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General and Efficient Indole Syntheses Based on Catalytic Amination Reactions

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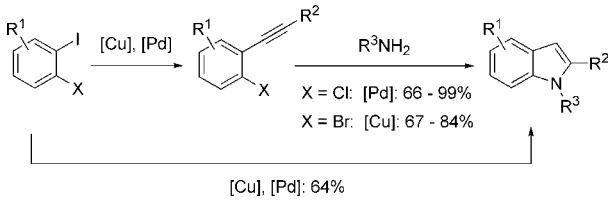
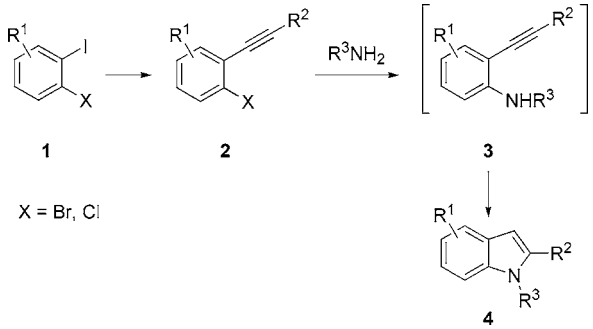
ABSTRACT



Highly flexible and efficient syntheses of the indole backbone are presented starting from *o*-alkynylhaloarenes. These transformations proceed via a palladium- or a copper-catalyzed amination reaction and a subsequent cyclization reaction in good to excellent yields. Furthermore, a multicatalytic one-pot indole synthesis starting from *o*-chloroiodobenzene is viable using a single catalyst consisting of an *N*-heterocyclic carbene palladium complex and CuI.

The prevalence of indoles in natural products and biologically active compounds results in a continued strong demand for the development of general, flexible, and especially regioselective synthetic methods of this structural moiety.[1] In this context, palladium-catalyzed transformations for the synthesis of the indole backbone, starting from *o*-alkynylanilines or derivatives thereof[2] as well as *o*-haloanilines,[3] have been studied intensively. However, much less attention has been paid to the use of *o*-dihaloarenes **1** or *o*-alkynylhaloarenes **2**,[4] although they are easily accessible from inexpensive starting materials. Transition metal-catalyzed C−N bond forming reactions using aryl halides have proved to be a versatile method for the synthesis of a variety of amines.[5] Additionally, cyclization reactions of *o*-alkynylanilines **3** have been mediated by strong bases[6] or catalyzed inter alia by palladium complexes[2] and Lewis acids,[7] such as CuI.[8] Herein, highly efficient, regioselective indole syntheses are reported, that are based on amination reactions of *o*-alkynylhaloarenes **2** (Scheme 1). Furthermore, a multicatalytic one-pot indole synthesis consisting of a Sonogashira reaction and an amination reaction with subsequent cyclization is presented. This multicatalytic reaction is accomplished by a single catalytic system.

Scheme 1. Indole Synthesis Using *o*-Dihaloarenes



(1) (a) Gilchrist, T. L. *Heterocyclic Chemistry*; Addison-Wesley Longman Limited: Singapore, 1997. (b) Joule, J. A.; Mills K.; Smith, G. F. *Heterocyclic Chemistry*; Stanley Thornes Ltd.: Cheltenham, 1995.

(2) (a) Utimoto, K.; Miwa, H.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 4277−4278. (b) Irtani, K.; Matsubara, S.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 1799−1802. (c) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1989**, *30*, 2581−2584. (d) Cacchi, S.; Carnicelli, V.; Marinelli, F. *J. Organomet. Chem.* **1994**, *475*, 289−296. (e) Tsuji, J. *Palladium Reagents and Catalysts*, 2nd ed.; Wiley: Chichester, 2004; pp 211−216. (f) Leni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285−2309.

(3) (a) For a review, see: Larock, R. C. *J. Organomet. Chem.* **1999**, *576*, 111−124. Selected recent examples: (b) Chen, C.; Lieberman, D. R.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1997**, *62*, 2676−2677. (c) Nazaré, M.; Schneider, C.; Lindenschmidt, A.; Will, D. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 4526−4528. (d) Ackermann, L.; Kaspar, L. T.; Gschrei, C. J. *Chem. Commun.* **2004**, 2824−2825.

