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Palladium-Catalyzed Heteroarylation of 1-(*tert*-Butyldimethylsilyl)-3-indolylzinc Chloride. Efficient Synthesis of 3-(2-Pyridyl)indoles

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Abstract: Palladium-catalyzed coupling of 1-(*tert*-butyldimethylsilyl)-3-indolylzinc chloride (**2**) with either π-deficient or π-excedent heteroaryl halides gives 3-arylindoles in good to excellent yields. The method is extensively applied to the preparation of 3-(2-pyridyl)indoles.

Palladium catalyzed cross-coupling reactions to give 3-vinyl-, 3-alkynyl-, or 3-allylindoles from 3-indoleboronic acids, 3-indolyl triflates, 3-(chloromercurio)indoles, 3-haloindoles, or indole itself are well documented.[1] However only a very few procedures for the palladium-catalyzed arylation at the indole 3-position are known.[2] In a recent paper,[2a] the cross-coupling reaction between 1-(benzenesulfonyl)-3-indolylzinc iodide, prepared by oxidative addition of active zinc to the corresponding 3-iodoindole, and aryl halides to give 3-arylindoles in moderate to good yields has been described. These results prompted us to report our findings[3] about the heteroarylation at the indole 3-position, especially for the preparation of 3-(2-pyridyl)indoles.[4]

As we recently reported,[5] 1-(benzenesulfonyl)-2-indolylzinc chloride, prepared by metathesis of 1-(benzenesulfonyl)-2-lithioindole with $ZnCl_2$, efficiently reacts with 2-halopyridines in the presence of Pd(0) to give 2-(2-pyridyl)indoles. However, initial attempts to extend this procedure to the synthesis of 3-(2-pyridyl)indoles from 1-(benzenesulfonyl)-3-indolylzinc chloride were unsuccessful due to the easy rearrangement of the intermediate 1-(benzenesulfonyl)-3-lithioindole to the 2-lithio isomer.[6,7]

Interestingly, we had observed[8] that 1-(*tert*-butyldimethylsilyl)-3-lithioindole is a stable species which does not rearrange to the 2-lithio isomer even upon warming at room temperature. For this reason we next decided to use the *tert*-butyldimethylsilyl group as the indole protecting group. The required 1-(*tert*-butyldimethylsilyl)-3-indolylzinc chloride (**2**) was prepared from 3-bromo-1-(*tert*-butyldimethylsilyl)indole[8] (**1**), by halogen-metal exchange with *tert*-BuLi at -78 °C followed by transmetallation (-78 °C → rt) of the resulting 3-lithioindole with anhydrous $ZnCl_2$. The reaction of **2** (1.5 equiv) with 2-bromopyridines **3a** and **3c** in the presence of 2 mol % of a catalyst prepared from $PdCl_2(PPh_3)_2$ and DIBAH (2 equiv) in refluxing THF under argon for 4 h led to the respective N-protected 3-(2-pyridyl)indoles **4a** and **4c** in about 95% yield. Further treatment with a refluxing ethanolic solution containing a catalytic amount of *p*-TsOH yielded the desilylated derivatives **5a** and **5c** in nearly quantitative yields. In all runs the corresponding 3,3′-biindole was formed in approximately 15% yield (based on **1**).

In order to evaluate the scope of the reaction both the effect of substituents of a different nature on the pyridine ring and the use of heteroaryl halides derived either from other π-deficient or from π-excedent heterocycles were investigated. Thus, 2-bromopyridines **3e-g**, having electron-releasing alkyl or methoxy substituents, and 2-chloropyridines **3i-m**, having strongly electron-withdrawing nitro and ester groups, were subjected to the above cross-coupling conditions and the resulting crude mixtures immediately desilylated as described above to avoid partial desilylation during purification of **4** by column chromatography. As can be observed in Table 1, the overall yields for the desilylated 3-(2-pyridyl)indoles **5** were always excellent. The reaction is even compatible with acidic hydroxy substituents: compound **5h** was obtained in 63% yield from 2-bromo-3-hydroxypyridine **3h**.

