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Palladium-catalyzed synthesis of 2-allylindole and 2-allylbenzofuran derivatives from 2-((trimethylsilyl)ethynyl)arenes

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ABSTRACT

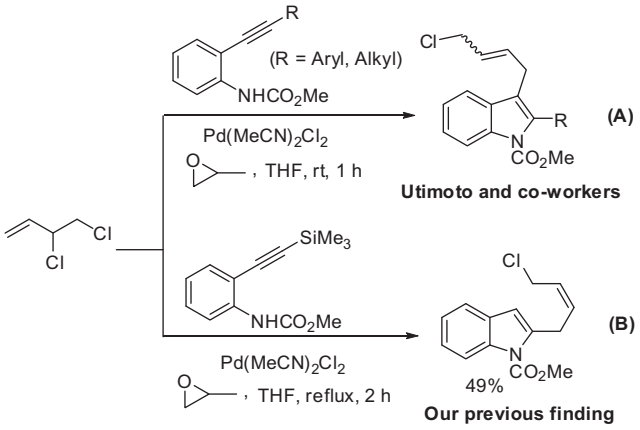
A new protocol for the synthesis of 2-allylindole and 2-allylbenzofuran derivatives has been developed from readily accessible starting material, 2-((trimethylsilyl)ethynyl)arenes via Pd-catalysis. The presence of trimethylsilyl group in the alkyne is vital for this reaction. Stereoselectivity of 2-allylindole derivatives is controlled by the use of different nitrogen-protecting groups for 2-((trimethylsilyl)ethynyl)aniline. The CO_2Me protection gives *Z-isomers*, whereas acetyl protection gives *E-isomers*.

Synthesis of functionalized indoles and benzofurans has been of considerable interest, because of their wide occurrence in natural products[1] and bioactive synthetic compounds.[2] In this context, the transition-metal catalyzed allylation has emerged as a powerful tool for access to functionalized indole and benzofuran derivatives.[3] Particularly, the allylative cyclization of 2-alkynylanilines or 2-alkynylphenols, mediated by palladium catalysts, is one of the most effective synthetic strategies for the construction of 2,3-disubstituted indoles and benzofuran rings.[4] In our earlier report[5] on indole-based heterocycle synthesis, we prepared several 3-allylindoles as starting materials by Utimoto's method[4a] in the presence of catalytic amount of $Pd(MeCN)_2Cl_2$ and propylene oxide in THF (Scheme 1A). Interestingly, a 2-allylated indole namely methyl 2-(4-chlorobut-2-enyl)-1*H*-indole-1-carboxylate was obtained in 49% yield[5] when methyl 2-((trimethylsilyl)ethynyl)phenylcarbamate was used as starting material under Utimoto's conditions (Scheme 1B).

Despite the obvious synthetic potential of 2-allylindoles,[6] the C2-allylation of indole[7] has been less explored compared to the C3-allylation.[8] This led us to a closer view of the regio- and stereo-selective syntheses of 2-allylindole and 2-allylbenzofuran derivatives further. Herein, we report a palladium-catalyzed synthesis of 2-allylindole and 2-allylbenzofuran derivatives from 2-((trimethylsilyl)ethynyl)anilines and 2-((trimethylsilyl)ethynyl) phenols, respectively, (Scheme 2).

As 2-((trimethylsilyl)ethynyl)arene derivatives **3** are the starting material for this reaction, a variety of 2-iodoarenes **1** were coupled with trimethylsilyl acetylene (**2**) under Sonogashira coupling conditions[9] to afford **3a**–**g** (Table 1, entries 1–7) in very good to excellent yields.

Next we focused our attention on the synthesis of 2-allylindoles via palladium-catalyzed coupling between 2-((trimethylsilyl)ethynyl)aniline derivatives and allyl chlorides. In order to improve the yield (Scheme 1 and 49%) for allylative cyclization, we tried to



Scheme 1. Reactions of 3,4-dichloro-1-butene with 2-alkynylanilines.

