Indole Synthesis

DOI: 10.1002/ange.200703763

Palladium-Catalyzed Aryl Amination–Heck Cyclization Cascade: A One-Flask Approach to 3-Substituted Indoles

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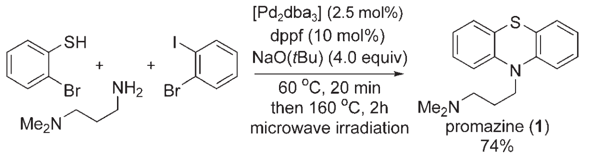
The indole nucleus is found in numerous biologically important natural products and synthetic drugs. Indoles with carbon substituents in the 3-position are of pivotal importance in central-nervous-system (CNS) drugs, particularly for antipsychotics.[1] Although many indole syntheses are known, a truly general approach has yet to be discovered.[2,3] Herein we report a route to 3-substituted indoles from *ortho*-dihalobenzenes and allylic amines with two distinct steps: intermolecular aryl amination and Heck cyclization. The aryl amination reaction was first reported by Kondratenko et al.[4] and has been developed extensively since the seminal work by Louie and Hartwig, and by Buchwald and co-workers.[5] The aryl amination has also been used in indole chemistry. Buchwald and co-workers used the Fischer indole synthesis to close the heterocyclic ring,[6] whereas Ackermann and co-workers used either a Sonogashira reaction or C–H bond activation.[7] The combination of a Heck reaction and a catalytic C–N coupling reaction was reported by Edmondson et al.[8] and by Kondo and co-workers.[9]

During our recent studies towards the development of a three-component approach to promazine (**1**; Scheme 1),[10] we observed that the inclusion of allylamine led to a complex mixture of products, among which was 3-methylindole (**3**; ca. 5%). Hegedus and co-workers, Terpko and Heck, and Mori et al. reported the synthesis of **3** and related compounds by intramolecular Heck reactions between 1977 and 1980.[11–13]



Scheme 1. One-flask approach to promazine (**1**). dba = dibenzylideneacetone, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene.

Following this serendipitous finding, we evaluated a selection of easily handled ligands for the one-flask synthesis of **3** (Figure 1).[14] We observed the best result with dppf;[15] davephos[16] and dpephos[17] were less efficient. The product **2** of aryl amination at the position with the iodide substituent dominated with binap[18] and xantphos.[19] The use of x-phos,[16] $PtBu_3$,[20] or N-heterocyclic carbenes[21] led to complex product mixtures. With the ligands PPh_3 and $P(o\text{-}tol)_3$, bromobenzene was obtained in approximately 50%

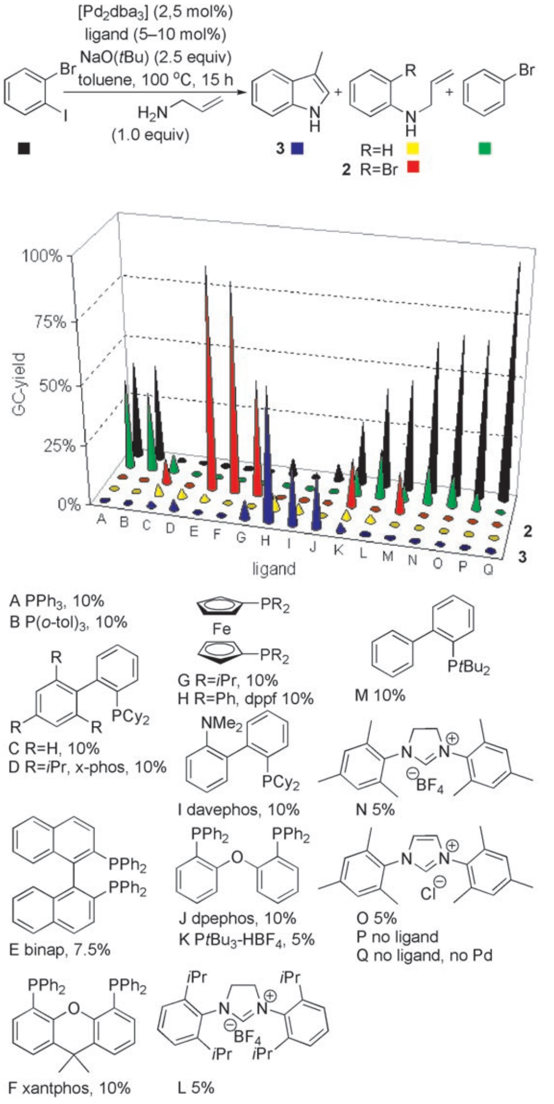


Figure 1. Ligand screening. Reactions were performed on a 0.33-mmol scale in toluene (2 mL) in closed vials. Cy = cyclohexyl.