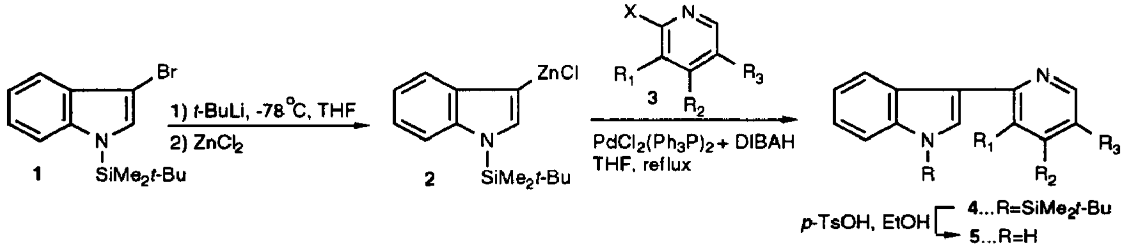


Table 1. The Palladium(0)-catalyzed Coupling of 3-Indolylzinc 2 with Halopyridines 3

	Halopyridine (3)				3-(2-Pyridyl)indole (5)	
	X	R_1	R_2	R_3	Product[a]	Yield(%)[b]
3a	Br	H	Me	H	**5a**	93
3b	Cl	H	Me	H	**5a**	52
3c	Br	H	H	H	**5c**[c]	95
3d	Cl	H	H	H	**5c**	84
3e	Br	Et	Me	H	**5e**[d]	88
3f	Br	H	Me	Et	**5f**[d]	89
3g	Br	OMe	H	H	**5g**	77
3h	Br	OH	H	H	**5h**	63
3i	Cl	CO_2Me	H	H	**5i**	90
3j	Cl	H	CO_2Me	H	**5j**[e]	95
3k	Cl	H	H	CO_2Me	**5k**[d]	97
3l	Cl	H	H	NO_2	**5l**	89
3m	Cl	NO_2	H	NO_2	**5m**	80

[a] All new compounds were identified by ^{1}H and ^{13}C NMR, IR, and elemental analysis. [b] Isolated yields (after column chromatography) based on **3**. [c] Reference 4i. [d] Reference 4d. [e] Reference 4e.

On the other hand, treatment of 2-chloropyrazine with 3-indolylzinc chloride **2** under the same set of reaction conditions afforded 3-(2-pyrazinyl)indole **7a** in 91% overall yield (Table 2). Similarly, halides derived from π-excedent heterocycles such as 2-bromothiophene, 3-bromothiophene, 3-bromofuran, and 3-bromo-(1-benzenesulfonyl)indole underwent cross-coupling reaction with **2** in the presence of Pd(0) to give the corresponding N-protected 3-(heteroaryl)indoles **6b-e**, although in lower yields. In these cases deprotection of indole had to be effected, after purification of **6**, by treatment with tetrabutylammonium fluoride (TBAF, 1.1 equiv, THF, 25 °C). Under these conditions, 3-(heteroaryl)indoles **7b-e** were obtained in good yields.

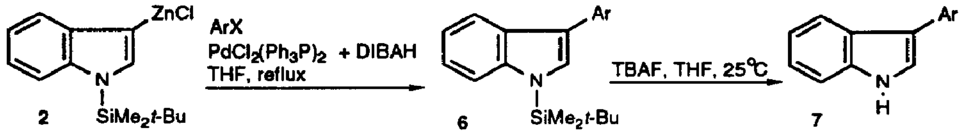
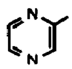
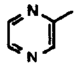
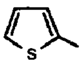
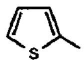
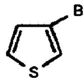
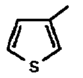
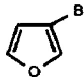
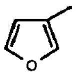
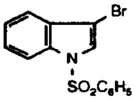
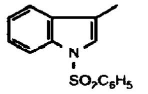


Table 2. The Palladium(0)-catalyzed Coupling of 3-Indolylzinc 2 with Heteroaryl Halides (ArX)

ArX	Product^a		
	Ar	6 (Yield)^b	7 (Yield)
		--	7a (91%)^b
		6b (50%)^c	7b (78%)^d
		6c (45%)^c	7c (80%)
		6d (12%)	7d (65%)^e
		6e (55%)	7e (78%)

[a] All new compounds were identified by ^{1}H and ^{13}C NMR, IR, and elemental analysis. [b] Isolated yields (after column chromatography) based on ArX. [c] The bithiophene dimer was formed in ~25% yield. [d] Reference 10. [e] Reference 11.

The above results not only further illustrate the usefulness of the *tert*-butyldimethylsilyl protecting group in the chemistry of 3-lithioindoles[8] and constitute an extensive application of 3-indolylzinc derivatives,[2a] a novel class of indole metal derivative,[9] but also provide a simple, efficient, and general procedure for the synthesis of 3-(2-pyridyl)indoles, a structural unit present in a large number of indole alkaloids belonging to several structural types.

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