A General Study of [(η^5-Cp′)$_2$Ti(η^2-Me$_3$SiC$_2$SiMe$_3$)]-Catalyzed Hydroamination of Terminal Alkynes: Regioselective Formation of Markovnikov and Anti-Markovnikov Products and Mechanistic Explanation (Cp′ = C$_5$H$_5$, C$_5$H$_4$Et, C$_5$Me$_5$)

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Abstract: A general study of the regioselective hydroamination of terminal alkynes in the presence of [(η^5-Cp)$_2$Ti(η^2-Me$_3$SiC$_2$SiMe$_3$)] (**1**), [(η^5-CpEt)$_2$Ti(η^2-Me$_3$SiC$_2$SiMe$_3$)] (CpEt = ethylcyclopentadienyl) (**2**), and [(η^5-Cp*)$_2$Ti(η^2-Me$_3$SiC$_2$SiMe$_3$)] (Cp* = pentamethylcyclopentadienyl) (**3**) is presented. While aliphatic amines give mainly the anti-Markovnikov products, anilines and aryl hydrazines yield the Markovnikov isomer as main products. Interestingly, using aliphatic amines such as *n*-butylamine and benzylamine the different catalysts lead to a significant change in the observed regioselectivity. Here, for the first time a highly selective switch from the Markovnikov to the anti-Markovnikov product is observed simply by changing the catalyst. Detailed theoretical calculations for the reaction of propyne with different substituted anilines and *tert*-butylamine in the presence of [(η^5-C$_5$H$_5$)Ti(=NR)(NHR)] (R = 4-C$_6$H$_4$X; X = H, F, Cl, CH$_3$, 2,6-dimethylphenyl) reveal that the experimentally observed regioselectivity is determined by the relative stability of the corresponding π-complexes **10**. While electrostatic stabilization favors the Markovnikov performance for aniline, the steric repulsive destabilization disfavors the Markovnikov performance for *tert*-butylamine.

Keywords: density functional calculations · hydroamination · regioselectivity · terminal alkynes · titanocene

Introduction

Amines and their derivatives are of importance as natural products, pharmacological agents, fine chemicals, and dyestuffs.[1] In general, a number of well-established "classic" organic methods, for example, nucleophilic substitution, reduction of amides, nitro compounds, azides, exist for their syntheses. However, apart from the reductive amination of carbonyl compounds, the catalytic formation of carbon–nitrogen bonds is rare. Clearly, there still exists considerable interest in the development of improved methodologies for the construction of carbon–nitrogen bonds. From an environmental point of view, transition metal catalyzed hydroamination of olefins and alkynes are particularly attractive methods for the synthesis of imines and amines (Scheme 1).[2]

Due to the 100% atom economy, that is, each atom from the starting material is present in the product, no by-products are formed. Easily available terminal olefins or alkynes provide, in principle, two regioisomeric amines or imines (Scheme 1, R′ = H). For simplicity we use the traditional Markovnikov and anti-Markovnikov terminology throughout the text to distinguish the regioisomeric products. In general, in polar hydroamination reactions the Markovnikov regioisomer is favored due to the higher stability of the secondary carbocation.

The negative entropy balance of the hydroamination reaction makes it necessary to use catalysts at lower temperatures. In the past strong bases,[3] both liquid and solid acids[4] and different types of transition-metal complexes[5,6] have been employed as catalysts for olefin hydroaminations. Despite considerable progress in recent years,[7] a general protocol for aliphatic intermolecular olefin hydroamination still needs to be developed. In contrast to olefins, alkynes are more reactive in hydroaminations, which is shown by the more exothermic (~70 kJ mol^{-1}) NH_3 addition to acetylene in comparison to ethylene.[8] Intramolecular cyclizations of

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Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author. Total electronic energies and bond parameters as well as natural charges are listed.

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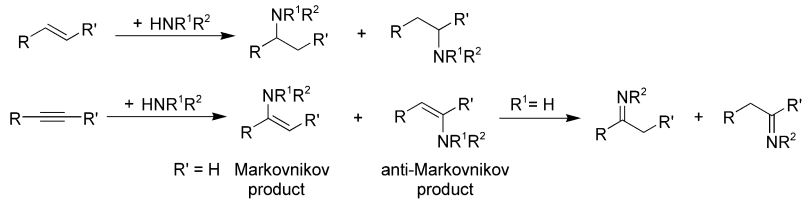
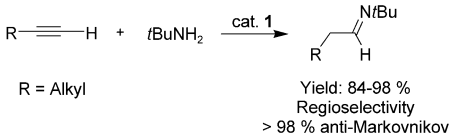


Scheme 1. Hydroamination of alkenes and alkynes.

aminoalkynes are easier to perform and provide different nitrogen-containing heterocycles. These reactions have been achieved using a broad variety of catalysts.[9] On the other hand, intermolecular aminations with alkynes have been realized in the presence of strong bases (Cs),[10] lanthanides (Nd),[11] actinides (U, Th),[12] and late transition metals (Ru, Pd, Rh, Au)[13a–g] as well as Hg, Tl[13h–j]. Based on the pioneering work of Bergman et al.[14] metallocenes have become popular as active catalysts in these reactions. More recently, the groups of Bergman,[15] Doye,[16] Odom[17] and Richeson[18] made significant contributions to the further development of titanocene and titanium amide catalysts with respect to hydroaminations. In most of these reactions aromatic, terminal alkynes or internal alkynes are treated with anilines as substrates. During our studies on the hydroamination of olefins[19] we also became interested in the selective amination of non-activated aliphatic alkynes. In a preliminary communication we reported the first anti-Markovnikov functionalization of terminal alkynes with aliphatic amines in the presence of $[(\eta^5\text{-Cp})_2\text{Ti}(\eta^2\text{-Me}_3\text{SiC}_2\text{SiMe}_3)]$ (**1**) as catalyst (Scheme 2).[20]



Scheme 2. Titanocene-catalyzed anti-Markovnikov hydroamination of terminal alkynes.

Outlined herein are new applications of hydroaminations in the presence of **1** and other titanocene catalysts. For the first time a systematic investigation of the effects of catalysts and substrates on the regioselectivity of the hydroamination of terminal alkynes is presented. The steric nature of the catalyst reveals a significant influence on the regioselectivity. Comparison of various anilines, arylhydrazines and aliphatic amines as the nitrogen source shows a general switch from anti-Markovnikov to Markovnikov products going from aliphatic to aromatic amines. This unusual behavior is explained by detailed theoretical investigations, which led to a new mechanistic rationale for the determination of the regiochemistry in titanocene-catalyzed hydroaminations of alkynes.

Results and Discussion

Hydroamination of aliphatic alkynes with aliphatic, benzylic and aromatic amines: Recently, we described the use of complex **1** (Rosenthal catalyst),[21] which is easily synthesized by the reaction of titanocene dichloride with the corresponding silylated alkyne,[22] for the hydroamination of aliphatic alkynes with aliphatic amines. An advantage of this catalyst[21a] is the relatively high stability at room temperature, however upon heating it looses easily the alkyne, thereby generating an active "Cp_2Ti"-intermediate within the proposed catalytic cycle. While reactions with the sterically hindered *tert*-butylamine proceeded in excellent yield and selectivity, the less crowded *sec*-alkylamines gave lower regioselectivities.

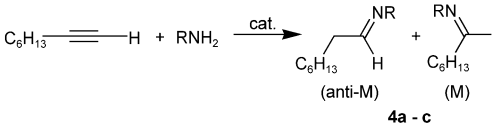
Despite the recent advancements in transition metal-catalyzed hydroamination of alkynes until to date, no detailed studies and general mechanistic explanation for the observed regioselectivity in hydroamination reactions of terminal alkynes are known. However, understanding and controlling of Markovnikov or anti-Markovnikov selectivity are of significant importance for further applications of this chemistry and also other refinement reactions of alkynes.[23] In order to study this chemistry more closely we investigated the aminations of 1-hexyne and 1-octyne with aliphatic and mainly aromatic amines further on (Tables 1 and 2). Initially, we thought that sterically more hindered titanocenes such as $[(\eta^5\text{-CpEt})_2\text{Ti}(\eta^2\text{-Me}_3\text{SiC}_2\text{SiMe}_3)]$ (CpEt = ethylcyclopentadienyl) (**2**) and $[(\eta^5\text{-Cp}^*)_2\text{Ti}(\eta^2\text{-Me}_3\text{SiC}_2\text{SiMe}_3)]$ (Cp* = pentamethylcyclopentadienyl) (**3**) should lead to improved regioselectivity applying less hindered primary amines. Here, we tested especially *n*-butylamine and benzylamine. The new titanocene complex **2** and the known complex **3**[22] were synthesized by straightforward reduction from the corresponding titanocene dichloride in the presence of magnesium and $Me_3SiC{\equiv}CSiMe_3$ in 73 and 77% yield, respectively.

In all catalytic reactions shown in Table 1 a slight excess of amine (1.2–1.5 equiv) was employed in order to suppress the oligomerization and polymerization of the alkynes. Nevertheless some dimerization, oligomerization and polymerization of the alkyne were observed. Competition experiments with isolated imines showed that decomposition of the imine to the corresponding aldehyde is no major side-reaction under the applied reaction conditions.

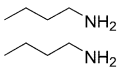
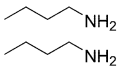
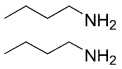
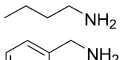
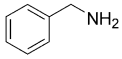
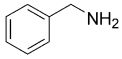
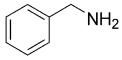
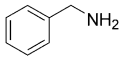
In the presence of **1** hydroaminations proceed at 85–120°C to give the anti-Markovnikov imines regioselectively (Table 1, entries 1, 6, 7 and 10). Even with simple non-hindered amines (*n*-butylamine and benzylamine) the anti-Markovnikov product dominates. However, the product yields were lower (up to 48%) as compared to hindered amines.

In the presence of **2** and **3** higher yields of imines were obtained both with *n*-butylamine and benzylamine (up to 62 and 66%, respectively). These results represent one of the few cases of titanium-catalyzed aminations with non-hindered amines.[17c,24] In the case of *tert*-butylamine **1** and **2** lead to excellent yields, while **3** is not active at all. Appa-

Table 1. Hydroamination of 1-octyne with aliphatic and benzylic amines in the presence of **1–3**.



