Heterocycles

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# Palladium-Catalyzed Coupling of *ortho*-Alkynylanilines with Terminal Alkynes Under Aerobic Conditions: Efficient Synthesis of 2,3-Disubstituted 3-Alkynylindoles**

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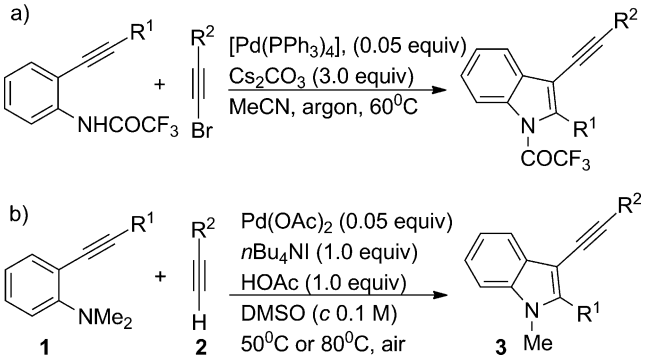
*Dedicated to Professor Lutz F. Tietze on the occasion of his 70th birthday*

The indole nucleus is an ubiquitous heterocycle found in many bioactive natural products, pharmaceuticals, and agrochemicals.[1] The synthesis and functionalization of indoles have attracted chemists for over a century and remain an active research area.[2] In this context, transition-metal-catalyzed transformations, notably the indole synthesis by Cacchi and co-workers[3] and the heteroannulation by Larock et al.,[4] among others,[5] have had a major impact on the field.

The 2- and 3-alkynylindoles are interesting synthetic targets because of their potential biological activities[6] and possibilities they can offer for further structural elaboration.[7] To access these compounds, several metal-catalyzed transformations have been developed, including a) the classic Sonogashira coupling using halogenated indoles,[7] b) direct C–H functionalization of indoles with alkynylhalides (pseudo halides)[8] or hypervalent iodine reagents,[9] and c) dehydrogenative coupling of indoles and terminal alkynes.[10] While these methods focused on the functionalization of the indole ring,[11] the palladium(0)-catalyzed domino indolization/alkynylation of *o*-alkynylanilines in the presence of 1-bromoalkynes has also been developed by Cacchi et al. for the synthesis of 2,3-disubstituted 3-alkynylindoles (Scheme 1 a).[12] In general, the indole synthesis by Cacchi and coworkers uses organic halides as electrophilic coupling partners and is performed under inert atmosphere in the presence of a phosphine ligand. We recently discovered that a nucleophile such as an internal amide could act as an effective reaction partner for *o*-alkynylaniline when the Cacchi cyclization was carried out under oxidative conditions.[13] Herein, we report that terminal alkynes can also enter into the oxidative catalytic cycle with the *o*-alkynylaniline **1**, and document an unprecedented palladium(II)-catalyzed coupling of **1** with the terminal alkynes **2** under mild aerobic conditions for the synthesis of 2,3-disubstituted 3-alkynylindoles (Scheme 1 b).




***Scheme 1.*** Alkynylation to 3-alkynylindoles. DMSO = dimethylsulfoxide.

By using *N*,*N*-dimethyl-*ortho*-(1-phenylethynyl)aniline (**1a**)[14] and 4-ethynyltoluene (**2a**) as test substrates, the optimum reaction conditions were found to involve performing the reaction in DMSO at 80 °C in the presence of $Pd(OAc)_2$ (0.05 equiv), $nBu_4NI$ (1.0 equiv), and HOAc (1.0 equiv) in air (Table 1, entry 9). Under these reaction conditions, the desired domino process occurred smoothly to provide 1-methyl-2-phenyl-3-(*p*-tolylethynyl)-1*H*-indole (**3aa**) in 88 % yield upon isolation.[15] Some points deserve additional comment: a) the presence of $Cu(OAc)_2$ as a cocatalyst was detrimental as it led to the formation of a significant amount of 3,3′-bisindole[16] and 1,4-di-*p*-tolylbuta-1,3-diyne resulting from the dimerization of **1a** and oxidative dimerization of **2a**,[17] respectively (entry 4); b) using 1.0 equivalent of HOAc and $nBu_4NI$ each is optimum. In the presence of 2.0 equivalents of HOAc (entry 5), the reaction became more complex, whereas with a substoichiometric amount of $nBu_4NI$, the yield of **3aa** was significantly reduced (entry 6 versus 7); c) higher concentration ($c = 0.2$; entry 10) and higher reaction temperature (100 °C; entry 11) under otherwise identical reaction conditions afforded **3aa** in a lower yield.

