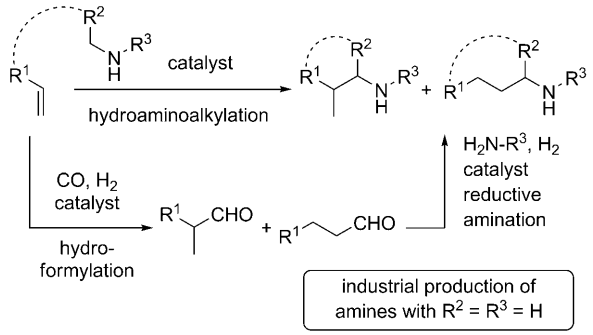
C–H Activation

DOI: 10.1002/anie.201101239

The Mechanism of the Titanium-Catalyzed Hydroaminoalkylation of Alkenes**

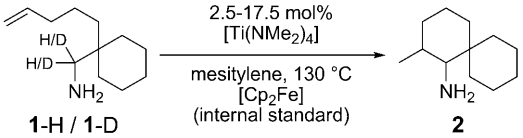
Insa Prochnow, Patrick Zark, Thomas Müller, and Sven Doye**

Catalytic C–H bond activation reactions at sp^3 centers in the α position to nitrogen atoms[1,2] have recently attracted much attention because they offer new and promising synthetic approaches for the functionalization of simple amines. Particularly important in this context are studies dealing with the development of methods for the hydroaminoalkylation of alkenes.[3–9] This highly atom efficient reaction, which does not lead to the formation of any side products, allows the addition of α-C–H bonds of primary or secondary amines to C–C double bonds in a single step (Scheme 1). The significance of this new reaction is clearly underlined by the fact that a hypothetical use of methylamine, which unfortunately could not be realized yet, would establish a waste-free one-step alternative for the industrial production of primary amines from alkenes, which nowadays requires two steps.



Scheme 1. Comparison of the hydroaminoalkylation of alkenes with the industrially established two-step process for the synthesis of amines from alkenes.

Although hydroaminoalkylation of alkenes has already been achieved with Ta,[4–7] Ti,[8] and Zr catalysts,[6b,9] the mechanism of the reaction remains unclear. So far only a few mechanistic suggestions have been published,[4b,5,6,8,9] but no detailed mechanistic data are available in the literature. For that reason and because we think that for any further optimization of the process it is vital to understand the reaction mechanism in detail we decided to perform an extensive kinetic investigation of the intramolecular hydroaminoalkylation of aminoalkenes **1**-H and **1**-D (Scheme 2) to reveal, for the first time, important mechanistic details of the new reaction. At the moment it is assumed that metallaaziridines are the key intermediates of the catalytic cycle. A corresponding monomeric tantallaaziridine complex[6a] and a bridging titanaaziridine[9] have already been isolated, and both derivatives turned out to be catalytically active.



Scheme 2. Kinetically investigated hydroaminoalkylation of aminoalkenes **1**-H and **1**-D. Preparative result with **1**-H and 5 mol% [Ti(NMe$_2$)$_4$] after 24 h: 83% yield of **2** (*cis*/*trans* = 17:83). Cp = C_5H_5.

At the beginning of our study we performed a number of intramolecular hydroaminoalkylation reactions of **1**-H in mesitylene at (130 ± 1) °C in the presence of various concentrations (2.5–17.5 mol%) of [Ti(NMe$_2$)$_4$].[10] To monitor the concentration of **1**-H by ^{1}H NMR spectroscopy ferrocene was used as an internal standard and samples were taken from the reaction mixture at regular time intervals. After dilution of these samples with a 1M solution of benzyl alcohol in C_6D_6 it was easily possible to determine the concentration of **1**-H by integration of the ^{1}H NMR signal of the terminal CH_2 group of **1**-H. However, it must be noted that the addition of alcohol, which was expected to result in cleavage of all the Ti–N bonds formed under the reaction conditions, was essential for a clean and reliable integration of the ^{1}H NMR signal. Otherwise, the corresponding signal showed a significant line broadening especially in cases of higher catalyst loadings.[11] This observation suggests that under the reaction conditions the aminoalkene **1**-H does not only exist in the free form but also bound to a large number and variety of Ti species. Selected plots of c(**1**-H) versus time, which clearly indicate that the reaction has a zero-order rate dependence on substrate concentration, are shown in Figure 1.[12,13]

