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Efficient Synthesis of 2-Substituted Indoles Based on Palladium(II) Acetate/Tri-*tert*-butylphosphine-Catalyzed Alkynylation/Amination of 1,2-Dihalobenzenes

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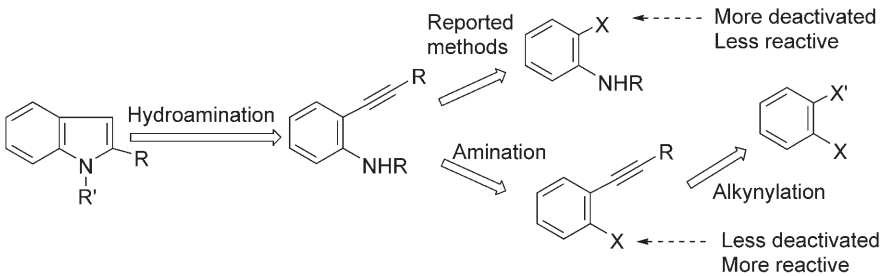
Abstract: A simple, efficient palladium(II) acetate/tri-*tert*-butylphosphine-catalyzed indole synthesis from *o*-alkynylhalobenzenes, readily available from 1,2-dihalobenzenes, has been achieved in good to excellent yields. A one-pot, $Pd(OAc)_2$/*t*-Bu_3P-catalyzed sequential reaction from 1-chloro-2-iodobenzene, phenylacetylene and amines has also been achieved in good yields.

Keywords: alkynylation; amination; 1,2-dihalobenzenes; indoles; palladium; phosphane ligands

Many natural products and biologically active compounds contain indole skeleton as their structural subunits.[1] Such a prevalence stimulated the development of a number of methods for indole synthesis in past decades.[1–3] Among the methods developed, the palladium-catalyzed transformations of *o*-haloanilines *via* alkynylation to form *o*-alkynylanilines followed by intramolecular hydroamination have been studied intensively and represent a fruitful strategy to access 2-substituted indoles.[2,3] As part of our program directed to develop new sequential and tandem reactions based on powerful cross-coupling reactions,[4,5] we became interested in developing sequential/tandem reactions for the efficient synthesis of heterocycles including indoles from readily available starting materials. Based on our analysis of possible routes to the key intermediate *o*-alkynylanilines for the synthesis of 2-substituted indoles, we reasoned that readily available 1,2-dihalobenzenes could be suitable starting materials to access *o*-alkynylanilines *via* an alkynylation followed by an amination sequence (Scheme 1). This possible route appeared to be very attractive considering: (a) due to the electronic nature of alkynyl groups, *o*-alkynylhalobenzenes are expected to be more reactive than strong deactivating amino group-containing *o*-haloanilines, and are thus expected to behave similarly like other *o*-substituted halobenzenes for the Buchwald–Hartwig aminations[6] and (b) *o*-alkynylhalobenzenes, especially *o*-alkynylchlorobenzenes, have been well-established to be readily accessible from the monoalkynylation of 1,2-dihalobenzenes.[7,8] Based on the fact that enormous progress has been achieved in Pd(0)-catalyzed amination reactions in recent years and different types of aryl halides including aryl chlorides have been demonstrated as suitable substrates,[6,9] we believed that the amination of *o*-alkynylhalobenzenes including *o*-alkynylchlorobenzenes could be possible and the strategy of alkynylation followed by amination of 1,2-dihalobenzenes would provide us an efficient and general method to access 2-substituted indoles.[10] Herein our results are reported.

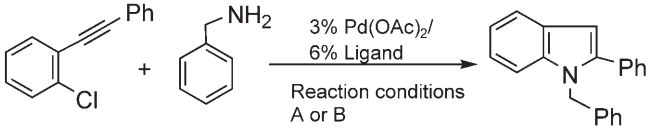


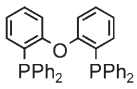
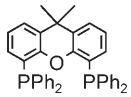
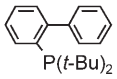
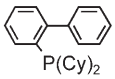
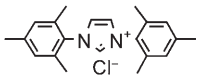
Scheme 1. Possible routes for the preparation of 2-substituted indoles.