4a - c

Entry	Amine	Catalyst [mol%]	*T* [°C]	Amine/Alkyne ratio	Yield [%][a] (anti-M:M)
1		**1** (2.5)	85	1.5:1	97 (99:1)[b] **4a**
2		**2** (2.5)	85	1.5:1	5 (98:2) **4a**
3		**2** (2.5)	100	1.5:1	97 (98:2) **4a**
4		**2** (2.5)	100	1.5:1	71 (98:2)[b,d] **4a**
5		**3** (2.5)	100	1.2:1	0[c] **4a**
6		**1** (10)	100	1.2:1	19 (79:21)[e] **4b**
7		**1** (10)	120	1.2:1	48 (72:28) **4b**
8		**2** (10)	100	1.2:1	62 (44:56) **4b**
9		**3** (10)	120	1.2:1	51 (22:78) **4b**
10		**1** (10)	120	1.2:1	46 (82:18) **4c**
11		**2** (10)	120	1.2:1	65 (45:55) **4c**
12		**2** (10)	100	1.2:1	66 (57:43) **4c**
13		**3** (10)	120	1.2:1	51 (19:81) **4c**

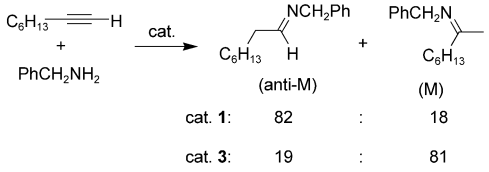
[a] Reaction in toluene, reaction time 24 h. Yield and mol% catalyst refer to the alkyne. Yield of imine was determined by GC analysis with an internal standard (hexadecane or dodecane). [b] 2 h reaction time. [c] 48 h reaction time. [d] 73% conversion. [e] 78% conversion.

rently the steric hindrance of both the catalyst and the amine precludes any reaction. Due to the stronger binding of alkynes to the titanium center with increased substitution of the cyclopentadienyl ring,[25] a higher reaction temperature (100–120 °C) has to be employed in the presence of **2** or **3** compared with **1**. Despite the increased binding from **1** to **3**, we observed in the GC/MS of the different catalytic reactions only $Me_3SiC{\equiv}CSiMe_3$ as the dissociation product. We have no proof for a protonolysis of this alkyne.

Interestingly, the different catalysts **1–3** introduce a significant change in the observed regioselectivity. For *n*-butylamine and benzylamine, catalyst **1** favors the anti-Markovnikov functionalization of 1-octyne as the main reaction pathway (anti-M:M 4–2.5:1). On the other hand, catalyst **3** favors the Markovnikov isomer being the main product (Scheme 3). Clearly, this simple control of regioselectivity in hydroaminations of terminal alkynes is interesting.

Next, we were interested in the amination of terminal aliphatic alkynes with aromatic amines. As shown in Table 2, ten different substituted anilines were treated with 1-hexyne and 1-octyne. In general, anilines react slower than aliphatic amines. Therefore, in some cases a slightly higher reaction temperature (up to 100 °C) and higher catalyst amount (5 mol%) were necessary, in order to achieve full conversion and high yield. Nevertheless, optimization of reaction conditions for a specific product was not done. With the exception of 3,4,5-trimethoxyaniline all other anilines gave the corresponding imines in the presence of **1** in good to very good conversion (61–94%). Surprisingly, the influence of steric effects is opposite for anilines and aliphatic amines. In the case of aliphatic alkynes increased steric bulk leads to a higher selectivity in favor of the anti-Markovnikov products. On the other hand, an increased steric bulk of the anilines gave a higher selectivity of the Markovnikov product!

For example, the reaction of 1-hexyne with 2,6-dimethylaniline gave the Markovnikov product with 99:1 selectivity, while aniline gave only 3:1 (Table 2; entries 1 and 2). The highest regioselectivities for the Markovnikov product (>99:1) were observed with 2,6-dimethylaniline (Table 2, entry 4) and 3,4,5-trimethoxyaniline (Table 2, entry 17). Apart from the steric bulk, the electronic factors of aniline also influence

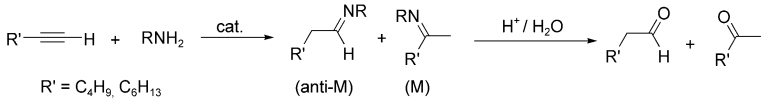


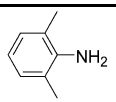
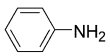
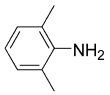
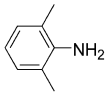
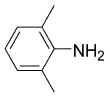
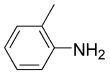
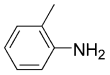
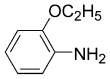
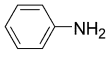
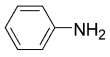
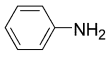
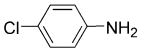
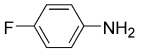
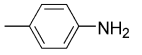
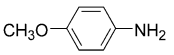
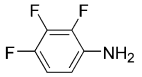
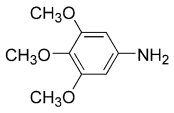
Scheme 3. Switch of regioselectivity.

the regioselectivity. This effect is nicely demonstrated by comparing the reactions of 4-chloroaniline, 4-fluoroaniline, 4-methylaniline, aniline, and 4-methoxyaniline with 1-octyne (Table 2, entries 11–17). Obviously, electron donating substituents favor the anti-Markovnikov products. Nevertheless, the steric bulk of the substrate seems to be the main determining effect as demonstrated by the reaction of 3,4,5-trimethoxyaniline. A comparison of catalysts **1**, **2** and **3** showed similar trends to the reactions of aliphatic amines. The more substituted complex **2** lead to higher Markovnikov selectivity, namely, the reaction of 1-octyne with aniline gave a selectivity of 75:25 and 83:17 in the presence of **1** and **2**, respectively (Table 1, entries 9–10).

Apart from 1-hexyne and 1-octyne also other terminal alkynes react with 2,6-dimethylaniline. In Table 3 the hydroamination of 3-phenyl-1-propyne, 3-cyclopentyl-1-propyne, 1,7-octadiyne, and phenylacetylene with 2,6-dimethylaniline

Table 2. Hydroamination of 1-hexyne and 1-octyne with aromatic amines in the presence of **1**–**3**.



Entry	Amine	Alkyne	Catalyst [mol%]	T [°C]	Amine/Alkyne ratio	Yield [%][a] (anti-M:M)
1			**1** (3.0)	85	1.5:1	94 (1:99)[b] **4d**
2			**1** (5.0)	85	1.2:1	94 (25:75)[b] **4e**
3			**1** (5.0)	85	1.5:1	68 (2:98)
4			**2** (5.0)	100	1.5:1	80 (1:>99)
5			**3** (5.0)	100	1.2:1	0[c]
6			**1** (5.0)	85	1.2:1	93 (12:88)
7			**2** (2.5)	100	1.2:1	96 (6:94)
8			**1** (5.0)	100	1.2:1	80 (9:91)
9			**1** (5.0)	100	1.2:1	80 (25:75)
10			**2** (2.5)	100	1.2:1	90 (17:83)
11			**1** (2.5)	85	1.2:1	72 (25:75)
12			**1** (2.5)	85	1.2:1	75 (20:80)
13			**1** (2.5)	85	1.2:1	67 (25:75)
14			**1** (2.5)	85	1.2:1	61 (33:67)
15			**1** (2.5)	85	1.2:1	61 (50:50)
16			**1** (2.5)	85	1.2:1	71 (3:97)
17			**1** (2.5)	85	1.2:1	43 (1:>99)

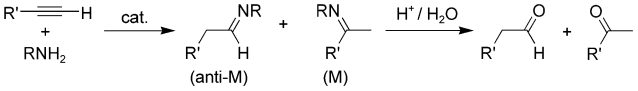
[a] 24 h reaction time in toluene. Yield and mol% catalyst refer to the limiting alkyne. Yield was determined by GC analysis with an internal standard (hexadecane or dodecane) after hydrolysis with 5% HCl and for 2-octanone/*n*-octanale. [b] Yield refers to the imine. [c] 48 h reaction time.

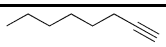
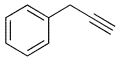
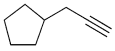
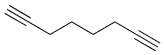
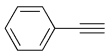
is shown. Except for phenylacetylene (Table 3, entry 5), which oligomerizes fast, reasonable to good yields (43–73%) and excellent regioselectivities for the Markovnikov products (M:anti-M >96:4) are obtained. Notably the double hydroamination of 1,7-octadiyne proceeds in 73% yield with excellent selectivity giving after hydrolysis 2,7-octadione, which is otherwise difficult to access.[26]

Hydroamination of terminal alkynes with hydrazines: Recently, Odom et al. described for the first time the titanium amide-catalyzed reaction of arylhydrazines with alkynes.[27] This reaction step in combination with the Fischer indole synthesis[28] allows for an elegant two-step (one-pot) synthesis of substituted indoles. Still today the development of new indole syntheses is subject of considerable efforts due to the great variety of indole units in natural products and pharmaceutical compounds. Apart from the synthetic challenge, it was of special interest for us to compare the regioselective attack of arylhydrazines on terminal alkynes with the above mentioned reactions of aliphatic amines and anilines. As a model system *N*-methyl-*N*-phenylhydrazine was used for amination reactions of different alkynes. In general, reactions were performed for 24 h at 85–100°C in the presence of 2.5–10 mol% of **1**.

Although no systematic optimization had been done, some screening reactions using 1-octyne demonstrated full conversion in the presence of 2.5 mol% catalyst after 2 h. As shown in Table 4 reaction of 1-octyne, 3-cyclopentyl-1-propyne, 3-phenyl-1-propyne and 5-chloro-1-pentyne with *N*-methyl-*N*-phenylhydrazine in the presence of **1** and subsequent treatment of the reaction mixture with an excess of $ZnCl_2$ gave directly the corresponding indoles in 52–90% yield. Except for phenylacetylene all reactions occurred with high Markovnikov selectivity leading to the 2-methyl-3-alkylsubstituted indoles. However, in the case of phenylacetylene both indole isomers were isolated in a ratio M:anti-M 4:1. 3-(2-Aminoethyl)-substituted indoles are of special interest to organic synthesis because of the biological activity of the tissue hormone melatonin and the neurotransmitter serotonin. Obviously, the reaction of commercially available 5-chloro-1-pentyne with arylhydrazines allows for a straightforward two-step preparation of this

Table 3. Hydroamination of terminal alkynes with 2,6-dimethylaniline in the presence of **1**.



Entry	Alkyne	*T* [°C]	Amine/Alkyne ratio	Yield [%][a] (anti-M:M)
1		85	1.5:1	68 (2:98)
2		85	1.5:1	72 (3:97)
3		85	1.2:1	43 (2:98)
4		100	4:1	73 (4:96)
5		85	1.5:1	28 (50:50)

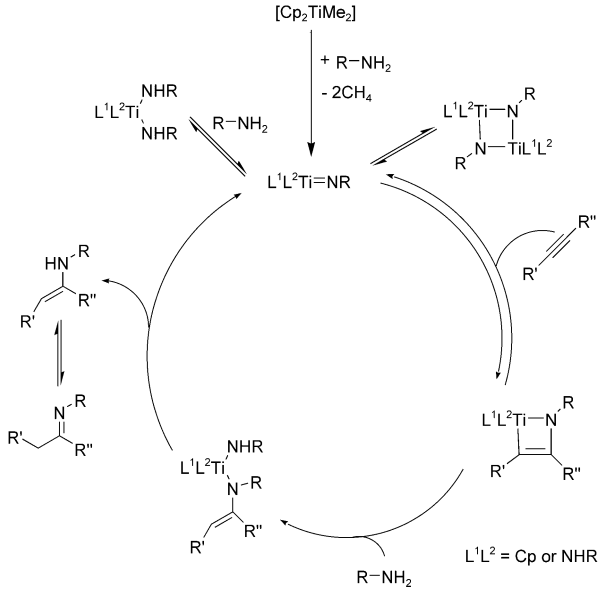
[a] 5 mol% catalyst **1**, 24 h reaction time in toluene. Yield and mol% catalyst refer to the alkyne. Yield was determined by GC analysis with an internal standard (hexadecane or dodecane) after hydrolysis with 5% HCl and for ketone/aldehyde.

class of indoles. Surprisingly, when we performed the reaction of *N*-methyl-*N*-phenylhydrazine with 5-chloro-1-pentyne in the presence of 10 mol% of **1** directly, the corresponding hydrochloride of *N*-methyl-3-(2-aminoethyl)-2-methylindole was obtained in good yield (Table 4, entry 6). After addition of NaOH the free indole (**9c**) was easily isolated and characterized. Keeping the commercial availability of different substituted aryl hydrazines in mind obviously this reaction can be extended to various other substituted serotonin products.

