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The First Regioselective Palladium-Catalyzed Indolization of 2-Bromo- or 2-Chloroanilines with Internal Alkynes: A New Approach to 2,3-Disubstituted Indoles

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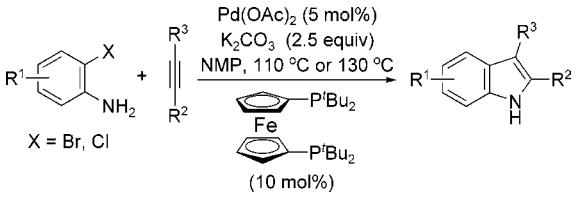
ABSTRACT



The first practical and economical process for synthesis of 2,3-disubstituted indole compounds has been developed with high regioselectivity by palladium-catalyzed indolization of 2-bromo- or chloroanilines and their derivatives with internal alkynes.

The indole nucleus is a prominent structural motif abundantly found in numerous natural products and pharmaceutically active compounds.[1] Many methods have been developed to meet the need of building indole structures.[2] However, regioselective formation of 2,3-disubstituted indoles is challenging with these classical approaches. The recently developed palladium-catalyzed indolization method by Larock et al.[3] provided a solution to the aforementioned issues of regioselectivity, and has been widely applied to preparation of heterocycles.[4] This versatile "ligandless" heteroannulation of internal alkynes with 2-iodoanilines allows easy access to a variety of indoles that may not be available by conventional methods in terms of substitution and functionality (eq 1). Inspired by Larock's work, we were interested in exploring the possibility of replacing the iodoanilines with the much cheaper 2-bromo or 2-chloro derivatives. If such a transformation were feasible, it would be of significant practical and economical value from a cost and throughput

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(1) For a recent review of indole-containing natural products, see: (a) Faulkner, D. J. *Nat. Prod. Rep.* **1999**, *16*, 155. (b) Lounasmaa, M.; Tolvanen, A. *Nat. Prod. Rep.* **2000**, *17*, 175.

(2) For reviews on indole syntheses, see: (a) Indoles; Sundberg, R. J., Ed.; Academic: London, 1996. (b) Sundberg, R. J. Pyrroles and Their Benzo Derivatives: Synthesis and Applications. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 4, pp 313−376. For a recent review on Fischer indole synthesis, see: Hughes, D. L. *Org. Prep. Proced. Int.* **1993**, *25*, 607.

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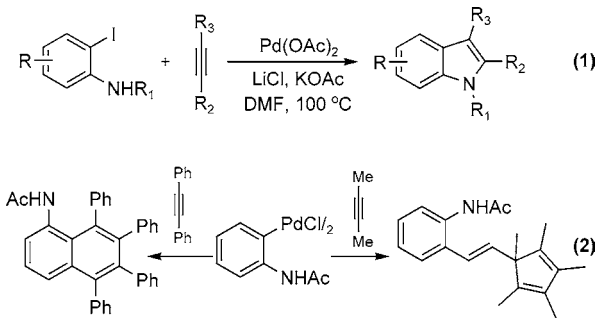
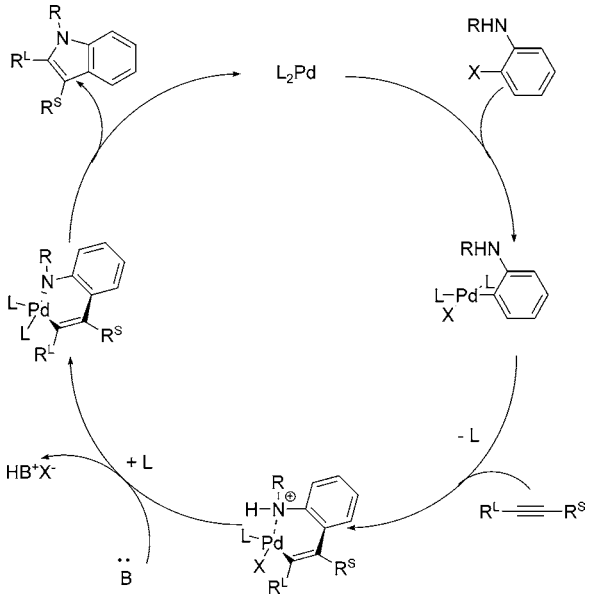
perspective. Unfortunately, the Larock protocol is not applicable to the indolization of acetylenes with 2-bromo or chloroanilines, because the oxidative insertion requires electron-rich palladium.[3] In addition, the presence of iodide was postulated to have a pronounced effect on the nature of the products in these alkyne insertion processes, as previous research on the reaction of ortho palladation complex with alkynes demonstrated the exclusive formation of multiple insertion products (eq 2).[3b,5]



