ChemComm

Cite this: *Chem. Commun.*, 2011, **47**, 6936–6938

www.rsc.org/chemcomm

COMMUNICATION

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

Pamela G. Alsabeh, Rylan J. Lundgren, Lauren E. Longobardi and Mark Stradiotto*

Received 1st April 2011, Accepted 19th April 2011
DOI: 10.1039/c1cc11874a

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 relevence,[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*t*Bu 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*t*Bu$_3$, D*i*PPF, Q-Phos, TrippyPhos, IPr, and selected CataCXium ligands gave poor results, Josiphos (CyPF*t*Bu) 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*t*Bu.[10] KOH, Cs_2CO_3 or NaO*t*Bu 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*t*Bu (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 $Pd[P(o\text{-}tolyl)_3]_2$ (73% and 83% GC yield, respectively).

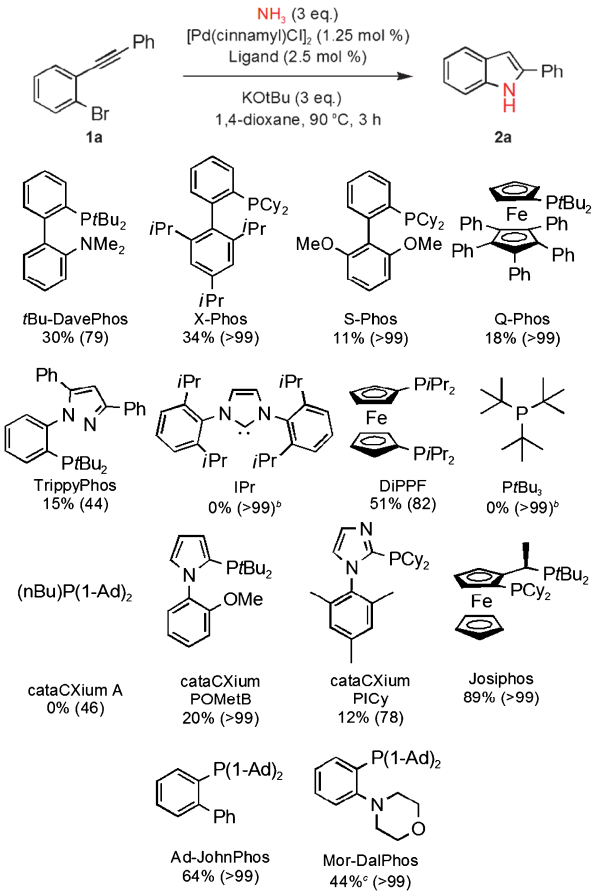
Having identified a suitable catalyst system for the direct synthesis of 2-phenylindole (**2a**) from ammonia using commercially available stock solutions (0.5 M in 1,4-dioxane), the scope of the reaction was explored with various 2-bromophenylalkynyl substrates (Table 2), which were generated *via*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

Department of Chemistry, Dalhousie University, Halifax, Nova Scotia, B3H 4J3, Canada. E-mail: mark.stradiotto@dal.ca; Fax: 1 902 494 1310; Tel: 1 902 494 7190

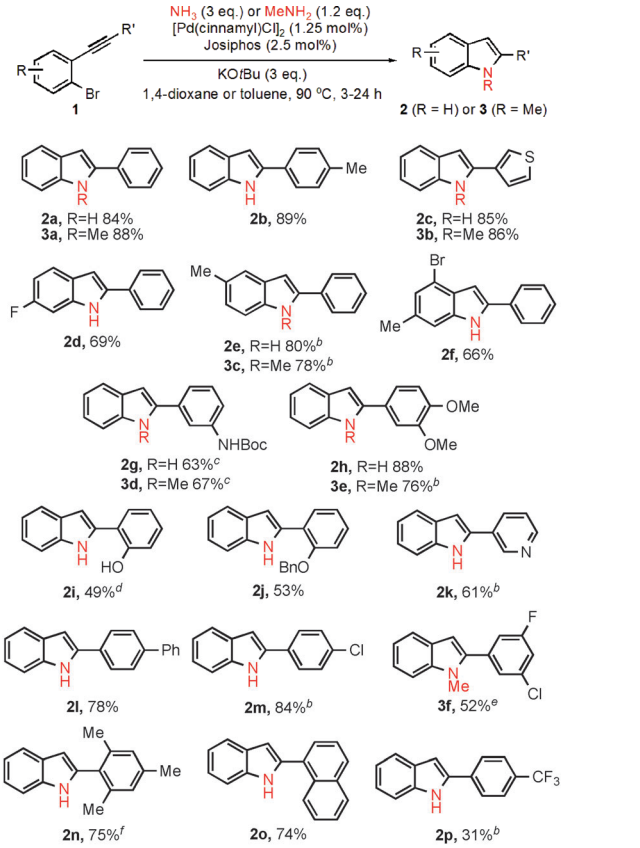
† Electronic supplementary information (ESI) available: Experimental procedures and NMR spectral data. See DOI: 10.1039/c1cc11874a

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



[a] 0.1 mmol scale, [Pd]/L = 1 : 1, NH_3 = 0.3 mmol, KO*t*Bu = 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.

