Titanium-Catalyzed Hydroamination of Propargyl Alcohol Derivatives: Synthesis of 3-Silyloxy-2-methylindoles via Hydrohydrazination

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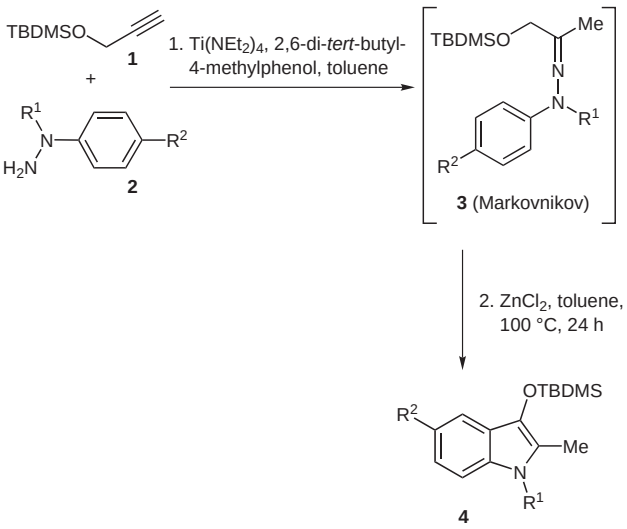
Abstract: A general method for the one-pot synthesis of substituted 3-(*tert*-butyldimethylsilyloxy)indoles via hydrohydrazination of alkynes and subsequent Fischer indole synthesis has been developed. For the first time titanium-catalyzed hydroaminations of propargyl alcohol derivatives are shown.

Key words: alkyne, hydrazine, hydroamination, indole, titanium

The addition of nitrogen compounds across carbon–carbon triple bonds continues to be an important subject for organic synthesis and catalysis.[1] Such addition reactions are perfectly suited to fulfill today's needs of green chemistry because atom economy or atom efficiency is in principle 100%. In recent years a variety of catalysts based on both early as well as late-transition-metal complexes has been developed. Based on the pioneering work of Bergman et al.[2] especially metallocenes have become popular catalysts in these reactions. More recently, Doye,[3] Odom,[4] Schafer[5] and other[6] made significant contributions to the further development of titanium catalysts with respect to intermolecular hydroaminations. However, in most reactions nonfunctionalized aromatic or simple aliphatic alkynes were reacted with primary amines as substrates. Thus, the hydroamination of more functionalized alkynes is still a challenging task. During our studies on the hydroamination of olefins and alkynes,[7] we became interested in the selective hydroamination of propargylic alcohols and their derivatives, which constitute probably the most prominent class of functionalized aliphatic alkynes. Here, we report the first examples of such reactions in the presence of titanium catalysts.

In addition to being environmentally benign, the hydroamination of alkynes opens up interesting possibilities for novel domino and one-pot reactions based on the resulting imines, enamines, or hydrazones. Recent examples include the combination of hydroamination coupled with direct nucleophilic addition of organometallic reagents[8] and electrocyclic rearrangements such as the Fischer indole synthesis.[9] For some time our group has been interested in the application of catalytic domino sequences such as hydrohydrazinomethylation of olefins,[10] carbonylations,[11] and hydrohydrazination of alkynes[12] for the synthesis and refinement of indoles.[13] Recently, we developed a one-pot synthesis of functionalized tryptamines and tryptophols starting from commercially available aryl hydrazines and chloroalkynes or 3- and 4-silyloxyalkynes.[12a,b] Based on this work, we studied the reaction of aniline, isobutylamine and *N*-methyl-*N*-phenylhydrazine with *tert*-butyldimethylsilyl-protected propargyl alcohol in the presence of a catalytic amount of tetrakis(diethylamino)titan [$Ti(NEt_2)_4$] and different phenols as ligands. While the former two model reactions gave only low yields (<5%) of the corresponding internal imine, the catalytic hydrohydrazination proceeded with significant conversion (>80%) in the presence of 2,6-di-*tert*-butyl-4-methylphenol as ligand! Interestingly, the resulting hydrazone is easily further converted in the presence of stoichiometric amounts of $ZnCl_2$ to give the corresponding siloxyindole in respectable yield (Scheme 1).



