A Dramatic Effect of Aryloxo Ligands on the Titanium-Catalyzed Hydroamination of Alkynes
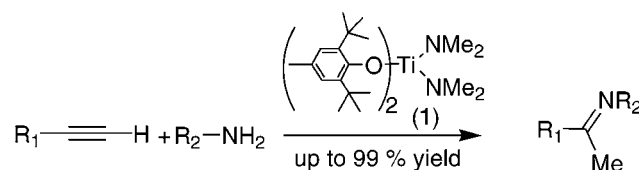
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ABSTRACT

The aryloxotitanium complex 1 is a highly chemo- and regioselective catalyst for intermolecular hydroamination of terminal alkynes. Branched imines are obtained in good to excellent yield (up to 99%) with various primary aromatic and aliphatic amines.

The direct addition of N–H bonds to alkenes and alkynes (hydroamination reaction) is a straightforward approach toward the synthesis of substituted nitrogen-containing products.[1] As a result of the 100%-atom economy of the reaction, no byproducts such as salts or water are produced. Apart from being environmentally benign, in the case of alkynes this method opens up interesting possibilities for new domino or one-pot reactions, e.g., a hydroamination coupled with direct nucleophilic addition of organometallic reagents.[2]

Originally, the catalytic intermolecular hydroamination of alkynes was carried out in the presence of Hg and Tl salts.[3] Later, alkali metals,[4] complexes of early-transition[5] and late-transition metals,[6] lanthanides,[7] and actinides[8] have been developed to promote these reactions.

Among the different catalysts for alkyne aminations, titanium compounds have found widespread interest due to their general reactivity and cheap and ubiquitous availability

as compared to toxic metals (Hg, Tl, U, and Th) or more expensive metal complexes (Ru, Pd, and Rh). Important progress in the intermolecular hydroamination of alkynes with titanium complexes has been reported by Bergman[9] and Doye.[10] In addition to synthetic applications, they also performed kinetic measurements[5e,10a] and established a general mechanism using dimethyltitanocene as catalyst. Inspired

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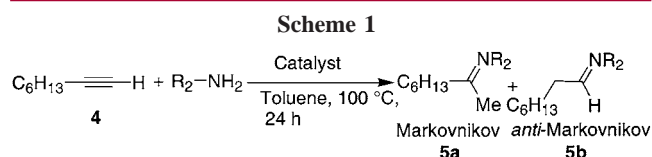
by this work, we described last year stable titanocene alkyne complexes of the type [Cp$_2$Ti(η^2-Me$_3$SiC$_2$R)] for the selective *anti*-Markovnikov hydroamination of terminal alkynes with aliphatic amines.[11]

More recently, non-Cp-based titanium complexes were studied for intermolecular hydroamination of alkynes. Odom and co-workers described Ti(NMe$_2$)$_4$ **2**[12] and pyrrolyl titanium complexes,[13] and Richeson et al. reported a guanidinate-supported titanium imido complex as precatalyst for these reactions.[14]

Despite the aforementioned advantages, known titanocene precatalysts exhibit in general high air and moisture sensitivity. Also mixtures of regioisomeric imines are often obtained as products using nonsymmetrical alkynes as starting materials. Thus, there exists a considerable interest in the improvement of titanium-based hydroamination catalysts. We wondered whether it was possible to improve the performance of Odom's useful catalyst **2** by addition of sterically hindered phenols as ligands. In general, free hydroxy groups are not tolerated by titanium complexes and catalyst activity breaks down. Nevertheless, sterically hindered phenols have been used in a few titanium-catalyzed reactions as controlling ligands.[15] However, to the best of our knowledge, apart from one example, phenols have not been applied as ligands in intermolecular hydroamination reactions.[16]

Here we report for the first time that bis(2,6-di-*tert*-butyl-4-methylphenoxo)-bisdimethyl-amide titanium **1** is a highly chemo- and regioselective hydroamination catalyst for terminal and internal alkynes with primary and secondary aliphatic amines, benzylamines, and anilines.

In first experiments, the addition of aniline and benzylamine to 1-octyne **4** was studied as a model reaction (Scheme 1). Initially the behaviors of complex **1**, Ti(NMe$_2$)$_4$ **2**, and **2**

Scheme 1

in the presence of 2,6-di-*tert*-butyl-4-methylphenol **3** were compared (Table 1).