After having established the resulting overall rate law $-dc(\mathbf{1}\text{-H})/dt = k_{obs(\mathbf{1}\text{-H})}$, a plot of the rate constants $k_{obs(\mathbf{1}\text{-H})}$ versus the catalyst concentration revealed that the reaction

[*] I. Prochnow, P. Zark, Prof. Dr. T. Müller, Prof. Dr. S. Doye
Institut für Reine und Angewandte Chemie, Universität Oldenburg
Carl-von-Ossietzky-Strasse 9–11, 26111 Oldenburg (Germany)
Fax: (+49) 441-798-3329
E-mail: thomas.mueller@uni-oldenburg.de
doye@uni-oldenburg.de

[**] We thank the Deutsche Forschungsgemeinschaft (DFG) and the Fonds der Chemischen Industrie (Chemiefonds fellowship for Patrick Zark) for financial support of our research. We further thank Andrea Tschirne and Prof. Dr. Markus Enders for their great help during the NMR spectroscopic studies.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201101239.

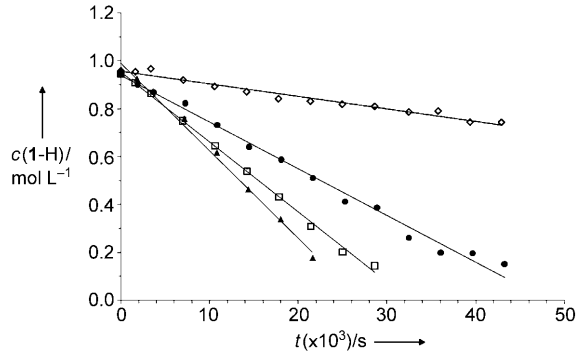


Figure 1. Representative plots of c(**1**-H) versus t for [Ti(NMe$_2$)$_4$] concentrations of 2.5 (◇), 5 (●), 7.5 (□), and 10 mol% (▲).

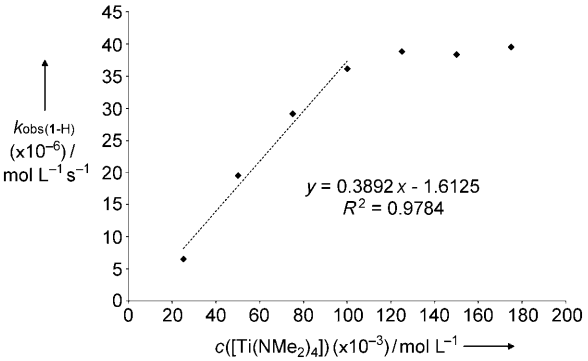


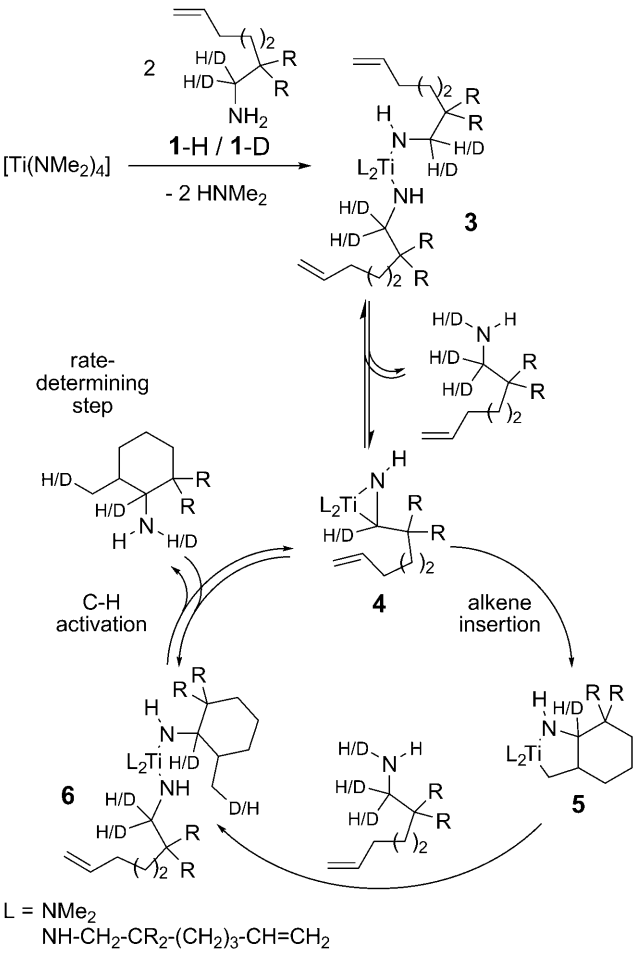
Figure 2. Plot of $k_{obs(1\text{-H})}$ (average of two kinetic runs) versus the [Ti(NMe$_2$)$_4$] concentration.

