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C2-Selective Direct Alkynylation of Indoles

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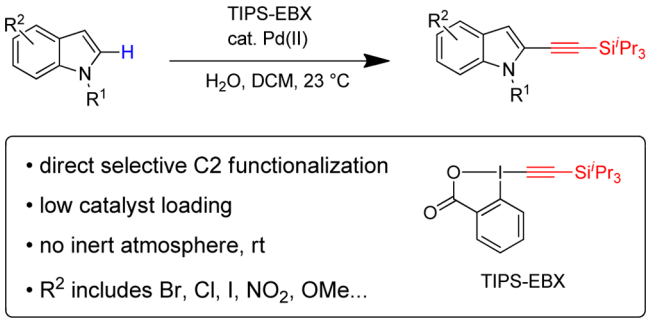
ABSTRACT



The first C2-selective alkynylation of indoles using the hypervalent iodine reagent triisopropylsilylethynyl-1,2-benziodoxol-3(1*H*)-one (TIPS-EBX) with Pd(II) as a catalyst is described. This convenient and robust method gives a single-step access to substituted alkynyl indoles with very high C2 selectivity. The reaction is orthogonal to classical Pd(0) cross-coupling reactions, as it is tolerant to bromide and iodide substituents. The used silyl protecting group can be easily removed to give terminal acetylenes.

Since the first synthesis of indole by Baeyer almost 150 years ago,[1] interest in the preparation and functionalization of this privileged heterocycle has constantly grown.[2] Indoles can indeed be found in numerous important molecules such as pharmaceuticals, dyes, and natural products. Consequently, methods to synthesize and modify this heterocycle are of utmost importance in organic chemistry.

Metal-catalyzed cross-coupling reactions constitute an efficient tool for the modification of aromatic rings,[3] but the need for prefunctionalization makes this method less efficient. In comparison, C−H functionalization constitutes a more direct alternative for the introduction of various valuable functional groups. Recently, the direct functionalization of indoles has been intensively examined using metal catalysts to complement traditional Friedel–Crafts reactions. Efficient methods have been developed to introduce vinyl,[4] aryl,[5] alkyl,[6] and cyano[7] groups among others.[8] In several cases, the C2/C3 regioselectivity of these functionalizations could be controlled by the reaction conditions or using directing groups.[4,9]

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(5) Selected examples: (a) Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897. (b) Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996. (c) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050. (d) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972. (e) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (f) Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008**, *130*, 2926. (g) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172. (h) Cornella, J.; Lu, P. F.; Larrosa, I. *Org. Lett.* **2009**, *11*, 5506. (i) Potavathri, S.; Pereira, K. C.; Gorelsky, S. I.; Pike, A.; LeBris, A. P.; DeBoef, B. *J. Am. Chem. Soc.* **2010**, *132*, 14676.

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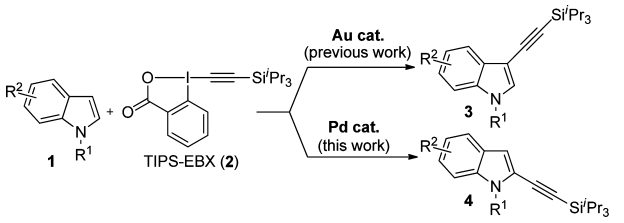
Despite the important applications of acetylenes in synthetic chemistry, biochemistry, and material sciences,[10] there are only a few methods for the direct alkynylation of the indole core.[11] In 2009, Gu and Wang first introduced the C3-selective alkynylation of indoles using bromoacetylenes and a Pd catalyst.[11a] C2-selective alkynylation is especially challenging, and only two examples have been reported so far. Li and co-workers described an oxidative Heck−Cassar−Sonogashira type method for the alkynylation of 1,3-dimethylindole.[11f] This reaction could be applied to a broad scope of acetylenes, but only 3-methylindoles were reported. More recently, a method for the alkynylation of lithiated indoles using ethynylsulfonates as reagents was reported by Garcia Ruano and co-workers.[11g,h] Depending on the sterical hindrance of the substituent on the indole nitrogen, C2 or C3 alkynylation could be obtained. Nevertheless, the requirement for a strong base such as butyl lithium limited the scope of this transformation. Consequently, the most frequently used methods to access 2-alkynylated indoles are often based on the formation of the heterocycles via cyclization reactions.[12]

