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$TiCl_4$-Catalyzed Intermolecular Hydroamination Reactions of Norbornene

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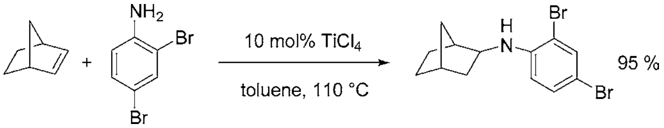
ABSTRACT



An intermolecular hydroamination reaction of norbornene is presented that uses catalytic amounts of user-friendly $TiCl_4$ and tolerates a variety of functional groups. In addition, a secondary amine is converted using this methodology.

The hydroamination reaction of carbon−carbon multiple bonds potentially provides an atom-economic access to substituted amines.[1] While a variety of protocols are available for the functionalization of alkynes,[2] a general procedure for the hydroamination of olefins remains elusive. Relatively few reports describe successful applications to unactivated olefins. Most prominent are lanthanide-catalyzed, often intramolecular,[3] hydroamination reactions[4,5] that, however, lack compatibility with a number of important functional groups. Significant research activity focused on the use of late transition metal complexes, featuring e.g., nickel,[6] palladium,[7] rhodium,[8,9] iridium,[10,11] and more recently, platinum[12] and ruthenium.[13] Yet for the most part, conjugated olefins were used in these studies. The hydroamination of norbornene (**1**) was found to be catalyzed by iridium[10,11] or rhodium[14,15] complexes.[16] Unfortunately, the high cost of these late transition metal catalysts as well as of their stabilizing ligands or additives is an important limitation of these methodologies.

Recently, several titanium complexes were shown to catalyze hydroamination reactions of alkynes.[17] These catalysts are significantly cheaper than known late transition metal catalysts, while tolerating a variety of functional groups. However, titanium-mediated hydroamination reac-

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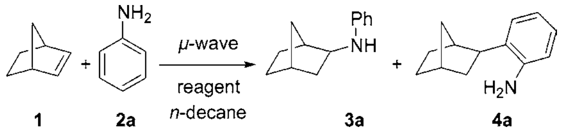
Table 1. Influence of Additives on the Hydroamination Reaction of Aniline (**2a**) onto Norbornene (**1**)[a]



entry	reagent (mmol)	*t* (h)	**3a**/**4a**[b]	conversion of **1**[b] (%)
1	$TiCl_4$ (2.0)	2	68/32	>98
2	$TiCl_4$ (2.0)[c]	2	65/35	>98
3	---	2	---	<2
4	$PhNH_3Cl$ (2.0)	2	---	<2
5	Cp_2TiCl_2 (2.0)[c]	2	---	<2
6	H_2SO_4 (4.0)[c]	2	---	<2
7	HCl (4.0)[c]	2	---	<2
8	$TiCl_4$ (2.0)[c,d]	2	68/32	>98

[a] Reaction conditions: 2 mmol of **1**, 8 mmol of **2a**, and 2 mL of toluene. [b] By GC using *n*-decane as internal standard. [c] Thermal reaction in an oil bath at 169 °C. [d] Without solvent.

tions are so far limited to alkynes and allenes, and no such transformation involving an unactivated olefin was described.[18] We reported $TiCl_4$-catalyzed intermolecular hydroamination reactions of alkynes.[19] In continuation of this work, we present herein $TiCl_4$-catalyzed hydroamination reactions of norbornene (**1**) and provide a mechanistic rationale for this transformation.[20]

