Hydroamination

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Titanium-Catalyzed Intermolecular Hydroamination of Vinylarenes**

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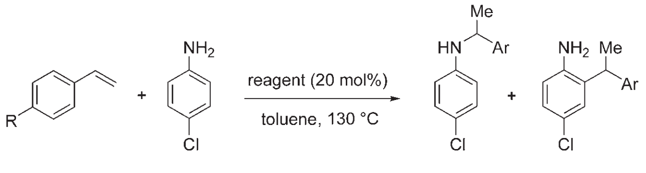
Most substituted amines are made today by multistep syntheses. Therefore, addition reactions of simple amines onto unsaturated carbon–carbon multiple bonds, hydroamination reactions,[1–6] are of considerable importance for industry and academia. Transformations of alkynes and allenes can be catalyzed by a variety of reagents.[7] However, protocols for intermolecular hydroamination reactions of more readily available olefins have thus far proven limited. Various lanthanide complexes catalyze hydroamination reactions of alkenes, but they lack compatibility with a number of important functional groups.[8,9] Significant research activity has focused on the use of late-transition-metal complexes for intermolecular hydroamination reactions of olefins, featuring iridium,[10–12] rhodium,[13–18] nickel,[19,20] palladium,[21–24] platinum,[25,26] and ruthenium.[27,28] The high cost of these complexes, their stabilizing ligands, or the additives constitute a limitation of these protocols. Recently, we reported a Group 4 metal catalyzed[29] intermolecular[30] hydroamination of norbornene.[31] Herein we present titanium-catalyzed[32] hydroamination reactions of vinylarenes as well as an application of this procedure to the synthesis of a tetrahydroisoquinoline.

Initial experiments showed that catalytic amounts of the Lewis acid $TiCl_4$ converted styrene (**1a**) in the presence of four equivalents of 4-chloroaniline (**2a**) efficiently at 130 °C (Table 1, entry 1). Control experiments indicated that a simple Brønsted acid mediated reaction is not operative (entries 3 and 4). These results are in agreement with observations made by Hartwig et al., who found that even the *intramolecular* addition of amines, not bearing an electron-withdrawing group, does not occur in the presence of concentrated sulfuric acid.[33,34]

Under the above reaction conditions, mixtures of hydroamination and *ortho*-hydroarylation products were obtained. While the reaction time for quantitative conversion could be reduced significantly with microwave irradiation, the amount of hydroarylation product increased (entries 6, 9, and 10). As the *ortho*-alkylated product was also predominantly formed when stoichiometric amounts of the Lewis acid $TiCl_4$ were employed (entry 7), we wondered if a rearrangement of the hydroamination product occurs. Accordingly, we synthesized secondary amine **3a** independently through a palladium-catalyzed amination reaction[35] and subjected it to the hydroamination reaction conditions [Eq. (1)]. Indeed, the secondary amine **3a** was quantitatively converted, while the primary amine **4a** remained unchanged under the reaction conditions [Eq. (2)].

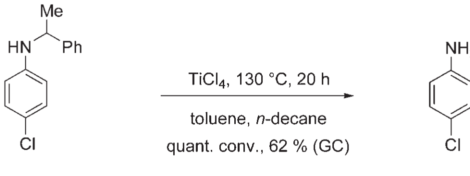
Table 1: Hydroamination of vinylarenes **1** with 4-chloroaniline (**2a**).[a]



1 **2a** **3** **4**

Entry	Reagent	R	*t* [h]	**3/4**[b]	Yield **3** [%][c]	Yield **4** [%][c]
1	$TiCl_4$	H (**1a**)	22	61:39	30 (**3a**)	32 (**4a**)
2	–	H (**1a**)	22	–	–	–
3	H_2SO_4	H (**1a**)	22	–	–	–
4	$4\text{-}ClC_6H_4NH_3Cl$	H (**1a**)	22	–	–	–
5	Cp_2TiCl_2	H (**1a**)	22	–	–	–
6	$TiCl_4$	H (**1a**)	4[d]	13:87	–	61 (**4a**)
7	$TiCl_4$	H (**1a**)	22[e]	16:84	–	52 (**4a**)
8	$TiCl_4$	Me (**1b**)	22	41:59	40 (**3b**)	40 (**4b**)
9	$TiCl_4$	Me (**1b**)	2[d]	7:93	–	68 (**4b**)
10	$TiCl_4$	F (**1c**)	6[d]	42:68	29 (**3c**)	37 (**4c**)

[a] Reaction conditions: **1** (1 mmol), **2a** (4 mmol), toluene (2 mL), 130 °C. [b] By GC analysis. [c] Yields of isolated product. [d] With microwave irridiation. [e] 1.0 equiv $TiCl_4$.



3a **4a**

(1)

Subsequently, we studied the scope of the catalytic intermolecular hydroamination of styrene derivatives (Table 2). A number of vinylarenes **1** and aniline derivatives **2** were efficiently converted with catalytic amounts of $TiCl_4$, leading to the functionalized products in high yields. Electron-poor amines underwent more efficient reactions

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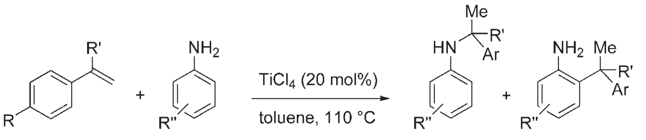
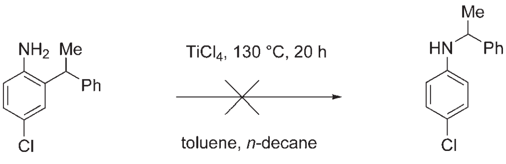
Table 2: Titanium-catalyzed hydroamination of vinylarenes **1**.[a]