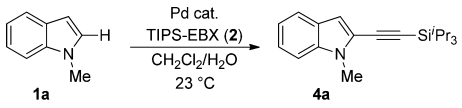
In 2009, our group introduced the hypervalent iodine compound triisopropylsilylethynyl-1,2-benziodoxol-3(1*H*)-one (TIPS-EBX, **2**)[13] as an efficient reagent for the gold-catalyzed C3 alkynylation of indoles (Scheme 1). During our first investigation, palladium catalysts gave only traces of product, albeit with very high C2 selectivity.[11b] We later demonstrated that efficient acetylene transfer with Pd catalysts was possible for the amino- and oxy-alkynylation of olefins.[14] Building upon these results, we report herein the first Pd-catalyzed C2-selective alkynylation of 3*H*-indoles using TIPS-EBX (**2**), which proceeds at room temperature under air in the presence of a broad range of functional groups (Scheme 1). In contrast to Gu and Wang's work, exclusive C2-alkynylation was observed. To the best of our knowledge, our work constitutes also the first example of Pd-catalyzed direct alkynylation of a heterocycle using a hypervalent iodine reagent.

Scheme 1. Regioselective Alkynylation of Indoles



During preliminary investigations on indole itself, a broad screen of Pd catalysts, solvents, and reaction conditions was not successful in improving the yield beyond 20%. More promising results were obtained in the case of *N*-methyl indole (**1a**) using a dichloromethane/water mixture as the solvent and 3 equiv of TIPS-EBX (**2**) (Table 1).[15] In this case, the reaction did not proceed without a catalyst (entry 1) or with the Pd(0) source $Pd(PPh_3)_4$ (entry 2), but Pd(II) salts such as $Pd(OAc)_2$ and $PdCl_2$ gave promising yields (entries 3 and 4). A further increase in yield was observed with $Pd(MeCN)_4(BF_4)_2$, which has a less coordinating counteranion (entry 5). In this case, the importance of water was confirmed, as a lower yield was obtained under dry conditions (entry 6). The catalyst loading had a strong influence on the yield, with 2% being the optimal amount (entries 7−9). Further screening of catalysts did not lead to better yields and confirmed that the reaction did not proceed in the presence of phosphine ligands (entries 10−12).

Table 1. Optimization of the C2 Selective Alkynylation



entry	catalyst loading	Pd source	yield (%)[a]
1		–	0
2	10%	$Pd(PPh_3)_4$	0
3	10%	$Pd(OAc)_2$	34
4	10%	$PdCl_2$	40
5	10%	$Pd(MeCN)_4(BF_4)_2$	50
6	10%	$Pd(MeCN)_4(BF_4)_2$	23[b]
7	25%	$Pd(MeCN)_4(BF_4)_2$	19
8	0.5%	$Pd(MeCN)_4(BF_4)_2$	37
9	2%	$Pd(MeCN)_4(BF_4)_2$	61
10	2%	$[Pd(allyl)Cl]_2$	60
11	2%	$Pd(PPh_3)_2Cl_2$	traces
12	2%	Pd_2dba_3	57
13	2%	$Pd(MeCN)_4(BF_4)_2$	66[c]

[a] 0.2 mmol of **1a**, 0.6 mmol of **2**, 2 mL of CH_2Cl_2, 0.04 mL of water, overnight; GC-MS yields, using dodecanitrile as standard. [b] In dry CH_2Cl_2. [c] Isolated yield on a 0.5 mmol scale.

(8) Reviews: (a) Beck, E. M.; Gaunt, M. J. Pd-Catalyzed C−H Bond Functionalization on the Indole and Pyrrole Nucleus. In *C−H Activation*; Yu, J. Q., Shi, Z., Eds.; Springer-Verlag Berlin: Berlin, 2010; Vol. 292, pp 85−121. (b) Lebrasseur, N.; Larrosa, I. Recent Advances in the C2 and C3 Regioselective Direct Arylation of Indoles. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Elsevier Academic Press Inc.: San Diego, 2012; Vol. 105, pp 309−351.