The hydroamination of 1-octyne with aniline in the presence of 5 mol % of commercially available **2** gave the corresponding imine in good yield (89%) but low regioselectivity (Markovnikov/*anti*-Markovnikov = 60:40) (Table 1, entry

Table 1. Hydroamination of 1-Octyne[a]

entry	R^2	catalyst (mol %)	temp (°C)	conv[b] (%)	yield (%)[c] (5a:5b)
1	Ph	**2** (5)	100	100	89 (60:40)
2		**2** (5)/**3** (10)	100	100	98 (93:7)
3		**1** (5)	100	100	99 (93:7)
4	PhCH$_2$	**2** (10)	100	74	0
5		**2** (10)/**3** (20)	100	100	98 (87:13)
6		**1** (10)	75	90	90 (63:37)[d]
7		**1** (5)	85	84	84 (60:40)
8		**1** (10)	85	97	90 (69:31)
9		**1** (5)	100	100	98 (72:28)
10		**1** (10)	100	100	99 (75:25)
11		**1** (5)	120	100	99 (81:19)
12		**1** (5)	140	100	96 (>99:1)

[a] Reaction conditions: 1-octyne (1.5 mmol), amine (1.8 mmol), time (24 h), toluene (2.0 mL). [b] Conversion is based on 1-octyne. [c] Yield is determined by GC analysis with dodecane or hexadecane as internal standard. [d] Time (48 h).

1). Simply adding 10 mol % of **3** improved the yield and selectivity in a remarkable manner. Similarly, precatalyst **1** gave an excellent yield (99%) and high regioselectivity of the Markovnikov imine (93:7) (Table 1, entry 3). Using benzylamine in the presence of 10 mol % of **2** did not lead to any imine product; however, oligomerization of **4** is observed (Table 1, entry 4). Again, by simply adding 20 mol % of **3** or by using complex **1** as catalyst, an excellent yield of the corresponding imines (98−99%) (Table 1, entries 5 and 10) is obtained. The model reaction also proceeds at lower temperature (75 °C) and with a lower amount of catalyst (Table 1, entries 6−8). Interestingly, the best regioselectivities (Markovnikov/*anti*-Markovnikov = >99:1) are achieved at 140 °C.
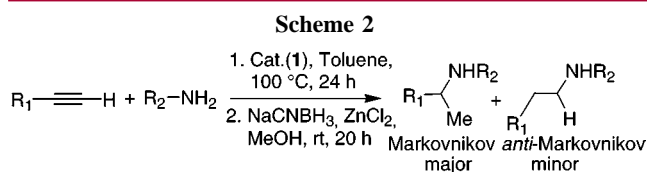
Next, we were interested in the behavior of complex **1** in the reaction of 1-octyne with other aromatic and aliphatic amines. Despite the possibility of using an in situ-catalyst (**2**/**3**) we decided to apply **1** as a catalyst due to the easier handling and increased stability compared to **2**. **1** is easily synthesized from commercially available 2,6-di-*tert*-butyl-4-methylphenol **3** and **2** in one step in good yield (72%).[17] Advantageously, the bisaryloxotitanium complex **1** can be handled without precautions for short time in air. Under argon at room temperature it is even stable for several months.

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Scheme 2

Scheme 2

As shown in Table 2, in all cases a highly regioselective hydroamination of 1-octyne **4** occurred. Reaction with different substituted anilines and subsequent reduction gave the corresponding secondary amines in good to excellent yield (92−99%). Typically the Markovnikov-isomer of the hydroamination reaction step is observed with a selectivity between 93:7 and 99:1. As a result of the slower hydrogenation of the linear imine compared to the branched imine, the selectivity for the branched amine is even higher. Our novel catalyst system tolerates a variety of functional groups. The reaction proceeded nicely for electron-rich anilines (Table 2, entries 2−4, 7−9) and anilines with electron-withdrawing groups (Table 2, entries 5, 6, 10). Sterical demanding groups, e.g., methyl or isopropyl at the *ortho* position, give the corresponding Markovnikov product in excellent yield and selectivity (Table 2, entries 3 and 9). However, 4-aminobenzonitrile gave the corresponding imine in lower yield (25%) under the same conditions.

Apart from arylamines we were also interested to explore the feasibility of catalyst **1** in hydroamination reactions with alkylamines (Table 3). Different primary and secondary alkyl

Instead of isolation of the resulting imines we favored a direct conversion of the alkyne to the corresponding amines (Scheme 2). The initially formed imine is reduced subsequently with NaCNBH₃ in the presence of ZnCl₂ to give the secondary amines in high yields.

Table 2. Amination of 1-Octyne with Anilines[a]

entry	amine	Markovnikov product	yield[b] [%]
1			92
2			98
3			94
4			91
5			97
6			98
7			96
8			95
9			98[c]
10			99[c]

[a] Reaction conditions. Hydroamination step: 1-octyne (1.5 mmol), amine (1.8 mmol), catalyst **1** (5 mol %), 100 °C, 24 h, toluene (2.0 mL). Reduction step: NaCNBH₃ (3.0 mmol), ZnCl₂ (1.5 mmol), room temperature, 15−20 h, MeOH (5.0 mL). [b] Yield is determined by GC analysis with dodecane as internal standard after reduction. [c] Catalyst **1** (10 mol %).