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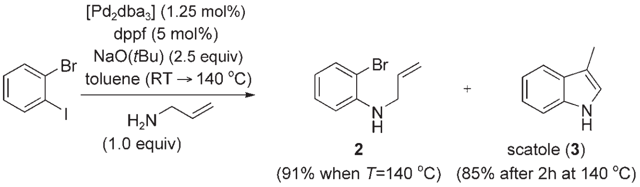
yield. Control experiments confirmed the importance of the ligand and the catalytic nature of the reaction.

The yield of **3** was improved from 59 to 85 % by starting the reaction at room temperature, heating to 140°C over about 0.5 h, and then heating at 140°C for 2 h. When [Pd$_2$dba$_3$] was replaced with Pd(OAc)$_2$, the yield decreased to 45 %, whereas [Pd(dppf)Cl$_2$]–CH$_2$Cl$_2$ did not promote the desired reaction at all. The Heck reaction did not proceed with K$_3$PO$_4$ as the base, and the yield decreased to 60 % with Cs$_2$CO$_3$.

On the basis of well-known intramolecular Heck approaches to indoles and related compounds[11–13,22] and the use of allylamine as an ammonia equivalent in aryl amination reactions,[23] it seemed plausible that the synthesis of **3** proceeds through an initial aryl amination. Indeed, the isolation of the aniline **2** indicated that a clean stepwise reaction takes place (Scheme 2). In accordance with this observation, all substrates that could react to give regioisomeric products were transformed only into the isomer that results from aryl amination at the position with the iodide substituent.

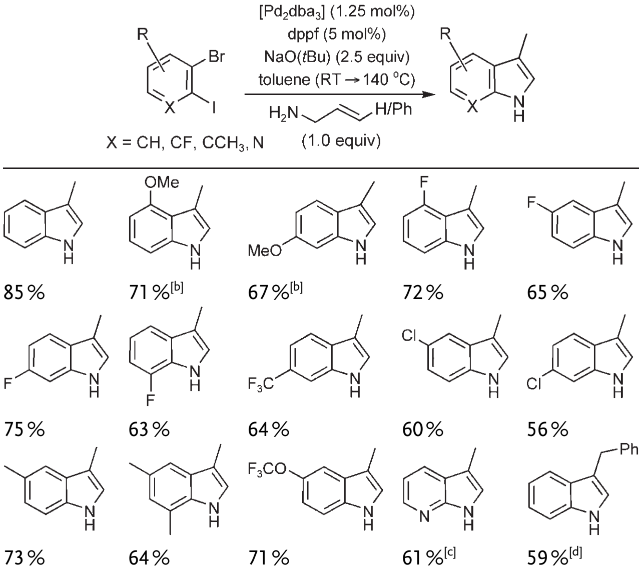


Scheme 2. The isolation of **2** suggests a stepwise reaction. The aniline **2** was obtained in 91 % yield when the reaction was stopped after 0.5 h (when the temperature reached 140°C), whereas scatole (**3**) was obtained in 85 % yield after 2 h at 140°C.