Mechanism and theoretical calculations of the hydroamination of terminal alkynes: Based on the original work by Bergman[15] the mechanism of the titanocene-catalyzed hydroamination has been recently defined more precisely by Doye et al.[29a] and Bergman et al.[29b] As shown in Scheme 4, the active catalyst is believed to be a titanium imido species, which is in equilibrium with the corresponding bisamidotitanium complex and dinuclear titanium complexes. A formal [2+2]-cycloaddition of the titanium imido species and the alkyne gives a titanaazacyclobutene derivative. Subsequent protonation by excess amine and tautomerization of the corresponding enamine leads to the imine product and the active catalyst is recovered.

Although the proposed catalytic cycle is in agreement with most previously reported observations, some questions remained considering our experimental results. For example, Bergman et al.[29b] concluded that the regioselectivity of the reaction is determined in the [2+2]-cycloaddition step, which should also be the rate-determining step. However, with regard to our results it is not clear why alkylamines favor the anti-Markovnikov products, while anilines and arylhydrazines favor the Markovnikov products. Which factors determine the regioselectivity of the process and how is it controlled? Not surprisingly, known mechanistic investigations and calculations used symmetrical alkynes as model systems in order to circumvent the problem of regioselectivity. In order to get insight into the origin of the unusual differences in regioselectivity reported above, we have carried out high level density functional theory computations. The calculated bond lengths, bond angles and natural charges as well as the energetic data for the π-complexes (**10**), transition states (**11**) and intermediates (**12**) of the [2+2]-cycloaddition are summarized in the Supporting Information.

The detailed mechanism of the catalytic hydroamination of alkynes has been computed previously by Straub and Bergman using the simplified [(η^5-C_5H_5)Ti(=NH)(NH_2)] and HC≡CH models.[29b] Along the reaction path on the potential

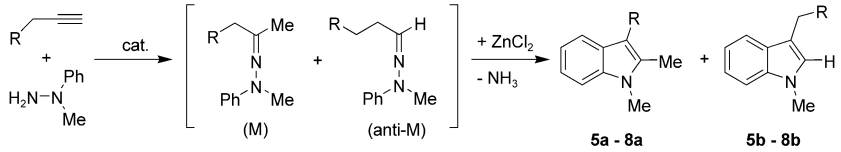


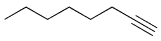
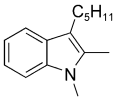
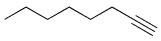
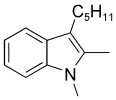
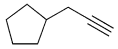
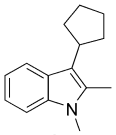
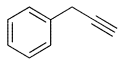
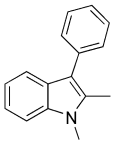
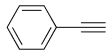
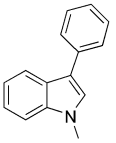
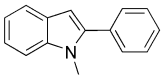
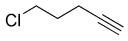
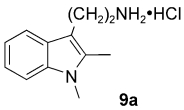
Scheme 4. Proposed mechanism of the titanocene-catalyzed amination of alkynes.

energy surface (PES), they found the formation of a π-complex between the metal complex and ethyne being the first step which is also endergonic, followed by a [2+2]-cycloaddition as the rate-determining step from the calculated activation parameters. They also postulated that the regioselectivity is controlled by the cycloaddition, and the related points on the PES of the first part of the ethyne hydroamination path is shown in Scheme 5. However, these simplified models do not explain the observed regioselectivity in case of terminal alkynes.

On the basis of Bergman's finding,[29b] we used the "real" complexes [(η^5-C_5H_5)Ti(=NR)(NHR)][30] to model the difference in regioselectivity of hydroamination between substituted anilines (R = 4-C_6H_4X (X = H, F, Cl, CH_3), and 2,6-dimethylphenyl) and *tert*-butylamine (R = $C(CH_3)_3$). Instead of HC≡CH, we used H_3C-C≡CH as a model for the employed terminal aliphatic alkynes. The related Markovnikov

Table 4. Hydroamination of terminal alkyne with *N*-methyl-*N*-phenylhydrazine in the presence of **1**.

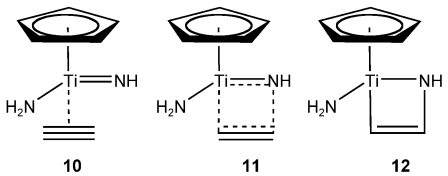


Entry	Alkyne	Indole	Catalyst [mol %]	*T* [°C]	Yield[a] [%]
1		 **5a**	5.0	100	90
2		 **5a**	2.5	100	88[b] (70)
3		 **6a**	3.0	100	82 (62)
4		 **7a**	5.0	85	84 (67)
5		 **8a**	5.0	100	42 (25)
		 **8b**			10 (5)
6		 **9a**	10.0	100	(64)[c]

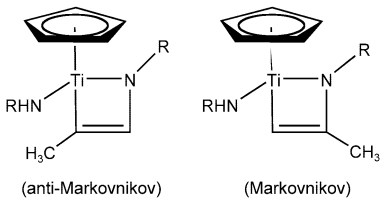
[a] Reaction in toluene, 24 h reaction time, alkyne/hydrazine ratio 1:1.2. 3–4 equiv $ZnCl_2$, reaction time 24 h. Yield and mol % catalyst refer to the alkyne. Yield was determined by GC analysis with an internal standard (hexadecane), isolated yield are given in parentheses [b] 2 h reaction time to hydrazone. [c] The indole was formed without $ZnCl_2$ and isolated as the hydrochloride (isolated yield).

activation and reaction. The results clearly show that Markovnikov (denoted as **M**) and anti-Markovnikov (denoted as **anti-M**) reactions have approximately the same Gibbs free energies for activation ($\Delta G^{\neq}$), and their negligible differences (< 0.3 kcal mol^{-1}) could not be responsible for the observed difference in the regioselectivity. For example, on the basis of the difference in the activation free energy (considering these two transition states in an equilibrium, and their equilibrium constant (K) is determined by their relative Gibbs free energy, $\Delta\Delta G^{\neq} = -RT\ln K$), the predicated product ratio would be roughly 60 to 40 in favor of the anti-Markovnikov pathway. This result gives the right trend for *tert*-butylamine, but the opposite trend for aniline. On the other hand, the predicated product ratios do not agree with the experimental finding in both cases (Tables 1 and 2). Therefore, the transition state of the [2+2]-cycloaddition step (**11**) does not control the regioselectivity.

Alternatively, one might expect that the regioselectivity can be explained by the thermodynamic effect or the difference of reaction free energies ($\Delta\Delta G$). As given in Table 5, the anti-Markovnikov products (**12**) of both *tert*-butylamine and aniline are more favored energetically than the Markovnikov isomers by 1.5 and 2.0 kcal mol^{-1}, and the predicated product ratio would be 93 to 7 for *tert*-butylamine and 97 to 3 for aniline. This is in good agreement with the experimental finding for *tert*-butylamine, but the result for aniline is totally wrong. Therefore, the regioselectivity also can not be ex-



Scheme 5. [2+2]-Cycloaddition: **10** (π-complex); **11** (transition state) and **12** (intermediate).



Scheme 6. [2+2]-Cycloaddition products with $CH_3C{=}CH$.

and anti-Markovnikov products of the [2+2]-addition are shown in Scheme 6.

Initially, the basic thermodynamic data for the reaction of *tert*-butylamine and aniline with propyne were calculated. Table 5 summarizes the computed Gibbs free energies for

Table 5. Gibbs free energies [kcal mol^{-1}][a] of activation ($\Delta G^{\neq}$, transition states, **11**) and reaction (ΔG, intermediates, **12**) relative to π-complexes (**10**).

Amine	Model	$\Delta G^{\neq}$	ΔG
$(H_3C)_3CNH_2$	anti-M	6.2 (**11a**)	−17.8 (**12a**)
	M	6.5 (**11b**)	−16.3 (**12b**)
$C_6H_5NH_2$	anti-M	3.2 (**11c**)	−15.7 (**12c**)
	M	3.5 (**11d**)	−13.7 (**12d**)
4-F-$C_6H_4NH_2$	anti-M	2.1 (**11e**)	−16.1 (**12e**)
	M	3.3 (**11f**)	−12.7 (**12f**)
4-Cl-$C_6H_4NH_2$	anti-M	3.2 (**11g**)	−15.7 (**12g**)
	M	4.0 (**11h**)	−13.0 (**12h**)
4-CH_3-$C_6H_4NH_2$	anti-M	2.5 (**11i**)	−16.2 (**12i**)
	M	3.0 (**11j**)	−14.4 (**12j**)
2,6-dimethyl-$C_6H_3NH_2$	anti-M	2.9 (**11k**)	−13.8 (**12k**)
	M	5.6 (**11l**)	−10.8 (**12l**)

[a] At B3LYP/LANL2DZp//B3LYP/LANL2DZ including the correction of thermal energy and entropy contribution at $T = 298.15$ K.

plained by the thermodynamic effect. However, what are the driving forces for these differences?

As the first step along the reaction path, we were wondering whether the relative stability of the Markovnikov and anti-Markovnikov π-complexes (**10**) should be responsible for the observed difference in the regioselectivity. One might consider that the two π-complexes should be in equilibrium during their formation, and their equilibrium constant (K) is determined by their relative Gibbs free energy ($\Delta G = -RT\ln K$), which is also the difference of the two competing reaction energies on the basis of the active catalyst [(η^5-C_5H_5)Ti(=NR)(NHR)]. The consequence is that the more stable the π-complex, the more dominant the product. These results are summarized in Table 6.

Table 6. Gibbs free energy [kcal mol^{-1}][a] difference between the anti-Markovnikov and Markovnikov π-complexes (**10**) and the related ratio (anti-M:M).

Amine	anti-M	M	Ratio[b]
$(H_3C)_3CNH_2$	0.00 (**10a**)	2.45 (**10b**)	98:2 (99:1))
$C_6H_5NH_2$	0.00 (**10c**)	−0.62 (**10d**)	26:74 (25:75)
4-F-$C_6H_4NH_2$	0.00 (**10e**)	−1.56 (**10f**)	7:93 (25:75)
4-Cl-$C_6H_4NH_2$	0.00 (**10g**)	−0.97 (**10h**)	16:84 (20:80)
4-CH_3-$C_6H_4NH_2$	0.00 (**10i**)	−0.73 (**10j**)	23:77 (33:67)
2,6-dimethyl-$C_6H_3NH_2$	0.00 (**10k**)	−2.56 (**10l**)	1:99 (2:98)

[a] At B3LYP/LANL2DZp//B3LYP/LANL2DZ including the correction of thermal energy and entropy contribution at $T = 298.15$ K. [b] The observed ratio is given in parenthesis.