Scheme 1 Hydrohydrazination of silyl-protected propargyl alcohol to 3-silyloxy-2-methylindoles

To our delight the catalytic hydrohydrazination proceeded smoothly with high regioselectivity to the Markovnikov isomer **3**,[14] which underwent a selective Fischer indole synthesis to yield exclusively the 2,3-disubstituted indole **4**. To the best of our knowledge there is only a characterization of 3-phenoxy- and 3-methoxyindoles established and one different preparation of a special 2-substituted 3-silyloxyindole known in literature.[15] Noteworthy, a similar structural motif is found in furo[3,2-*b*]indoles, which are known to have potent analgesic and anti-inflammatory

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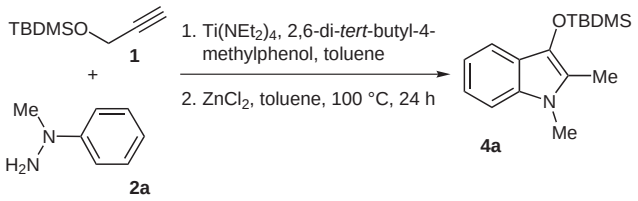
Table 1 Reaction of *tert*-Butyldimethylsiloxy-2-propyne (**1**) with *N*-Methyl-*N*-phenylhydrazine (**2a**)[a]



Entry	$Ti(NEt_2)_4$ (mol%)	Ligand (mol%)	Temp (°C)	Ratio hydrazine/alkyne	Time (h)	Yield (%)[b]
1	5	–	100	1.3:1	24	42
2	10	20	100	1.3:1	24	51
3	5	10	80	1.3:1	24	60
4	5	10	100	1.3:1	24	65
5	5	10	120	1.3:1	24	42
6	5	10	100	1:1.3	24	50
7	5	10	100	1.3:1	4	53

[a] *Reaction conditions*: hydrohydrazination: see Table 1; Fischer indole cyclization: $ZnCl_2$ (3.0 equiv), 100 °C, 24 h.
[b] Isolated yield based on *tert*-butyldimethylsiloxy-2-propyne.

activity[16] and act as potent BK_{Ca} channel openers for the treatment of neuronal damages or to treat cardiovascular diseases.[17]

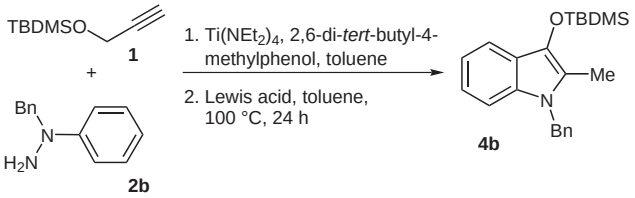
Selected results of the model reaction of *tert*-butyldimethylsiloxy-2-propyne (**1**)[18] with *N*-methyl-*N*-phenylhydrazine (**2a**) are shown in Table 1. The best yield of indole **4** (65%) is achieved applying 5 mol% $Ti(NEt_2)_4$ and 10 mol% 2,6-*tert*-butyl-4-methyl-phenol at 100 °C in the presence of a slight excess of hydrazine (Table 1, entry 4). Next, the effect of different Lewis acids on the Fischer indole cyclization was investigated. Therefore the hydrohydrazination of *tert*-butyldimethylsiloxy-2-propyne (**1**) and *N*-benzyl-*N*-phenylhydrazine (**2b**) was performed in the presence of different Lewis and Brønsted acids like *p*-toluenesulfonic acid (PTSA),[19] polyphosphoric acid (PPA),[20] and iron(III)chloride[21] instead of zinc chloride (Table 2).

However, none of the tested acids gave a better result compared to $ZnCl_2$ (50%).

