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A novel palladium catalyst for the amination of electron-rich indole derivatives

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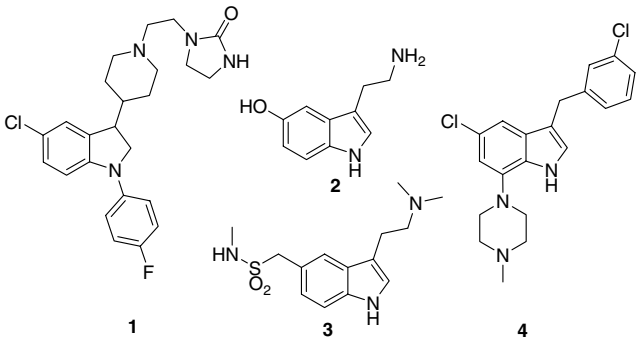
Abstract—The palladium-catalyzed amination of a 3-silyloxy-substituted bromo-indole with primary and secondary amines is described for the first time. In the presence of the novel catalyst system of $Pd(OAc)_2$/*N*-phenyl-2-(di-1-adamantylphosphino)pyrrole potentially bioactive amino-functionalized indole derivatives are obtained in a general manner in high yield.

The indole ring system constitutes one of the most important heterocycles in nature and substituted indoles have been referred to as 'privileged pharmaceutical structures' since they are capable of binding to many biological receptors with high affinity.[1] Due to their importance as building blocks for pharmaceuticals and natural products the preparation of new indole derivatives is an actual topic in organic chemistry. Owing to the great structural diversity of biologically active indoles, there is also a continuing interest in the development of improved methods for the synthesis of indoles.[2]

Among the numerous known indoles, especially amino-functionalized derivatives represent key structures for various biologically active compounds (Scheme 1). In particular tryptamine derivatives are involved in several biological processes, for example, melatonin in the control of the circadian rhythm and serotonin **2** in neurological processes. Thus, amino-functionalized indoles are used for the medical treatment of diverse diseases like migraine (Sumatriptan **3**), schizophrenia (Sertindole **1**), and many others. Due to the pharmaceutical relevance of amino-substituted tryptamine and its analogues, numerous syntheses have been reported and the development of new methods is still a subject of intensive research.[3]



Scheme 1. Examples of amino-substituted indole derivatives.

Based on our long standing interest in indole syntheses[4] as well as in palladium-catalyzed coupling reactions,[5] we became interested in the preparation of new functionalized indole derivatives via Buchwald–Hartwig aminations.

Clearly, palladium-catalyzed C–N-bond formation (Buchwald–Hartwig reaction) of aryl halides with amines has been extensively studied in the past few years.[6] In general, these processes have excellent functional group tolerance and wide substrate scope, which make them ideally suited for applications in the pharmaceutical area. However, there is relatively little known on the coupling reactions of electron-rich indoles.

Clearly, the palladium-catalyzed activation is more difficult here compared to electron-poor substrates.

Keywords: Amination; C–N coupling; Palladium; Indoles.
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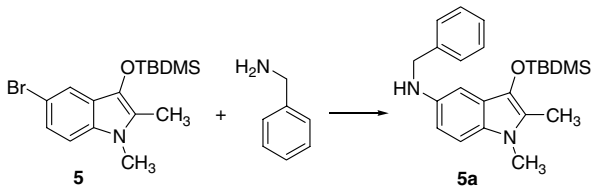
Table 1. Reaction of 3-*tert*-butyldimethylsilyloxy-5-bromo-indole with benzylamine in the presence of different ligands and bases[a]



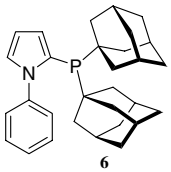
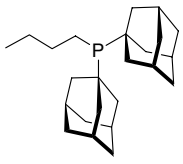
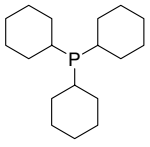
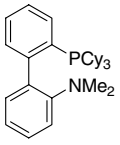
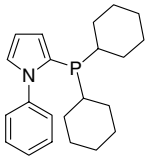
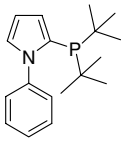
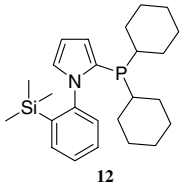
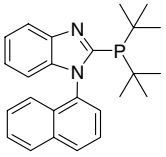
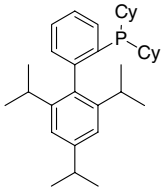
Entry	Ligand	Base	Yield[b] (%)
1		LiHMDS[c]	85
2		K_3PO_4	5
3		Cs_2CO_3	70
4		NaO^{t}Bu	40
5		Without	0
6		LiHMDS	<10
7		LiHMDS	<10
8		LiHMDS	51
9		LiHMDS	25
10		LiHMDS	75
11		LiHMDS	95