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Preliminary studies showed that a palladium complex generated from the sterically hindered *N*-heterocyclic carbene precursor **5** (Figure 1), in combination with KO-*t*-Bu,[9] was

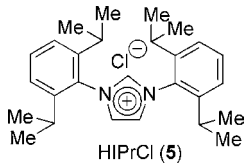
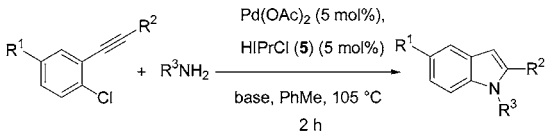


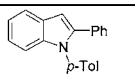
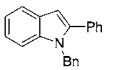
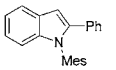
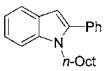
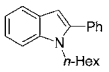
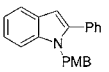
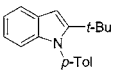
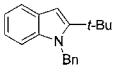
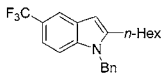
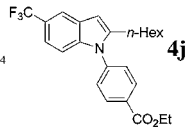
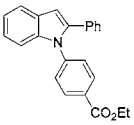
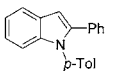
Figure 1. Imidazolium salt **5**.

an efficient catalyst for the direct conversion of alkynes **2**[10] to the corresponding indoles **4** in 2 h with excellent isolated yields (Table 1).[11] In contrast to the previously described method,[4] the protocol was not only applicable to sterically hindered amines (entry 3), but to simple less sterically demanding alkyl-substituted amines (entries 4 and 5).

Furthermore, it was not limited to simple alkyl-substituted alkynes, but was used for the conversion of aryl- and *t*-Bu-substituted derivatives with excellent yields. Different *N*-protecting groups, such as benzyl- (entries 2, 8, and 9) or *p*-methoxybenzyl (PMB) (entry 6), could be introduced via the corresponding amine, allowing for further elaboration of the resulting indoles. Additionally, mild bases, such as Cs_2CO_3[12] or less expensive and less toxic K_3PO_4 could be employed (entry 9), thereby expanding the functional group tolerance significantly.[13] Longer reaction times, and in some cases, incomplete cyclization of the amination product **3** were observed using these bases,[14] suggesting an acceleration of the ring closing reaction by KO-*t*-Bu.[6] Because copper salts were frequently used for the cyclization of *o*-alkynylanilines

Table 1. Palladium-Catalyzed Indole Synthesis[a]



entry[b]		R^1	R^2	R^3	product		Isolated yield (%)
1	A	H	Ph	*p*-Tol		**4a**	99
2	A	H	Ph	$PhCH_2$		**4b**	92
3	A	H	Ph	Mes		**4c**	99
4	A	H	Ph	*n*-Oct		**4d**	93
5	A	H	Ph	*n*-Hex		**4e**	93
6	A	H	Ph	PMB		**4f**	78
7	A	H	*t*-Bu	*p*-Tol		**4g**	83
8	A	H	*t*-Bu	$PhCH_2$		**4h**	74
9	B	CF_3	*n*-Hex	$PhCH_2$		**4i**	66
10	C	CF_3	*n*-Hex	4-$EtCO_2C_6H_4$		**4j**	67
11	C	H	Ph	4-$EtCO_2C_6H_4$		**4k**	92
12	C	H	Ph	*p*-Tol		**4a**	95

[a] Alkyne (1.0 mmol), amine (1.2 mmol), $Pd(OAc)_2$ (5 mol %), HIPrCl (**5**) (5 mol %) in PhMe (3 mL), 105 °C. [b] A: KO-*t*-Bu (3 mmol); B: K_3PO_4 (3 mmol), 16 h; C: CuI (5 mol %), K_3PO_4 (3 mmol), 5−18 h.

(4) For a two-step, one-pot approach consisting of a hydroamination and a subsequent intramolecular palladium-catalyzed amination reaction, see: Siebenreicher, H.; Bytschkov, I.; Doye, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3042−3044.

(5) (a) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125−146. (b) Hartwig, J. F. In *Modern Amination Methods*; Ricci, A., Ed.; Wiley-VCH: Weinheim, 2000; pp 195−262. (c) Tsuji, J. *Palladium Reagents and Catalysts*, 2nd ed.; Wiley: Chichester, 2004; pp 373−391.

(6) (a) Rodriguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2488−2490. (b) For a review, see: Seayad, J.; Tillack, A.; Hartung, C. G.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 795−813.