For the reaction with *tert*-butylamine, the anti-Markovnikov π-complex (**10a**) is computed to be lower in energy than the Markovnikov one (**10b**) by 2.45 kcal mol^{-1}, and, therefore, **10a** should be more dominant over **10b**, and this should also be the case for the subsequent products. This free energy difference gives a percentage ratio of 98:2 for anti-Markovnikov to Markovnikov products, and this ratio matches the experimental finding (99:1) perfectly (Table 1)!

In contrast to *tert*-butylamine, the anti-Markovnikov π-complex (**10c**) of aniline is computed to be higher in energy than the Markovnikov one (**10d**) by 0.62 kcal mol^{-1}, and this energy difference favors the Markovnikov over anti-Markovnikov products with a percentage ratio of 76 to 24, again in perfect agreement with the experimental result (75 to 25, Table 1). As for aniline, *para*-substituted anilines also favor Markovnikov over anti-Markovnikov products, and it is very interesting to see that the ratio of Markovnikov to anti-Markovnikov depends on the electronegativity of the substituent, as also found experimentally. For example, the most electronegative F substituent results in a higher Markovnikov to anti-Markovnikov ratio (**10f**:**10e** 93:7) than the less electronegative Cl (**10h**:**10g** 84:16) or H (**10d**:**10c** 74:26). Therefore, the energetic difference between the π-complexes reproduces the regioselectively not only qualitatively, but also quantitatively.

Apart from this perfect agreement between theory and experiment, it is interesting and also unavoidable to look for the driving force and insight of these differences. Are these results due to steric or electronic effects? To answer this question, we analyzed the structural parameters and natural charge distributions. The optimized structures and natural charges (bold and italics) of *tert*-butylamine and aniline as substrates are shown in Figure 1, and selected bond parameters and the atomic natural charges from NBO analyses are summarized in the Supporting Information.

Initially, we were interested in the distances between the C≡C triple bond of propyne and the formal Ti=N double bond of [(η^5-C_5H_5)Ti(=NR)(NHR)]. For *tert*-butylamine, the Ti–C_1 and Ti–C_2 distances (2.621 and 2.711 Å) of the anti-Markovnikov π-complex **10a** are shorter than those (2.644 and 2.753 Å) of the Markovnikov isomer (**10b**). This difference indicates a stronger interaction between metal center and substrate in **10a** than in **10b**. Therefore, the former should be favored energetically, and this is confirmed by the calculated energy difference of 2.45 kcal mol^{-1}. For aniline, however, the Ti–C_1 distance (2.563 Å) of the anti-Markovnikov π-complex (**10c**) is longer than that (2.412 Å) of the Markovnikov isomer (**10d**), while the Ti–C_2 distance of the former (2.596 Å) is shorter than that (2.685 Å) of the latter. This mixed behavior agrees with their rather small energetic order by 0.62 kcal mol^{-1}.

Secondly, we were interested in the orientation of propyne with respect to the metal complexes [(η^5-C_5H_5)Ti(=NR)(NHR)]. In both anti-Markovnikov π-complexes (**10a** and **10c**) (R = $C(CH_3)_3$ and C_6H_5), propyne has nearly the same orientation as indicated by the calculated $N_1TiC_1C_2$ torsion angles (−161.5 vs −165.1°), and the formal four-membered rings have very close bond angles (see Supporting Information). Therefore, there is no significant difference in conformation between **10a** and **10c**.

However, the propyne unit has different orientations in the Markovnikov π-complexes (**10b** and **10d**) as indicated by the calculated $N_1TiC_1C_2$ torsion angles. For example, the $N_1TiC_1C_2$ torsion angle for **10d** (R = C_6H_5) of only −0.2° shows that the formal four-membered ring is nearly planar, and this also indicates that there is no steric interaction between the methyl group and the phenyl ring. In contrast, the $N_1TiC_1C_2$ torsion angle for **10b** (R = $C(CH_3)_3$) of −38.4° shows the non-planarity of the four-membered ring and reveals at the same time the steric repulsive interaction between the methyl groups of propyne and the *tert*-butyl

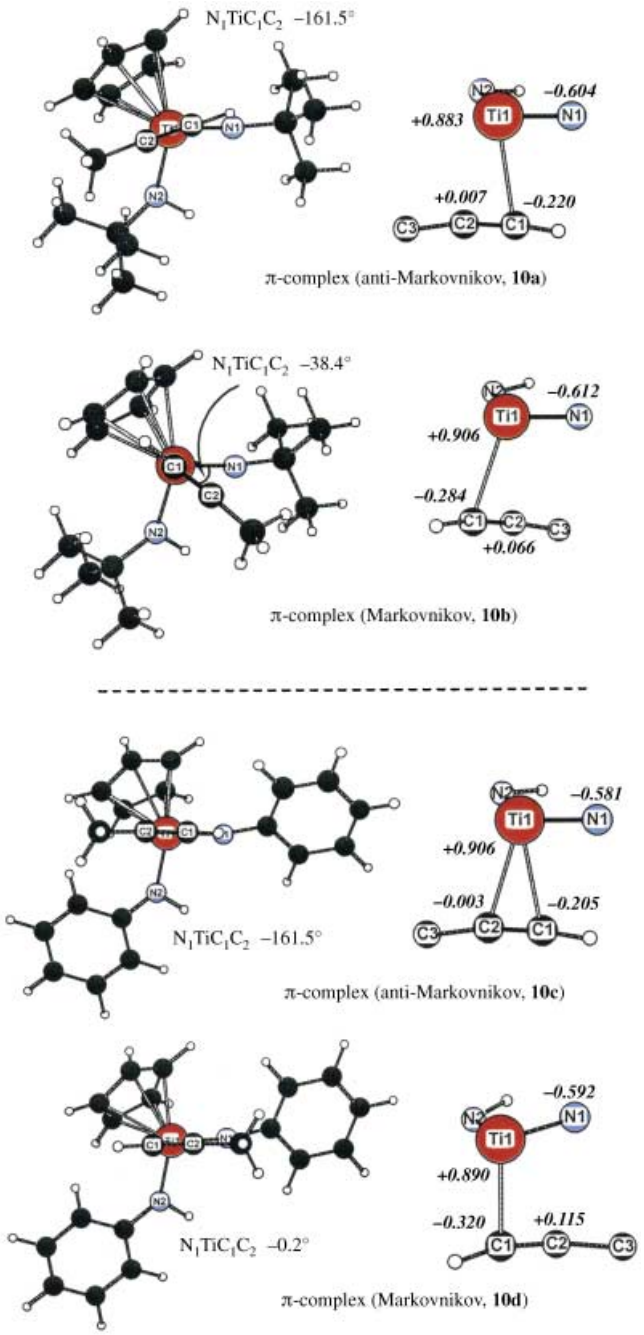


Figure 1. The computed $N_1TiC_1C_2$ torsion angles and natural charges (bold and italics) for the π-complexes of *tert*-butylamine (top) and aniline (bottom) as substrates.

group. Therefore, the orientation of propyne in the π-complexes **10b** and **10d** might be indicative for their stability.

That *tert*-butyl is more bulky than phenyl is also shown by the longer Ti–C_1 and Ti–C_2 distances in **10a** (2.621 and 2.711 Å) and **10b** (2.644 and 2.753 Å) than in **10c** (2.563 and 2.596 Å) and **10d** (2.412 and 2.685 Å), respectively. This is consistent with the difference of the calculated Gibbs free activation energies for both substrates (6.2 and 6.5 kcal mol^{-1} for R = $C(CH_3)_3$ vs 3.2 and 3.5 kcal mol^{-1} for R = C_6H_5, Table 5), that is propyne is stronger activated in the π-complexes with R = C_6H_5 than with R = $C(CH_3)_3$.

Apart from the orientation of propyne, the calculated natural charge distributions are informative for understanding the energetic difference and, therefore, the difference in the regioselectivity between *tert*-butylamine and aniline as substrates. As shown in Figure 1, the π-complexes **10a–d** are electrostatic in nature as indicated by the calculated natural charges from NBO analysis. In **10a–d**, the formal Ti=N double is highly polarized with positively charged titanium and negatively charged nitrogen centers. The terminal ≡CH (C_1) carbon is negative charged in all these π-complexes, while ≡C_2 is nearly neutral.

For *tert*-butylamine as substrate, the electrostatic stabilizing interaction in the Markovnikov π-complex (**10b**) should be weaker than in the anti-Markovnikov isomer (**10a**) due to the steric repulsive interaction between the methyl groups in propyne and *tert*-butyl unit and the resulting longer Ti–C_1 and Ti–C_2 distances. This is indicated by the $N_1TiC_1C_2$ dihedral angle of −38.4 and the rather long N_1–C_2 distance of 3.160 Å in **10b**, and, therefore, is responsible for the reduced electronic stabilization.

For aniline as substrate, no such steric repulsive interaction in the π-complexes (**10c** and **10d**) is observed, and the alternating positive and negative charge interaction of the Markovnikov π-complex (**10d**) in the nearly planar four-membered ring is the decisive factor for the enhanced stability over the anti-Markovnikov isomer (**10c**).

It is, therefore, to conclude that the experimentally observed difference in the regioselectivity between *tert*-butylamine and aniline as substrates is determined by their relative stability of their π-complexes (**10**) with terminal aliphatic alkynes, that is, electrostatic stabilization favors the Markovnikov performance for aniline, while the steric repulsive destabilization disfavors the Markovnikov performance for *tert*-butylamine.

In addition to this insight comparison, we have also calculated the effect of substituted anilines. As given in Table 5, all substituted anilines favor Markovnikov π-complexes (**10f**, **h**, **j** and **l**), and, therefore, the Markovnikov hydroamination products (the related structural parameters and natural charges are given in the Supporting Information). This agrees with the experimental results. As shown in Table 5, the Gibbs free energy difference between the anti-Markovnikov (**10k**) and Markovnikov (**10l**) π-complexes for 2,6-dimethyl aniline (2.65 kcal mol^{-1}) is much larger than that for aniline (**10c** and **10d**; 0.62 kcal mol^{-1}). This large energetic difference can be ascribed to the steric repulsive interaction among the methyl groups of propyne, 2,6-dimethyl phenyl ring and the (η^5-C_5H_5) ligand, and this is indicated by the shortest H···H distances among these ligands (H_{sub}···H_{Cp} = 2.300, H_{sub}···H_{Me} = 2.286 and H_{Me}···H_{Cp} = 2.365 Å; see Supporting Information) in **10k**. The direct consequence is the elongation of Ti–C_1 and Ti–C_2 distances (2.594 and 2.702 Å), as compared to corresponding values (2.563 and 2.596 Å) of anilines, as shown in Figure 2. In contrast, the Ti–C_1 and Ti–C_2 distances are very close for aniline and 2,6-dimethylaniline in the Markovnikov π-complexes.

