Palladium-Catalyzed, One-Pot, Three-Component Approach to α-Alkynyl Indoles from *o*-Bromo-(2,2-dibromovinyl)benzenes, Terminal Alkynes and Arylamines

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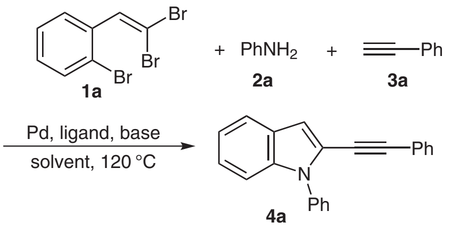
Abstract: α-Alkynyl indoles were efficiently synthesized in one pot from *o*-bromo-(2,2-dibromovinyl)benzenes, terminal alkynes, and arylamines via a palladium-catalyzed three-component coupling process.

Key words: multi-component coupling, *o*-halo-(2,2-dihalovinyl)-benzene, alkyne, arylamine, indole, palladium-catalyzed reaction

We have been interested in the preparation and synthetic applications of polyfunctional conjugated compounds, such as polyhalo compounds, with the aim of utilizing the cooperative effect among functional groups on conjugated systems.[1,2] We envisioned that polyhalo compounds, such as *o*-halo-(2,2-dihalovinyl)benzenes, might be useful building blocks for the construction of heterocyclic compounds via multi-step coupling of the different C–X bonds.[1] Herein, we would like to disclose a useful application of *o*-bromo(2,2-dibromovinyl)benzenes **1** and a novel synthetic method for the production of indoles.

Indoles are very important compounds in many aspects. Consequently, the research and development of synthetic methods for indoles continues to be one of the most active areas in synthetic chemistry.[3–10] Recently, useful and unique syntheses of indoles have been developed by applying Pd-catalyzed protocols.[5–10] For example, *o*-haloaniline and *o*-alkynylaniline,[6] *o*-dihaloarenes, alkynes, and primary amine[7] have been applied to the synthesis of indoles. Barluenga et al. reported that *o*-dihaloarenes reacted with imines to form indoles.[8] Lautens and co-workers developed a series of methods to construct indole rings starting from *o*-amino-*gem*-dihalostyrenes.[9] Willis and co-workers used *o*-halo-β-sulfonyl-styrenes and primary amines to synthesize indoles.[10] Although these reported methods are useful and interesting, synthetic methods for the synthesis of indoles, especially for indole rings substituted with functional groups such as alkynyl groups, are

Table 1 Reaction Optimization[a]



Entry	Ligand	Base	Solvent	Yield (%)[b]
1	Xantphos	Cs_2CO_3	NMP	80
2	Ph_3P	Cs_2CO_3	NMP	trace
3	*t*-Bu_3P	Cs_2CO_3	NMP	trace
4	Dppf	Cs_2CO_3	NMP	trace
5	DPEphos	Cs_2CO_3	NMP	7
6	X-phos	Cs_2CO_3	NMP	26
7	Xantphos	*t*-BuONa	NMP	trace
8	Xantphos	K_2CO_3	NMP	trace
9	Xantphos	KOH	NMP	trace
10	Xantphos	Cs_2CO_3	Toluene	13
11	Xantphos	Cs_2CO_3	DMF	9
12	Xantphos	Cs_2CO_3	Dioxane	5
13[c]	Xantphos	Cs_2CO_3	NMP	5
14[d]	Xantphos	Cs_2CO_3	NMP	45
15[e]	Xantphos	Cs_2CO_3	NMP	21

[a] *Reaction conditions:* **1a** (0.4 mmol), **2a** (0.3 mmol), **3a** (0.4 mmol), $Pd(OAc)_2$ (5 mol%), base (0.9 mmol), solvent (2 mL).
[b] Isolated yield.
[c] $[Pd_2(dba)_3]$ was used as catalyst.
[d] With CuI (5 mol%).
[e] Reaction performed at 100 °C.