The mechanism of the transformation is generally recognized as involving the following three steps: (a) oxidation insertion of carbon−halide bond to L_2Pd, (b) coordination and regioselective addition to the C−C alkyne bond, and (c) subsequent Pd extrusion via reductive elimination (Scheme 1).[3b,6] Recent developments have shown that bulky, electron-rich phosphines readily allow previously unreactive aryl chlorides to undergo cross-coupling and Heck chemistry,[7] as well as amination reactions.[8]

These precedents therefore suggest that extension of the Larock chemistry to highly deactivated *o*-chloroanilines may be possible. However, it is not at all obvious that expected side reactions such as multiple insertions (eq 2) and amination/dimerization of the substrates could be brought under control. Indeed, one would expect that the ligands that are necessary to activate aryl chlorides would also be capable of promoting amination of the substrates, a reaction that is never seen with the traditional Larock substrates under "ligandless" conditions. Indeed, this side reaction proved to be a major problem for the development of the new indolization protocol, but suitable conditions could be found that partially suppressed it. Therefore, we are pleased to report herein on the first effective palladium-catalyzed

Scheme 1. Mechanistic Working Model



indolization of 2-bromo or chloroaniline derivatives with internal alkynes.

To develop this protocol into a practical method, we had to address another aspect in addition to chemoselectivity, i.e., regioselectivity. Although regioselectivity is generally attributed to the inherent steric hindrance of the alkyne substrates, the use of ligands, introduced in order to activate the C−Cl bond, will most likely lead to unpredictable regiochemical issues, which have never been studied before in this type of reaction. To this end, we first conducted a ligand screen with a deactivated 2-chloroaniline and a nonsymmetrical alkyne (Scheme 1). In addition to the desired product, we observed that the major side reaction was indeed the homocoupling of the 2-chloroaniline via two consecutive amination reactions.[9] Our primary objective became identifying conditions that not only minimize formation of amination byproduct **3** but also result in optimal regioselectivity.

Several types of well-documented, highly active phosphine ligands such as trialkylphosphines (Cy_3P, *t*-Bu_3P), ferrocenyl phosphines (**4**−**6**), and biaryl phosphines (**7**−**10**) were examined, among which 1,1′-bis(di-*tert*-butylphosphino) ferrocene (**6**) gave superior results, albeit with formation of 19% of **3** (entry 5a). With tricyclohexylphosphine, the reaction was clean and no byproduct **3** was formed. However, this ligand negatively affected the desired regioselectivity (entry 1). With either biaryl ligands (**7**−**10**) or *t*-Bu_3P, the unwanted amination reaction occurred to a large extent (entries 2, 6−9). With D^{t}BPF (**6**) as the ligand, several bases, both inorganic and organic, were evaluated. K_2CO_3 proved to be the best choice with regards to reaction rate, reaction profile, and regioselectivity. Further optimization indicated that lower temperature or nonpolar solvents had little influence in reducing formation of side product **3**. Eventually,

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(6) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 412.

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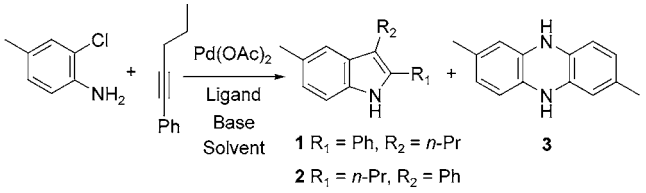
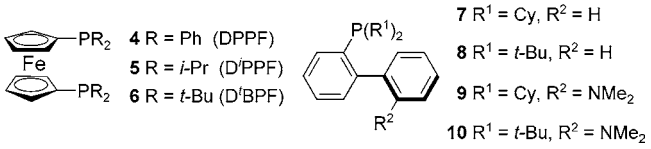
(9) Application of this double-amination reaction to the preparation of dihydrophenazine and analogues is under current investigation.