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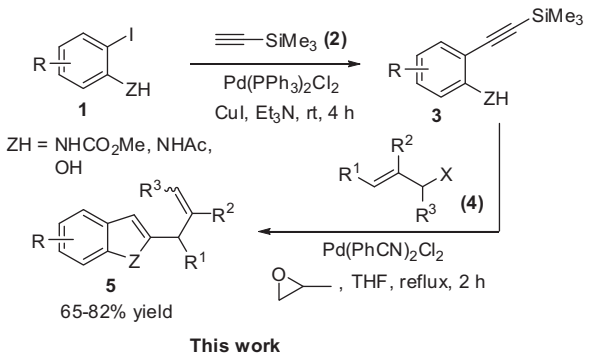
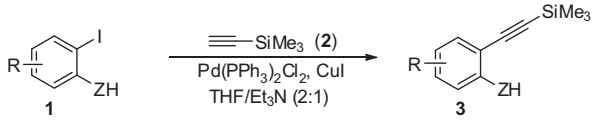


Scheme 2. Palladium-catalyzed synthesis of 2-allyl heteroarenes.

Table 1
Synthesis of 2-((trimethylsilyl)ethynyl)arenes



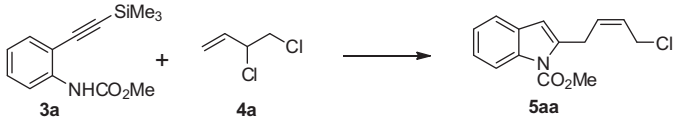
Entry	R	ZH	Product	Yield[a,b] (%)
1	H	$NHCO_2Me$	**3a**	89
2	4-Cl	$NHCO_2Me$	**3b**	85
3	5-Cl	$NHCO_2Me$	**3c**	86
4	H	NHAc	**3d**	77
5	4-Me	NHAc	**3e**	79
6	H	NHAc	**3f**	87
7	4-Me	$NHCO_2Me$	**3g**	86

[a] All reactions were carried out with substrate (1 mmol), alkyne (1.2 equiv), CuI (5 mol %), and $Pd(PPh_3)_2Cl_2$ (2.5 mol %) in THF/Et_3N (2:1) mixture at room temperature under Ar atmosphere for 4 h.
[b] Isolated yield.

optimize the reaction conditions with **3a** (Table 2). The choice of solvent proved to be crucial and only THF promoted this reaction (Table 2, entries 1–3). Notably, treatment with common bases such as CsF, KOAc, K_2CO_3, and Cs_2CO_3 instead of propylene oxide (used as a proton scavenger[4a]), gave cyclized product in poor yields (Table 2, entries 4, 5, 13, and 14). When a higher equivalent (10 equiv) of 3,4-dichloro-1-butene (**4a**) was used, yield was substantially increased to 68% (Table 2, entry 6). A variety of other palladium catalysts were also screened to check whether less concentration of **4a** can provide comparable yield (Table 2, entries 7–10). Among them $Pd(PhCN)_2Cl_2$ was found to be the best catalyst to give the product in a higher yield (76%, Table 2, entry 10). Further, the effect of catalyst loading was checked and it was observed that the yield got reduced to 35% when 2.5 mol % of catalyst (Table 2, entry 11) was used and no significant improvement was observed with 10 mol% catalyst (Table 2, entry 12).