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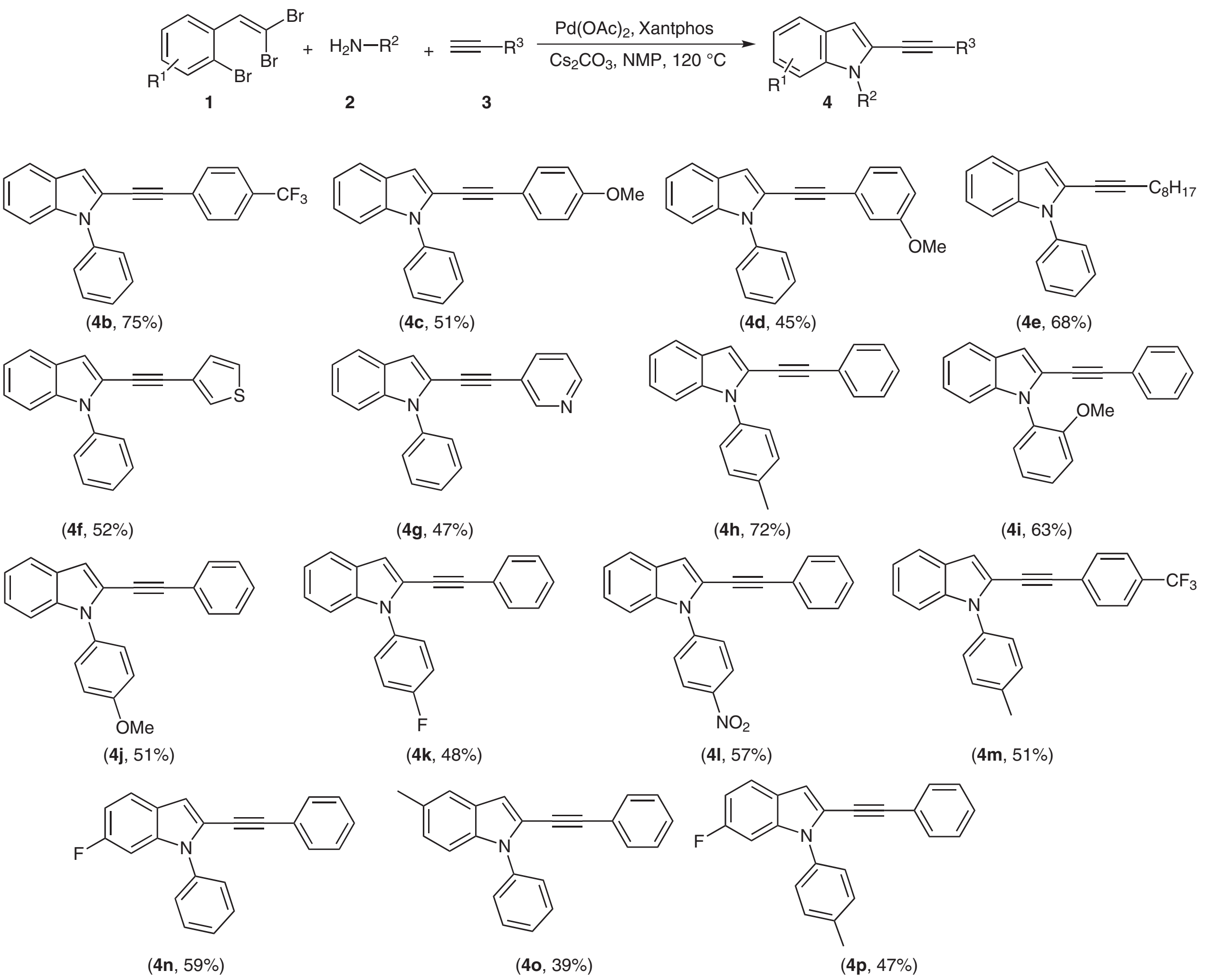
still in great demand. In addition, diverse starting materials and synthetic strategies are desired to make indole derivatives more readily accessible.

In our present work, α-alkynyl indoles were formed in good yields from polyhalo compounds **1**, arylamines, and alkynes in one-pot, via a Pd-catalyzed, three-component coupling reaction. One Csp^2–Csp bond and two Csp^2–N bonds are constructed in the one-pot process. Table 1 shows the screening results obtained for optimization of the reaction conditions in the one-pot, three-component coupling reaction of **1a**, aniline **2a**, and phenylacetylene **3a** using $Pd(OAc)_2$ as the catalyst.

First, we screened the efficiency of ligands. The results indicated that Xantphos ligand was the best for this coupling reaction. Next, it was observed that solvents significantly affected this reaction. Toluene, dioxane, and DMF were tested, but they were found to be much less effective than NMP. Several bases, such as *t*-BuONa, K_2CO_3 and KOH, were also examined. The results showed that all were less efficient compared with Cs_2CO_3. Finally, in addition to $Pd(OAc)_2$, we also tested $[Pd_2(dba)_3]$ (Table 1, entry 13) and CuI (entry 14) as catalysts. Although the use of $[Pd_2(dba)_3]$ and CuI benefited the construction of the C–N bond and the Sonogashira reaction, the simple $Pd(OAc)_2$ catalyst was found to be much more efficient in this three-component coupling reaction. Thus, the optimized reaction conditions were as follows: **1a** (0.4 mmol), **2a** (0.3 mmol), **3a** (0.4 mmol), $Pd(OAc)_2$ (5 mol%), Cs_2CO_3 (0.9 mmol), in NMP (2 mL) at 120 °C.

