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Mechanism of the Intramolecular Hydroamination of Alkenes Catalyzed by Neutral Indenyltitanium Complexes: A DFT Study

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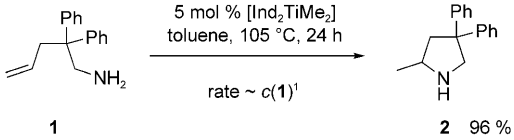
Abstract: Three mechanistic pathways for the [Ind_2TiMe_2]-catalyzed intramolecular hydroamination of alkenes have been investigated by employing density functional theory calculations on the possible intermediates and transition states. The results indicate that the reaction cycle proceeds via a Ti–imido–amido complex as the catalytically active species. However, at the moment, the question as to whether this imido–amido complex is involved in a [2+2]-cycloaddition with the alkene or a newly proposed insertion of the alkene into a Ti–N single bond cannot be answered; the calculated barriers of both the insertion mechanism and the [2+2]-cycloaddition mechanism are similar (143 vs. 136 kJ mol^{-1}), and both pathways are in accordance with the experimentally observed rate law (first-order dependence on the aminoalkene concentration). Interestingly, the newly proposed insertion mechanism that takes place by an insertion of the alkene moiety into the Ti–N single bond of an imido–amido complex seems to be much more likely than a mechanism that involves an alkene insertion into a Ti–N single bond of a corresponding trisamide. The latter mechanism, which has been proposed in analogy to rare-earth-metal-catalyzed hydroamination reactions, can be ruled out for two reasons: a surprisingly high activation barrier (164 kJ mol^{-1}) and the fact that the rate-limiting insertion step is independent of the aminoalkene concentration. This is in sharp contrast to the experimental findings for indenyltitanium catalysts.

Keywords: alkenes · amines · hydroamination · reaction mechanisms · titanium

Introduction

The catalytic hydroamination of alkenes, alkynes, and allenes has attracted much attention during the past 15 years.[1] Among the various catalysts,[1] rare-earth metal[2a–i] and late transition-metal[2j–w] complexes were used most extensively for alkene hydroamination. On the other hand, the use of Group IV metal catalysts has been limited to the hydroamination of alkynes,[3] until in 2004 it was found that cationic Zr and Ti complexes catalyze intramolecular hydroamination reactions of aminoalkenes containing a secondary amino group.[4] Subsequently, neutral Group IV metal complexes,[5] such as [$Ti(NMe_2)_4$][5a] were found to catalyze intramolecular hydroaminations of aminoalkenes containing primary amino groups. Based on some of these reports and our studies with [Ind_2TiMe_2] (Ind = Indenyl) as a highly efficient catalyst for the intermolecular hydroamination of alkynes,[6] we recently reported that [Ind_2TiMe_2] is also a suitable catalyst for the intramolecular hydroamination of alkenes (Scheme 1).[7] In the presence of 5 mol % of this catalyst, the geminally disubstituted aminoalkene **1** undergoes a successful hydroamination reaction within 24 h at 105 °C to give the pyrrolidine product **2** in 96 % yield.



1 **2** 96 %

Scheme 1. Intramolecular hydroamination of aminoalkene **1** catalyzed by [Ind_2TiMe_2].

An additional kinetic investigation performed with aminoalkene **1** showed that after a relatively long induction period of approximately 3 h, the [Ind_2TiMe_2]-catalyzed hydroamination is first order in the concentration of substrate **1**. The

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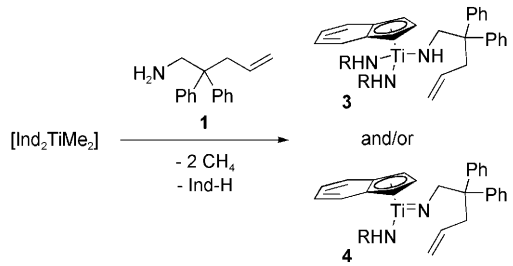
significant induction period suggests that under the reaction conditions, the catalytically active species is formed slowly from [Ind_2TiMe_2] and the aminoalkene **1**. As the cleavage of the metal–carbon σ bonds that liberates methane and generates catalytically active imido- or amidometal complexes is usually a fast process, one possible explanation is that during the induction period one indenyl ligand is also exchanged by the amine (Scheme 2). This interpretation is