Table 1. Effect of Ligand on the Indolization of Alkynes with 2-Chloroanilines[a]





entry	ligand	*t* (h)/conversion (%)	**1**:**2**[b]	**3** (%)[c]
1	Cy_3P	14/>99	67:33	0
2	*t*-Bu_3P	4/>99	76:14	79
3	**4**	15/50	80:20	20[d]
4	**5**	14/90	79:21	10
5a	**6**	4/>99	91:9	19
5b	**6**	18/>99	91:9	8[e]
6	**7**	4/>99	71:29	21
7	**8**	4/>99	80:20	55
8	**9**	4/95	72:28	29
9	**10**	4/>99	84:16	62

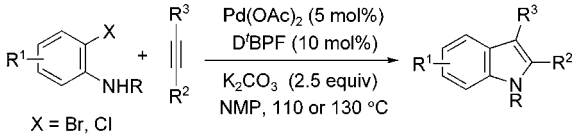
[a] All reactions were carried out with aniline (1.0 mmol), alkyne (1.2 mmol), $Pd(OAc)_2$ (5 mol %), ligand (Pd/L 1/4), and K_2CO_3 (2.5 equiv), in NMP (2 mL). [b] Ratios were determined by HPLC at $\lambda = 228$ nm. [c] Yields were determined by HPLC at $\lambda = 248$ nm. [d] Multiple insertion byproduct. [e] Reaction was run at 0.1 M concentration of aniline (instead of 0.5 M).

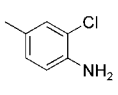
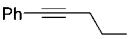
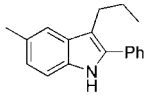
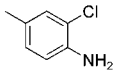
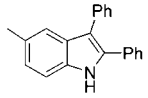
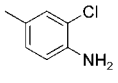
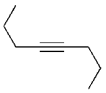
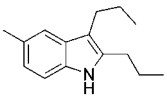
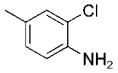
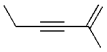
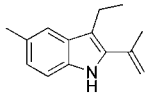
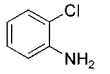
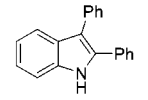
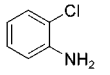
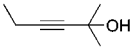
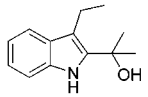
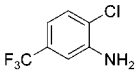
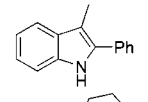
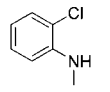
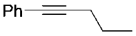
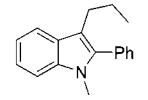
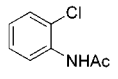
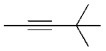
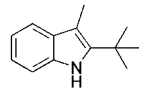
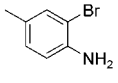
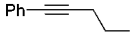
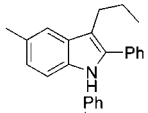
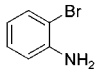
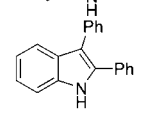
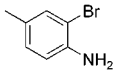
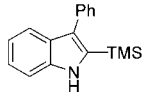
it was found that this problem could be alleviated by simply using a more dilute solution. Only 8% of amination byproduct **3** was observed when the reaction was performed at 0.1 M concentration in NMP under otherwise similar conditions (entry 5b). This point has clear mechanistic implications, which are being actively investigated.