Based on our recently developed protocol for $TiCl_4$-catalyzed intermolecular hydroamination reactions of alkynes,[19] we focused our attention on the use of olefinic substrates. Therefore, we studied the influence of microwave irradiation[21] on the addition of aniline (**2a**) onto norbornene (**1**). Microwave-assistance allowed for a $TiCl_4$-mediated intermolecular hydroamination of norbornene (**1**) (Table 1, entry 1). In addition to amine **3a**, side product **4a**, generated via regioselective activation of a C−H bond, was formed in a **3a**/**4a** ratio of ca. 7:3. Such hydroarylation products were previously observed in rhodium-catalyzed addition reactions of aniline (**2a**) onto norbornene (**1**)[14,15] as well as iridium-mediated transformations of norbornene (**1**) with benzamide[22] or phenol.[23] Nonthermal microwave effects found controversial interpretation in the literature.[24] Here, quantitative conversion of alkene **1** was also achieved by applying conventional heating in an oil bath at 169 °C (entry 2). A number of reactions were performed to test the likelihood of a Brønsted acid-mediated reaction. Neither the use of chlorides $PhNH_3Cl$ (entry 4) or Cp_2TiCl_2 (entry 5) nor of 2 equiv of concentrated sulfuric (entry 6) or hydrochloric acid (entry 7) gave rise to significant amounts of products **3a** or **4a**. These results are in agreement with observations made by Hartwig, showing that the *intramolecular* addition of amines, not bearing an electron-withdrawing group, even onto *activated* olefins does not occur using concentrated sulfuric acid.[25] Therefore, a plain Brønsted acid mediated reaction seems unlikely to be operative. Importantly, the reaction could be carried out in the absence of toluene in neat aniline (entry 8). Next we studied the scope of the stoichiometric hydroamination reaction (Table 2).

Reactions were generally conducted until quantitative conversion of norbornene (**1**) was obtained.[26]

Some aspects are noteworthy: (i) The chemoselectivity of the transformation depended upon the electron density at the nitrogen moiety in the aniline derivative, giving rise to highly selective hydroamination reactions for electron-poor aniline derivatives.[27] (ii) A variety of functional groups, such as F- (entries 4 and 5), Cl- (entries 6 and 7), Br- (entries 8 and 9), CF_3- (entry 10), and CN-substituents (entry 11), were tolerated. (iii) While norbornene (**1**) was completely converted using mesitylamine (**2c**) (entry 3), 2,4,6-trichloroaniline (**2l**) did not yield any hydrofunctionalization products, even after prolonged heating at 169 °C (entry 12). (iv) Only a directed hydroarylation in the ortho position of the aniline derivative was observed, and no products stemming from a meta or para functionalization were obtained as judged by inspection of the crude reaction mixtures. (v) *N*-Deuterated