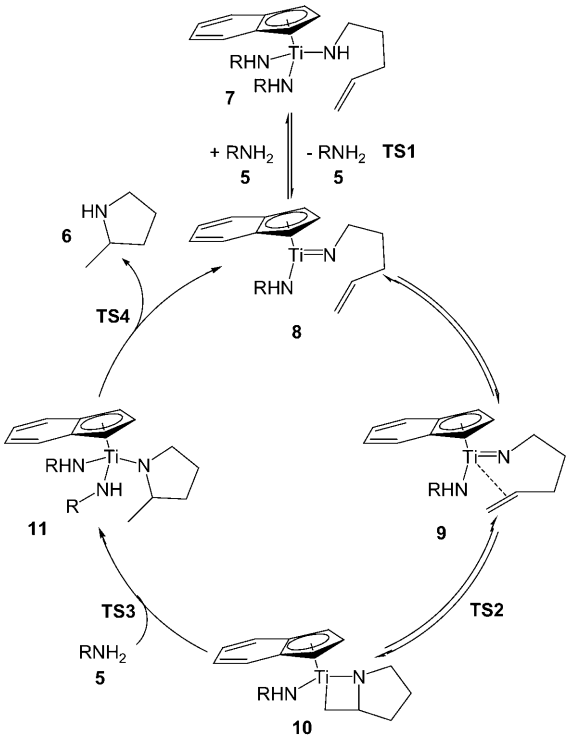
Scheme 2. Formation of the possible catalytically active species from [Ind_2TiMe_2] and 1-amino-2,2-diphenylpent-4-ene (**1**). R = CH_2–CPh_2–CH_2–CH=CH_2.

strongly supported by the fact that free indene (approximately 1 equiv relative to the amount of [Ind_2TiMe_2]) could be observed by NMR spectroscopy during our kinetic studies. Furthermore, a comparable ligand exchange process has already been observed for the [Cp_2TiMe_2]-catalyzed hydroamination of allenes.[8] Correspondingly, it is assumed that either amidometal complexes of type **3** or imido complexes of type **4** act as the catalytically active species.

Results and Discussion

According to the mechanism established for the Ti-catalyzed intermolecular hydroamination of alkynes,[9] it was initially proposed that the mechanism of the cyclization of aminoalkenes in the presence of neutral titanium catalysts takes place by an intramolecular [2+2]-cycloaddition of a Ti–imido moiety to the C–C double bond of the substrate.[5a–c,e–g] Scheme 3 shows the corresponding general catalytic cycle for an indenyl catalyst that converts the simplified model substrate 1-amino-4-pentene (**5**) into the pyrrolidine product **6**. The catalytically active Ti–imido complex **8** can either react with additional aminoalkene **5** to give the trisamide **7** or the C=C linkage can coordinate to the electrophilic Ti center to give the π-complex **9**, which subsequently undergoes a [2+2]-cycloaddition. The resulting azatitanacyclobutane **10** then undergoes protonolysis with aminoalkene **5** to give the trisamide **11**. Finally, elimination of the hydroamination product **6** from **11** regenerates the catalytically active imido complex **8**.

To gain more detailed mechanistic information, we carried out DFT calculations on the intermediates and transition states involved in the proposed [2+2]-cycloaddition mechanism,[10] employing the B3LYP functional[11] with a basis set



Scheme 3. [2+2]-cycloaddition mechanism for the intramolecular hydroamination of 1-amino-4-pentene catalyzed by a neutral indenyl titanium complex. R = $(CH_2)_3$CH=CH_2.

combination of Pople's 6-31G(d)[12] for ligand atoms (C, H, N atoms) and SDD[13] for titanium atoms together with the corresponding SDD pseudopotentials. To assess the influence of a larger basis set, additional calculations were performed with the triple-ζ basis set 6-311+G(d,p)[14] for several rate-determining steps. However, this basis set led to only very minor changes of the relative energies and for computational reasons is, therefore, not used herein. A self-consistent reaction field approach using the default settings (PCM)[15] with the solvent explicitly set to toluene was evaluated to give almost no effect of the solvent. Values given in the text are free Gibbs energies at 298 K under inclusion of zero-point vibrational energies, unless otherwise mentioned.