Although the monoalkynylation of 1,2-dihalobenzenes with terminal alkynes to form *o*-alkynylhalobenzenes has been well-established,[7,8] we were surprised to find that the amination of *o*-alkynylhalobenzenes for the synthesis of 2-substituted indoles was rarely studied.[10,11] We thus began our study to identify palladium catalyst systems that could efficiently catalyze the amination reaction of *o*-alkynylhalobenzenes. 1-Chloro-2-(2-phenylethynyl)benzene was chosen as the model substrate because of (a) its high yield, selective formation from readily available 1-bromo-2-chlorobenzene (81%) and 1-chloro-2-iodobenzene (95%),[8] and (b) the consideration that catalyst systems that work for 1-chloro-2-(2-phenylethynyl)benzene which contains a very inert C–Cl bond should also work for other more reactive *o*-alkynylhalobenzenes. A number of commercially available ligands that have been demonstrated as suitable for the amination of aryl halides were screened for the Pd(0)-catalyzed amination of 1-chloro-2-(2-phenylethynyl)benzene with benzylamine, which yielded 1-benzyl-2-phenylindole as the final product after intramolecular hydroamination reaction (Table 1). We found that under the conditions of KO-*t*-Bu as base and toluene as solvent at 110 °C, bidentate bis(2-diphenylphosphinophenyl) ether (DPEphos) and 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (XantPhos) were ineffective ligands (Table 1, entries 1 and 2).[12] Buchwald's aryldialkylphosphines proved to be excellent ligands for the reaction (Table 1, entries 3 and 4).[13] An N-heterocyclic carbene, *in situ* generated from 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride, was also tested and a moderate yield was observed (Table 1, entry 5).[9c, d] We found that the best result was obtained when $(t\text{-Bu})_3$P was employed as ligand (Table 1, entry 6). Other monodentate ligands such as $(Cy)_3$P and $(sec\text{-Bu})_3$P were also tested and no desired cyclization product was observed (Table 1, entry 7).

With Pd(0)/P(t-Bu)$_3$ as the catalyst system,[14] several *o*-alkynylhaloarenes, which were prepared from 1-bromo-2-iodobenzene, 1-bromo-2-chlorobenzene and 1-chloro-2-iodobenzene by following reported methods,[7,8] were tested for the amination followed by the intramolecular hydroamination and our results are listed in Table 2. We found that 1-bromo-2-(2-phenylethynyl)-benzene and 1-chloro-2-(2-phenylethynyl)benzene reacted smoothly with both alkylamines and anilines to give 2-substitued indoles in excellent isolated yields (Table 2, entries 1–6). We also found that although *o*-chlorooctynylbenzene and *o*-chlorohexynylbenzene also reacted with benzylamine and octylamine to give 2-substituted indoles with satisfactory results, they appeared to be less reactive than 1-chloro-2-(2-phenylethynyl)benzene (Table 2, entries 7–10). In the reaction of aniline with *o*-chlorohexynylbenzene, the uncyclized product 2-(1-hexynyl)-*N*-phenylaniline was isolated as the main product (Table 2, entry 11). Our results suggested that alkyl groups, which are more electron-donating than the phenyl group, likely through the triple bond, retarded the amination reaction and also slowed down the intramolecular hydroamination process.

Table 1. Ligand screening.[a]

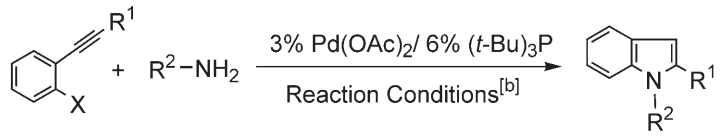


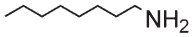
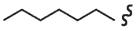
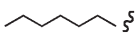
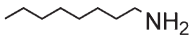
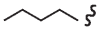
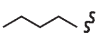
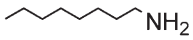
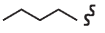
Entry	Ligands	Reaction Condition[b]	Yields [%][c]
1		A	0
2		A	0
3		A	88
4		A	93
5		A	59
6	$(t\text{-Bu}_3)$P	A or B	91 – 95
7	$(Cy)_3$P and $(sec\text{-Bu})_3$P	A	0