Table 3. Amination of 1-Octyne with Aliphatic Amines[a]

entry	amine	Markovnikov product	yield[b] (%)
1			70
2			81
3			85
4			89
5			72[c]

[a] Reaction conditions. Hydroamination step: 1-octyne (1.5 mmol), amine (1.8 mmol), catalyst **1** (10 mol %), 100 °C, 24 h, toluene (2.0 mL). Reduction step: NaCNBH₃ (3.0 mmol), ZnCl₂ (1.5 mmol), room temperature, 15−20 h, MeOH (5.0 mL). [b] Yield is determined by GC analysis with dodecane as internal standard after reduction. [c] The ee value of the two obtained distereomers has not been determined.

amines and benzylamine reacted smoothly with **4** in the presence of 10 mol % of **1**.

After subsequent reduction the Markovnikov products are obtained preferentially. Unfortunately, hydroamination with enantiomerically pure (*S*)-1-phenylethylamine and subsequent reduction yielded two diastereomeric Markovnikov products in nearly 1:1 ratio.

In general the alkylamines favored the Markovnikov addition products with somewhat lower selectivity compared to that of the aromatic amines. Nevertheless all secondary amines shown in Table 3 were obtained in good to very good yields (70−89%).

Table 4. Hydroamination of Different Alkynes with Various Aromatic and Aliphatic Amines and Subsequent Reduction or Hydrolysis [a]

entry	alkyne	Amine	yield[b] of Markovnikov product (%)
1	phenylacetylene	aniline (NH_2)	72[c]
2	3-phenyl-1-propyne	4-fluoroaniline (F, NH_2)	89
3	N,N-dimethyl-propargylamine	4-methoxyaniline (MeO, NH_2)	69[c,d]
4	3-cyclopentyl-1-propyne	4-chloroaniline (Cl, NH_2)	97
5	3-phenyl-1-propyne	cyclooctylamine (NH_2)	71
6	3-cyclopentyl-1-propyne	benzylamine (NH_2)	88
7	Ph——Ph	n-propylamine (NH_2)	99[e]
8	Ph——Me	aniline (NH_2)	97[f]

[a] Reaction conditions. Hydroamination step: 1-octyne (1.5 mmol), amine (1.8 mmol), catalyst **1** (5 mol %), 100 °C, 24 h, toluene (2.0 mL). Reduction step: NaCNBH$_3$ (3.0 mmol), ZnCl$_2$ (1.5 mmol), room temperature, 15−20 h, MeOH (5.0 mL). [b] Yields are determined by GC analysis with dodecane or hexadecane as internal standard after reduction or after hydrolysis with 5% HCl for correponding ketone. [c] 115 °C. [d] Catalyst (10 mol %). [e] Catalyst (10 mol %), 48 h, 120 °C; yield for 1,2-diphenylethanone. [f] Catalyst (10 mol %), 48 h, 130 °C, yield for phenylacetone.

Furthermore we explored the scope of catalyst **1** in hydroaminations of other alkynes. Here, we have tested the reaction of various aliphatic, aromatic, and functionalized alkynes with different aryl and alkylamines (Table 4). In all cases complete conversion of the alkyne is observed. Phenyl acetylene undergoes hydroamination with aniline to yield the Markovnikov product in 72% yield. Here small amounts (<5%) of oligomers and polymers have been observed as side-products. 1-Phenyl-3-propyne gave the corresponding product in 89% yield under similar reaction conditions. *N,N*-Dimethyl-propargylamine needed a catalyst loading of 10 mol % and higher reaction temperature (115 °C) to give 69% of the Markovnikov addition product (Table 4, entry 3). Unfortunately, methyl propargyl ether did not react under these conditions; however, 3-cyclopentyl-1-propyne gave the Markovnikov amines in very good yield (Table 4, entries 4 and 6). Also, internal alkynes gave the corresponding imines in high yield albeit at reaction temperatures >120 °C (Table 4, entries 7 and 8).

In summary, we have introduced the stable aryloxotitanium complex **1** as a novel pre-catalyst for hydroamination of terminal and internal alkynes.

In general, highly selective hydroaminations of terminal alkynes to give the Markovnikov products are obtained. Further work using other aryloxotitanium complexes for hydroamination reactions is currently in progress.

Supporting Information Available: Synthesis and characterization of complex **1**, experimental procedures, and characterization data for all new compounds and references for the compounds generated. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035653+