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



[a] 0.5 mmol scale, [Pd]/L = 1 : 1, NH_3 = 1.5 mmol or $MeNH_2$ = 0.6 mmol, KO*t*Bu = 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. KO*t*Bu, 48 h. [f] 6.0 eq. KO*t*Bu, 110 °C, 60 h.

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

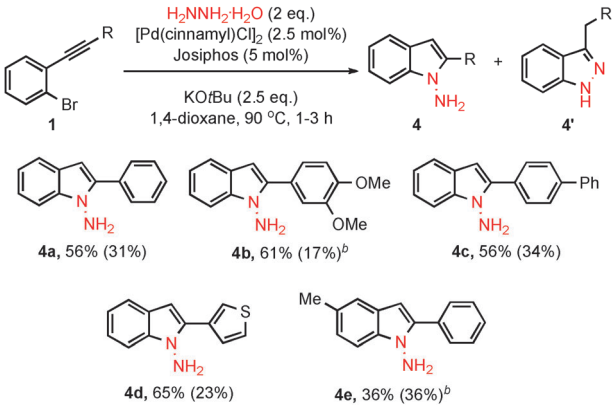
Brief examination of the reactivity of substrates with substitution on the bromoarene resulted in 4, 5, or 6-substituted indoles in generally good yields, including an example containing 1,6-dibromo-substitution to yield the mono-cross-coupled product **2f**—a viable precursor for further metal-catalyzed 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.

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. Methylamine[13] 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 KO*t*Bu 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-alkynylbromoarenes[a]



[a] 0.5 mmol scale, [Pd]/L = 1 : 1, $N_2H_4{\cdot}H_2O$ = 1.0 mmol, KO*t*Bu = 1.25 mmol, 90 °C in 1,4-dioxane; isolated yield of **4** (**4′** in parentheses). [b] ^{1}H 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-arylindoles 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.

Acknowledgment is made to the NSERC of Canada, and Dalhousie University for their support of this work. Solvias is acknowledged for the gift of the Josiphos ligand.

Notes and references

1 For recent reviews see: (*a*) J. L. Klinkenberg and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2011, **50**, 86; (*b*) Y. Aubin, C. Fischmeister, C. M. Thomas and J.-L. Renaud, *Chem. Soc. Rev.*, 2010, **39**, 4130; (*c*) J. I. van der Vlugt, *Chem. Soc. Rev.*, 2010, **39**, 2302.

2 (*a*) J. E. R. Sadig and M. C. Willis, *Synthesis*, 2011, 1; (*b*) G. R. Humphrey and J. T. Kuethe, *Chem. Rev.*, 2006, **106**, 2875; (*c*) S. Cacchi and G. Fabrizi, *Chem. Rev.*, 2005, **105**, 2873.

3 (*a*) J. L. Klinkenberg and J. F. Hartwig, *J. Am. Chem. Soc.*, 2010, **132**, 11830; (*b*) G. D. Vo and J. F. Hartwig, *J. Am. Chem. Soc.*, 2009, **131**, 11049; (*c*) Q. Shen and J. F. Hartwig, *J. Am. Chem. Soc.*, 2006, **128**, 10028; (*d*) D. S. Surry and S. L. Buchwald, *J. Am. Chem. Soc.*, 2007, **129**, 10354; (*e*) T. Schulz, C. Torborg, S. Enthaler, B. Schäffner, A. Dumrath, A. Spannenberg, H. Neumann, A. Börner and M. Beller, *Chem.–Eur. J.*, 2009, **15**, 4528; (*f*) R. J. Lundgren, B. D. Peters, P. G. Alsabeh and M. Stradiotto, *Angew. Chem., Int. Ed.*, 2010, **49**, 4071.

4 For selected reviews see: (*a*) D. S. Surry and S. L. Buchwald, *Chem. Sci.*, 2011, **2**, 27; (*b*) J. F. Hartwig, *Organotransition Metal Chemistry*, University Science Books, Sausalito, 2010, p. 907; (*c*) J. F. Hartwig, *Acc. Chem. Res.*, 2008, **41**, 1534.