The reaction proceeded well when electron-withdrawing or electron-donating groups were present on the aromatic ring of the substrate, and substitution *ortho* to the iodine or bromine substituent was possible (Table 1). The 3-substituted indoles were formed in yields ranging from 56 to 85 %, which correspond to yields of 75–92 % per bond formed. The scope of the reaction could be extended to the synthesis of an azaindole when 2,3-dichloropyridine was used.[24] No azaindole was formed from other dihalogenated pyridines. The reaction was also applicable to simple functionalized allylic amines, as exemplified by the formation of 3-benzylindole in good yield. The desired product was not formed from the nonaflate derived from 2-bromophenol, and the use of 2-iodobromobenzenes with an additional bromine substituent led to complex product mixtures. Attempts to prepare chain-elongated, functionalized indoles were largely unsuccessful.[24]

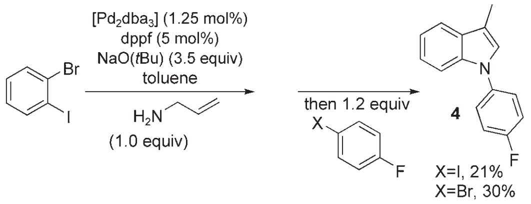
Although the regiochemistry of the reaction was controlled by the selective amination of the aryl iodide, **3** could also be prepared from 2-bromochlorobenzene (in 66 % yield), 2-chloroiodobenzene (47 %), 1,2-dichlorobenzene (43 %), 1,2-dibromobenzene (70 %), and 1,2-diiodobenzene (15 %). Thus, the preparation of functionalized products is limited by the accessibility of the corresponding 1,2-dihalo arenes. The reaction could be scaled up to produce **3** in a quantity of 10 g (76 % yield) from 2-bromoiodobenzene by treatment with allylamine in the presence of [Pd$_2$dba$_3$] (1.25 mol %) in *p*-xylene at reflux for 5 h.

Table 1: Synthesis of 3-substituted indoles.[a]



[a] Reactions were performed on a 1.5-mmol scale in dry toluene (4 mL) in closed vials. [b] [Pd$_2$dba$_3$]: 2.5 mol %; dppf: 10 mol %. [c] 2,3-Dichloropyridine was used as the substrate. (No product was observed in the absence of the catalyst). [d] (*E*)-3-Phenylallylammonium chloride was used as the allylic substrate in the presence of 3.5 equivalents of NaO*t*Bu.

It was possible to functionalize **3** through in situ N arylation by adding either an aryl iodide or an aryl bromide after the completion of the first two steps (Scheme 3).[25] One C–C and two C–N bonds were formed in this way in approximately 60 % yield per step. For comparison, **3** can be coupled to 4-bromofluorobenzene in 62 % yield under conditions described by Hartwig and co-workers ([Pd$_2$dba$_3$] (1.25 mol %), dppf (5 mol %), 140°C).[26]



Scheme 3. In situ N arylation.

In summary, we have developed a novel approach to indoles on the basis of sequential aryl amination and Heck cyclization reactions in a one-flask operation with a single catalyst.

Experimental Section

General procedure: [Pd$_2$dba$_3$] (1.25 mol %), dppf (5 mol %), NaO(*t*Bu) (3.75 mmol), the aryl halide (1.5 mmol), toluene (4 mL), and allylamine (1.5 mmol) were placed in a 7-mL screw-cap vial. The resulting mixture was heated from room temperature to 140 °C over approximately 0.5 h and then stirred at 140 °C for 5 h.

Received: August 16, 2007

Keywords: amination · Heck reaction · indoles · palladium · phosphane ligands

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[14] All chemicals were weighed out in air, and no precautions were taken to exclude air from the reaction mixture. Abbreviations: binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl; davephos = 2-dicyclohexylphosphanyl-2′-(*N,N*′-dimethylamino)biphenyl; dpephos = bis(2-diphenylphosphanyl)ether; xantphos = 4,5-bis(diphenylphosphanyl)-9,9-dimethylxanthene; x-phos = 2-dicyclohexylphosphanyl-2′,4′,6′-triisopropyl-1,1′-biphenyl.

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[24] See the Supporting Information for experimental details.

[25] For X = I, the reaction mixture was heated from room temperature to 160 °C, then maintained at 160 °C for 1 h. The aryl iodide for N arylation of the indole was then added, and the mixture was stirred at 160 °C for an additional 16 h. For X = Br, the reaction mixture was heated from room temperature to 140 °C, then maintained at 140 °C for 2 h. Further [Pd$_2$dba$_3$] (1.25 mol %) and dppf (5 mol %) were then added, as well as the aryl bromide for N arylation of the indole, and the mixture was stirred at 140 °C for an additional 18 h.

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