is not first order in the concentration of [Ti(NMe$_2$)$_4$] over the entire range of catalyst concentration (Figure 2).

While an expected and almost linear acceleration of the reaction with increasing catalyst concentration is observed over the range 2.5–10 mol% [Ti(NMe$_2$)$_4$] which corresponds to a first-order rate law $\{k_{obs(\mathbf{1}\text{-H})} = k_{\mathbf{1}\text{-H}}c([Ti(NMe_2)_4])\}$, the reaction order becomes zero $\{k_{obs(\mathbf{1}\text{-H})} = k_{\mathbf{1}\text{-H}}\}$ above a catalyst concentration of 12.5 mol%. A plausible explanation for this fairly sharp decrease in reaction order could be that the formation of multidimensionally linked titanium amido oligomers containing Ti-N-Ti bridges[14] is possible at higher catalyst loadings because of the primary amino group of **1**-H. This aggregation process should be clearly favored as the concentration of Ti species in solution increases, and an important indication of such an aggregation is provided by the ^{1}H NMR spectra of mixtures of **1**-H and [Ti(NMe$_2$)$_4$]. With increasing Ti content in solution and especially at a [Ti(NMe$_2$)$_4$] concentration above 10 mol%, many and broadened ^{1}H NMR signals are observed at $\delta = 3$–4 ppm which can be assigned to the α-CH$_2$ group of many different titanium amido species formed under the reaction conditions.[15,16] Ultimately, the formation of titanium oligomers could lead to a situation in which the addition of additional amounts of [Ti(NMe$_2$)$_4$] does not lead to a further increase in the number of catalytically active molecules, which then results in a constant reaction rate.[17] The possibility that dimethylamine, which is formed from [Ti(NMe$_2$)$_4$] and the aminoalkene substrate under the reaction conditions, is responsible for the constant rate at high catalyst concentrations[18] can be ruled out because an analogous rate-dependence on the catalyst concentration was found for the catalyst [TiBn$_4$] (Bn = benzyl).[10]

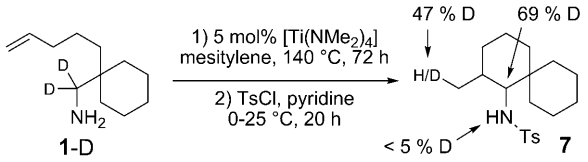
Additional kinetic studies were conducted at 120 °C and 140 °C in the presence of 5 mol% and 10 mol% [Ti(NMe$_2$)$_4$] to determine the activation parameter of the hydroaminoalkylation of **1**-H. With the presumption that the reaction is first-order in respect of [Ti(NMe$_2$)$_4$] for these catalyst loadings, an Eyring-type analysis[10] of the obtained data revealed that the enthalpy of activation is high ($\Delta H^{\neq} = (110.2 \pm 3.0)$ kJ mol^{-1}) and that the reaction passes through a moderately ordered transition state ($\Delta S^{\neq} = -(39.7 \pm 6.4)$ J mol^{-1} K^{-1}). This results in a substantial Gibbs free activation energy of $\Delta G^{\neq}(403.15\text{ K}) = (128.3 \pm 2.6)$ kJ mol^{-1}.

