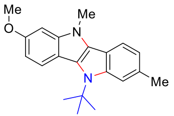
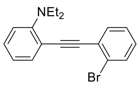
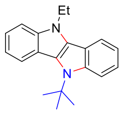


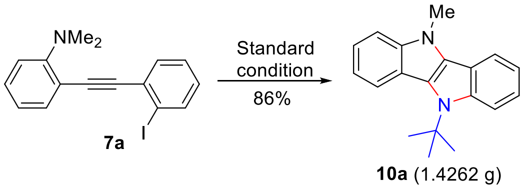
Table 2. Substrate Scope[a]



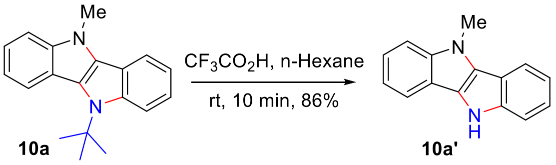
Entry	7	10	Yield[b]
			
1	**7a**, R^{1}=H, X=I	**10a**	93
	7a′, R^{1}=H, X=Br	**10a**	83
2	**7b**, R^{1}=Me, X=Br	**10b**	83
3	**7c**, R^{1} = Cl, X =Br	**10c**	79
4	**7d**, R^{1}=CF$_3$, X=Br	**10d**	91
5	 **7e**	 **10e**	70
			
6	**7f**, R=Me, X=I	**10f**	85
7	**7g**, R=F, X=I	**10g**	84
8	**7h**, R=Cl, X=I	**10h**	72
9	**7i**, R=NO$_2$, X=Br	**10i**	58
10	**7j**, R=CN, X=Br	**10j**	81
11	**7k**, R=CO$_2$Me, X=I	**10k**	52
12	**7l**, R=Ph, X=I	**10l**	71
13	 **7m**	 **10m**	77
			
14	**7n**, R=R^{1}= Me	**10n**	81
15	**7o**, R=Me, R^{1}=Cl	**10o**	81
16	**7p**, R=Me, R^{1}=CF$_3$	**10p**	83
17	**7q**, R=F, R^{1}=Me	**10q**	77
18	**7r**, R=F, R^{1}=CF$_3$	**10r** (X-ray)	87
19	**7s**, R=F, R^{1}=Cl	**10s**	89
20	 **7t**	 **10t**	93
21	 **7u**	 **10u**	69
22	 **7v**	 **10v**	78

[a]All reactions were carried out with **7** (0.30 mmol), Pd (0.015 mol), PPhCy$_2$ (0.060 mmol), **1** (0.45 mmol), and Cs$_2$CO$_3$ (0.45 mmol) in DMF (3 mL) at 110 °C under N$_2$ for 48 h. [b]Isolated yield (%).

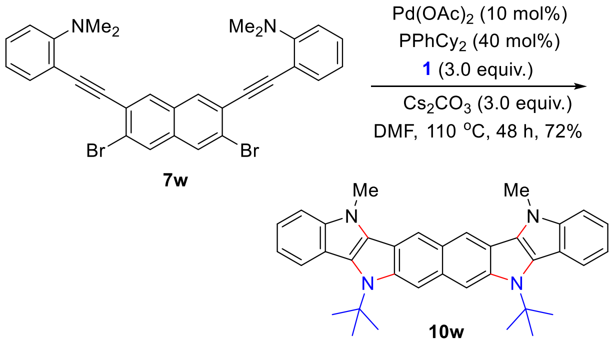
Scheme 4. Gram Scale Reaction with Substrate 7a



Scheme 5. Removal of the *tert*-Butyl Group of Product 10a

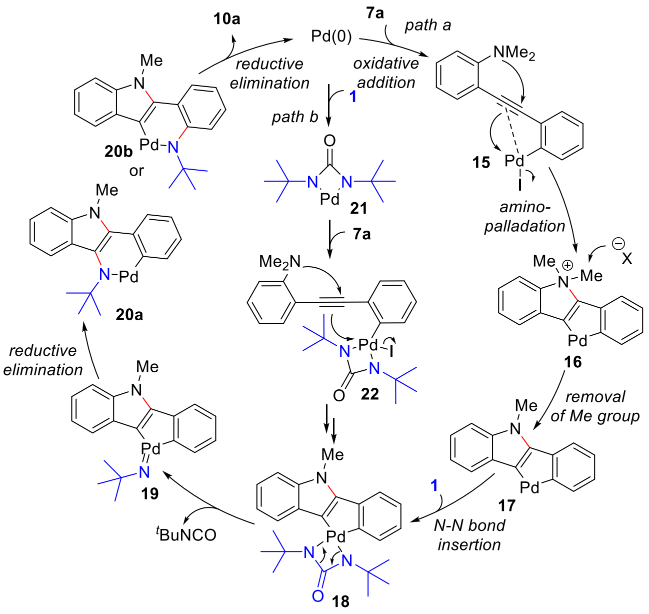


Scheme 6. Formation of Highly Conjugated Bisindolo[3,2-*b*]indole



A precise understanding of the reaction mechanism requires further study. On the basis of earlier studies,[3] a plausible catalytic cycle is proposed in Scheme 7 (with **7a** as an example). The process starts with the coordination of the Pd(0) to the substrate (**7a**), followed by the oxidative addition of the Pd(0) to the C−I bond to give Pd(II) species **15** (path

Scheme 7. A Proposed Catalytic Cycle



a), which undergoes nucleophilic aminopalladation and demethylation to form indole-fused pallada(II)cycle **17**. The oxidative addition of **17** to di-*tert*-butyldiaziridinone (**1**) gives pallada(IV)cycle **18**, which is converted to pallada(IV)nitrene species **19** with release of ^{t}BuNCO. Indolo[3,2-*b*]indole **10a** is formed from **19** by two consecutive reductive eliminations via **20a** or **20b** with regeneration of the Pd catalyst. Alternatively, the Pd(0) could be oxidatively inserted into the N−N bond of di-*tert*-butyldiaziridinone (**1**) to form four-membered Pd species **21** (path b). The oxidative addition of **21** to substrate **7a** gives Pd intermediate **22**, which is converted to pallada(IV)cycle **18**, upon nucleophilic aminopalladation and subsequent demethylation.

In summary, we have developed an efficient palladium-catalyzed nucleophilic aminopalladation and bisamination sequence with 2-[(2-haloaryl)ethynyl]-*N*,*N*-dialkylanilines (**7**) and di-*tert*-butyl-diaziridinone (**1**), affording a wide variety of substituted indolo[3,2-*b*]indoles in 52−93% yields. To the best of our knowledge, this is the first example in which an indole-fused palladacycle is formed through intramolecular nucleophilic aminopalladation to form overall two rings with generation of three C−N bonds. Highly conjugated linear bisindolo[3,2-*b*]indole can also be achieved via the aforementioned process. Further exploration of new reaction processes with the indole-fused palladacycle 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.1c00466.

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

Accession Codes

CCDC 2051396 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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