These results also give a nice explanation about the reactivity and regioselectivity of catalyst **3** with the permethylated cyclopentadienyl ring as ligand. For example, there is no

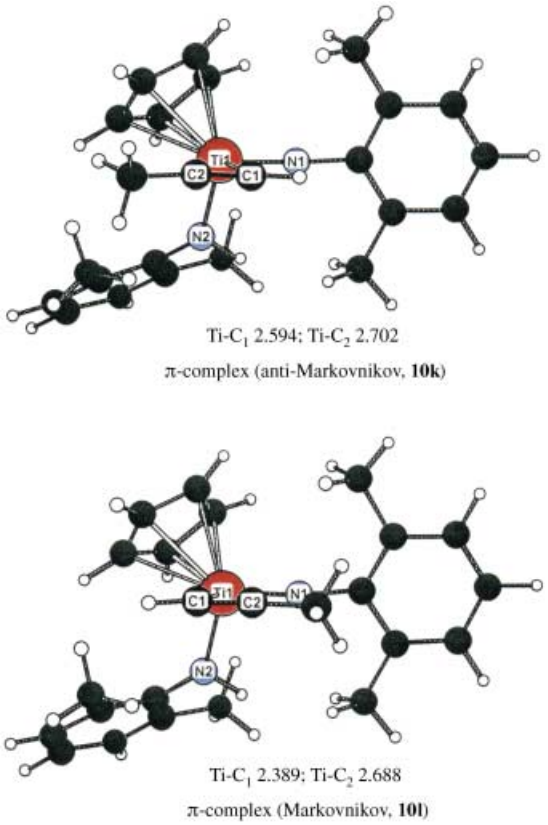


Figure 2. The conformation for the π-complexes of 2,6-dimethyl amine substrate [Å].

reaction for catalyst **3** with *tert*-butylamine as substrate, and this is apparently due to the bulky property of the active catalyst, $[(\eta^5\ C_5(CH_3)_5)Ti(=N(C(CH_3)_3)(NH(C(CH_3)_3)]$, which hinders the effective coordination between the titanium center and the alkyne. Using *n*-butylamine and benzylamine as substrates, on the other hand, the less bulky catalyst **1** favors the anti-Markovnikov products, while the more bulky catalyst **3** favors the Markovnikov pathway.

Conclusion

In conclusion we have presented the first general study of the regioselective hydroamination of terminal alkynes. As nitrogen source aliphatic amines, anilines and arylhydrazines were used. Depending on the amine the Markovnikov or the anti-Markovnikov regioisomer is formed preferentially. The experimentally observed isomer distribution is explained perfectly by detailed theoretical investigations which demonstrate, that the regioselectivity is determined by the relative stability of the corresponding π-complexes **10**. This leads to a general understanding of titanocene-catalyzed hydroaminations of unsymmetrical alkynes. Interestingly, electrostatic stabilization favors the Markovnikov performance for aromatic amines, while steric repulsive destabilization disfavors the Markovnikov performance for sterically hindered aliphatic amines.

Significant changes in the regioselectivity are also observed using different titanocene catalysts **1**–**3** with aliphatic amines, for example, *n*-butylamine and benzylamine favor the anti-Markovnikov functionalization of 1-octyne in the presence of catalyst **1**, while catalyst **3** favors the Markovnikov isomer being the main product. Clearly, such an easy control of regioselectivity in hydroaminations of terminal alkynes has not been reported previously.

Experimental Section

Computation: All calculations were carried out by using the Gaussian 98 program.[31] All structures were first optimized at the Hartree–Fock (HF) level of theory with the LANL2DZ[32] basis set, and the nature of the optimized structures on the potential energy surface (PES) was characterized by the calculated number of imaginary frequency (NImag) at the same level of theory (HF/LANL2DZ), i.e., minimum structures without (NImag = 0), and transition states with only one imaginary frequency (NImag = 1).[33] This moderate theoretical method was used to make a systematic comparison for large systems possible. The related frequency calculations provided at the same time zero-point energies (ZPE) and thermal energies as well as entropies at given temperature (T = 298.15 K), and all these data were scaled by an empirical factor of 0.8929 and used for the calculations of the thermodynamic parameters.[33] The HF structures obtained were further refined at the electron correlated B3LYP DFT level of theory with the LANL2DZ basis set (B3LYP/LANL2DZ), and the final energies were the single-point energies at the B3LYP level with the B3LYP/LANL2DZ geometries and the LANL2DZ basis set by adding a set of polarization functions (LANL2DZp[32c]). This combination (B3LYP/LANL2DZp) is found to be appropriate for the accurate determination of the structural isomer ratios on the basis of the computed relative energies in titanium and ziconium complexes.[34] The energies for discussion and interpretation are the Gibbs free energies ($\Delta G = \Delta H - T\Delta S$). Natural charges were obtained with the method of Natural Bond Orbital (NBO) analyses.[35] The calculated total electronic energies, ZPE, NImag, thermal energies and entropies of the π-complexes, transition states and products of [2+2] cycloadditions are summarized in the Supporting Information.

General: Chemicals were obtained from Aldrich, Fluka, Acros and Strem and unless otherwise noted were used without further purification. Amines were distilled from CaH_2. Alkynes were degassed, flushed with argon and stored over molecular sieves (4 Å). Absolute solvents were purchased from Fluka. All operations were carried out under an argon atmosphere.

Catalysts **1** and **3** were synthesized according to a literature procedure.[22] Imines **4a**–**d** were isolated after distillation of the crude hydroamination mixtures, indoles **5a**–**8a** and **8b** were isolated by column chromatography, compound **9a** was isolated as hydrochloride adduct and all products were characterized by NMR, MS, IR and elemental analyses. The ^{1}H and ^{13}C NMR chemical shifts are reported relative to the center of solvent peak ($CDCl_3$: 7.25 (^{1}H), 77.0 (^{13}C); [D$_8$]THF: 1.73 (^{1}H), 25.2 (^{13}C)). Identification of all other products was performed via comparison with authentic products. **4e** was synthesized according to ref. [13c]. Not commercially available ketones, such as octan-2,7-dione and cyclopentylacetone, were isolated after amination and hydrolysis. The analytical data is in agreement with literature data.[26,36]

Synthesis of complex 2: [(CpEt)$_2$TiCl$_2$] (1.0 g, 3.3 mmol), finely shaved magnesium (95 mg, 3.9 mmol) and bis(trimethylsilyl)acetylene (0.61 g, 3.6 mmol) were stirred in THF (10 mL) at room temperature under argon for 2 h. The resulting dark solution was filtered and evaporated in vacuo to dryness at room temperature. Then the residue was dissolved in pentane (10 mL) and the solution again filtered. Cooling the pentane filtrate to −78 °C gave yellow-green crystals of complex **2** which were separated from the mother liquor by decanting and drying in vacuo at room temperature to yield the title compound (0.98 g, 73 %). ^{1}H NMR ([D$_8$]THF, 400 MHz): δ = 6.58 (t, J = 2.6 Hz, 4H), 5.75 (t, J = 2.6 Hz, 4H), 2.26 (q, J = 7.5 Hz, 4H), 1.30 (t, J = 7.7 Hz, 6H), −0.34 (s, 18H); ^{13}C NMR ([D$_8$]THF, 100 MHz): δ = 245.1, 137.7, 115.2, 114.9, 25.1, 15.3, 1.1; ^{29}Si NMR ([D$_8$]THF, 79 MHz): δ = −13.9; MS (EI, 70 eV): m/z: 404 (1) [M^+], 234 (100) [M^+−Me$_3$SiC$_2$SiMe$_3$], 170 (5) [Me$_3$SiC$_2$SiMe$_3^+$], 155

(50) [$Me_3SiC_2SiMe_3^+-Me$]; FT IR (nujol): $\tilde{\nu}$ = 1677, 1639, 1243, 860, 832, 787, 750 cm^{-1}; elemental analysis calcd (%) for $C_{22}H_{36}Si_2Ti$: C 65.31, H 8.97; found: C 65.60, H 9.02.

General procedure for the reaction of alkynes with amines: In an Ace-pressure tube under an argon atmosphere a solution of the catalyst in toluene was added to a mixture of the alkyne and the amine. This mixture was heated at the given temperature for the specified time (see Tables 1–3). Isolation of the product was done by fractional distillation in vacuo.

***N*-*tert*-Butyl-octylidene-amine (4a)**: According to the general procedure 1-octyne (3.2 mL, 21.5 mmol) and *tert*-butylamine (3.5 mL, 32.2 mmol) were treated in the presence of 2.5 mol% **1** (188 mg, 0.54 mmol) in toluene (8 mL) at 85°C for 2 h. Fractional distillation afforded **4a** as a colorless oil. GC yield: 97% (isolated yield: 2.8 g (71%)); b.p. 48–49°C/0.1 mbar; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.56 (t, J = 5.3 Hz, 1H), 2.20 (m, 2H), 1.46 (m, 2H), 1.34–1.21 (m, 8H), 1.14 (s, 9H), 0.85 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 159.3, 56.4, 36.4, 31.7, 29.6, 29.2, 29.1, 26.4, 22.6, 14.0; MS (EI, 70 eV): *m*/*z* (%): 184 (15) [M^++H], 183 (2) [M^+], 168 (30) [M^+-CH_3], 112 (14), 99 (100) [$C_7H_{15}^+$], 84 (86) [$C_4H_9NCH^+$], 57 (91) [$C_4H_9^+$], 43 (38), 41 (36); FT IR (neat): $\tilde{\nu}$ = 1671 cm^{-1} (C=N); elemental analysis calcd (%) for $C_{12}H_{25}N$: C 78.62, H 13.74, N 7.64; found: C 78.19, H 13.99, N 7.42.

***N*-*n*-Butyl-octylidene-amine/*N*-*n*-butyl-2-octylidene-2-amine (ratio 2.6:1) (4b)**: According to the general procedure 1-octyne (2.4 mL, 16.0 mmol) and *n*-butylamine (1.9 mL, 19.2 mmol) were treated in the presence of 10.0 mol% **1** (558 mg, 1.60 mmol) in toluene (6 mL) at 120°C for 24 h. Fractional distillation afforded **4b** as a colorless oil. GC yield: 48%; b.p. 44–45°C/0.1 mbar. ^{1}H NMR for main product ($CDCl_3$, 400 MHz): δ = 7.59 (t, J = 5.0 Hz, 1H), 3.32 (t, J = 6.9 Hz, 2H), 2.24–1.99 (m, 2H), 1.62–1.20 (m, 14H), 0.95–0.80 (m, 6H); ^{13}C NMR for main product ($CDCl_3$, 100 MHz): δ = 164.8, 61.1, 35.8, 32.8, 31.7, 29.2, 29.0, 26.1, 22.6, 20.3, 14.0, 13.8; MS (EI, 70 eV): *m*/*z* (%): 183 (0.7) [M^+], 182 (1.4) [M^+-H], 168 (0.9) [M^+-CH_3], 154 (3) [$M^+-C_2H_5$], 140 (12) [$M^+-C_3H_7$], 112 (30), 99 (26), 84 (100) [$CH{=}NC_4H_9^+$], 57 (40) [$C_4H_9^+$], 56 (23), 41 (17) [$C_3H_5^+$]; FT IR (neat): $\tilde{\nu}$ = 1662 cm^{-1} (C=N); elemental analysis calcd (%) for $C_{12}H_{25}N$: C 78.62, H 13.74, N 7.64; found: C 78.28, H 14.03, N 7.47.