Figure 1 shows the calculated thermodynamic data for the [2+2]-cycloaddition mechanism. To form the catalytically active imido complex **8**, one equivalent of the aminoalkene **5** has to be cleaved from the trisamido complex **7** (**TS1**). This process has a barrier of 128 kJ mol^{-1} and despite of an entropy gain (ca. 10 J K^{-1} mol^{-1}) the process is highly endergonic (+72 kJ mol^{-1}). After pre-coordination of the terminal alkene group to the Ti center (**9**), which is favored by about 20 kJ mol^{-1}, [2+2]-cycloaddition (**TS2**) leads to the azacylcobutane **10**. The endergonic formation of **10** from **7** is fully reversible, thus it can be expected that the equilibrium between the trisamido complex **7** and the azacyclobutane **10** is almost completely on the side of the former. This reversibility of related [2+2]-cycloadditions with alkenes has already been shown experimentally for Zr–imido complexes.[16] In addition, two molecules of the imido complex **8** can also

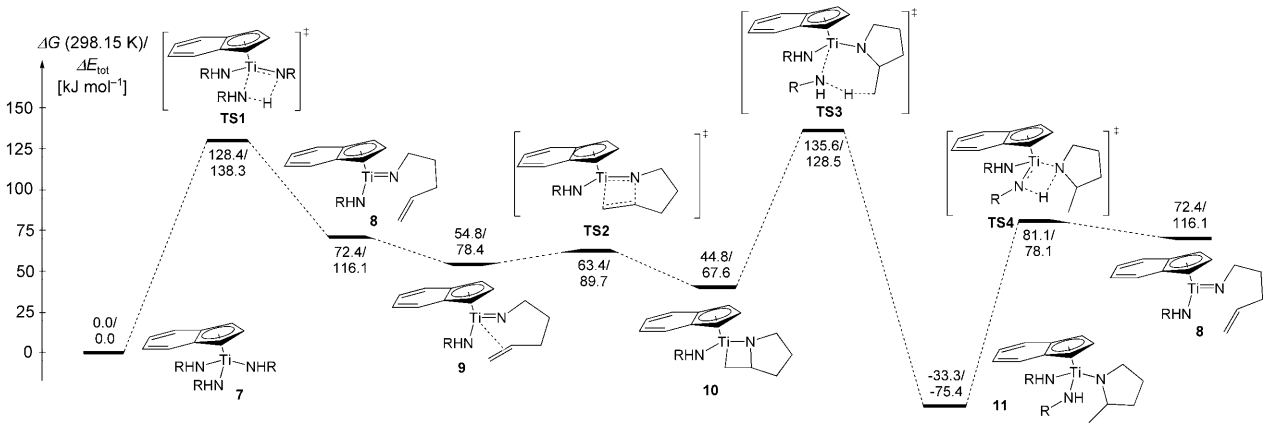


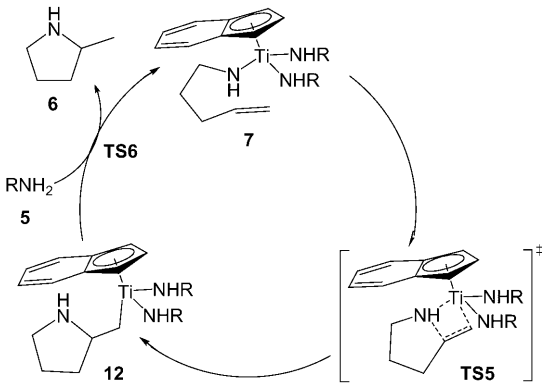
Figure 1. Thermodynamic data (B3LYP/6-31G(d)) for the [2+2]-cycloaddition mechanism. R = $(CH_2)_3CH{=}CH_2$.

form a dimer[9b,10a] (**8**-dimer, not shown in Figure 1), which is approximately 22 kJ mol^{-1} more stable than the trisamide **7**. This dimerization reduces the available amount of catalytically active amido complex **8** leading to longer reaction times. Within the catalytic cycle, the subsequent aminolysis of **10** by an aminoalkene **5**, which is considered to be irreversible, can—in principle—be achieved by two mechanistic pathways[10a] and should shift the overall reaction to the side of the products.