With the optimum reaction conditions in hand, the scope of the reaction was next investigated. As expected, aromatic substituents in both starting materials ($R^1$, $R^2$ = aromatic) having different electronic properties were well tolerated and the reaction between the diarylacetylenes **1** and arylethynes **2** gave 3-alkynylindoles in good to excellent yields (**3aa**–**3af** and **3ba**–**3da**; Scheme 2). The reaction conditions were applicable to aliphatic alkynes ($R^1$, $R^2$ = alkyl) as well, and various functionalities such as chlorine, hydroxy, benzyloxy,

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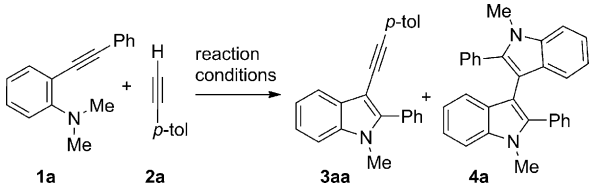
***Table 1:*** Condition survey for the palladium-catalyzed coupling of **1a** and **2a**.[a]

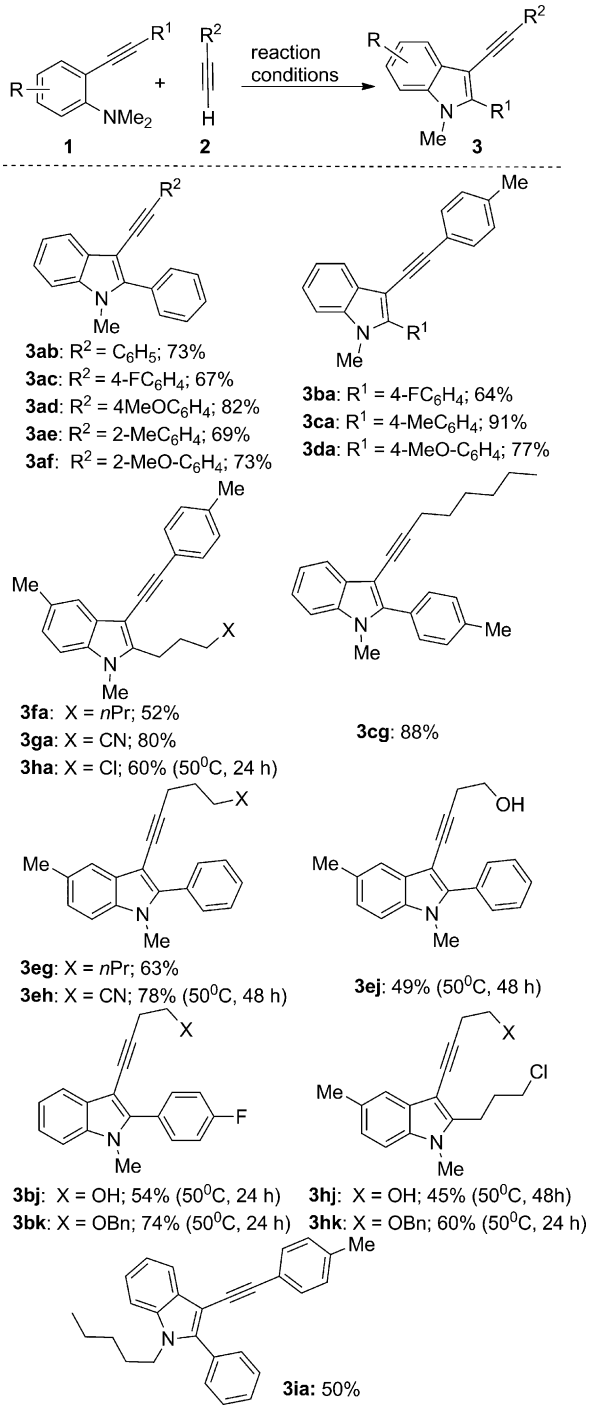



| Entry | $Pd^{II}$ (equiv) | $nBu_4NI$ (equiv) | AcOH (equiv) | **2a** (equiv) | Yield [%][b] | | |
|---|---|---|---|---|---|---|---|
| | | | | | **1a** | **4a** | **3aa** |
| 1 | 0.025 | 0.1 | 1.0 | 2.0 | 36 | 4 | 31 |
| 2 | 0.025 | 0.3 | 1.0 | 2.0 | 23 | 10 | 39 |
| 3 | 0.025 | 0.5 | 1.0 | 2.0 | 6 | 19 | 54(41) |
| 4[c] | 0.025 | 0.5 | 1.0 | 2.0 | 28 | 36 | 13 |
| 5[d] | 0.025 | 0.5 | 2.0 | 2.0 | 0 | 20 | 14 |