Taken together, the obtained kinetic data are in agreement with the catalytic cycle shown in Scheme 3. A similar mechanism with a metallaaziridine[6a,9] as the key intermediate was proposed for analogous tantalum-catalyzed reactions.[4b,5,6] This mechanistic scenario suggests that the titanium-bisamide complex **3** is initially formed from the precatalyst [Ti(NMe$_2$)$_4$] by substitution of dimethylamine



Scheme 3. Simplified mechanism of the titanium-catalyzed intramolecular hydroaminoalkylation of alkenes.

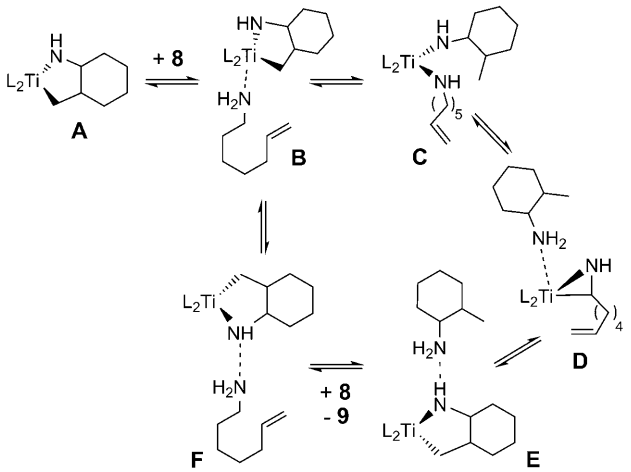
with the reactive amine. This amine exchange reaction is fast at room temperature and it is detectable by ^{1}H NMR spectroscopy.[15] The titanaaziridine **4** is subsequently produced from complex **3** by a C–H activation reaction. The intramolecular alkene insertion into the Ti–C bond then results in the formation of 2-titanapyrrolidine **5**, which subsequently undergoes aminolysis to the tetraamido species **6** and product-forming C–H activation with regeneration of the catalytically active complex **4**. The observed independence of the reaction rate on the aminoalkene concentration indicates that either the alkene insertion or the C–H activation, but not the aminolysis of 2-titanapyrrolidine **5**, is the rate-determining step of the catalytic cycle. In the case of a rate-determining C–H activation of the α-C–H bond, a significant primary kinetic isotope effect would be expected when the deuterated aminoalkene **1**-D is used. For this reason, this substrate was also included in the kinetic study. The determined isotope effect of $k_{obs(\mathbf{1}\text{-H})}/k_{obs(\mathbf{1}\text{-D})} = 7.3$ at 130 °C observed with 5 mol % and 10 mol % [$Ti(NMe_2)_4$] shows impressively that the C–H activation step **6**→**4** and not the alkene insertion is rate-determining. In a complementary hydroaminoalkylation reaction of **1**-D on a preparative scale, significant deuterium loss in the α position to the nitrogen atom from > 98 % in **1**-D to 69 % in the tosylated product **7** (Scheme 4) was established. This clearly indicates that besides



Scheme 4. Preparative reaction of the deuterated aminoalkene **1**-D. Ts = toluene-4-sulfonyl.

the productive alkene insertion, the intermediate titanaaziridine **4** also undergoes a noticeable amount of aminolysis by N–H proton transfer from the starting or product amine, and it confirms unequivocally the reversibility of the C–H/C–D activation steps. The additionally observed incorporation of deuterium atoms into the methyl group of the product **7** is explained by the aminolysis of titanapyrrolidine **5** to give tetraamido complex **6** by N-deuterated aminoalkene. The latter is formed by C–D activation of **1**-D.