The transition-state **TS3** for the protonation of the titanium-coordinated exocyclic carbon atom in **10**, which takes place by coordination of aminoalkene **5** and subsequent intramolecular proton transfer, possesses a Gibbs free energy of 136 kJ mol^{-1}, which is even higher than the barrier for the generation of the imido complex **8** from the trisamido complex **7**. The aminolysis yields a trisamido complex **11**, which finally liberates the product **6** and regenerates the imido complex **8** via a low-energy transition state, **TS4** (81 kJ mol^{-1}). In this context, it is worth mentioning that DFT studies by Straub and Bergman[10a] already demonstrated that the proton transfer from an external amine, which is pre-coordinated to the titanium center and hence acidified, is thermodynamically strongly preferred over the alternative pathway in which the proton transfer occurs from the remaining amido ligand in **10**. This finding is in agreement with our results; we calculated the alternative pathway to be less favorable by 40 kJ mol^{-1}.

Overall, it can be seen from Figure 1 that the suggested [2+2]-cycloaddition mechanism describes a plausible mechanistic scenario for the [Ind_2TiMe_2]-catalyzed hydroamination/cyclization of aminoalkenes. The transition-state **TS3** for the titanaazacyclobutane protonation by a pre-coordinated aminoalkene (aminolysis) is the highest point in the catalytic pathway ($\Delta G_{\mathbf{TS3}}(298.15\ \mathrm{K}) = 136$ kJ mol^{-1}) and thus is rate determining. This conclusion is in good agreement with the experimental rate law (first order in the concentration of the aminoalkene) and with DFT calculations of the hypothetical ethene hydroamination with ammonia catalyzed by CpTi–imido complexes, which have been reported by Straub and Bergman.[10a]

Recently, an alternative mechanism for the Group IV metal-catalyzed intramolecular hydroamination of alkenes has been proposed by Stubbert and Marks.[5h] In analogy to rare-earth-metal-catalyzed hydroamination reactions,[2a–i,17] it is suggested that a Group IV metal–amido complex (e.g., of type **7**, Scheme 4) undergoes an irreversible, rate-limiting intramolecular insertion of the alkene into the Group IV metal–amido bond, presumably via a four-centered transition state (**TS5**). A final rapid protonation of the resulting metal–alkyl species (**12**) delivers the cyclization product (**6**) and regenerates the catalytically active species (**7**). For rare-earth-metal-catalyzed hydroamination reactions, the proposed catalytic cycle is in agreement with experimental data and density functional theory analysis.[17d] Kinetic investigations that have been performed with neutral zirconium "constrained geometry" catalysts showed that these reactions are first order in the catalyst concentration and zero order in the aminoalkene concentration,[5h] a behavior that is consistent with the proposed insertive pathway. However, a number of other studies involving various Ti catalysts revealed that the hydroamination reactions are first order in



Scheme 4. Insertion mechanism for the intramolecular hydroamination of 1-amino-4-pentene catalyzed by a neutral indenyl titanium complex. R = $(CH_2)_3CH{=}CH_2$.

the concentration of the aminoalkene substrate.[5c,7b] To get some more information regarding a possible insertive pathway, we performed calculations on the catalytic cycle shown in Scheme 4. The corresponding calculated thermodynamic data are presented in Figure 2.

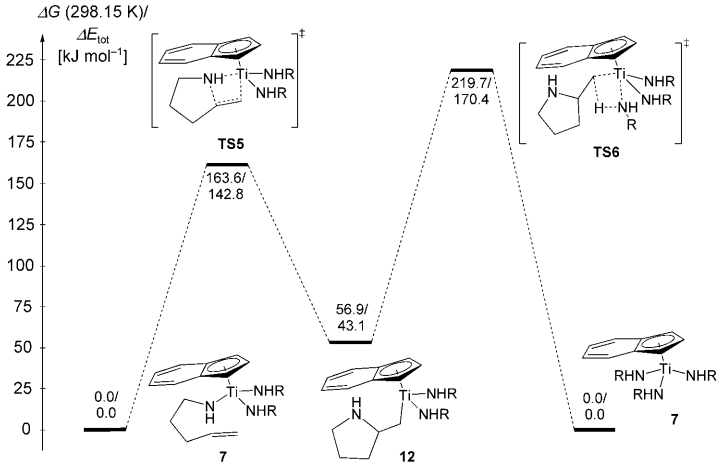


Figure 2. Thermodynamic data (B3LYP/6-31G(d)) for the insertion mechanism involving a proton transfer from an external amine. R = $(CH_2)_3CH{=}CH_2$.