| 6[d] | 0.05 | 0.5 | 1.0 | 2.0 | 0 | 8 | 64 |
| 7[d] | 0.05 | 1.0 | 1.0 | 2.0 | 0 | 3 | 80 (72) |
| 8[d] | 0.05 | 1.0 | 1.0 | 1.5 | 0 | 8 | 62 |
| 9 | 0.05 | 1.0 | 1.0 | 2.0 | – | – | (88) |
| 10[e] | 0.05 | 1.0 | 1.0 | 2.0 | – | – | (65) |
| 11[f] | 0.05 | 1.0 | 1.0 | 2.0 | – | – | (74) |

[a] Reaction conditions: **1a** (0.1 mmol), **2a**, $Pd(OAc)_2$, $nBu_4NI$, and AcOH in DMSO (1.0 mL) was heated at 80 °C under air atmosphere (1 atm) for 24 h. [b] Yields were determined by $^1H$ NMR spectroscopy using $CH_2Br_2$ as an internal standard. The value within parentheses is yield of the isolated **3aa**. [c] $Cu(OAc)_2$ (0.1 equiv) was added. [d] 36 h. [e] 0.5 mL of DMSO was used. [f] Reaction was performed at 100 °C.

and cyano groups were tolerated. Since the preparation of unsymmetrical 2,3-dialkyl-substituted indoles represents a significant synthetic challenge,[18] it was thus delightful to find that the 2-alkyl-3-(1-alkylethynyl)indoles (**3hj** and **3hk**; $R^1$ and $R^2$ = alkyl) could also be synthesized in good yields using this method.[19,20] *N*-methyl-*N*-pentyl-*ortho*-(1-phenylethynyl)aniline coupled effectively with 4-ethynyltoluene to afford *N*-pentyl-2-phenyl-3-(*p*-tolylethynyl)-1*H*-indole (**3ia**) in 50% yield.[21]