With the optimum conditions on hand,[10] the substrate scope of our present procedure was investigated and the results are summarized in Table 3. A wide range of both 2-((trimethylsilyl)ethynyl)arenes (**3a**–**g**) and allyl halides (**4a**–**g**) were deployed to prove the general applicability of the allylative cyclization process (Table 3, entries 1–13). In accordance with Utimoto's proposition[4a] for a related reaction (Scheme 1) the coupling took place between 2-((trimethylsilyl)ethynyl)arenes and γ-position of allyl halides regioselectively to afford the desired products in good yields. The reaction is equally effective for indole rings and benzofurans as well. The most significant feature of the reaction is the stereochemical control of the allylindole derivatives by suitable choice of the protecting group either carbomethoxy or acetyl of 2-((trimethylsilyl)ethynyl)aniline (Table 3, entries 1–5). Thus carbomethoxy protected substrates provided selectively (*Z*)-2-allylindole derivatives (Table 3, entries 1–3) whereas acetyl protected substrates produced the corresponding (*E*)-isomers (Table 3, entries 4 and 5). However, 2-allylbenzofurans were obtained as *E*/*Z* mixtures (Table 3, entries 6 and 7). Using this standard reaction conditions, when indolization reactions were carried out with allyl halides **4d**, **4e**, and **4f**, the desired products were obtained in poor yields (12–18%). In an attempt to solve this problem, excess amount of allyl halides (**4d**, **4e**, and **4f**), propylene oxide, and palladium catalyst were employed in the allylation reaction. Under this modified conditions, **3g** and **3a** furnished very good yields of **5gd**, **5ge**, and **5af** (Table 3, entries 10–12). In case of allyl halides **4d** and **4e**, a trace amount of 2,3-diallylindoles (Table 3, entries

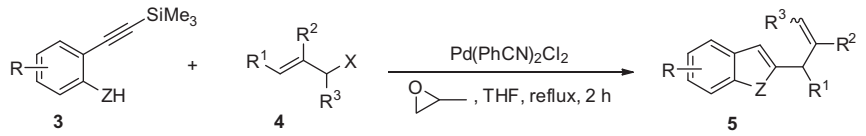
Table 2
Optimization of the reaction conditions for the allylative cyclization of **3a**

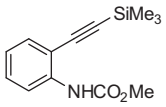
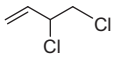
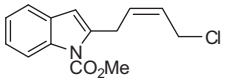
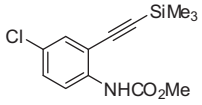
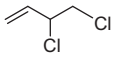
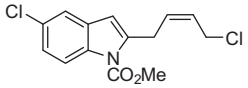
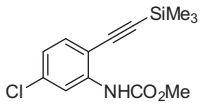
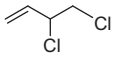
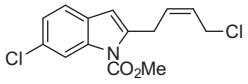
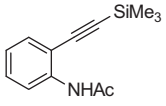
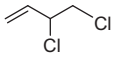
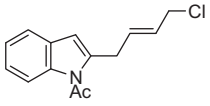
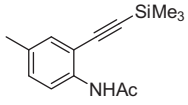
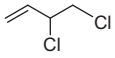
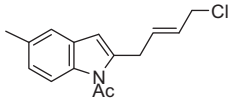
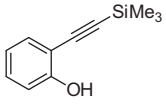
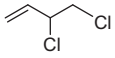
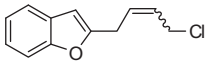
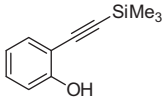
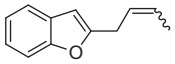
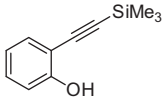
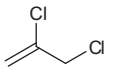
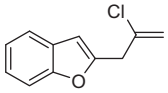
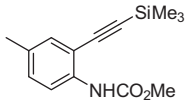
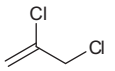
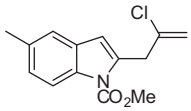
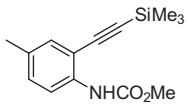
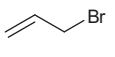
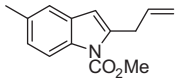
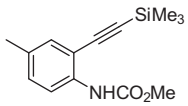
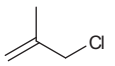
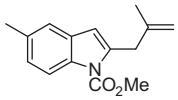
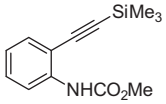
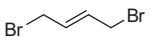
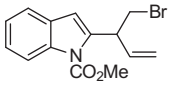
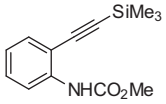
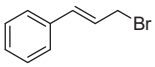
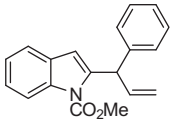