Starting from the trisamido complex **7**, for which no π complex (similar to structure **9** in Figure 1) could be located, a Gibbs free energy barrier of 164 kJ mol^{-1} (**TS5**) is required to form the alkyl–amido complex **12**. A subsequent protonation by an additional aminoalkene **5**—as proposed by Stubbert and Marks—recycles the starting complex **7**; however, the barrier required (**TS6**, 220 kJ mol^{-1}) is distinctively higher than those of the initial insertion. A rate-determining aminolysis would be in agreement with the experimentally observed first-order dependency on the aminoalkene concentration of the $[Ind_2TiMe_2]$-catalyzed reaction. However, the unexpectedly high activation barrier for the proton transfer step prompted a search for alternative variations of the protonolytic product separation.

We therefore investigated the possibility of a proton transfer from an amido ligand to the Ti coordinated carbon atom in **12**.[10a] This "α elimination of the product" would give imido complex **8**, which then could add another aminoalkene **5** to form the initial trisamido complex **7**. Figure 3 presents the relevant thermodynamic data for this process. One can clearly see that this product cleavage, which takes place by a proton transfer from an amido ligand to the exocyclic carbon atom (**TS7**), possesses a much lower barrier with 155 kJ mol^{-1}, compared to the 220 kJ mol^{-1} in the initially proposed pathway.

Comparison of the two aminolysis variations indicates that the insertion mechanism originally proposed by Stubbert and Marks could include a proton transfer from an amido ligand to a carbon atom, as shown in Figure 3. This would imply that the hydroamination is expected to be zero order with respect to the aminoalkene because **5** is not involved in the rate-determining step (**TS5**). However, this is in sharp contrast to the experimental findings for indenyltitanium catalysts. Additionally, this mechanism is energetically less favorable than the [2+2]-cycloaddition mechanism presented in Figure 1; it requires 164 kJ mol^{-1} compared to only 136 kJ mol^{-1} in the latter case. On the basis of these results, we can rule out the possibility that the reaction takes place by means of the mechanisms shown in Figures 2 and 3.

The surprisingly high barrier for the alkene insertion (**TS5**) appears to result from steric hindrance: an additional Ti–C bond is formed when going from the already crowded trisamide **7** to the transition state **TS5**. The question is, therefore, can this insertion of an alkene into the titanium amido bond happen with a sterically less demanding species, such as the coordinatively unsaturated imido-amido complex **8**? A new mechanism with the insertion of the alkene moiety into the Ti–N single bond of this imido–amido complex **8** as the new key step is proposed in Scheme 5, whereas Figure 4 shows the respective calculated thermodynamic data. In this context it is worth mentioning that preparative and theoretical studies of vanadium imido–amido complexes have recently revealed that these compounds prefer to react with alkynes by an insertion into the V–N single bond. The alternative [2+2]-cycloaddition between the V–imido moiety and the alkyne is not observed.[18]

In analogy to the already studied [2+2]-cycloaddition mechanism, an equilibrium between the trisamido complex **7** and the imido complex **8** exists in this alternative insertive mechanism. Again, a pre-coordinative π-complex **13** between the alkene moiety and the titanium center is located