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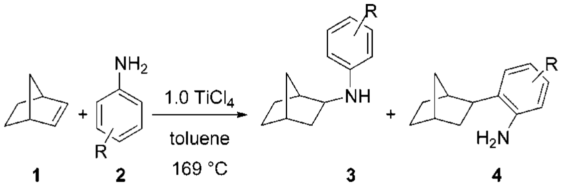
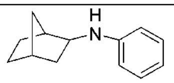
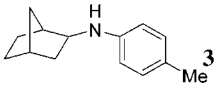
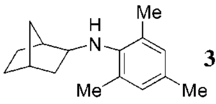
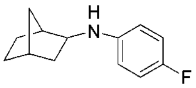
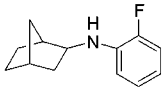
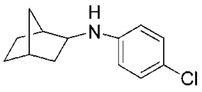
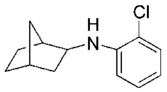
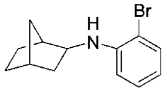
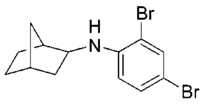
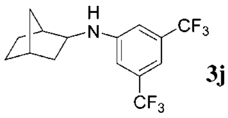
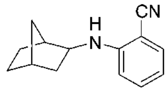
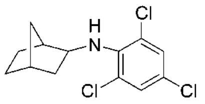
(26) **Representative Procedure for Hydroamination of Norbornene (1): *N*-(*exo*-Bicyclo[2.2.1]hept-2-yl)-*N*-(2-chlorophenyl)amine (3g).** $TiCl_4$ (0.22 mL, 2.00 mmol) was added to a solution of norbornene (**1**) (0.188 mg, 2.00 mmol) and 2-chloroaniline (1.02 g, 8.00 mmol) (**2g**) in toluene (2 mL) under N_2. The suspension was stirred at 169 °C for 2 h in a sealed tube, after which GC/MS analysis indicated complete conversion of norbornene (**1**). CH_2Cl_2 (50 mL) and saturated aqueous $NaHCO_3$ (20 mL) were added to the cooled reaction mixture. The separated aqueous phase was extracted with CH_2Cl_2 (2 × 75 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The remaining residue was purified by column chromatography on silica gel (*n*-pentane/Et_2O, 200/1) to yield **3g** as a pale yellow oil (346 mg, 78%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (dd, 1H, $J = 7.9, 1.4$ Hz), 7.13 (ddd, 1H, $J = 7.9, 7.9, 1.4$ Hz), 6.65 (dd, 1H, $J = 7.9, 1.4$ Hz), 6.60 (ddd, 1H, $J = 7.9, 7.9, 1.4$ Hz), 4.18 (s, 1H), 3.28 (m, 1H), 2.35−2.20 (m, 2H), 1.87 (ddd, 1H, $J = 12.8, 7.6, 2.4$ Hz), 1.65−1.45 (m, 3H), 1.35−1.10 (m, 4H); ^{13}C NMR (75 MHz, DEPT, $CDCl_3$) δ 143.6 (C), 129.0 (CH), 127.8 (CH), 118.9 (C), 116.7 (CH), 112.0 (CH), 56.5 (CH), 41.4 (CH), 41.0 (CH_2), 35.8 (CH), 35.3 (CH_2), 28.5 (CH_2), 26.3 (CH_2); IR (KBr) 3420, 3069, 2954, 2870, 1598, 1510, 1326, 1034, 739 cm^{-1}; MS (EI) *m*/*z* (relative intensity) 221 (55) [M^+], 166 (21), 153 (53), 127 (100), 67 (46); HR-MS (EI) *m*/*z* calcd for $C_{13}H_{16}NCl$ 221.0971, found 221.0972.

(27) Comparison of NMR and MS data for **3a** and **4a** with those reported in the literature confirmed unambiguously formation of the corresponding *exo*-diastereomers.

Table 2. Scope of Stoichiometric Hydroamination Reactions of Norbornene (**1**)[a]

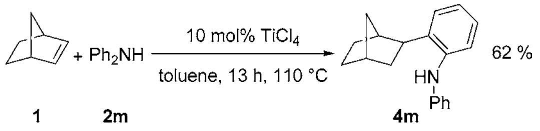


entry	*t* [h]	ratio **3/4**[b]	product		isolated yield **3**
1	2	65/35		**3a**	48 %[c]
2	12	59/41		**3b**	24 %[c]
3	6	100/0		**3c**	60 %
4	4	76/24		**3d**	56 %[c]
5	2	95/5		**3e**	80 %
6	4	83/17		**3f**	67 %[c]
7	2	89/11		**3g**	78 %
8	3	91/9		**3h**	81 %
9	3	96/4		**3i**	83 %
10	1	98/2		**3j**	54 %[c]
11	12	98/2		**3k**	47 %[d]
12	30	---		**3l**	---

[a] Reaction conditions: 2 mmol of **1**, 8 mmol of **2**, 2 mL of toluene. [b] By GC/MS analysis of the crude mixture. [c] Isolated yield for the corresponding tosylated compound, after subsequent reaction with TsCl in pyridine at room temperature. [d] Using 1.0 equiv of amine.

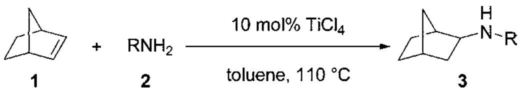
p-toluidine **2b** (70% D) yielded hydroamination product **3b** with incorporation of deuterium in the ortho position of the aniline derivative (70% D). (vi) An indication of reduction of titanium(IV) to titanium(III) was not observed. (vii) Norbornene (**1**) was converted quantitatively using *secondary amine* **2m** (Scheme 1) and hydroarylation product **4m** was formed as the major product.