Entry	Catalyst (mol %)	Proton scavenger/base (equiv)	**4a** (equiv)	Solvent	Temp (°C)	Time (h)	Yield[a,b] (%)
1	$Pd(MeCN)_2Cl_2$ (5)	Propylene oxide (5)	4	THF	66	2	49
2	$Pd(MeCN)_2Cl_2$ (5)	Propylene oxide (5)	4	MeCN	75	12	nr[c]
3	$Pd(MeCN)_2Cl_2$ (5)	Propylene oxide (5)	4	DMF	100	12	nr[c]
4	$Pd(MeCN)_2Cl_2$ (5)	KOAc (2.5)	4	THF	66	12	19
5	$Pd(MeCN)_2Cl_2$ (5)	CsF (2.5)	4	THF	66	12	22
6	$Pd(MeCN)_2Cl_2$ (5)	Propylene oxide (5)	10	THF	66	2	68
7	$Pd(PPh_3)_2Cl_2$ (5)	Propylene oxide (5)	5	THF	66	12	nr[c]
8	$PdCl_2$ (5)	Propylene oxide (5)	5	THF	66	10	16
9	$Pd(OAc)_2$ (5)	Propylene oxide (5)	5	THF	66	10	37
10	**$Pd(PhCN)_2Cl_2$ (5)**	**Propylene oxide (5)**	**5**	**THF**	**66**	**2**	**76**
11	$Pd(PhCN)_2Cl_2$ (2.5)	Propylene oxide (5)	5	THF	66	2	35
12	$Pd(PhCN)_2Cl_2$ (5)	Propylene oxide (5)	5	THF	66	2	76
13	$Pd(PhCN)_2Cl_2$ (5)	K_2CO_3 (2.5)	5	THF	66	12	22
14	$Pd(PhCN)_2Cl_2$ (5)	Cs_2CO_3 (2.5)	5	THF	66	12	18

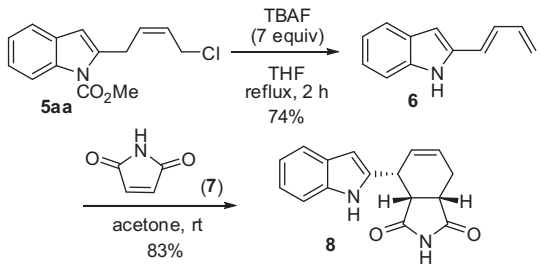
Entry 10 is showing the optimum conditions of this reaction.
[a] All reactions were carried out in 0.20 mmol scale in solvent (2 mL) under Ar atmosphere.
[b] Isolated yield.
[c] No conversion was observed.

Table 3
Synthesis of 2-allylindole and 2-allylbenzofuran derivatives



Entry		Substrate (**3**)		Allyl halide (**4**)		Product (**5**)	Yield[a,b] (%)	Stereoselectivity (**5**)
1	**3a**		**4a**		**5aa**		76	*Z*
2	**3b**		**4a**		**5ba**		72	*Z*
3	**3c**		**4a**		**5ca**		79	*Z*
4	**3d**		**4a**		**5da**		74	*E*
5	**3e**		**4a**		**5ea**		71	*E*
6	**3f**		**4a**		**5fa**		82	*E*/*Z*
7	**3f**		**4b**		**5fb**		80	*E*/*Z*
8	**3f**		**4c**		**5fe**		65	—
9	**3g**		**4c**		**5gc**		77	—
10[c,d]	**3g**		**4d**		**5gd**		66	—
11[c,d]	**3g**		**4e**		**5ge**		73	—
12[c]	**3a**		**4f**		**5af**		68	—
13	**3a**		**4g**		**5ag**		0	—

[a] All reactions were carried out with substrate **3** (0.50 mmol), allyl halide **4** (5 equiv), propylene oxide (5 equiv), and $Pd(PhCN)_2Cl_2$ (5 mol %) in THF (5 mL) under Ar atmosphere at 66 °C for 2 h unless otherwise mentioned.
[b] Isolated yield.
[c] Reactions were carried out with allyl halide (>15 equiv), propylene oxide (>15 equiv), and $Pd(PhCN)_2Cl_2$ (10 mol %).
[d] Trace amounts of 2,3-diallylindole derivatives were obtained.