***N*-Benzyl-octylidene-amine/*N*-benzyl-2-octylidene-amine (ratio 4.6:1) (4c)**: According to the general procedure 1-octyne (2.4 mL, 15.8 mmol) and benzylamine (2.1 mL, 19.0 mmol) were treated in the presence of 10.0 mol% **1** (544 mg, 1.56 mmol) in toluene (6 mL) at 120°C for 24 h. Fractional distillation afforded **4c** as a colorless oil. GC yield: 46%; b.p. 97–98°C/0.1 mbar. ^{1}H NMR for main product ($CDCl_3$, 400 MHz): δ = 7.78 (t, J = 5.0 Hz, 1H), 7.30–7.14 (m, 5H), 4.56 (s, 2H), 2.30–2.20 (m, 2H), 1.60–1.40 (m, 2H), 1.25 (m, 8H), 0.88 (t, 3H); ^{13}C NMR for main product ($CDCl_3$, 100 MHz): δ = 166.3, 139.3, 128.4, 127.8, 126.8, 65.1, 35.9, 31.5, 29.4, 29.2, 26.0, 22.5, 14.0; MS (EI, 70 eV): *m*/*z* (%): 217 (1) [M^+], 202 (0.4) [M^+-CH_3], 188 (2) [$M^+-C_2H_5$], 174 (3) [$M^+-C_3H_7$], 160 (3) [$M^+-C_4H_9$], 146 (20), 133 (83) [$M^+-C_6H_{12}$], 132 (49) [$M^+-C_6H_{13}$], 91 (100) [$PhCH_2^+$]; FT IR (neat): $\tilde{\nu}$ = 1663 cm^{-1} (C=N).

***N*-(2-Hexylidene)-2,6-dimethylaniline (4d)**: According to the general procedure 1-hexyne (1.5 mL, 12.9 mmol) and 2,6-dimethylaniline (2.4 mL, 19.4 mmol) were treated in the presence of 3.0 mol% **1** (140 mg, 0.39 mmol) in toluene (5 mL) at 85°C for 24 h. Fractional distillation afforded **4d** as a colorless oil. GC yield: 94% (isolated yield: 1.4 g (54%)); b.p. 65–66°C/0.1 mbar; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.97 (d, J = 7.5 Hz, 2H), 6.83 (t, J = 7.5 Hz, 1H), 2.44 (t, J = 7.7 Hz, 2H), 1.97 (s, 6H), 1.69 (m, 2H), 1.59 (s, 3H), 1.44 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 172.2, 149.2, 128.2, 126.3, 122.9, 41.2, 29.2, 23.1, 20.1, 18.3, 14.4; MS (EI, 70 eV): *m*/*z* (%): 203 (14) [M^+], 188 (7) [M^+-CH_3], 161 (14), 146 (100) [$M^+-C_4H_9$], 121 (20), 105 (21), 77 (16) [Ph^+]; FT IR (neat): $\tilde{\nu}$ = 1664 cm^{-1} (C=N); elemental analysis calcd (%) for $C_{14}H_{21}N$: C 82.70, H 10.41, N 6.89; found: C 82.62, H 10.59, N 6.85.

General procedure for the reaction of alkynes with hydrazines: In an Ace-pressure tube under an argon atmosphere a solution of the catalyst in toluene was added to a mixture of alkyne and hydrazine. This mixture was heated at the given temperature for the specified time (see Table 4). Then 3–4 equiv of $ZnCl_2$ were added. The pressure tube was heated again at 100°C for 24 h. After filtration and removal of the solvent in vacuo, the product was isolated by column chromatography.

1,2-Dimethyl-3-pentylindole (5a): According to the general procedure 1-octyne (0.8 mL, 5.4 mmol) and *N*-methyl-*N*-phenylhydrazine (0.76 mL, 6.5 mmol) were treated in the presence of 2.5 mol% **1** (45 mg, 0.13 mmol) in toluene (4 mL) at 100°C for 2 h. Then $ZnCl_2$ (2.9 g, 21.6 mmol) was added. The residue was purified by column chromatography (*n*-hexane/ethyl acetate 5:1) to afford **5a** as a pale yellow oil. GC yield: 88% (isolated yield: 814 mg (70%)). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.59 (d, J = 7.7 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.24–7.18 (m, 1H), 7.16–7.11 (m, 1H), 3.69 (s, 3H), 2.78 (t, J = 7.7 Hz, 2H), 2.41 (s, 3H), 1.68 (m, 2H), 1.46–1.39 (m, 4H), 0.97 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 136.5, 132.5, 127.8, 120.3, 118.4, 118.0, 111.7, 108.4, 31.8, 30.8, 29.4, 24.4, 22.6, 14.1, 10.2; MS (EI, 70 eV): *m*/*z* (%): 215 (12) [M^+], 158 (100) [$M^+-C_4H_9$]; FT IR (neat): $\tilde{\nu}$ = 736 cm^{-1} (ArH *o*-disubst.); elemental analysis calcd (%) for $C_{15}H_{21}N$: C 83.67, H 9.83, N 6.50; found: C 84.03, H 10.14, N 6.60.

1,2-Dimethyl-3-cyclopentylindole (6a): According to the general procedure 3-cyclopentyl-1-propyne (0.76 mL, 5.7 mmol) and *N*-methyl-*N*-phenylhydrazine (0.82 mL, 6.9 mmol) were treated in the presence of 3.0 mol% **1** (60 mg, 0.17 mmol) in toluene (4 mL) at 100°C for 24 h. Thereafter $ZnCl_2$ (2.3 g, 17.2 mmol) was added. The residue was purified by column chromatography (*n*-hexane/ethyl acetate 5:1) to afford **6a** as a colorless solid. M.p. 102–104°C; GC yield: 82% (isolated yield: 754 mg (62%)). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.68 (d, J = 7.9 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.20 (m, 1H), 7.10 (m, 1H), 3.68 (s, 3H), 3.35–3.25 (m, 1H), 2.43 (s, 3H), 2.11–1.96 (m, 6H), 1.86–1.77 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 136.9, 132.0, 126.1, 120.2, 119.1, 118.2, 114.1, 108.7, 37.4, 32.9, 29.4, 26.4, 10.4; MS (EI, 70 eV): *m*/*z* (%): 213 (67) [M^+], 198 (21) [M^+-CH_3], 184 (100) [$M^+-C_2H_5$], 170 (19) [$M^+-C_3H_7$], 158 (29); FT IR (KBr): $\tilde{\nu}$ = 738 cm^{-1} (ArH *o*-disubst.); elemental analysis calcd (%) for $C_{15}H_{19}N$: C 84.46, H 8.98, N 6.57; found: C 84.81, H 9.27, N 6.45.

1,2-Dimethyl-3-phenylindole (7a): According to the general procedure 3-phenyl-1-propyne (0.43 mL, 3.5 mmol) and *N*-methyl-*N*-phenylhydrazine (0.49 mL, 4.2 mmol) were treated in the presence of 5.0 mol% **1** (61 mg, 0.17 mmol) in toluene (2.5 mL) at 85°C for 24 h. Then $ZnCl_2$ (1.9 g, 14.0 mmol) was added. The residue was purified by column chromatography (*n*-hexane/ethyl acetate 10:1) to afford **7a** as colorless needles. M.p. 107°C (lit.[37] 113–114°C); GC yield: 84% (isolated yield: 519 mg (67%)). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.76 (d, J = 7.9 Hz, 1H), 7.60–7.51 (m, 4H), 7.40–7.35 (m, 2H), 7.29 (m, 1H), 7.20 (m, 1H), 3.76 (s, 3H), 2.54 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 136.6, 135.8, 133.3, 129.6, 128.4, 126.9, 125.6, 121.1, 119.6, 118.6, 113.9, 108.7, 29.5, 11.0; MS (EI, 70 eV): *m*/*z* (%): 221 (100) [M^+], 204 (11), 144 (10); FT IR (KBr): $\tilde{\nu}$ = 742 (ArH *o*-disubst.), 704, 772 cm^{-1} (ArH monosubst.).

1-Methyl-3-phenylindole (8a):[38] According to the general procedure phenylacetylene (0.8 mL, 7.3 mmol) and *N*-methyl-*N*-phenylhydrazine (1.0 mL, 8.7 mmol) were reacted in the presence of 5.0 mol% **1** (125 mg, 0.36 mmol) in toluene (5.5 mL) at 100°C for 24 h. Then $ZnCl_2$ (2.9 g, 21.6 mmol) was added. The residue was purified by column chromatography (*n*-hexane/ethyl acetate 10:1) to afford **8a** as a green yellow oil. GC yield: 42% (isolated yield: 378 mg, 25%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.05 (d, J = 7.9 Hz, 1H), 7.74 (m, 2H), 7.52 (m, 2H), 7.43–7.28 (m, 4H), 7.27 (s, 1H), 3.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 137.4, 135.6, 128.7, 127.2, 126.5, 126.1, 125.6, 121.9, 119.9, 119.8, 116.6, 109.5, 32.7; MS (EI, 70 eV): *m*/*z* (%): 207 (100) [M^+], 192 (15) [M^+-CH_3], 165 (29), 104 (13); FT IR (KBr): $\tilde{\nu}$ = 744 (ArH *o*-disubst.), 698, 766 cm^{-1} (ArH monosubst.).

Together with **8a** another product was isolated, which after comparison with previously reported NMR data[39] could be characterized as 1-methyl-2-phenylindole (**8b**): GC yield: 10% (isolated yield: 76 mg (5%)). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.74 (d, J = 7.9 Hz, 1H), 7.63–7.22 (m, 8H), 6.67 (s, 1H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 141.5, 138.3, 132.8, 129.3, 128.4, 127.9, 127.8, 121.6, 120.4, 119.8, 109.6, 101.6, 31.1; MS (EI, 70 eV): *m*/*z* (%): 207 (100) [M^+], 165 (12), 104 (11), 102 (14).

2-(1,2-Dimethyl-indole-3-yl)ethylamine hydrochloride (9a)[40] **and 2-(1,2-dimethyl-indole-3-yl)ethylamine (9c)**:[41] According to the general procedure 5-chloro-1-pentyne (0.15 mL, 1.4 mmol) and *N*-methyl-*N*-phenylhydrazine (0.21 mL, 1.7 mmol) were reacted in the presence of 10.0 mol% **1** (51 mg, 0.14 mmol) in toluene (4 mL) at 100°C for 24 h. During this

time the corresponding hydrochloride **9a** precipitated. The mixture was diluted with hexane (5 mL) and the precipitate was filtered. M.p. 224–226 °C (lit.[40] 239–240 °C). Yield 210 mg (64 %). For the isolation of amine **9c**, the corresponding hydrochloride was dissolved in water (20 mL). This solution was treated with CH_2Cl_2 (20 mL) and subsequently with NaOH (to pH 9). Both layers were separated and the aqueous phase was washed twice with CH_2Cl_2 (10 mL). All organic phases were combined and dried over $MgSO_4$. After evaporation of the solvent the free amine **9c** was obtained as an colorless oil (159 mg, 58 %). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.54 (d, J = 7.7 Hz, 1H), 7.26 (d, J = 8.1 Hz, 1H), 7.17 (m, 1H), 7.09 (m, 1H), 3.65 (s, 3H), 2.96 (m, 2H), 2.88 (m, 2H), 2.38 (s, 3H), 1.39 (brs, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 136.5, 133.5, 127.7, 120.4, 118.6, 117.8, 108.4, 108.3, 42.7, 29.4, 28.6, 10.2; MS (EI, 70 eV): m/z (%): 188 (22) [M^+], 158 (100) [$M^+ - CH_2NH_2$], 143 (8); FT IR (neat): $\tilde{\nu}$ = 3359, 3290, 1653 (NH_2), 739 cm^{-1} (ArH *o*-disubst.).

