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Palladium-catalyzed synthesis of indoles *via* ammonia cross-coupling–alkyne cyclization†

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The synthesis of indoles *via* the metal-catalyzed cross-coupling of ammonia is reported for the first time; the developed protocol also allows for the unprecedented use of methylamine or hydrazine as coupling partners. These Pd/Josiphos-catalyzed reactions proceed under relatively mild conditions for a range of 2-alkynylbromoarenes.

The functionalization of ammonia by use of transition-metal catalysis is emerging as a useful means of streamlining the synthesis of nitrogen-containing organic molecules.¹ Although the inexpensive and readily available nature of ammonia makes it an attractive nitrogen source, the use of ammonia presents considerable difficulties in most metal-catalyzed reactions, especially in comparison to other classes of substituted amines. Despite considerable research efforts directed towards the metal-catalyzed synthesis of indoles and related heterocycles,² the direct use of ammonia in such transformations has, to the best of our knowledge, not been reported. Indeed, the Pd-catalyzed cross-coupling of ammonia and aryl (pseudo)halides has only recently been developed,^{1,3} and such catalyst systems generally lack the activity and versatility that can be achieved in the arylation of primary or secondary amines.⁴ Given the importance of the indole framework in molecules of biological relevance,^{2,5} and inspired by the work of Ackermann in the field of tandem arylation–hydroamination involving primary amines or amides,⁶ we sought to develop a tandem ammonia cross-coupling/cyclization protocol to deliver NH-indoles. We report herein the first Pd-catalyzed synthesis of 2-arylindoles from ammonia and bromophenylacetylenes. Extension of this methodology enables the utilization of methylamine as a substrate, while the use of hydrazine hydrate allows for the preparation of N-aminoindoles.

We envisioned the synthesis of 2-substituted NH-indoles could be achieved by the union of the Pd-catalyzed cross-coupling of ammonia, followed by base-mediated cyclization of the resultant 2-aminophenylacetylene.⁷ After screening a range of conditions, we found mixtures of [Pd(cinnamyl)Cl]₂/Mor-DalPhos^{3f,8} to yield the desired 2-arylindole **2a** in a

maximum of 44% yield after 18 h using 5 mol% Pd and 3 equivalents of KO^tBu at 90 °C.^{9,10}

In an effort to develop a more effective catalytic process, active and commonly employed ligands for Pd-catalyzed amination reactions were screened (Table 1). While ligands such as *t*Bu-DavePhos, S-Phos, X-Phos, P^tBu₃, D^tPPF, Q-Phos, TrippyPhos, IPr, and selected CataCXium ligands gave poor results, Josiphos (CyPF^tBu) provided the desired indole product in 89% GC yield. Josiphos has been shown by Hartwig and co-workers to be a highly effective ligand for amine cross-coupling,^{4b,11} including ammonia.^{3a–c}

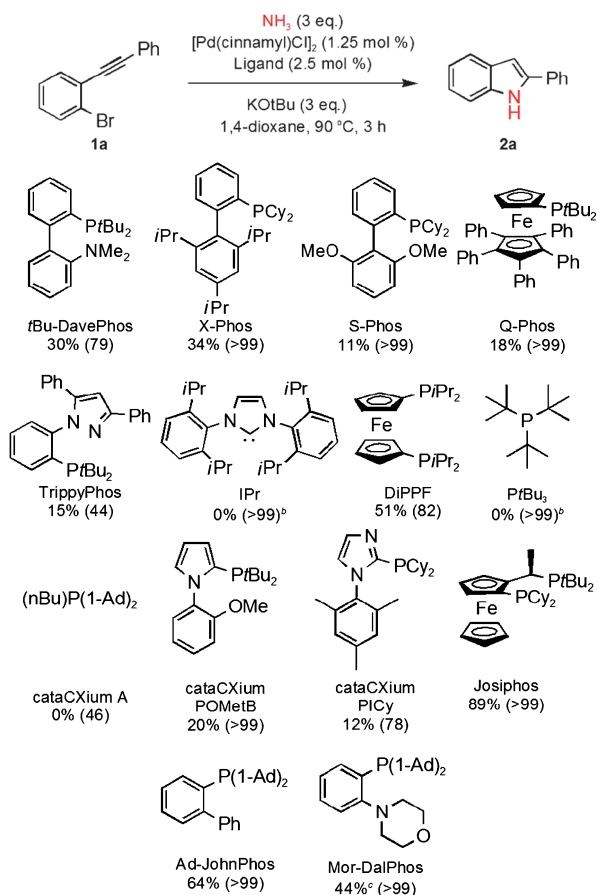
Using Josiphos as the optimal ligand, variation of the standard reaction conditions (Table 1) demonstrated the importance of using KO^tBu.¹⁰ KOH, Cs₂CO₃ or NaO^tBu failed to deliver **2a** in high yields, but in some cases delivered the uncyclized aniline; for example, 2-(phenylethynyl)aniline **2a'** could be isolated in 89% yield when using NaO^tBu (2 equiv).¹² The use of a lower catalyst loading (0.5 mol% [Pd(cinnamyl)Cl]₂) resulted in a lower yield of the desired product (56% yield by GC), although full conversion of the starting material was still observed. Aryl chlorides or tosylates were not suitable substrates. While [Pd(cinnamyl)Cl]₂ provided the highest yield of **2a**, other Pd-sources could be employed such as Pd(dba)₂ or Pd[P(o-tolyl)₃]₂ (73% and 83% GC yield, respectively).