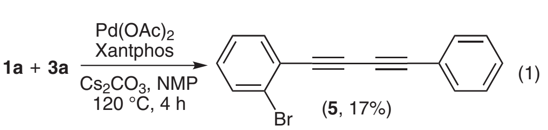
As shown in Scheme 1, a variety of α-alkynyl indoles could be obtained from **1**, arylamines **2** and alkynes **3** under the optimal reaction conditions. In terms of terminal alkynes, both aliphatic alkynes (**4e**) and aromatic alkynes could be used. Aromatic alkynes with both electron-withdrawing groups, such as CF_3 (**4b** and **4m**), and electron-donating groups, such as OMe (**4c**, **4d**), on the phenyl ring afforded the corresponding indole derivatives. Heteroatom aromatic alkynes (**4f** and **4g**) could also be used in this reaction. A wide variety of anilines were examined. The results showed that anilines with either electron-donating or electron-withdrawing groups were tolerated in the three component coupling reaction. Substituted *o*-bromo(2,2-dibromovinyl)benzenes were also investigated. It was found that both F- and Me-substituted substrates also reacted smoothly with aniline and phenylacetylene under

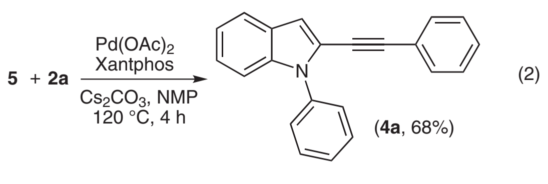


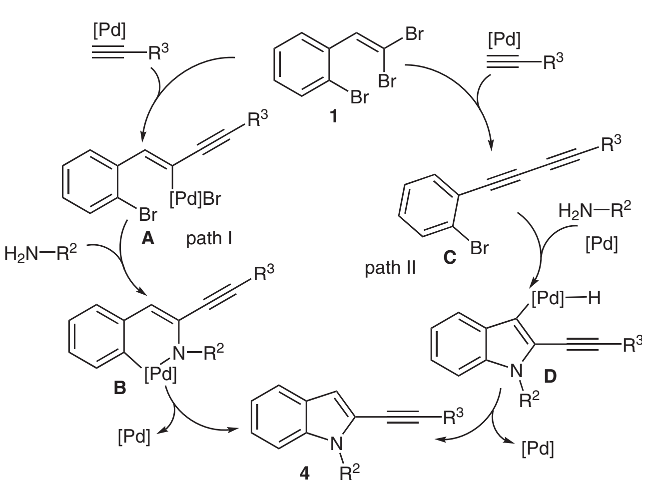
Scheme 1 Palladium-catalyzed cross-coupling of *o*-bromo-(2,2-dibromovinyl)benzenes **1** with arylamine **2** and alkyne **3**. *Reagents and conditions*: **1** (0.4 mmol), **2** (0.3 mmol), **3** (0.4 mmol), $Pd(OAc)_2$ (5 mol%), Xantphos (10 mol%), Cs_2CO_3 (0.9 mmol), NMP (2 mL). Isolated yields.

the conditions described above to generate the corresponding indoles **4n**, **4o**, and **4p**, respectively. To the best of our knowledge, this three-component one-pot coupling reaction represents the first example of such type,[11] especially using the polyhalo compounds *o*-bromo-(2,2-dibromovinyl)benzenes.

It should be noted that all three components are present at the same time in the reaction system. The chemical selectivity of the reaction is thus very high. Clearly, compared with previously reported reactions involving one or two of these components,[6–10,12] the reaction mechanism of this process is intriguing. We found that, without aniline, **1a** reacted with phenylacetene to form **5** in 17% isolated yield (eq. 1). We also found that compound **5** could further react with aniline smoothly to form 2-alkynylindole **4a** in 68% isolated yield (eq. 2). Therefore, although the reaction path I as proposed in Scheme 2 is more likely, the reaction path II cannot be ruled out.







Scheme 2 Proposed reaction pathways

In conclusion, we have described a novel and efficient method for the synthesis of α-alkynyl indoles[13] via a palladium-catalyzed, multi-component coupling of *o*-bromo-(2,2-dibromovinyl)benzenes with arylamines and alkynes.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(13) **Typical Procedure for the preparation of α-alkynyl-indole 4a**: Under the protection of nitrogen, $Pd(OAc)_2$ (5 mol%) and Xantphos (10 mol%) were added to NMP (2 mL). The reaction mixture was stirred at r.t. for 15 min, then *o*-bromo-2-(2,2-dibromovinyl)benzene (0.4 mmol), phenylacetylene (0.4 mmol), and aniline (0.3 mmol) were added and the reaction mixture was stirred at 120 °C for 5 h. The reaction mixture was quenched with water and extracted with Et_2O. The organic extract was washed with brine and dried over $MgSO_4$. The solvent was then evaporated in vacuo and the residue was purified by using a SiO_2 column (petroleum ether–ethyl acetate, 100:1) to afford 1-phenyl-2-(phenylethynyl)-1*H*-indole (**4a**) as a colorless solid (80%, 70 mg). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.99$ (s, 1 H), 7.12–7.16 (m, 1 H), 7.17–7.22 (m, 4 H), 7.27–7.30 (m, 3 H), 7.38 (t, $J = 8.0$ Hz, 1 H), 7.46–7.54 (m, 4 H), 7.62 (d, $J = 7.2$ Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 81.78$, 95.25, 109.35, 110.48, 120.89, 120.95, 121.88, 122.64, 123.63, 127.25, 127.49, 127.56, 128.25, 128.30, 128.95, 131.04, 137.47, 137.56; HRMS (ESI): m/z calcd for $C_{22}H_{16}N^+$: 294.1277; found: 294.1274