(9) Huestis, M. P.; Chan, L.; Stuart, D. R.; Fagnou, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 1338.

(10) Diederich, F.; Stang, P. J.; Tykwinsky, R. R. *Acetylene Chemistry*; Wiley-WCH: Weinheim, Germany, 2004.

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(12) Mothe, S. R.; Kothandaraman, P.; Lauw, S. J.; Chin, S. M.; Chan, P. W. *Chem.—Eur. J.* **2012**, *18*, 6133 and references herein.

(13) TIPS-EBX is commercially available and easily prepared in a two-step protocol from iodobenzoic acid in high yield on a 30 g scale: Brand, J. P.; Waser, J. *Synthesis* **2012**, *44*, 1155.

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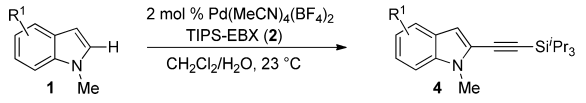
When the reaction was scaled up to 0.5 mmol, the alkynylation product was obtained in 66% isolated yield with $Pd(MeCN)_4(BF_4)_2$ (entry 13). In contrast to the work of Gu and Wang,[11a] only the C2-alkynylated product was isolated from the reaction mixture. This transformation consequently was the first C2-selective direct alkynylation of 3-unsubstituted indoles.

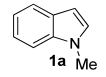
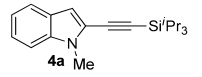
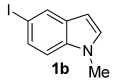
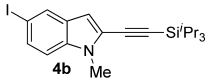
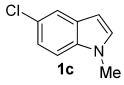
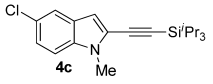
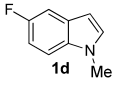
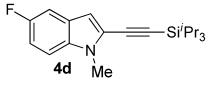
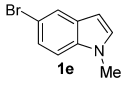
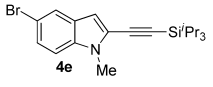
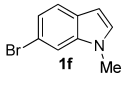
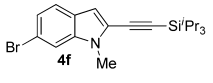
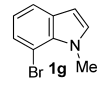
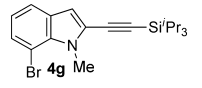
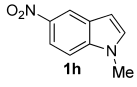
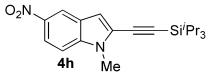
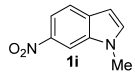
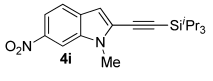
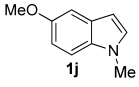
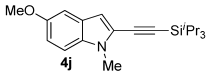
The reaction worked well with different halogens on various positions on the benzene ring (Table 2, entries 2−7), which has two main advantages. First, halogen substituents can be used to adjust the polarity, lipophilicity, and metabolic stability of dyes or pharmaceuticals. Second, halogens allow further modification using cross-coupling reactions for the elaboration of molecule libraries. These results also indicated that the reaction most likely did not proceed via a Pd(0) intermediate, as oxidative addition on the carbon−halogen bond would have been expected in this case. This is an important advantage when compared with previously published methods involving Pd(0) catalysis.[11a] Furthermore, both electron-withdrawing (entries 8−9) and electron-donating (entry 10) groups were tolerated on the benzene ring.

In general, N-alkylated indoles are very important building blocks for the synthesis of bioactive compounds, in particular for natural indole alkaloids. We consequently decided to further examine the scope of alkyl groups on the nitrogen (Table 3).[16] Propylphenyl substituted indole **1k** gave a 58% yield, demonstrating that the reaction was not limited to the small methyl group (entry 1). Allyl or benzyl groups on nitrogen could present a serious issue in the presence of a palladium catalyst. Nevertheless, the alkynylation products could still be obtained in moderate yields in this case (entries 2−4). Conversely, a TIPSO-ethyl and a sensitive bromo ethyl group gave good yields, opening the door for a wide range of further synthetic modifications (entries 5−6). Finally, indole **1q**, bearing an acetal protected aldehyde, could also be alkynylated in 66% yield (entry 7).

Based on precedence from other Pd-mediated transformations, in particular arylation,[5] a speculative mechanism may possibly involve a Pd(II)/(IV) cycle (Scheme 2).