[a] Alkyne (1 mmol), amine (1.2 mmol), 3% Pd(OAc)$_2$, 6% ligands.
[b] *Reaction conditions:* A: *t*-BuOK (3 equivs.), toluene (2 mL), 110–120 °C. B: K_3PO_4 (3 equivs.), DMA (2 mL), 130 °C.
[c] Yields of isolated products.

With Pd(0)/P(t-Bu)$_3$ as the catalyst system, we have also carried out the indole synthesis in a sequential fashion from 1-chloro-2-iodobenzene, alkynes and amines.[10] We found that conditions for the first alkynylation step played an important role for the successful sequential reactions. When Et_3N was employed as base for the first alkynylation step, no cyclization product was obtained. Fortunately, when inorganic bases such as Cs_2CO_3 or *t*-BuOK were used, 2-substituted indoles were obtained in good yields for phenylacetylene as the alkyne source (Table 3). However, with 1-octyne as the alkyne source, lower yields of 2-substituted indoles were observed, along with significant amounts of uncyclized *N*-benzyl-2-(1-octynyl)aniline. Such lower yield observation was probably due, at least in part, to the electron-donating alkyl group which might make

Table 2. Pd(0)-catalyzed synthesis of 2-substituted indoles from *o*-alkynylhalobenzenes.[a]



Entry	X	R^1	R^2NH_2	Method[b]	Yield [%][c]
1	Br		$PhCH_2NH_2$	A	95
2	Br		$PhNH_2$	A	95
3	Cl		$PhCH_2NH_2$	B	95
4	Cl		$PhNH_2$	B	99
5	Cl		4-MeO-$PhNH_2$	B	95[d]
6	Cl			A	99
7	Cl		$PhCH_2NH_2$	A	85
8	Cl			A	74
9	Cl		$PhCH_2NH_2$	A	85
10	Cl			A	90
11	Cl		$PhNH_2$	A	23[e]

[a] 3% $Pd(OAc)_2$, 6% $(t\text{-}Bu)_3P$, 1 mmol alkyne, 1.2 mmol amine.
[b] Method A: *t*-BuOK (3 equivs.), toluene (2 mL), 110–12 °C, 14 h; Method B: K_3PO_4 (3 equivs.), DMA (2 mL), 130 °C, 14 h.
[c] Yields of isolated products.
[d] 5% $Pd(OAc)_2$ and 10% $(t\text{-}Bu)_3P$ were used.
[e] 2-(1-Hexynyl)-*N*-phenylaniline was obtained in 55% yield.

the amination and hydroamination less effective. We have also attempted to carry out the reaction by loading 1-chloro-2-iodobenzene, phenylacetylene and benzylamine at the same time, but no desired indole product was observed.

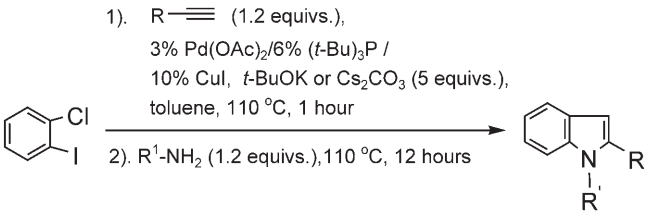
In summary, based on our analysis that readily available *o*-alkynylhalobenzenes would be more reactive than strong deactivating amino group-containing *o*-haloanilines and would behave similarly like other *o*-substituted halobenzenes for the Buchwald–Hartwig aminations, we have successfully developed a simple, efficient $Pd(OAc)_2/(t\text{-}Bu)_3P$-catalyzed indole synthesis from *o*-alkynylhalobenzenes including *o*-alkynylchlorobenzenes. A one-pot, $Pd(OAc)_2/(t\text{-}Bu)_3P$-catalyzed sequential reaction from 1-chloro-2-iodobenzene, phenylacetylene and amines has also been developed. Further investigations on Pd(0)-catalyzed sequential/tandem reactions of 1,2-dihalobenzenes for the synthesis of other types of heterocyclic compounds are currently underway.