Table 1 (*continued*)

Entry	Ligand	Base	Yield[b] (%)
12		LiHMDS	40
13		LiHMDS	85

[a] Reaction conditions: 3-*tert*-butyldimethylsilyloxy-5-bromo-2-methylindole (0.56 mmol), benzylamine (0.67 mmol), solvent: toluene (3 mL), 1 mol % $Pd(OAc)_2$, 2 mol % ligand, base (0.73 mmol), 24 h, 100 °C.

[b] Isolated yield based on 3-*tert*-butyldimethylsilyloxy-5-bromo-2-methylindole.

[c] 1 M solution of lithium-bis(trimethylsilyl)amide in toluene.

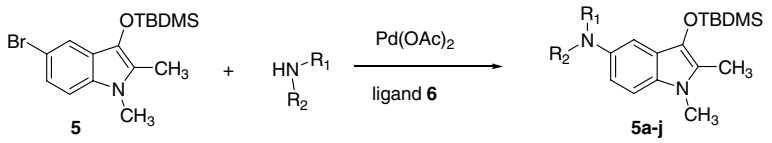
In the present Letter we describe for the first time the palladium-catalyzed amination of 3-silyloxy-5-bromo-indole with primary and secondary amines in the presence of $Pd(OAc)_2$ and *N*-phenyl-2-(di-1-adamantylphosphino)-pyrrole as ligand to give new indole derivatives.

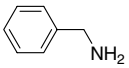
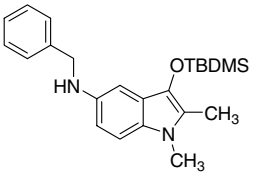
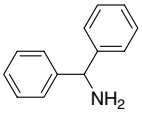
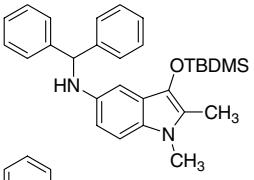
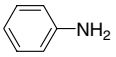
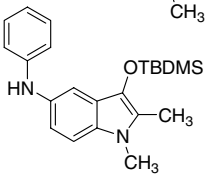
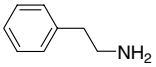
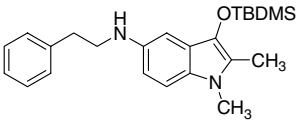
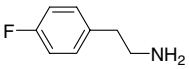
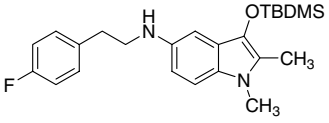
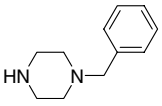
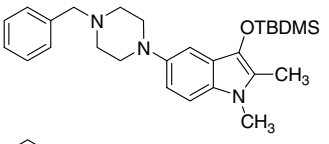
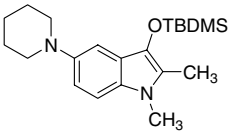
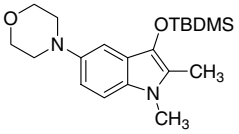
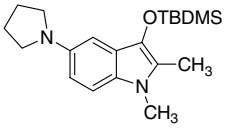
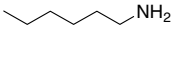
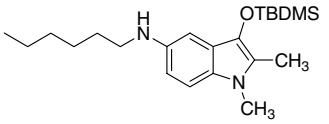
In exploratory experiments, we studied the effect of base and ligands on the reaction of 3-*tert*-butyldimethylsilyloxy-5-bromo-2-methylindole **5** and benzylamine to the corresponding indole **5a**. As shown in Table 1 the best yield of indole **5a** (85%) is achieved with 1.3 equiv of 1 M solution of LiHMDS in toluene. Further variation of the base revealed only lower yields (5–70%) of the corresponding indole (Table 1, entries 2–5). As expected the reaction without any base was not successful (Table 1, entry 5). Next, we were interested in the influence of different sterically demanding ligands on our model reaction. All reactions were performed at 100 °C for 24 h in toluene in the presence of 1 mol % $Pd(OAc)_2$ and 1.3 equiv of LiHMDS (Table 1, entries 6–13). In general, sterically hindered biaryl-type ligands gave the best yields. Thus, using ligands **11**, **12**, and **14** gave 75–95% yield of the corresponding indole. Employing di-1-adamantyl-*n*-butylphosphine **7** or tricyclohexylphosphine **8** the isolated yield decreased to <10%. Here, we observed mainly reductive dehalogenation via β-hydride-elimination as competing reaction pathway.