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[1] For general references, see: a) J. March, *Advanced Organic Chemistry*, 4th ed., Wiley, New York, **1992**, pp. 768, and references therein; b) J. P. Collman, B. M. Trost, T. R. Veroeven, in *Comprehensive Organometallic Chemistry, Vol. 8* (Eds.: G. Wilkinson, F. G. A. Stone), Pergamon Press, Oxford, **1982**, pp. 892, and references therein; c) M. S. Gibson, in *The Chemistry of Amino Group* (Ed.: S. Patai), Wiley, New York, **1968**, pp. 61.

[2] For leading reviews on hydroamination, see: a) F. Pohlki, S. Doye, *Chem. Soc. Rev.* **2003**, *32*, 104; b) I. Bytschkov, S. Doye, *Eur. J. Org. Chem.* **2003**, 935; c) M. Beller, C. Breindl, M. Eichberger, C. G. Hartung, J. Seayad, O. R. Thiel, A. Tillack, H. Trauthwein, *Synlett* **2002**, 1579; d) M. Nobis, B. Drießen-Hölscher, *Angew. Chem.* **2001**, *113*, 4105; *Angew. Chem. Int. Ed.* **2001**, *40*, 3983; e) J.-J. Brunet, D. Neibecker, in *Catalytic Heterofunctionalization*, (Eds.: A. Togni, H. Grützmacher), Wiley-VCH, Weinheim, **2001**, p. 91; f) T. E. Müller, M. Beller, *Chem. Rev.* **1998**, *98*, 675; g) J. J. Brunet, D. Neibecker, F. Niedercorn, *J. Mol. Catal.* **1989**, *49*, 235.

[3] For alkalimetal and base catalyzed hydroamination, see: a) A. Ates, C. Quinet, *Eur. J. Org. Chem.* **2003**, 1623; b) B. M. Trost, W. Tang, *J. Am. Chem. Soc.* **2003**, *125*, 8744; c) J. Seayad, A. Tillack, C. G. Hartung, M. Beller, *Adv. Synth. Catal.* **2002**, *344*, 795; d) M. Beller, C. Breindl, *Chemosphere* **2001**, *43*, 21; e) C. G. Hartung, C. Breindl, A. Tillack, M. Beller, *Tetrahedron* **2000**, *56*, 5157; f) M. Beller, C. Breindl, T. H. Riermeier, M. Eichberger, H. Trauthwein, *Angew. Chem.* **1998**, *110*, 3571; *Angew. Chem. Int. Ed.* **1998**, *37*, 3389; g) M. Beller, C. Breindl, *Tetrahedron* **1998**, *54*, 6359; h) D. Steinborn, B. Dies, I. Wagner, R. Taube, *Z. Chem.* **1989**, *29*, 333; i) G. P. Pez, J. E. Galle, *Pure Appl. Chem.* **1985**, *57*, 1917; j) J. Wollensak, R. D. Closson, *Org. Synth.* **1963**, *43*, 45; k) R. Stroh, J. Ebersberger, H. Haberland, W. Hahn, *Angew. Chem.* **1957**, *69*, 124; l) B. W. Howk, E. L. Little, S. L. Scott, G. M. Whitman, *J. Am. Chem. Soc.* **1954**, *76*, 1899.

[4] For acid-catalyzed hydroamination, see: a) M. Lequitte, F. Figueras, C. Moreau, S. Hub, *J. Catal.* **1996**, *163*, 255; b) A. Cermona, A. Corma, M. Iglesias, A. San José, F. Sánchez, *J. Organomet. Chem.* **1995**, *492*, 11; c) N. Mizuno, M. Tabata, T. Uematsu, M. Iwamoto, *J. Catal.* **1994**, *146*, 249; d) N. Mizuno, M. Tabata, T. Uematsu, M. Iwamoto, *J. Chem. Soc. Faraday Trans. 1* **1993**, *89*, 3513; e) P. Fink, J. Datka, *J. Chem. Soc. Faraday Trans. 1* **1989**, *85*, 3079; f) M. Deeba, M. E. Ford, T. A. Johnson, *J. Chem. Soc. Chem. Commun.* **1987**, 562.

[5] For hydroamination mediated by early transition metals and lanthanoid complexes, see: a) D. V. Gribkov, K. C. Hultzsch, F. Hampel, *Chem. Eur. J.* **2003**, *9*, 4796; b) Y. K. Kim, T. Livinghouse, Y. Horino, *J. Am. Chem. Soc.* **2003**, *125*, 9560; c) P. N. O'Shaughnessy, P. Scott, *Tetrahedron: Asymmetry* **2003**, *14*, 1979; d) G. A. Molander, J. A. C. Romero, *Chem. Rev.* **2002**, *102*, 2161; e) S. Hong, T. J. Marks, *J. Am. Chem. Soc.* **2002**, *124*, 7886; f) M. R. Douglass, M. Ogasawara, S. Hong, M. V. Metz, T. J. Marks, *Organometallics* **2002**, *21*, 283; g) Y. K. Kim, T. Livinghouse, *Angew. Chem.* **2002**, *114*, 3797; *Angew. Chem. Int. Ed.* **2002**, *41*, 3645; h) Y. K. Kim, T. Livinghouse, J. E. Bercaw, *Tetrahedron Lett.* **2001**, *42*, 2933; i) S. Tian, V. M. Arredondo, C. L. Stern, T. J. Marks, *Organometallics* **1999**, *18*, 2568; j) E. L. Eliel, S. H. Wilen, L. N. Mander, *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**, 682; k) M. A. Giardell, V. P. Conticello, L. Brard, M. R. Gagné, T. J. Marks, *J. Am. Chem. Soc.* **1994**, *116*, 10241; l) M. R. Gagné, C. L. Stern, T. J. Marks, *J. Am. Chem. Soc.* **1992**, *114*, 275; m) M. R. Gagné, T. J. Marks, *J. Am. Chem. Soc.* **1989**, *111*, 4108.

[6] a) For hydroamination catalyzed by late transition metals, see R. Dorta, P. Egli, F. Zürcher, A. Togni, *J. Am. Chem. Soc.* **1997**, *119*, 10857; b) M. Beller, M. Eichberger, H. Trauthwein, *Angew. Chem.* **1997**, *109*, 2306; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2225; c) J.-J. Brunet, G. Commenges, D. Neibecker, K. Philippot, *J. Organomet. Chem.* **1994**, *469*, 221; d) J.-J. Brunet, D. Neibecker, K. Philippot, *Tetrahedron Lett.* **1993**, *34*, 3877; e) J.-J. Brunet, D. Neibecker, K. Philippot, *J. Chem. Soc. Chem. Commun.* **1992**, 1215; f) D. Selent, D. Scharfenberg-Pfeiffer, G. Reck, R. Taube, *J. Organomet. Chem.* **1991**, *415*, 417; g) A. L. Casalnuovo, J. L. Calabrese, D. Milstein, *J. Am. Chem. Soc.* **1988**, *110*, 6738; h) D. Steinborn, R. Taube, *Z. Chem.* **1986**, *26*, 349; i) L. S. Hegedus, J. M. McKearin, *J. Am. Chem. Soc.* **1982**, *104*, 2444; j) B. Pugin, L. M. Venanzi, *J. Organomet. Chem.* **1981**, *214*, 125, and references therein; k) D. R. Coulson, *Tetrahedron Lett.* **1971**, *12*, 429.

[7] a) M. Utsunomiya, R. Kuwano, M. Kawatsura, J. F. Hartwig, *J. Am. Chem. Soc.* **2003**, *125*, 5608; b) J.-J. Brunet, N. C. Chu, O. Diallo, E. Mothes, *J. Mol. Catal. A* **2003**, *198*, 107; c) K. Li, P. N. Horton, M. B. Hursthouse, K. K. Hii, *J. Organomet. Chem.* **2003**, *665*, 250; d) U. Nettekoven, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 1166; e) X. Cheng, K. K. Hii, *Tetrahedron* **2001**, *57*, 5445; f) M. Kawatsura, J. F. Hartwig, *J. Am. Chem. Soc.* **2000**, *122*, 9546; g) H. M. Senn, P. E. Blöchl, A. Togni, *J. Am. Chem. Soc.* **2000**, *122*, 4098; h) A. Tillack, H. Trauthwein, C. G. Hartung, M. Eichberger, S. Pitter, A. Jansen, M. Beller, *Monatsh. Chem.* **2000**, *131*, 1327; i) M. Beller, O. R. Thiel, H. Trauthwein, C. G. Hartung, *Chem. Eur. J.* **2000**, *6*, 2513.

[8] a) Y. Li, T. J. Marks, *J. Am. Chem. Soc.* **1996**, *118*, 9295; b) J. B. Pedley, R. D. Naylor, S. P. Kirby, *Thermochemical Data of Organic Compounds*, Chapman and Hall, London, **1986**, Appendix Tables 1, 3.

[9] a) S. Burling, L. D. Field, H. L. Li, B. A. Messerle, P. Turner, *Eur. J. Inorg. Chem.* **2003**, 3179; b) C. Li, R. K. Thomson, B. Gillon, B. O. Patrick, L. L. Schafer, *Chem. Commun.* **2003**, 2462; c) J. Barluenga, M. Trincado, E. Rubio, J. M. González, *Angew. Chem.* **2003**, *115*, 2508; *Angew. Chem. Int. Ed.* **2003**, *42*, 2406; d) C. Koradin, W. Dohle, A. L. Rodriguez, B. Schmid, P. Knochel, *Tetrahedron* **2003**, *59*, 1571; e) L. Ackermann, R. G. Bergman, *Org. Lett.* **2002**, *4*, 1475; f) I. Bytschkov, S. Doye, *Tetrahedron Lett.* **2002**, *43*, 3715; g) V. Neff, T. E. Müller, J. A. Lercher, *Chem. Commun.* **2002**, 906; h) J. Penzien, R. Q. Su, T. S. Müller, *J. Mol. Catal. A* **2002**, *182–183*, 489; i) T. Kondo, T. Okada, T. Suzuki, T. Mitsudo, *J. Organomet. Chem.* **2001**, *622*, 149, and references therein; j) M. Tokunaga, M. Ota, M.-A. Haga, Y. Wakatsuki, *Tetrahedron Lett.* **2001**, *42*, 3865; k) T. E. Müller, M. Grosche, E. Herdtweck, A.-K. Pleier, E. Walter, Y.-K. Yan, *Organometallics* **2000**, *19*, 170; l) J. Penzien, T. E. Müller, J. A. Lercher, *Chem. Commun.* **2000**, 1753; m) S. Burling, L. D. Field, B. A. Messerle, *Organometallics* **2000**, *19*, 87; n) T. E. Müller, A.-K. Pleier, *J. Chem. Soc. Dalton Trans.* **1999**, 583; o) D. Duncan, T. Livinghouse, *Organometallics* **1999**, *18*, 4421; p) M. R. Bürgstein, H. Berberich, P. W. Roesky, *Organometallics* **1998**, *17*, 1452; q) L. S. Hegedus, *Angew. Chem.* **1988**, *100*, 1147; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1113.