(7) (a) For a recent example, see: Hiroya, K.; Itoh, S.; Sakamoto, T. *J. Org. Chem.* **2004**, *69*, 1126−1136. (b) See also: Barluenga, J.; Trincado, M.; González, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 2406−2409 and references therein.

(8) Early examples: (a) Castro, C. E.; Stephens, R. D. *J. Org. Chem.* **1963**, *28*, 2163. (b) Castro, C. E.; Gaughan, E. J.; Owsley, D. C. *J. Org. Chem.* **1966**, *31*, 4071−4078.

(9) For the use of heterocyclic carbene ligands in C−N bond-forming processes, see: (a) Huang, J.; Grasa, G.; Nolan, S. P. *Org. Lett.* **1999**, *1*, 1307−1309. (b) Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423−1426.

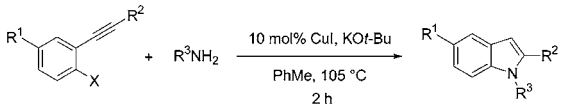
(10) Alkynes **2** were obtained from *o*-dihaloarenes **1** with excellent selectivity in 73−96% isolated yields by Sonogashira coupling reactions using $Pd(PPh_3)_2Cl_2$ and CuI. For a review, see: Marsden, J. A.; Haley, M. M. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; pp 317−394.

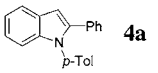
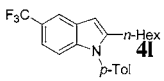
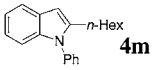
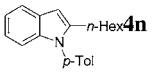
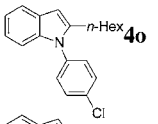
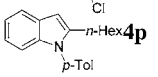
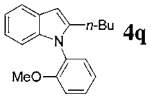
(11) **Representative Procedure for Palladium-Catalyzed Indole Synthesis: 2-Phenyl-1-*p*-tolyl-1*H*-indole (4a).** To a solution of $Pd(OAc)_2$ (11 mg, 0.05 mmol, 5 mol %), HIPrCl (**5**) (21 mg, 0.05 mmol, 5 mol %), and KO*t*-Bu (336 mg, 3.0 mmol) in PhMe (3 mL) were added 1-chloro-2-phenylethynylbenzene (212 mg, 1.0 mmol) and 4-methylaniline (129 mg, 1.2 mmol) at room temperature. The resulting red mixture was stirred at 105 °C for 2 h, after which GC/MS analysis indicated complete conversion of the starting material. CH_2Cl_2 (50 mL) and aq HCl (2 N, 50 mL) were added to the cooled reaction mixture. The separated aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The remaining residue was purified by column chromatography on silica gel (*n*-pentane/Et_2O, 200/1) to yield **4a** as a white solid (282 mg, 99%).

3,[8] such problems could be circumvented by addition of 5 mol % CuI to the catalytic system, leading to quantitative conversion to the corresponding indoles **4j**, **4k**, and **4a**, when using K_3PO_4 (entries 10−12).

Recently, renewed interest has focused on the copper-catalyzed Ullman−Goldberg amination reaction.[15] "Ligand-free" CuI-catalyzed amination reactions employing KO-*t*-Bu as base have also been described.[16] Consequently, the possibility of accomplishing a copper-catalyzed indole synthesis was explored (Table 2).

Table 2. CuI-Catalyzed Indole Synthesis[a]



entry	X	R^1	R^2	R^3	product	yield (%)
1	Cl	H	Ph	4-MeC_6H_4	 **4a**	21 (51)[b]
2	Cl	CF_3	*n*-Hex	4-MeC_6H_4	 **4l**	(53)[b]
3	Br	H	*n*-Hex	Ph	 **4m**	84
4	Br	H	*n*-Hex	4-MeC_6H_4	 **4n**	67
5	Br	H	*n*-Hex	4-ClC_6H_4	 **4o**	70
6	Br	H	*n*-Hex	4-MeC_6H_4	 **4p**	75
7	Br	H	*n*-Bu	2-$MeOC_6H_4$	 **4q**	69

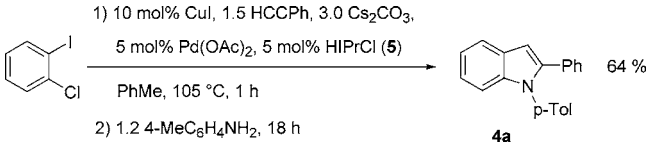
[a] Isolated yields; alkyne (1.0 mmol), amine (1.2 mmol), KO-*t*-Bu (3.0 mmol), and CuI (10 mol %) in PhMe (3 mL), 105 °C. [b] Conversion of **2** by GC analysis, 48 h.