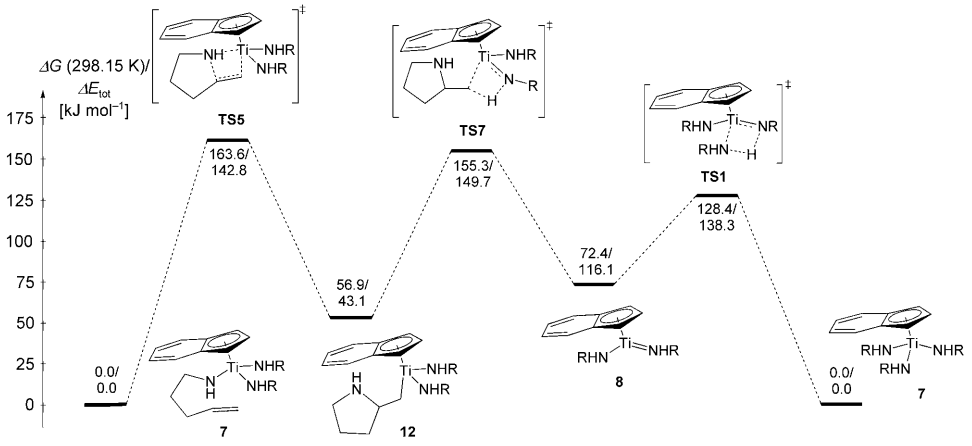
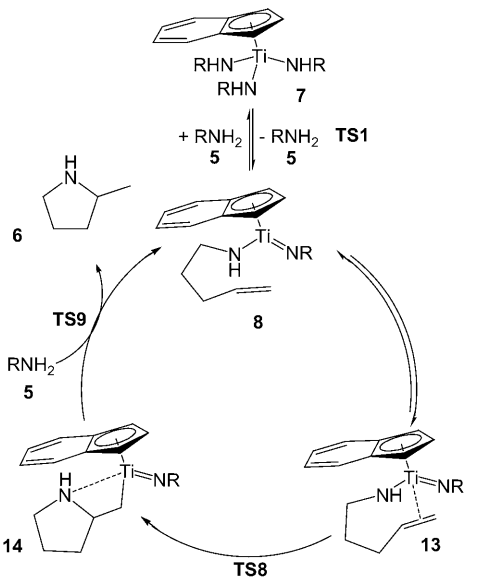


Figure 3. Thermodynamic data (B3LYP/6-31G(d)) for the insertion mechanism involving a proton transfer from an amido ligand. R = $(CH_2)_3CH{=}CH_2$.



Scheme 5. Alternative insertion mechanism for the intramolecular hydroamination of 1-amino-4-pentene catalyzed by a neutral indenyl titanium complex that takes place by an insertion of the alkene into the Ti–N single bond of the imido complex **8**. R = $(CH_2)_3CH{=}CH_2$.

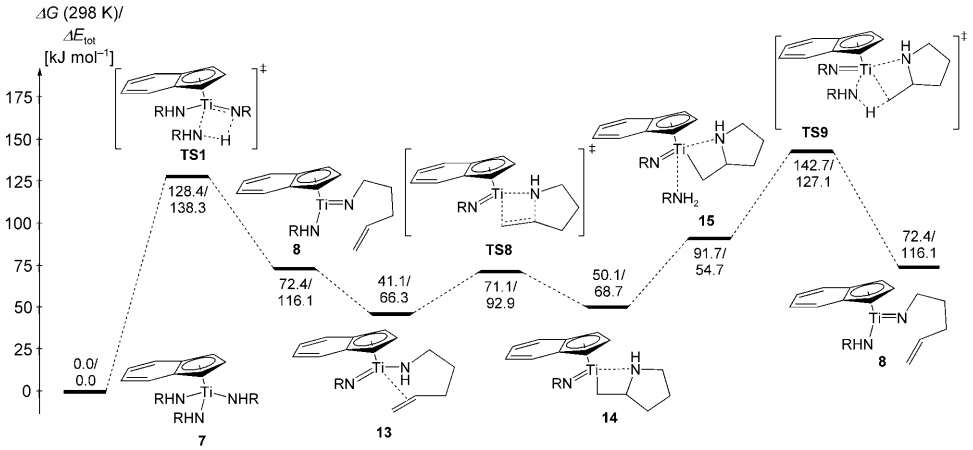


Figure 4. Thermodynamic data (B3LYP/6-31G(d)) for the alternative insertion mechanism that takes place by an insertion of the alkene into the Ti–N single bond of the imido complex **8**. R = $(CH_2)_3CH{=}CH_2$.