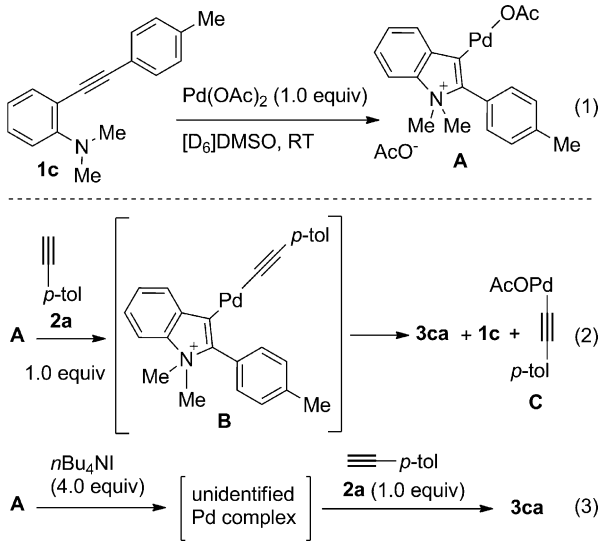
Two possible elementary steps could initiate the present alkynylation process: a) formation of a σ-alkynylpalladium(II) complex, b) the aminopalladation of *o*-alkynylaniline leading to a σ-indolylpalladium(II) intermediate. To gain insight into the mechanism, a series of experiments have been performed. Mixing **1c** and $Pd(OAc)_2$ (1.0 equiv) in [$D_6$]DMSO at room temperature rapidly produced a new compound, whose structure was assigned as the σ-indolylpalladium(II) intermediate **A** on the basis of detailed spectroscopic studies [Eq. (1), Scheme 3; see the Supporting Information]. To capitalize on the reactivity of this intermediate, the following control experiments were carried out. Firstly, addition of 4-ethynyltoluene (**2a**, 1.0 equiv) to a [$D_6$]DMSO solution of **A** produced a mixture of the cross-coupled product **3ca** and the starting material **1c** [Eq. (2), Scheme 3]. Since **A** was stable in the absence of the terminal alkyne **2a**, we assumed that **1c** was produced by a retro-aminopalladation of the σ-indolyl-σ-alkynylpalladium **B**, which was generated in situ from **A** and **2a**. Secondly, addition of $nBu_4NI$ (4.0 equiv) to the solution of **A** produced an unidentified complex [Eq. (3), Scheme 3]. Neither




***Scheme 2.*** General conditions: a solution of **1** (0.1 mmol) and **2** (0.2 mmol) in DMSO (1.0 mL) was heated at 80 °C in the presence of $Pd(OAc)_2$ (0.05 equiv), $nBu_4NI$ (1.0 equiv), and HOAc (1.0 equiv) under air atmosphere (1 atm) for 24 h.

AcOMe nor **1c** were detectable by $^1H$ NMR spectroscopy of the crude reaction mixture, thus indicating that N-demethylation and retro-aminopalladation did not take place in this case. However, addition of **2a** to the above mixture generated **3ca** as well as AcOMe which was detected by $^1H$ NMR spectroscopy. These control experiments indicated that a) the σ-indolylpalladium(II) complex **A** is a viable

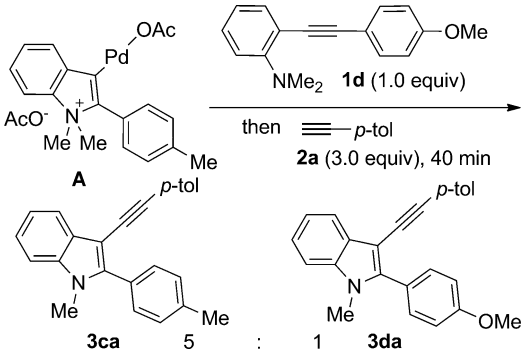
  




***Scheme 3.*** Identification of a key intermediate and control experiments. Neutral ligands on Pd were omitted for clarity.

intermediate on the way to **3ca**, b) the intermediate **B** is susceptible to retro-aminopalladation, presumably because of a more pronounced *trans* effect of the alkynyl group,[22] and thus could lead to a nonproductive pathway, c) **B** is more susceptible than **A** towards N-demethylation which drove the reaction toward the formation of the desired product, and d) the present domino alkynylation went through a $Pd^{II}/Pd^{0}$ catalytic cycle.