[10] D. Tzalis, C. Koradin, P. Knochel, *Tetrahedron Lett.* **1999**, *40*, 6193.

[11] a) Y. Li, T. J. Marks, *Organometallics* **1996**, *15*, 3370; b) Y. Li, T. J. Marks, *J. Am. Chem. Soc.* **1998**, *120*, 1757.

[12] a) J. Wang, A. K. Dash, M. Kapon, J.-C. Berthet, M. Ephritikhine, M. S. Eisen, *Chem. Eur. J.* **2002**, *8*, 5384; b) T. Straub, A. Haskel,

T. G. Neyroud, M. Kapon, M. Botoshansky, M. S. Eisen, *Organometallics* **2001**, *20*, 5017; c) M. S. Eisen, T. Straub, Haskel, A. *J. Alloys Compd.* **1998**, *271–273*, 116; d) A. Haskel, T. Straub, M. S. Eisen, *Organometallics* **1996**, *15*, 3773.

[13] a) E. Mizushima, T. Hayashi, M. Tanaka, *Org. Lett.* **2003**, *5*, 3349; b) T. Shimada, Y. Yamamoto, *J. Am. Chem. Soc.* **2002**, *124*, 12670; c) C. G Hartung, H. Trauthwein, A. Tillack, M. Beller, *J. Org. Chem.* **2001**, *66*, 6339; d) M. Tokunaga, Y. Wakatsuki, *J. Synth. Org. Chem. Jpn.* **2000**, *58*, 587; e) M. Tokunaga, M. Eckert, Y. Wakatsuki, *Angew. Chem.* **1999**, *111*, 3416; *Angew. Chem. Int. Ed.* **1999**, *38*, 3222; f) Y. Uchimaru, *Chem. Commun.* **1999**, 1133; g) I. Kadota, A. Shibuya, L. M. Lutete, Y. Yamamoto, *J. Org. Chem.* **1999**, *64*, 4570; h) J. Barluenga, A. Aznar, R. Liz, R. Rodes, *J. Chem. Soc. Perkin Trans. 1* **1980**, 2732; i) J. Barluenga, A. Aznar, *Synthesis* **1977**, 195; j) J. Barluenga, A. Aznar, *Synthesis* **1975**, 704.

[14] a) A. M. Baranger, P. J. Walsh, R. G. Bergman, *J. Am. Chem. Soc.* **1993**, *115*, 2753; b) P. J. Walsh, A. M. Baranger, R. G. Bergman, *J. Am. Chem. Soc.* **1992**, *114*, 1708.

[15] J. S. Johnson, R. G. Bergman, *J. Am. Chem. Soc.* **2001**, *123*, 2923.

[16] a) F. Pohlki, A. Heutling, I. Bytschkov, T. Hotopp, S. Doye, *Synlett* **2002**, 799; b) I. Bytschkov, S. Doye, *Eur. J. Org. Chem.* **2001**, 4411; c) E. Haak, H. Siebeneicher, S. Doye, *Org. Lett.* **2000**, *2*, 1935; d) E. Haak, I. Bytschkov, S. Doye, *Angew. Chem.* **1999**, *111*, 3584; *Angew. Chem. Int. Ed.* **1999**, *38*, 3389.

[17] a) Y. Shi, C. Hall, J. T. Ciszewski, C. Cao, A. L. Odom, *Chem. Commun.* **2003**, 586; b) Y. Shi, J. T. Ciszewski, A. L. Odom, *Organometallics* **2001**, *20*, 3967; c) C. Cao, J. T. Ciszewski, A. L. Odom, *Organometallics* **2001**, *20*, 5011.

[18] T.-G. Ong, G. P. A. Yap, D. S. Richeson, *Organometallics* **2002**, *21*, 2839.

[19] a) H. Trauthwein, A. Tillack, M. Beller, *Chem. Commun.* **1999**, 2029; b) M. Beller, O. R. Thiel, H. Trauthwein, *Synlett* **1999**, 243; c) M. Beller, H. Trauthwein, M. Eichberger, C. Breindl, T. E. Müller, *Eur. J. Inorg. Chem.* **1999**, 1121; d) M. Beller, H. Trauthwein, M. Eichberger, C. Breindl, J. Herwig, T. E. Müller, O. R. Thiel, *Chem. Eur. J.* **1999**, *5*, 1306; e) M. Beller, H. Trauthwein, M. Eichberger, C. Breindl, A. Zapf, T. E. Müller, *J. Organomet. Chem.* **1998**, *566*, 277.

[20] A. Tillack, I. Garcia Castro, C. G. Hartung, M. Beller, *Angew. Chem.* **2002**, *114*, 2646; *Angew. Chem. Int. Ed.* **2002**, *41*, 2541.

[21] For reviews, see: a) U. Rosenthal, V. V. Burlakov, P. Arndt, W. Baumann, A. Spannenberg, *Organometallics* **2003**, *22*, 884; b) U. Rosenthal, V. V. Burlakov, in *Titanium and Zirconium in Organic Synthesis* (Ed.: I. Marek), Wiley-VCH, Weinheim, **2002**, p. 355. The Rosenthal catalysts are now commercially available from Fluka.

[22] V. V. Burlakov, A. V. Polyakov, A. I. Yanovsky, Y. T. Struchkov, V. B. Shur, M. E. Vol'pin, U. Rosenthal, H. Görls, *J. Organomet. Chem.* **1994**, *476*, 197.

[23] For a recent review on selective Markovnikov and anti-Markovnikov functionalization reactions, see: J. Seayad, A. Tillack, H. Jiao, M. Beller, *Angew. Chem.* **2004**, *116*, in press; *Angew. Chem. Int. Ed.* **2004**, *43*, in press.

[24] A. Heutling, S. Doye, *J. Org. Chem.* **2002**, *67*, 1961.

[25] V. Varga, K. Mach, M. Polašek, P. Sedmera, J. Hiller, U. Thewalt, S. I. Troyanov, *J. Organomet. Chem.* **1996**, *506*, 241.

[26] J.-L. Jiang, Z. Shi, *Synth. Commun.* **1998**, *28*, 4137.

[27] C. Cao, Y. Shi, A. L. Odom, *Org. Lett.* **2002**, *4*, 2853.

[28] a) B. Robinson, *The Fischer Indole Synthesis*, Wiley, Chichester, **1982**; b) D. L. Hughes, *Org. Prep. Proced. Int.* **1993**, *25*, 607.

[29] a) F. Pohlki, S. Doye, *Angew. Chem.* **2001**, *113*, 2361; *Angew. Chem. Int. Ed.* **2001**, *40*, 2305; b) B. F. Straub, R. G. Bergman, *Angew. Chem.* **2001**, *113*, 4768; *Angew. Chem. Int. Ed.* **2001**, *40*, 4632.

[30] In addition to $[(\eta^5\text{-}C_5H_5)Ti(=NR)(NHR)]$, we have calculated the reactions with $(\eta^5\text{-}C_5H_5)_2Ti(=NR)$ as the active catalyst ($R = C(CH_3)_3$, C_6H_5). However, no energetic difference is found between the Markovnikov and anti-Markovnikov π-complexes using $[(\eta^5\text{-}C_5H_5)_2Ti(=NR)(HC{\equiv}CCH_3)]$. In addition, the ligand exchange reaction between $[(\eta^5\text{-}C_5H_5)_2Ti(=NR)(HC{\equiv}CCH_3)]$ and NH_2R to give $[(\eta^5\text{-}C_5H_5)Ti(=NR)(NHR)(HC{\equiv}CCH_3)]$ and C_5H_6 is exothermic by 15.4 kcal mol^{-1} for $R = C_6H_5$, and by 12.8 kcal mol^{-1} for $R = C(CH_3)_3$, and therefore the release of C_5H_6 is favored energetically. This result agrees with the experimental and theoretical finding by Bergman (ref. [15]) for a release of C_5H_6 under catalytic conditions. Hence, the active catalyst under our conditions should be $[(\eta^5\text{-}C_5H_5)Ti(=NR)(NHR)]$ rather than $[(\eta^5\text{-}C_5H_5)_2Ti(=NR)]$.

[31] *Gaussian 98*, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle, J. A. Pople, Gaussian, Inc., Pittsburgh PA, **1998**.

[32] a) P. J. Hay, W. R. Wadt, *J. Chem. Phys.* **1985**, *82*, 299; b) T. H. Dunning, Jr., P. J. Hay, *Modern Theoretical Chemistry* (Ed.: H. F. Schaefer, III), Plenum, New York, **1976**, pp. 1; c) for polarization functions see: S. Huzinaga, J. Anzelm, M. Klobukowski, E. Radzio-Andzelm, Y. Sakai, H. Tatewaki, *Gaussian Basis Sets for Molecular Calculations*, Elsevier, Amsterdam, **1984**.

[33] J. B. Foresman, Æ. Frisch, *Exploring Chemistry with Electronic Structure Methods: A Guide to Using Gaussian*, 2nd ed., Gaussian, Inc., Pittsburgh PA, **1996**.

[34] E. D. Jemmis, A. K. Phukan, J. Jiao, U. Rosenthal, *Organometallics* **2003**, *22*, 1958.

[35] a) NBO Program, 3.1, E. D. Glendening, A. E. Reed, J. E. Carpenter, F. Weinhold; b) A. E. Reed, L. A. Curtiss, F. Weinhold, *Chem. Rev.* **1988**, *88*, 899.

[36] R. Jaouhari, C. Filliatre, B. Maillard, J. J. Villenave, *Tetrahedron* **1982**, *38*, 3137.

[37] a) P. E. Verkade, E. F. Janetzky, *Recl. Trav. Chim. Pays-Bas* **1943**, *62*, 775; b) C. Berti, L. Greci, M. Poloni, *J. Chem. Soc. Perkin Trans. 1* **1981**, 1610.

[38] a) J. Rodriguez, A. Lafuente, P. Garcia-Almaraz, *J. Heterocycl. Chem.* **2000**, *37*, 1281; b) A. Couture, E. Deniau, Y. Gimbert, P. Grandclaudon, *J. Chem. Soc. Perkin Trans. 1* **1993**, 2463; c) T. Nishio, *J. Org. Chem.* **1988**, *53*, 1323.

[39] M. Ishikura, I. Agata, N. Katagiri, *J. Heterocycl. Chem.* **1999**, *36*, 873.

[40] R. V. Heinzelman, J. Szmuszkovicz, *Prog. Drug Res.* **1963**, *75*, 6; *Chem. Abstr.* **1964**, *60*, 13215b.

[41] I. I. Grandberg, N. I. Afonina, T. I. Zuyanova, *Khim. Geterosikl. Soedin.* **1968**, 1038.

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