1 **2** **3** **4**

Entry	R	R′	Amine	*t* [h]	**3**/**4**[b]	Yield **3** [%][c]	Yield **4** [%][c]	Yield **3**+**4** [%][c]
1	H	H (**1a**)	3,5-$(CF_3)_2C_6H_3NH_2$ (**2b**)	30	>99:1	87 (**3d**)	–	87
2	Cl	H (**1d**)	3,5-$(CF_3)_2C_6H_3NH_2$ (**2b**)	30	99:1	68 (**3e**)	–	68
3	F	H (**1c**)	3,5-$(CF_3)_2C_6H_3NH_2$ (**2b**)	30	>99:1	81 (**3f**)	–	81
4	H	H (**1a**)	2-$CNC_6H_4NH_2$ (**2c**)	22[d,e]	91:9	62 (**3g**)	–	62
5	H	H (**1a**)	2,4-$Br_2C_6H_3NH_2$ (**2d**)	20[d]	7:93	–	65 (**4h**)	65
6	H	H (**1a**)	4-$FC_6H_4NH_2$ (**2e**)	3[f,g]	32:68	21 (**3i**)	47 (**4i**)	68
7	H	H (**1a**)	3,5-$(CH_3)_2C_6H_3NH_2$ (**2f**)	20[g,h]	8:92	–	50 (**4j**)	50
8	H	Me (**1e**)	2-$ClC_6H_4NH_2$ (**2g**)	19[d]	<1:99	–	85 (**4k**)	85
9	H	H (**1a**)	2,4,6-$Cl_3C_6H_2NH_2$ (**2h**)	16[g]	–	–	–	–
10	OMe	H (**1f**)	2,4-$Br_2C_6H_3NH_2$ (**2d**)	22	<1:99	–	51 (**4l**)	51
11	H	H (**1a**)	3,5-$(CF_3)_2C_6H_3NH_2$ (**2b**)	22[i]	>99:1	85 (**3d**)	–	85

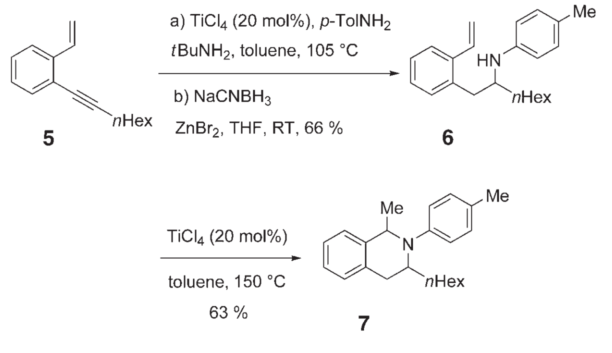
[a] Reaction conditions: **1** (1 mmol), **2** (4 mmol), $TiCl_4$ (20 mol%), toluene (2 mL). [b] By GC analysis. [c] Yields of isolated product. [d] 130°C. [e] **1a** (4 mmol), **2c** (1 mmol). [f] With microwave irridiation. [g] 170°C. [h] $TiCl_4$ (1 mmol). [i] $HfCl_4$ (20 mol%).



4a **3a** (2)

(entries 1–6). A variety of functional groups was tolerated by the catalyst, such as CF_3 (entries 1–3), Cl (entry 2), CN (entry 4), F (entries 3 and 6), and Br substituents (entries 5 and 10). Additionally, α-methylstyrene (**1e**) was quantitatively converted into product **4k**, which contains a quarternary carbon center (entry 8). Interestingly, di-*ortho*-substituted aniline **2h** was not converted (entry 9).[31] In the reaction of aniline **2b** catalytic amounts of the Lewis acid $HfCl_4$ led to comparable results (entry 11).

Finally, we applied the titanium-catalyzed hydroamination reaction to a regioselective synthesis of a tetrahydroisoquinoline (Scheme 1).[36] The highly regio- and chemoselective titanium-catalyzed hydroamination[37,38] of enyne **5** and subsequent one-pot reduction gave aminoalkene **6** in good yield. Intramolecular hydroamination of the remaining double bond yielded the desired tetrahydroisoquinoline **7** with excellent regioselectivity and a diastereoselectivity of 4:1.[39]



Scheme 1. Titanium-catalyzed synthesis of tetrahydroisoquinoline **7**.

In summary, we have described a protocol for titanium-catalyzed hydroamination reactions of styrene derivatives. A subsequent rearrangement gives rise to *ortho*-alkylated products. The catalytic system was applied to the synthesis of a tetrahydroisoquinoline derivative.

Experimental Section

Representative procedure for titanium-catalyzed hydroamination: A sealed tube was equipped with a septum and purged with N_2. The tube was charged with dry toluene (2 mL), 3,5-bis(trifluoromethyl)aniline (**2b**; 917 mg, 4.00 mmol), and styrene (**1a**; 104 mg, 1.00 mmol). $TiCl_4$ (0.022 mL, 0.20 mmol, 20 mol%) was added, the tube was sealed, and the resulting mixture was stirred for 30 h at 110°C. CH_2Cl_2 (5 mL), Et_2O (60 mL), aq NH_4OH (1N, 15 mL), and brine (50 mL) were added to the cold suspension. The separated aqueous phase was washed with Et_2O (2 × 60 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (silica gel, *n*-pentane/Et_2O 100:1) yielded *N*-1-phenylethyl-3,5-bis(trifluoromethyl)aniline (**3d**) as a yellow oil (290 mg, 87%).

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