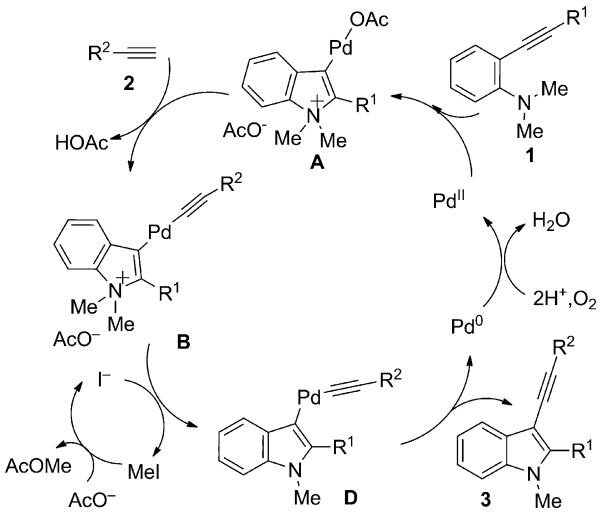
The retro-aminopalladation from **B** should produce the σ-alkynylpalladium complex **C**[23] in addition to **1c** [Eq. (2), Scheme 3]. As it was difficult to discern its presence by $^{1}H$ NMR spectroscopy, an additional experiment was performed to trap this reactive intermediate (Scheme 4). Addition of **2a** to a solution of **A** and *N*,*N*-dimethyl-2-(4′-methoxyphenylethynyl)aniline (**1d**) in [$D_6$]DMSO afforded, after 40 minutes at RT, the two 3-alkynylindoles **3ca** and **3da** (ratio 5:1) in addition to the two anilines **1c** and **1d**. This result indicated that **B** was a second possible intermediate in our alkynylation process and that this intermediate readily underwent the retro-aminopalladation process. While σ-indolyl-σ-arylpalladium of type **B** has been frequently




***Scheme 4.*** Further evidence of retro-aminopalladation by a cross-over experiment.

invoked as an intermediate in the paladium-catalyzed synthesis of functionalized indoles, the retro-aminopalladation has, to the best of our knowledge, never been unequivocally identified previously.

The ability of a palladium complex of the type **C** to trigger the indole formation has been amply demonstrated by Cacchi and co-workers. In view of the observed facile aminopalladation process and the fact that $Pd(OAc)_2$ is more electron deficient than the σ-alkynylpalladium complex,[24] we think that a catalytic cycle involving **C** may not be a predominant one under our oxidative conditions. A more plausible catalytic cycle was therefore proposed as shown in Scheme 5. $Pd(OAc)_2$-catalyzed intramolecular aminopalladation of **1** led to the formation of the σ-indolylpalladium intermediate **A**. Coordination of **A** to the terminal alkyne **2**




***Scheme 5.*** Palladium(II)-catalyzed alkynylation: a plausible reaction pathway. Neutral ligands on Pd were omitted for clarity.

and subsequent deprotonation afforded the σ-indolyl-σ-alkynylpalladium **B**, which underwent N-demethylation by $S_N2$ attack of iodide onto the indolium to furnish **D** and MeI. Reductive elimination from **D** provided the product **3** and $Pd^{0}$. The oxidation of $Pd^{0}$ to $Pd^{II}$ by air completes the catalytic cycle. Since iodide is regenerated under the reaction conditions by its reaction with acetate, only a catalytic amount of iodide is in principle needed. Although this is indeed the case, the reduced efficiency (entry 3 versus 7, Table 1) implied that a fast iodide-mediated N-demethylation (conversion of **B** into **D**) is important to ensure the occurrence of the desired domino process. Otherwise, **B** could undergo the retro-aminopalladation, thus reducing the yield of **3**. The fact that dimerization of terminal alkynes was effectively minimized in this domino process is also supportive of the proposed mechanism as this pathway did not involve the formation of a discrete σ-alkynylpalladium(II) complex which is prone to dimerization and degradation under oxidative conditions.