To illustrate the embodiments of this methodology, several indoles were synthesized using D*t*BPF as the ligand (Table 2).[10] Good regioselectivities and yields were achieved in all the examples. It is interesting to observe that under the optimal conditions except using Cy_3P as the ligand, the reaction of 4-methyl-2-chloroaniline and diphenylacetylene

(10) Preparation of 5-methyl-2-phenyl-3-propyl-1*H*-indole (entry 1, Table 2) as the representative experimental procedure: $Pd(OAc)_2$ (11 mg, 0.05 mmol), 1,1′-bis(di-*tert*-butylphosphino)ferrocene (47 mg, 0.1 mmol), and potassium carbonate (346 mg, 2.5 mmol) were charged to an oven-dried reaction vial. The vial was purged with argon. 2-Chloro-4-methylaniline (123 μL, 1 mmol), 1-pentyl-1-pentyne (192 μL, 1.2 mmol), and NMP (2 mL) were added via syringe. The reaction was heated to 130 °C, while stirring and monitoring by HPLC. The reaction was complete after 4 h. The ratio of the regioisomers was 91:9. The mixture was filtered through a pad of Celite. The Celite was washed with ethyl acetate. The organic phase was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to give a brown residue. The product was purified via column chromatography: yield 76%; off-white solid; mp 120−123 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.60−7.40 (m, 5H), 7.34−7.29 (m, 1H), 7.21−7.18 (m, 1H), 7.01−6.98 (m, 1H), 2.80 (t, $J = 7.0$ Hz, 2 H), 2.48 (s, 3H), 1.75−1.64 (m, 2H), 0.86 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.31, 134.27, 133.67, 129.62, 128.81, 128.67, 127.92, 127.38, 123.78, 119.05, 113.60, 110.48, 26.80, 24.30, 21.66, 14.53; LC-MSD (API-ES, positive) $m/z = 250$ (M + H$^+$); HR-MS calcd 249.1517, found 249.1515.

Table 2. Synthesis of 2,3-Disubstituted Indoles via Pd-Catalyzed Heteroannulation of Internal Alkynes with 2-Chloro- or Bromoanilines[a]



entry	aniline	alkyne	major isomer	yield[b] (Ratio[c])
1				76 (91:9)
2				86 (n/a)[d]
3				82 (n/a)
4				60 (>99:1)
5				97 (n/a)[d]
6				60 (>99:1)
7				65 (89:11)
8				68 (91:9)
9				73[e] (>99:1)
10				86% (78:22)
11				99% (n/a)[d]
12				63% (>99:1)[f]

[a] All reactions were carried out with aniline (1.0 mmol), alkyne (1.2 mmol), $Pd(OAc)_2$ (5 mol %), D*t*BPF (6 mol %), and K_2CO_3 (2.5 equiv), in NMP (10 mL). [b] Isolated yield of major isomer. [c] Ratios were determined by HPLC at $\lambda = 228$ nm. [d] Cy_3P as ligand. [e] Yield is based on the recovery of the starting material. [f] $KHCO_3$ as base.

afforded the desired indole product in 86% isolated yield (entry 2). Thus, this ligand can safely be employed if regiochemistry issues are not a concern. A similar reaction with 2-iodoaniline produced no desired indole product as reported in Larock's previous work.[3] Use of dialkyl acetylenes led to a clean reaction (entry 3).

Reactions of different anilines with a variety of alkynes afforded the desired products. Reaction of a trimethylsilyl-substituted acetylene with 2-chloroaniline did not yield satisfactory results, due to desilylation of the product under the reaction conditions. In this case, 2-bromoaniline gave the desired product in better yield (entry 12).

Although we have demonstrated that D^{t}BPF is a more generally applicable ligand than the other ones examined, one should keep in mind that, as in most palladium-catalyzed reactions, fine-tuning of individual reaction conditions may be necessary in order to obtain the optimal result for each substrate.

In summary, we have developed the first palladium-catalyzed indolization of 2-bromo- or 2-chloroanilines with internal alkynes by proper choice of ligand, base, solvent, and concentration. Our results illustrate the concept that by careful choice of ligand, a novel, multistep, metal-catalyzed transformation can be successfully developed. Further studies to expand the scope of this methodology are in progress.

Acknowledgment. We acknowledge Professors Scott Denmark (University of Illinois at Urbana) and Peter Wipf (University of Pittsburgh) for helpful suggestions.

Supporting Information Available: Reaction procedures and characterization of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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