5 For selected examples see: (*a*) F.-R. Alexandre, A. Amador, S. Bot, C. Caillet, T. Convard, J. Jakubik, C. Musiu, B. Poddesu, L. Vargiu, M. Liuzzi, A. Roland, M. Seifer, D. Standring, R. Storer and C. B. Dousson, *J. Med. Chem.*, 2011, **54**, 392; (*b*) K.-H. Lim, O. Hiraku, K. Komiyama, T. Koyano, M. Hayashi and T.-S. Kam, *J. Nat. Prod.*, 2007, **70**, 1302.

6 Selected reports: (*a*) L. Ackermann, R. Sandmann and M. V. Kondrashov, *Synlett*, 2009, 1219; (*b*) L. Ackermann, R. Sandmann, M. Schinkel and M. V. Kondrashov, *Tetrahedron*, 2009, **65**, 8930; (*c*) L. T. Kaspar and L. Ackermann, *Tetrahedron*, 2005, **61**, 11311; (*d*) L. Ackermann, *Org. Lett.*, 2005, **7**, 439; (*e*) L. Ackermann, S. Barfüßer and H. K. Potukuchia, *Adv. Synth. Catal.*, 2009, **351**, 1064.

7 (*a*) A. L. Rodriguez, C. Koradin, W. Dohle and P. Knochel, *Angew. Chem., Int. Ed.*, 2000, **39**, 2488; (*b*) C. Koradin, W. Dohle, A. L. Rodriguez, B. Schmid and P. Knochel, *Tetrahedron*, 2003, **59**, 1571; (*c*) A. H. Stoll and P. Knochel, *Org. Lett.*, 2008, **10**, 113; (*d*) R. Sanz, V. Guilarte and M. P. Castroviejo, *Synlett*, 2008, 3006.

8 (*a*) R. J. Lundgren and M. Stradiotto, *Angew. Chem., Int. Ed.*, 2010, **49**, 8686; (*b*) K. D. Hesp, R. J. Lundgren and M. Stradiotto, *J. Am. Chem. Soc.*, 2011, **133**, 5194.

9 The low yields of **2a** were the result of hydrodehalogenation as well as conversion to other unidentified products. In the course of this study we found that the presence of the alkyne functionality slowed catalytic turnover and promoted the reduction of the haloarene substrate[10].

10 See the ESI† for additional details.

11 (*a*) E. Avaro and J. F. Hartwig, *J. Am. Chem. Soc.*, 2009, **131**, 7858; (*b*) Q. Shen and J. F. Hartwig, *Org. Lett.*, 2008, **10**, 4109; (*c*) M. A. Fernández-Rodríguez, Q. Shen and J. F. Hartwig, *Chem.–Eur. J.*, 2006, **12**, 7782; (*d*) Q. Shen, S. Shekhar, J. P. Stambuli and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2005, **44**, 1371.

12 Beller and co-workers[3e] have reported the cross-coupling of a 2-alkynyl substrate to yield the corresponding aniline in modest yield.

13 For some examples of the use of methylamine in Buchwald–Hartwig amination, see: (*a*) B. P. Fors and S. L. Buchwald, *J. Am. Chem. Soc.*, 2010, **132**, 15914; (*b*) R. J. Lundgren, A. Sappong-Kumankumah and M. Stradiotto, *Chem.–Eur. J.*, 2010, **16**, 1983; (*c*) B. P. Fors, D. A. Watson, M. R. Biscoe and S. L. Buchwald, *J. Am. Chem. Soc.*, 2008, **130**, 13552.

14 Disubstituted hydrazines have been employed in tandem cross-coupling/cyclization reactions to yield either indazoles or N-aminoindoles, although the substitution pattern of the hydrazine substrates precludes the formation of indole/indazole mixtures, see: (*a*) N. Halland, M. Nazaré, O. R'kyek, J. Alonso, M. Urmann and A. Lindenschmidt, *Angew. Chem., Int. Ed.*, 2009, **48**, 6879; (*b*) N. Halland, M. Nazaré, J. Alonso, O. R'kyek and A. Lindenschmidt, *Chem. Commun.*, 2011, **47**, 1042.

15 For a report concerning Cu-catalyzed cross-coupling/cyclization of substituted hydrazines to yield either pyrroles or pyrazoles see: R. Martín, M. Rodríguez Rivero and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2006, **45**, 7079.