In conclusion, we have reported an efficient synthesis of 2,3-disubstituted 3-alkynylindoles by a novel palladium(II)-catalyzed domino reaction[25] between two alkynes under aerobic oxidative conditions. A σ-indolylpalladium(II) com-

plex (**A**) was characterized and its intermediacy in the transformation was illustrated. We also identified the N-demethylation step that took place right after the formation of the σ-indolyl-σ-alkynylpalladium intermediate (**B**). The rapid N-demethylation of **B** by $n$Bu$_4$NI is important as it prevents the occurrence of retro-aminopalladation of complex **B**. The present domino reaction displayed broad substrate scope, good functional group tolerance, and high synthetic efficiency. The so-developed oxidative conditions allow the use of nucleophiles (terminal alkynes) instead of electrophiles (organic halides) as the reaction partners for *o*-alkynylanilines, and are therefore complementary to indole synthesis by Cacchi and co-workers.

## Experimental Section

General procedure: A 5 mL vial was charged with **1a** (0.1 mmol), **2a** (0.2 equiv), $Pd(OAc)_2$ (5 mol%), $n$Bu$_4$NI (1.0 equiv), acetic acid (1.0 equiv), and DMSO (1.0 mL). After being heating at 80 °C under air (1 atm) for 24 h, the reaction mixture was quenched with water and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/dichloromethane = 10:1) to give the product **3aa** (28.3 mg, 88%) as a brown oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.90–7.85 (m, 1H), 7.73–7.68 (m, 2H), 7.58–7.51 (m, 2H), 7.50–7.44 (m, 1H), 7.41–7.24 (m, 5H), 7.12 (d, $J$ = 7.8 Hz, 2H), 3.77 (s, 3H), 2.36 ppm (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta$ = 143.7, 137.3, 131.1, 131.0, 130.4, 129.1, 128.9, 128.6, 128.5, 123.0, 121.6, 120.9, 120.2, 109.9, 97.1, 91.9, 83.5, 31.8, 21.6 ppm; ATR-IR $\nu$ 3054 (w), 2918 (w), 2201 (w), 1489 (w), 1487 (m), 1468 (m), 1367 (m), 1264 (m), 816 (s), 741 (s), 699 (s); HRMS (ESI) calcd for $C_{24}H_{20}N^+$ $[M+H]^+$ 322.1590; found 322.1581.

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[17] Palladium-catalyzed dimerization of terminal alkynes: X. Feng, Z. Zhao, F. Yang, T. Jin, Y. Ma, M. Bao, *J. Organomet. Chem.* **2011**, *696*, 1479 – 1482; see also: S. V. Damle, D. Seomoon, P. H. Lee, *J. Org. Chem.* **2003**, *68*, 7085 – 7087. Under our optimized reaction conditions, dimerization of **2a** to 1,4-di-*p*-tolyl-buta-1,3-diyne was also observed in the $^1$H NMR spectrum of the crude reaction mixture. Nevertheless, the dimerization was significantly slower than the desired alkynylation process.

[18] For a recent achievements and insightful discussions, see: M. P. Huestis, L. Chan, D. R. Stuart, K. Fagnou, *Angew. Chem.* **2011**, *123*, 1374 – 1377; *Angew. Chem. Int. Ed.* **2011**, *50*, 1338 – 1341.

[19] 2-alkyl-3-(1-alkylethynyl)indoles were not reported in the paper by Cacchi and co-workers; see Ref. [12].

[20] Hydrogenation of **3ga** under standard conditions (Pd/C, MeOH, 1 atm $H_2$) afforded the 2,3-dialkylated indole; see the Supporting Information.

[21] Under standard reaction conditions using 4-ethynyltoluene as a coupling partner, the *ortho*-(1-phenylethynyl)aniline, its N-methyl, and N-methyl-N-benzyl derivatives gave the NH and *N*-methyl 3-unsubstituted indoles (65%, 64%, 48%, respectively). The 4-ethynyltoluene was not incoporated into the product with these substrates. The N,N-dibenzyl derivative gave the corresponding *N*-benzyl-3-alkynyl indole in 11% yield. In contast, no reaction occurred when the N-methyl-N-phenyl derivative was submitted to the standard reaction conditions.

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