Having identified a suitable catalyst system for the direct synthesis of 2-phenylindole (**2a**) from ammonia using commercially available stock solutions (0.5 M in 1,4-dioxane), the scope of the reaction was explored with various 2-bromophenylalkynyl substrates (Table 2), which were generated *via* Sonogashira coupling reactions.¹⁰

A variety of substituents on the remote arene ring of the alkyne were tolerated; for instance, heterocycle-containing examples such as 3-thiophene (**2c**) and 3-pyridine (**2k**) proceeded in good yields (85% and 61%), as did phenylacetylenes with alkyl, ether, or halogen groups. The reaction appears relatively insensitive to *ortho*-substitution of the arene ring at the 2-position, as compounds **1i**, **1j**, **1n**, and **1o** formed the corresponding 2-arylindoles in moderate to good yields. An indole featuring an NHBoc-group (**2g**) could be prepared without complication from the additional amine functionality in 63% yield. We observed the *tert*-butyldimethylsilyl-protected bromoalkyne substrate **1i** to undergo concurrent deprotection to yield the phenol-containing product **2i**, albeit in slightly reduced yield (49%), while use of a benzyl

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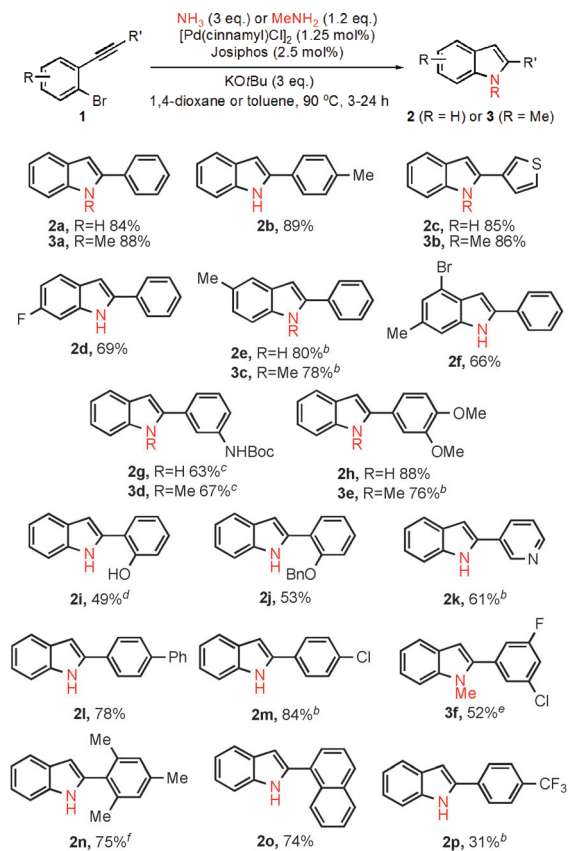
Table 1 Ligand screen for the Pd-catalyzed synthesis of 2-phenylindole from ammonia and 2-bromophenylacetylene^a

^a 0.1 mmol scale, $[\text{Pd}]/\text{L} = 1:1$, $\text{NH}_3 = 0.3$ mmol, $\text{KOtBu} = 0.3$ mmol, 90 °C in 1,4-dioxane. Conversions of **1a** in parentheses and yields of **2a** are based on calibrated GC data using dodecane as an internal standard. ^b Starting material consumed; product not observed by GC. ^c Isolated yield using 5 mol% Pd after 18 h reaction time.

protecting group gave the corresponding indole **2j** in 53% yield with the protecting group intact.

Brief examination of the reactivity of substrates with substitution on the bromoarene resulted in 4-, 5-, or 6-substituted indoles in generally good yields, including an example containing 1,6-dibromo-substitution to yield the mono-cross-coupled product **2f**—a viable precursor for further metal-catalyzed cross-coupling. While for convenience we employed an inert atmosphere glovebox for the setup of most catalytic experiments, use of a glovebox is not necessary. For example, in the reaction of **1a** the catalyst components and base could be weighed out in air and placed under dinitrogen prior to introduction of the reactants and solvent to give **2a** in 84% yield by GC.