In addition to the experimental investigations, DFT studies for the titanium-catalyzed cyclization of the model aminoalkene **8** to give *trans*-1-amino-2-methylcyclohexane (**9**) were conducted (Figure 3).[19] The computations reveal that the isomerization reaction to give amine **9** is exothermic by $\Delta H_R^{298} = 76\ kJ\,mol^{-1}$ [B3LYP/6-311 + G(d,p)(C,H);SDD-(Ti)]. Starting from the simplified mechanism for the hydroaminoalkylation reaction shown in Scheme 3 and from previous mechanistic suggestions,[4b,5,6,8,9] the theoretical investigations resulted in a more detailed proposal for the catalytic cycle, which is depicted in Scheme 5. The corresponding calculated reaction coordinates are shown in Figure 4.



Scheme 5. Detailed mechanistic proposal for the titanium-catalyzed intramolecular hydroaminoalkylation based on DFT calculations (L: NMe_2).

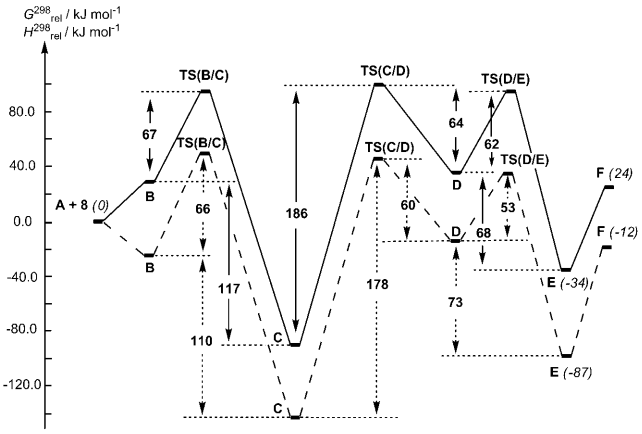


Figure 4. Calculated reaction coordinates of the titanium-catalyzed intramolecular hydroaminoalkylation (Scheme 5). The course of the calculated Gibbs free energy G^{298} is given by a solid line, that of the enthalpy H^{298} by a dashed line (relative to **A** + **8**). Differences in the enthalpies and Gibbs free energies between isomers are given in italics and in parentheses. Differences in the enthalpies and Gibbs free energies between ground and transition states are shown in boldface [B3LYP/6-311 + G(d,p)(C,H);SDD(Ti)].

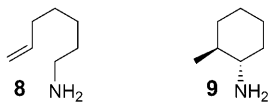


Figure 3. Model compound **8** and product amine **9** used in DFT calculations.

The suggested reaction sequence (Scheme 5) starts with coordination of the starting amine **8** to the 2-titanapyrrolidine **A**, which corresponds to the key intermediate **5** in Scheme 3. The so-formed pentacoordinated species **B** is stabilized by 23 kJ mol^{-1}, while the negative entropy of the bimolecular reaction results in a 29 kJ mol^{-1} increase in the Gibbs free energy (Figure 4). The subsequent intramolecular aminolysis

of the Ti–C bond in **B** yields the extremely stable tetraamido complex **C**. The consecutive rate-determining step transforms the titanium complex **C** to the titanaaziridine **D** by hydrogen atom transfer from the α carbon atom of the coordinated starting amine to the nitrogen atom of the product amine. The formed product amine **9** stays coordinatively bonded at the titanium center (binding energy $\Delta H_R^{298} = 71\ kJ\,mol^{-1}$). The significant calculated activation barrier for this step is in qualitative agreement[20] with the high reaction temperatures applied in the experiment. The fact that the rate-determining step of the catalytic cycle corresponds to an isomerization reaction of the tetraamido complex **C** to give the titanaaziridine **D** is consistent with the experimentally observed zero-order kinetics with respect to the starting amine **8**. The calculated structure of the transition state **TS(C/D)** for the C–H activation step indicates a considerably advanced C–H bond cleavage, while the new N–H bond is developed only to a small extent (bond elongation C–H: 140%; N–H 129%; Figure 5).[21] For this step, the calculations for the model