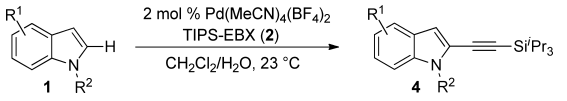
Table 2. Scope of Substituents on the Benzene Ring

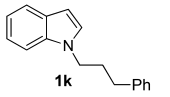
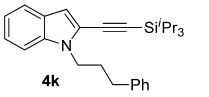
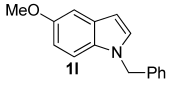
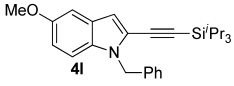
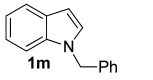
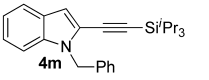
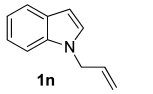
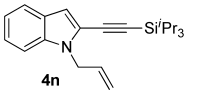
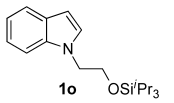
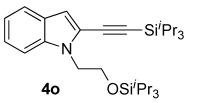
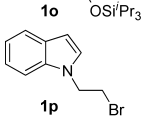
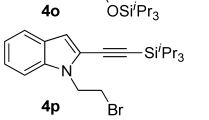
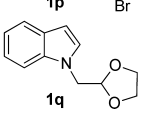
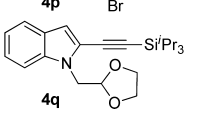


entry	indole	product	yield(%)[a]
1			66
2			68
3			54
4			45
5			54
6			72
7			72
8			48
9			45
10			55

[a] Isolated yields with 0.5 mmol of indole **1**, 1.5 mmol of (**2**), 5 mL of CH_2Cl_2, 0.1 mL of water, 10 μmol of $Pd(MeCN)_4(BF_4)_2$.

Table 3. Scope of Substituents on the Nitrogen



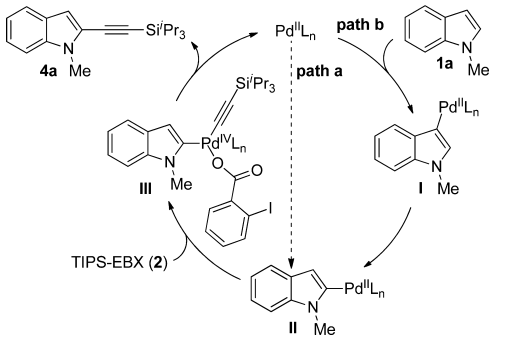
entry	indole	product	yield(%)[a]
1			58
2			41
3			41
4			44
5			68
6			61
7			66

[a] Isolated yields, 0.5 mmol of indole **1**, 1.5 mmol of **2**, 5 mL of CH_2Cl_2, 0.1 mL of water, 10 μmol of $Pd(MeCN)_4(BF_4)_2$.

The reaction could be initiated by a C2-palladation to give intermediate **II**, either via direct concerted metalation–deprotonation (CMD, path **a**)[5i,17] or via electrophilic palladation at the C3 position to give **I**, followed by Pd migration (path **b**).[5c,18] Water or water clusters could play a key role in promoting this metalation–deprotonation step. The indole Pd complex **II** can then be oxidatively alkynylated by TIPS-EBX (**2**), to give Pd(IV) intermediate **III**,[19] which undergoes reductive elimination to give the product **4a** and regenerate the Pd(II) catalyst.

In conclusion, we have described the first Pd-catalyzed alkynylation of indoles proceeding with high C2 regioselectivity. The reaction is orthogonal to classical cross-coupling reactions and has a broad functional group tolerance on both the indole core and the alkyl substituent on the nitrogen. The mild and neutral reaction conditions and the tolerance of the process toward air and moisture lead to a convenient method for the direct C2 alkynylation of indoles.

Scheme 2. Speculative Mechanism for the Alkynylation Reaction



Supporting Information Available. Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.

(15) A broad range of other solvents and additives were examined, but without a positive effect on the reaction outcome. A steady improvement in the yield was observed with increasing amounts of TIPS-EBX (**2**) up to 3 equiv. Other silyl substituted alkynes gave lower yields, and no product was observed with aryl or alkyl substituted acetylenes. See Supporting Information for details.

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