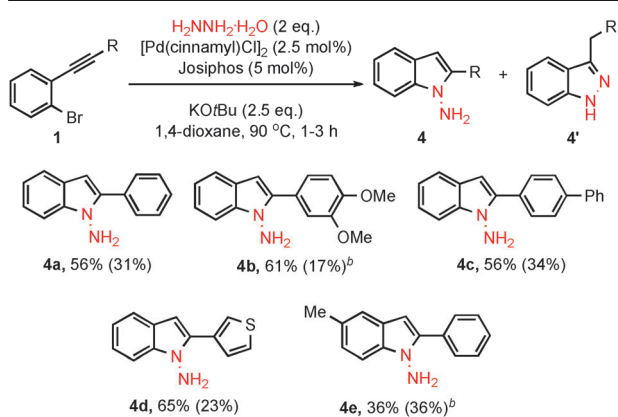
Some limitations to the current method were established during substrate scope studies. Heterocyclic substrates with the heteroatom *ortho* to the bromo or alkyne group gave low yields. The reaction appears limited to aryl-substituted alkyne groups, as replacement at this position (R' , Table 2) with silyl (TMS), alkyl (propyl or hexyl) or alkenyl groups resulted in degradation of the starting material without significant product formation.

Table 2 Scope of the Pd-catalyzed cross-coupling of ammonia or methylamine with 2-alkynylbromoarenes^a

^a 0.5 mmol scale, $[\text{Pd}]/\text{L} = 1:1$, $\text{NH}_3 = 1.5$ mmol or $\text{MeNH}_2 = 0.6$ mmol, $\text{KOtBu} = 1.5$ mmol, 90 °C in 1,4-dioxane (NH indoles, 3 h reaction time) or in toluene (NMe indoles, 16–24 h). Yields are of isolated products. ^b 5 mol% Pd used. ^c **2g** = 3.5 eq. base, **3d** = 4.0 eq. base. ^d From TBS-protected alcohol substrate. ^e 4.0 eq. Cs_2CO_3 , 3.0 eq. KOtBu , 48 h. ^f 6.0 eq. KOtBu , 110 °C, 60 h.

Given the success of the Pd/Josiphos system to deliver NH-indoles from ammonia, we sought to expand the scope of the reaction to other challenging amine partners. Methylamine¹³ could be employed to directly prepare N-methylated indoles, with yields similar to that of ammonia for select substrates (Table 2, **3a–3f**). Notably, dihalogenated indole **3f** was obtained using a two-step one-pot procedure, in which amine cross-coupling was first achieved by using Cs_2CO_3 as base followed by treatment with KOtBu to mediate cyclization to indole. These results, combined with the comprehensive studies of Hartwig,^{3a–c,4b,11} suggest that Pd/Josiphos mixtures may have broad-ranging scope for tandem cross-coupling/cyclization reactions to yield N-functionalized indoles.

We recently reported the first example of Pd-catalyzed hydrazine cross-coupling to generate aryl hydrazines^{8a} and were pleased to find that hydrazine hydrate could be employed to generate NH_2 -substituted aminoindoles from 2-bromophenylalkynes (Table 3).^{14,15} Under the standard conditions using 5 mol% Pd, the N-aminoindole **4a** was formed in 56% yield, along with the indazole product **4a'** (31%) after 1 h. Attempts to bias the product ratio by altering the base, solvent, or

Table 3 Pd-catalyzed cross-coupling of hydrazine with 2-alkynyl-bromoarenes^a

^a 0.5 mmol scale, $[\text{Pd}]/\text{L} = 1:1$, $\text{N}_2\text{H}_4\cdot\text{H}_2\text{O} = 1.0$ mmol, $\text{KOtBu} = 1.25$ mmol, 90 °C in 1,4-dioxane; isolated yield of **4** (**4'** in parentheses).

^b ¹H NMR yield of **4** (**4'**) relative to 1,3,5-trimethoxybenzene.

including additives (CuCl_2 or Ag_2CO_3) were not successful. A brief survey of additional substrates proved other N-aminoindoles could be formed in moderate yields (36–65%). Given the difficulties associated with the use of hydrazine as a nitrogen-source in cross-coupling reactions, we view this transformation as representing a significant contribution towards the establishment of direct routes to hydrazine-containing heterocycles.

In summary, we have developed a straightforward method for the synthesis of 2-arylaminoindoles directly from ammonia through a tandem cross-coupling/alkyne amination sequence. Additionally, the challenging amine partners methylamine and hydrazine have been shown to form indole structures using the same catalyst system. We believe that this protocol represents an important contribution towards the development of a more direct and benign synthesis of the ubiquitous indole substructure, and continued improvements to the described reaction should engender the process as a viable alternative to more traditional syntheses of NH-, NMe- and N-aminoindoles.

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