Aryl chlorides reacted sluggishly and low isolated yields were obtained due to the formation of byproducts (entries 1 and 2). However, complete conversion was obtained for the corresponding aryl bromides, allowing isolation of the indoles in high yields after only 2 h (entries 3−7).[17]

Subjecting the *o*-alkynylbromoarene **2** employed in Table 2, entries 3−6, and the secondary amine *N*-methylaniline to these reaction conditions gave mainly rise to the corresponding hydroamination product. This suggests that here a sequence consisting of an intermolecular hydroamination and a subsequent intramolecular amination[18,19] is predominantly operative.

As the palladium amination catalyst was found compatible with the addition of substoichiometric amounts of CuI, a multicatalytic[20] one-pot indole synthesis consisting of a Sonogashira coupling reaction, an amination and an intramolecular hydroamination sequence was probed (Scheme 2).[21] A combination of commercially available imidazolium salt **5**, $Pd(OAc)_2$, CuI, and Cs_2CO_3 enabled quantitative conversion to **4a**, which was isolated in 64% yield.

Scheme 2. Multicatalytic One-Pot Indole Synthesis



In conclusion, general and efficient approaches to the indole framework starting from *o*-alkynylhaloarenes **2** are presented. These transformations proceed via either a palladium- or a copper-catalyzed amination reaction, and are applicable to alkyl- and aryl-substituted alkynes and amines. Furthermore, they allow for the use of mild bases, such as K_3PO_4, and the introduction of different protecting groups at nitrogen of the indole moiety. Remarkably, a one-pot indole synthesis starting from *ortho*-chloroiodobenzene is viable using a single catalytic system consisting of $Pd(OAc)_2$, CuI, HIPrCl (**5**), and Cs_2CO_3.

(12) Under otherwise identical reaction conditions to the ones outlined in Table 1, entry 9, the use of Cs_2CO_3 or KOAc instead of K_3PO_4 led to complete conversion (**4j**: 40% isolated yield) and no conversion of the corresponding alkyne, respectively.

(13) Wolfe, J. P.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6359−6362.

(14) The use of K_3PO_4 instead of KO-*t*-Bu under otherwise identical conditions to the one outlined in Table 1, entry 8, yielded exclusively the corresponding amine **3**, supporting the sequence outlined in Scheme 1.

(15) (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400−5449. (b) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428−2439.

(16) Kelkar, A. A.; Patil, N. M.; Chaudhari, R. V. *Tetrahedron Lett.* **2002**, *43*, 7143−7146.

(17) **Representative Procedure for CuI-Catalyzed Indole Synthesis: 2-*n*-Hexyl-1-*p*-tolyl-1*H*-indole (4n).** To a solution of CuI (18 mg, 0.10 mmol, 10 mol %) and KO-*t*-Bu (336 mg, 3.0 mmol) in PhMe (3 mL) were added 1-bromo-2-oct-1-ynylbenzene (265 mg, 1.0 mmol) and 4-methylaniline (129 mg, 1.2 mmol) at room temperature. The resulting mixture was stirred at 105 °C for 2 h, after which GC/MS analysis indicated complete conversion of the starting material. CH_2Cl_2 (50 mL) and aq HCl (2 N, 50 mL) were added to the cooled reaction mixture. The separated aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The remaining residue was purified by column chromatography on silica gel (*n*-pentane/Et_2O, 200/1 → 50/1) to yield **4n** as a yellow oil (195 mg, 67%).

(18) For copper-catalyzed intramolecular amination reactions of aryl chlorides under mild conditions, see: Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793−796.

(19) KO-*t*-Bu can assist similar cyclization reactions via formation of an aryne intermediate. See, for example: Beller, M.; Breindl, C.; Riermeier, T. H.; Tillack, A. *J. Org. Chem.* **2001**, *66*, 1403−1412.

(20) Lee, J. M.; Na, Y.; Han, H.; Chang, S. *Chem. Soc. Rev.* **2004**, *33*, 302−312.

(21) For the use of *N*-heterocyclic carbene palladium complexes for Sonogashira coupling reactions, see: Yang, C.; Nolan, S. P. *Organometallics* **2002**, *21*, 1020−1022.

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Supporting Information Available: Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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