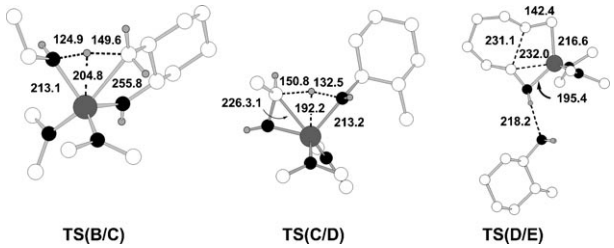


Figure 5. Calculated structures of transition states **TS(B/C)**, **TS(C/D)**, and **TS(D/E)** [B3LYP/6-311 + G(d,p)(C,H);SDD(Ti)]. Code: Ti (dark gray), N (black), C (white), H (light gray). For the sake of clarity, H atoms bonded to C atoms are not shown, if not essential for the understanding of the structure. For the same reason, the 4-pentenyl groups are omitted in the structures of **TS(B/C)** and of **TS(C/D)**.

system predict a deuterium isotope effect of 4.3, which is slightly lower than the experimental result of $k_{obs(\mathbf{1}\text{-H})}/k_{obs(\mathbf{1}\text{-D})} = 7.3$. The subsequent insertion of the alkene group into the Ti–C bond of the titanaaziridine **D** displaces the product amine **9** from the coordination sphere of the titanium atom. It remains, however, bound to the 2-titanapyrrolidine through a NH···N bridge (adduct **E**). Substitution of product amine **9** by starting amine **8** and extension of the coordination sphere of complex **F** regenerates the pentacoordinate complex **B** and closes the catalytic cycle.

In summary, we have presented the first detailed study on the reaction mechanism of the hydroaminoalkylation of alkenes that takes place by C–H bond activation in the α position to a nitrogen atom. We believe that the kinetic data, which are consistent with the theoretical studies, will guide the further optimization of this new and economically promising process.

Received: February 18, 2011
Revised: April 12, 2011
Published online: May 31, 2011