After testing different ligands and bases, we were interested in the scope and limitations of the catalyst system for different amines. For this purpose we used the silyl-protected 3-oxy-5-bromo-2-methylindole **5** and diverse primary and secondary amines.

Although ligands **12** and **14** gave comparable or even improved results in the model coupling reaction, nevertheless, we used **6** for the further synthesis of

Table 2. Reaction of different amines with the silyl-protected 3-oxy-5-bromo-2-methylindole[a]



Entry	Amine	Product		Yield[b] (%)
1			**5a**	85
2			**5b**	40
3			**5c**	85
4			**5d**	60
5			**5e**	91
6			**5f**	50
7			**5g**[8]	75
8			**5h**	55
9			**5i**	73
10			**5j**	91

[a] Reaction conditions: 3-*tert*-butyldimethylsilyloxy-5-bromo-2-methylindole (0.56 mmol), amine (0.67 mmol), solvent: toluene (3 mL), 1 mol % $Pd(OAc)_2$, 2 mol % ligand **6**, 1 M solution of lithium-bis(trimethylsilyl)amide in toluene (0.73 mmol), 24 h, 100 °C.

[b] Isolated yield based on 3-*tert*-butyldimethylsilyloxy-5-bromo-2-methylindole.

amino-functionalized indoles, because of the easier availability of this in-house developed ligand.[7] As shown in Table 2 the corresponding indole products are obtained in 40–91% yield. The novel catalyst system works well with different primary and secondary amines which are all commercially available. With respect to the yield there is no clear trend on the electronic or steric factors of the amine.

In conclusion, we presented the first palladium-catalyzed amination of silyl-protected 3-oxyhaloindoles, a novel class of electron-rich indoles. Different amines reacted smoothly in the presence of $Pd(OAc)_2$, *N*-phenyl-2-(diadamantyl-phosphino)pyrrole **6** to give potentially bioactive amino-functionalized indoles.

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8. Preparative procedure for the Pd-catalyzed amination reaction (**5g**): In an Ace-pressure tube under an argon atmosphere 3-*tert*-butyldimethylsilyloxy-5-bromo-2-methylindole (0.56 mmol), $Pd(OAc)_2$ (1 mol %) and ligand **6** (2 mol %) were dissolved in toluene (3 mL). To this solution LiHMDS (0.73 mmol) and piperidine (0.67 mmol) were added. The pressure tube was fitted with a Teflon cap and heated at 100 °C for 24 h. After removal of the solvent in vacuo, the desired indole product was isolated by column chromatography in hexane/ethyl acetate. Isolated yield: 150 mg (75%), (mp: 85–88 °C). ^{1}H NMR (300.13, $CDCl_3$) $\delta = -0.17$ (s, 6H, H-12a,b); 1.09 (s, 9H, H-13a,b,c); 1.5–1.9 (m, 7H, H-16a,b; H-17); 2.28 (s, 3H, H-11); 3.08 (t, 4H, $^3J_{15,16} = 5.4$ Hz, H-15a,b); 3.57 (s, 3H, H-10); 6.92 (dd, 1H, $^4J_{4,6} = 2.2$ Hz, $^3J_{6,7} = 8.8$ Hz, H-6); 7.01 (d, 1H, $^4J_{4,6} = 2.2$ Hz, H-4); 7.11 (d, 1H, $^3J_{6,7} = 8.8$ Hz, H-7) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz,) $\delta = -3.9$ (C-12); 9.4 (C-11); 18.4 (C-14); 24.6 (C-17); 26.1 (C-13); 26.6 (C-16a,b); 29.7 (C-10); 53.8 (C-15a,b); 105.1 (C-4); 108.9 (C-6); 115.2 (C-7); 121.8, 122.9, 129.8, 130.4, 146.1 (C-9, C-8, C-5, C-3, C-2) ppm. MS (EI, 70 eV) *m*/*z* (rel. intensity): 358 (100) [M^+], 343 (3), 301 (6), 228 (12). HRMS calcd for $C_{21}H_{34}N_2OSi$: 358.24349. Found: 358.242665.