Scheme 3. Diels–Alder reaction of indolyl-1,3-butadiene **6**.

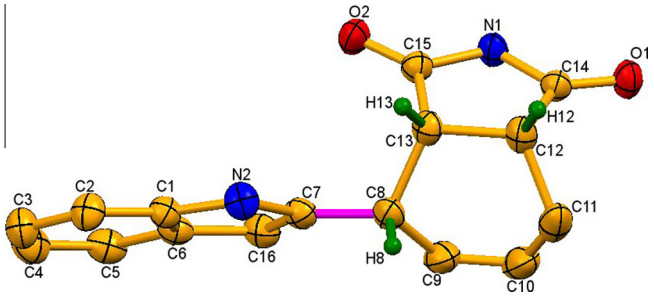


Figure 1. X-ray crystal structure of **8** (thermal ellipsoids are drawn at 30% probability level).

10 and 11) were obtained. We also tried to extend the synthetic scope of this reaction by including cinnamyl bromide **4g**; however this did not give any positive result under our present experimental conditions (Table 3, entry 13).

In order to establish the regioselectivity of **5aa**, we prepared 2-(buta-1,3-dienyl)-1*H*-indole **6** by applying our previously developed methodology.[9] Next, the Diels–Alder reaction was performed between diene **6** and maleimide **7** at room temperature, which led to the formation of crystallizable *endo* adduct **8**[11] in 83% yield (Scheme 3). The structure of the compound **8** was confirmed by the X-ray crystallographic analysis (Fig. 1).

In summary, we have found a general method for the efficient synthesis of 2-allylindoles and 2-allylbenzofurans from readily accessible starting materials. Significantly, the stereoselectivity of 2-(4-chlorobut-2-enyl)-1*H*-indoles can be controlled by proper choice of the nitrogen-protecting group of the corresponding 2-((trimethylsilyl)ethynyl)anilines leading to either *E* or *Z isomers*. To the best of our knowledge we are not aware of any report for such a selective formation of 2-allylindole derivatives.

Acknowledgments

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Supplementary data

Supplementary data (procedures of compounds **3**, **5gd**, **5ge**, **5af**, **6** and **8**, spectral data, copies of NMR spectra, crystal data of compound **8**, copies of decoupled spectra of compound **5aa** and proposed mechanism of allylative cyclization reaction) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.10.049.

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10. *General procedure for the synthesis of 2-allyl heteroarenes* **5**: To a stirred degassed solution of silyl ethynylarenes **3** (0.50 mmol) in dry THF (3.0 mL) under argon were added propylene oxide (2.5 mmol), allyl halides **4** (2.5 mmol), and $Pd(PhCN)_2Cl_2$ (0.025 mmol). The yellowish solution was degassed again and stirred under reflux for 2 h (TLC). Then the crude reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel using diethyl ether in petroleum ether (0–4%) as eluent to furnish 2-allyl heteroarenes **5** in good yields.
This procedure was followed for the preparation of **5aa**–**5gc** (Table 3, entries 1–9).
Characterization data for the compound **5aa** are given below:
A colorless liquid (94 mg, 76% yield) was isolated by flash column chromatography over silica gel (1% diethyl ether/petroleum ether). IR (neat/$CHCl_3$) ν 3070, 3045, 3030, 2954, 2906, 2852, 1739, 1653, 1593, 1568, 1456, 1440, 1375, 1327, 1306 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.07 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.29–7.20 (m, 2H), 6.41 (s, 1H), 5.92–5.81 (m, 2H), 4.19 (dd, J = 5.2, 2.8 Hz, 2H), 4.06 (s, 3H), 3.87 (d, J = 6.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.6, 139.2, 136.7, 130.8, 129.4, 127.6, 124.0, 123.3, 120.2, 115.8, 108.8, 53.8, 39.4, 28.1; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{15}ClNO_2$: 264.0791, found: 264.0786.
11. X-ray crystallographic data for compound **8** have been deposited to the Cambridge Crystallographic Data Centre and assigned the deposition numbers CCDC 1002032 for **8**.