Keywords: alkenes · amines · C–H activation · homogeneous catalysis · titanium

[1] For reviews on catalytic C–H activation in the α position to a nitrogen atom, see a) K. R. Campos, *Chem. Soc. Rev.* **2007**, *36*, 1069–1084; b) S. Doye, *Angew. Chem.* **2001**, *113*, 3455–3457; *Angew. Chem. Int. Ed.* **2001**, *40*, 3351–3353.
[2] For selected examples of catalytic C–H activation in the α position to a nitrogen atom, see a) Y. Zhang, H. Peng, M. Zhang, Y. Cheng, C. Zhu, *Chem. Commun.* **2011**, *47*, 2354–2356; b) M. Ghobrial, K. Harhammer, M. D. Mihovilovic, M. Schnürch, *Chem. Commun.* **2010**, *46*, 8836–8838; c) F. Yang, J. Li, J. Xie, Z.-Z. Huang, *Org. Lett.* **2010**, *12*, 5214–5217; d) M.-Z. Wang, C.-Y. Zhou, M.-K. Wong, C.-M. Che, *Chem. Eur. J.* **2010**, *16*, 5723–5735; e) D. Sureshkumar, A. Sud, M. Klussmann, *Synlett* **2009**, 1558–1561.
[3] For a review on the hydroaminoalkylation of alkenes, see P. W. Roesky, *Angew. Chem.* **2009**, *121*, 4988–4991; *Angew. Chem. Int. Ed.* **2009**, *48*, 4892–4894.
[4] a) M. G. Clerici, F. Maspero, *Synthesis* **1980**, 305–306; b) W. A. Nugent, D. W. Ovenall, S. J. Holmes, *Organometallics* **1983**, *2*, 161–162.
[5] a) S. B. Herzon, J. F. Hartwig, *J. Am. Chem. Soc.* **2007**, *129*, 6690–6691; b) S. B. Herzon, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 14940–14941.
[6] a) P. Eisenberger, R. O. Ayinla, J. M. P. Lauzon, L. L. Schafer, *Angew. Chem.* **2009**, *121*, 8511–8515; *Angew. Chem. Int. Ed.* **2009**, *48*, 8361–8365; b) P. Eisenberger, L. L. Schafer, *Pure Appl. Chem.* **2010**, *82*, 1503–1515.
[7] G. Zi, F. Zhang, H. Song, *Chem. Commun.* **2010**, *46*, 6296–6298.
[8] a) C. Müller, W. Saak, S. Doye, *Eur. J. Org. Chem.* **2008**, 2731–2739; b) R. Kubiak, I. Prochnow, S. Doye, *Angew. Chem.* **2009**, *121*, 1173–1176; *Angew. Chem. Int. Ed.* **2009**, *48*, 1153–1156; c) I. Prochnow, R. Kubiak, O. N. Frey, R. Beckhaus, S. Doye, *ChemCatChem* **2009**, *1*, 162–172; d) R. Kubiak, I. Prochnow, S. Doye, *Angew. Chem.* **2010**, *122*, 2683–2686; *Angew. Chem. Int. Ed.* **2010**, *49*, 2626–2629.
[9] J. A. Bexrud, P. Eisenberger, D. C. Leitch, P. R. Payne, L. L. Schafer, *J. Am. Chem. Soc.* **2009**, *131*, 2116–2118.
[10] For details, see the Supporting Information.
[11] The broad ^{1}H NMR signals for the terminal CH_2 group of **1**-H are shown in the Supporting Information.
[12] All plots can be found in the Supporting Information.
[13] Additional experiments performed with various initial concentrations of **1**-H [$c(\mathbf{1}\text{-H}) = 0.5$–$1.0\ mol\,L^{-1}$] confirmed that the rate does not depend on the concentration of **1**-H.
[14] For examples of complexes with Ti-N-Ti moieties, see a) Y. Li, Y. Shi, A. L. Odom, *J. Am. Chem. Soc.* **2004**, *126*, 1794–1803; b) A. Abarca, M. V. Galakhov, J. Gracia, A. Martín, M. Mena, J.-M. Poblet, J. P. Sarasa, C. Yélamos, *Chem. Eur. J.* **2003**, *9*, 2337–2346; c) P. Gómez-Sal, A. Martín, M. Mena, C. Yélamos, *J. Chem. Soc. Chem. Commun.* **1995**, 2185–2186.
[15] The ^{1}H NMR spectra of mixtures of **1**-H and $[Ti(NMe_2)_4]$ (< 1–50 mol%) in C_6D_6 are presented in the Supporting Information.
[16] ^{1}H DOSY NMR experiments performed with mixtures of **1**-H and $[Ti(NMe_2)_4]$ also suggest that Ti compounds of increased molecular weight are formed. The corresponding spectra are shown in the Supporting Information. In addition, the isolation of a dimeric, bridging imido-titanium complex from a mixture of a monomeric amido-titanium complex and benzylamine by Schafer and co-workers (see Ref. [9]) and its catalytic activity in a hydroaminoalkylation reaction strongly support the possible formation of amido titanium oligomers.
[17] An analogous explanation was recently proposed for the comparably sharp decrease in reaction order from one to zero that was observed during a copper-catalyzed reaction: P.-F.

Larsson, C. Bolm, P.-O. Norrby, *Chem. Eur. J.* **2010**, *16*, 13613 – 13616.
[18] The inhibition of closely related titanium-catalyzed hydroamination reactions by dimethylamine is described in detail in: K. Gräbe, F. Pohlki, S. Doye, *Eur. J. Org. Chem.* **2008**, 4815 – 4823.
[19] All calculations were performed with the program package Gaussian 03 (M. J. Frisch et al., Gaussian 03, Inc., Wallingford, CT, **2009**). For technical details, see the Supporting Information.
[20] The results of the DFT calculations are only discussed qualitatively because they were obtained for the gas-phase reaction only. Although it is possible to apply them to reactions in nonpolar solvents, one should keep in mind that the presence of large amounts of highly polar amines and amido derivatives in the reaction mixture as well as their aggregation processes are expected to significantly influence the experimentally observed kinetic parameters. For technical reasons, this influence could not be considered during the calculations.
[21] Calculated from the following standard bond lengths: C–H 107 pm, N–H 103; P. Pyykkö, M. Atsumi, *Chem. Eur. J.* **2009**, *15*, 12770 – 12779.