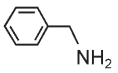
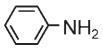
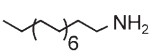
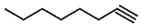
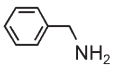
Experimental Section

General Procedures for Pd(0)/$(t\text{-}Bu)_3P$-Catalyzed Indole Synthesis from *o*-Alkynylchlorobenzene

Method A: Under an N_2 atmosphere, to a mixture of *o*-alkynylchlorobenzene (1 mmol), *t*-BuOK (3 mmol), $Pd(OAc)_2$ (0.03 mmol) and $(t\text{-}Bu)_3P$ (0.06 mmol) were added an amine

Table 3. Indole synthesis in an one-pot, sequential fashion.



Entry	R≡	R'–NH_2	Yields [%][a]
1	Ph≡		64
2	Ph≡		71
3	Ph≡		80
4	Ph≡		47
5			23[b]

[a] Yield of isolated product.
[b] *N*-Benzyl-2-(1-octynyl)aniline was observed in 14% yield.

(1.2 mmol) and toluene (2 mL). The resulting mixture was heated to 110–120 °C for 14 hours. After quenching with water, the reaction mixture was extracted with ethyl acetate and the organic layer was washed with brine. Rota-evaporation and flash chromatography on silica gel (hexane: ethyl acetate = 5:95 to 15:85) gave 2-substituted indoles as the product.

Method B: Under an N_2 atmosphere, to a mixture of *o*-alkynylchlorobenzene (1 mmol), K_3PO_4 (3 mmol), $Pd(OAc)_2$ (0.03 mmol) and $(t\text{-Bu})_3P$ (0.06 mmol) were added an amine (1.2 mmol) and dimethylacetamide (2 mL). The resulting mixture was heated to 130 °C for 14 hours. After quenching with water, the reaction mixture was extracted with ethyl acetate and the organic layer was washed with brine. Rota-evaporation and flash chromatography on silica gel (hexane: ethyl acetate = 5:95 to 15:85) gave 2-substituted indoles as the product.

General Procedure for One-Pot, Sequential Preparation of 2-Substituted Indoles

Under an N_2 atmosphere, to a mixture of 1-iodo-2-chlorobenze (1 mmol), $Pd(OAc)_2$ (0.03 mmol), CuI (0.1 mmol), *t*-BuOK (3 mmol), and $(t\text{-Bu})_3P$ (0.06 mmol) were added an alkyne (1.2 mmol) and toluene (2 mL). After the resulting mixture was heated to 110 °C for 1 hour, an amine (1.2 mmol) was added and the mixture was heated at 110 °C for another 12 h. After quenching with water, the reaction mixture was extracted with ethyl acetate and the organic layer was washed with brine. Rota-evaporation and flash chromatography on silica gel (hexane: ethyl acetate = 5:95 to 15:85) gave 2-substituted indoles as the product.

For detailed procedures and characterization data, see Supporting Information.

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[14] Pd(OAc)$_2$/(t-Bu$_3$)P catalyst system appears to be more active than that of Pd(OAc)$_2$/1,3-bis(2,6-diisopropylphenyl)imidazolium chloride system for the preparation of 2-substituted indoles from *o*-alkynylhalobenzenes and 1,2-dihalobenzenes because comparable yields were observed from a 3% Pd(OAc)$_2$/(t-Bu)$_3$P catalyst loading or a 5–10% Pd(OAc)$_2$/1,3-bis(2,6-diisopropylphenyl)-imidazolium chloride catalyst loading (ref.[10]). In addition, tri-*tert*-butylphosphine is cheaper than the sterically hindered 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride: For example, the prices from the 2004–2006 Strem's catalog: tri-*tert*-phosphine: $ 37.0/g; 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride: $ 58.0/500 mg.