Scheme 1. $TiCl_4$-Catalyzed Reaction with a Secondary Amine



For all functionalized amines, an optimization of the reaction conditions was performed, highlighting that *catalytic* amounts of $TiCl_4$ allow for complete conversion of norbornene (**1**) even at 110 °C (Table 3).

Table 3. $TiCl_4$-Catalyzed Hydroamination of Norbornene (**1**)[a]



entry	R	*t* (h)	product	isolated yield (%)
1	2-FC_6H_4	21	**3e**	70[b]
2	2-ClC_6H_4	18	**3g**	89[b]
3	2-BrC_6H_4	18	**3h**	88
4	2,4-$Br_2C_6H_3$	20	**3i**	95
5	3,5-$(CF_3)_2C_6H_3$	21	**3j**	83[c]
6	2-$(CN)C_6H_4$	20	**3k**	45[b,d]

[a] Reaction conditions: 2 mmol of **1**, 8 mmol of **2**, and 2 mL of toluene. [b] 130 °C. [c] 5 mol % of $TiCl_4$. [d] Using 1.0 equiv of amine.

A mechanistic hypothesis, which accounts for the formation of the hydroamination product, the conversion of a secondary amine and the regioselective ortho-functionalization reaction, is provided in Scheme 2.

Titaniumdiamide **5** can give rise to imido complex **6** through elimination of aniline. Analogous imido species are the active catalytic species in titanocene-based hydroamination reactions.[28,29] Wolczanski showed elegantly that comparable titaniumimido complexes even undergo intermolecular C−H bond activation reactions.[30] If such an activation reaction occurs intramolecularly, cyclometalated complex **7** is formed. Alternatively, metallacycle **7** might be formed directly from diamide **5**. This direct route is likely to be operative when $HNPh_2$ is the substrate. A formal insertion of norbornene (**1**) constitutes the chemose-

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(29) Pohlki, F.; Doye, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 2305.
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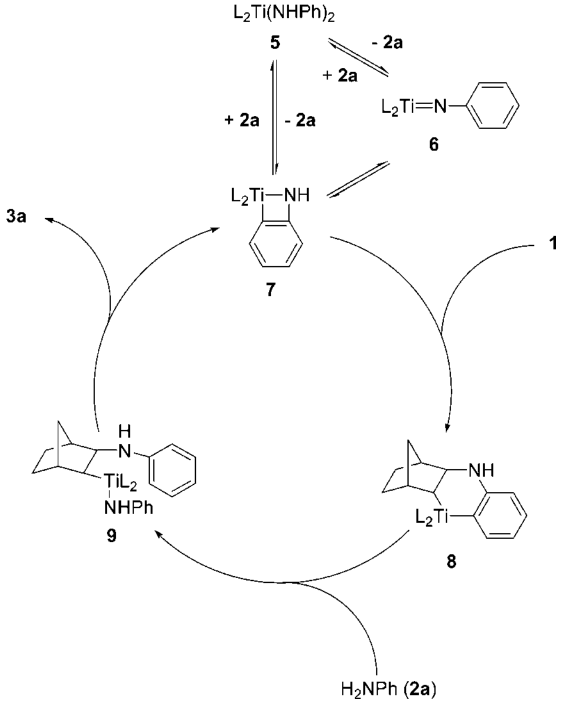
Scheme 2. Proposed Mechanism for $TiCl_4$-Catalyzed Hydroamination Reactions of Norbornene (**1**)



lectivity-determining step. Through an insertion into the titanium−nitrogen bond, metallacycle **8** is formed, which yields hydroamination product **3a** after subsequent protonolysis.

In summary, we present a user-friendly $TiCl_4$-catalyzed hydroamination reaction of norbornene (**1**), which tolerates a variety of functional groups. Regioselective hydroarylation occurs as a competing reaction, and secondary amines can be used as well. This represents one of the first two catalytic systems based on early transition metals for the intermolecular hydroamination of norbornene (**1**).[20]

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Supporting Information Available: Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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