Finally, we applied the optimized hydrohydrazination–cyclization protocol to ten different indole products (Table 3).[22] Commercially available aryl hydrazines with different substituents in the *para* position such as Me, OMe, F, Cl, Br, and SO_2Me were alkylated with methyl iodide or benzyl bromide in the presence of base and reacted with the in situ titanium catalyst and $ZnCl_2$ to give the desired 3-siloxyindole derivatives in good to moderate yields.

In general, the *N*-methyl-protected indoles gave a higher yield compared to the *N*-benzyl-protected indoles. Noteworthy, the reaction sequence can be performed easily up to a 10 g scale without loss in yield.

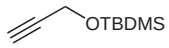
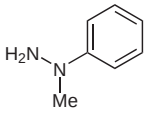
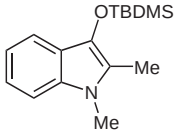
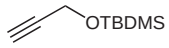
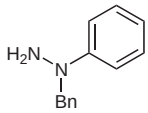
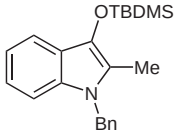
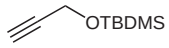
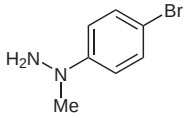
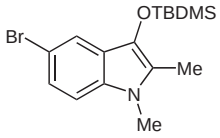
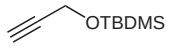
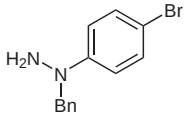
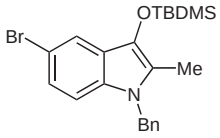
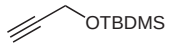
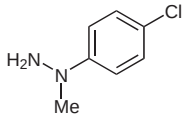
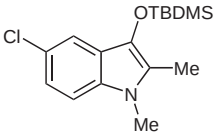
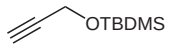
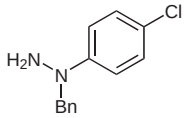
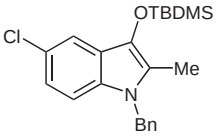
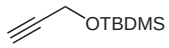
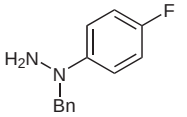
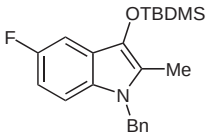
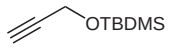
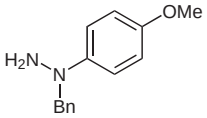
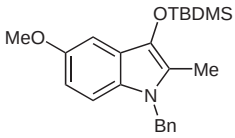
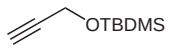
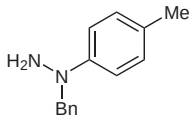
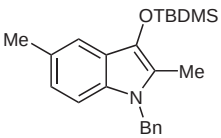
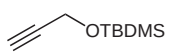
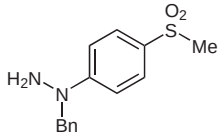
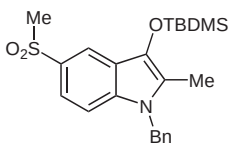
Table 2 Reaction of *tert*-butyldimethylsiloxy-2-propyne (**1**) with *N*-Benzyl-*N*-phenylhydrazine (**2b**)[a]



Entry	Lewis acid	Yield (%)[b]
1	$FeCl_3$	<1
2	NH_4Cl	<10
3	SO_2Cl_2	<1
4	AcOH	<1
5	PPA	<1
6	PTSA	<1
7	$Y(OTf)_3$	<10
8	$Zn(OTf)_2$	28
9	$ZnCl_2$	50

[a] *Reaction conditions*: hydrohydrazination: *tert*-butyl-dimethylsiloxy-2-propyne (1.0 mmol), *N*-benzyl-*N*-phenylhydrazine (1.3 mmol), $Ti(NEt_2)_4$ (5 mol%), 2,6-di-*tert*-butyl-4-methylphenol (10 mol%), toluene (2 mL), 100 °C, 24 h; Fischer indole cyclization: Lewis acid (3.0 mmol), 100 °C, 24 h.
[b] Isolated yield based on *tert*-butyldimethylsiloxy-2-propyne.

Table 3 Reaction of *tert*-Butyldimethylsiloxy-2-propyne (**1**) with Various Substituted Hydrazines (**2a**–**j**)[a]

Entry	Alkyne **1**	Hydrazine **2**		Product **4**		Yield (%)[b]
1			**2a**		**4a**	65
2			**2b**		**4b**	50
3			**2c**		**4c**	45
4			**2d**		**4d**	40
5			**2e**		**4e**	40
6			**2f**		**4f**	40
7			**2g**		**4g**	35
8			**2h**		**4h**	60
9			**2i**		**4i**	40
10			**2j**		**4j**	20

[a] *Reaction conditions*: hydrohydrazination: *tert*-butyldimethylsiloxy-2-propyne (1.0 mmol), arylhydrazine (1.3 mmol), $Ti(NEt_2)_4$ (5 mol%), 2,6-di-*tert*-butyl-4-methyl-phenol (10 mol%), toluene (2 mL), 100 °C, 24 h; Fischer indole cyclization: $ZnCl_2$ (3.0 mmol), 100 °C, 24 h.
[b] Isolated yield based on *tert*-butyldimethylsiloxy-2-propyne.

In conclusion, a new efficient method for the synthesis of functionalized 3-silyloxy-2-methylindoles has been developed. As key step the first titanium-catalyzed hydroamination of a propargylic alcohol derivative is applied. Starting from commercially available aryl hydrazines and silyl-protected propargyl alcohol a variety of new electron-rich indole derivatives are accessible with high regioselectivity in the presence of $Ti(NEt_2)_4$ and

2,6-di-*tert*-butyl-4-methylphenol. Further use of these 3-silyl-oxyindoles as intermediates for potential pharmaceuticals is currently under way in our laboratory.

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(22) **Representative Procedure: Synthesis of 1-Benzyl-3-(*tert*-butyldimethylsilyloxy)-2-methyl-1*H*-indole (4b)**

In an ACE pressure tube under an argon atmosphere the ligand 2,6-di-*tert*-butyl-4-methylphenol (22.0 mg, 0.1 mmol) is dissolved in 3 mL dry toluene. To this solution *N*-benzyl-*N*-phenylhydrazine (257.7 mg, 1.3 mmol), *tert*-butyldimethylsiloxy-2-propyne (209.0 mL, 1.0 mmol) and $Ti(NEt_2)_4$ (18 μL, 0.05 mmol) were added. The reaction mixture was heated at 100 °C for 24 h. Then the pressure tube was opened under argon to add $ZnCl_2$ (410.0 mg, 3.0 mmol). The reaction mixture was heated at 100 °C for further 24 h. After cooling to r.t. the solution was decanted and the dark residue was washed with toluene and EtOAc. After removal of the combined solvents in vacuo and purification by column chromatography (eluent: hexane–EtOAc = 10:1) yielded 1-benzyl-3-(*tert*-butyldimethylsilyloxy)-2-methyl-1*H*-indole (175.8 mg, 50%) as light yellow solid (mp 69 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.40 (m, 1 H), 7.27–7.21 (m, 3 H, *m*-, *p*-Ph), 7.10 (m, 1 H), 6.93 (m, 2 H), 6.86–6.87 (m, 2 H, *o*-Ph), 5.22 (s, 2 H, CH_2Ph), 2.20 (s, 3 H), 0.83 (s, 12 H), 0.15 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.4 (*i*-Ph), 135.6, 133.6, 128.9 (*m*-Ph), 128.4, 127.8 (*p*-Ph), 125.8 (*o*-Ph), 121.7, 120.6, 120.8, 120.7, 108.7, 46.9, 25.8, 18.2, 9.1, –5.3 ppm. MS (EI, 70 eV): *m/z* (relative intensity) = 351 (100) [M^+], 294 (27), 260 (13), 221 (25), 204 (12), 177 (8), 115 (15), 91 (90), 73 (71), 65 (8), 43 (6). HRMS (EI): *m/z* calcd for $C_{22}H_{29}NOSi$: 351.2013; found: 351.1999.