with the amido-bound alkene group being coordinated, in contrast to the [2+2]-cycloaddition mechanism in which the respective complex **9** is formed with an imido-bound alkene. This complex is stabilized by about 30 kJ mol^{-1} relative to **8**, which is significantly more effective compared to the energy gain from pre-coordination in Figure 1 (17 kJ mol^{-1}). This could be attributed to a higher conformational flexibility of the N-bound group in the case of the amido-bound alkene and hence lower strain in **13** compared to complex **9**. The most surprising feature of this new mechanism, however, is the low Gibbs free activation energy required for the insertion (**TS8**), which is only about 71 kJ mol^{-1}, relative to **7**. The energy of this transition state is similar to that of the imido complex **8**, rendering this insertion more than 90 kJ mol^{-1} more favorable than the comparable transition-state **TS5** of the trisamido-based insertion in Figure 2. The Ti–alkyl complex **14** can then coordinate another aminoalkene **5**, liberate the product **6** via **TS9** (143 kJ mol^{-1}), and recycle the imido complex **8**. Since the transition state for the protonation (aminolysis) of the Ti–alkyl complex **TS9**, which involves a pre-coordinated aminoalkene, is the highest point in the catalytic pathway, it must be rate determining. Correspondingly, the new mechanism is in good agreement with the experimental rate law (first order in the concentration of the aminoalkene).

Conclusion

The newly proposed insertion mechanism that takes place by an insertion of the alkene moiety into the Ti–N single bond of the imido–amido complex **8** (Scheme 5, Figure 4) seems to be much more likely than a mechanism that involves an alkene insertion into a Ti–N single bond of the trisamide **7**: not only is the required activation barrier significantly lower (143 vs. 164 kJ mol^{-1}), but it can also explain the experimentally observed rate law. The kinetic studies[7b] suggest that the reaction shows a first-order dependence on the aminoalkene concentration. The rate-determining step of the new insertion pathway, the product liberation (**TS9**), involves an aminoalkene, whereas the rate-limiting insertion step in the mechanism proposed by Stubbert and Marks (**TS5**) is independent thereof. The calculated barriers of both the alternative insertion mechanism and the [2+2]-cycloaddition mechanism are similar (143 vs. 136 kJ mol^{-1}), and both pathways are in accordance with the measured reaction order. On the current basis of experiments and calculations, it cannot be decided which of the two mechanisms is applicable for [Ind_2TiMe$_2$]-catalyzed hydroaminations of alkenes. However, the simple insertion mechanism originally proposed by Stubbert and Marks in analogy to rare-earth-metal-catalyzed hydroamination reactions can be ruled out for the reasons given above. On the other hand, this mechanism can be responsible for the fact that a few cyclizations of secondary aminoalkenes that cannot proceed via imido species have been achieved in the presence of selected neutral Zr and Ti catalysts.[5h,l,7b] Since our calculations suggest that such a mechanistic change results in a significantly increased activation barrier of the process, the decreased reactivity of secondary aminoalkenes compared to primary aminoalkenes[5l,7b] can easily be understood.[19]

In summary, our experimental[7b] and computational results of the [Ind_2TiMe_2]-catalyst system indicate that the reaction cycle proceeds via a Ti–imido–amido complex as the catalytically active species. However, at the moment, the question as to whether this complex is involved in a [2+2]-cycloaddition with the alkene or the newly proposed insertion of the alkene into a Ti–N single bond cannot be answered; the energy profiles of both pathways are too similar. However, in this context, it is worth mentioning that Scott et al. have recently presented a Zr-catalyzed hydroamination of primary aminoalkenes that seems to proceed via an imido [2+2]-cycloaddition mechanism.[5m] At the moment, additional kinetic and computational mechanistic studies are underway in our laboratories, which will address the issue of mechanistic changes when going from the small Ti to its larger counterpart Zr or changing the aminoalkene.

Experimental Section

General: All calculations were performed with the program package Gaussian 03.[20] DFT with the B3LYP functional[11] was used for the optimizations of the ground-state geometries in the gas phase. The default convergence criteria and integration grid of the program were used. The basis set employed a combination of Pople's 6-31G(d)[12] for the ligand atoms (C, H, N atoms) and SDD[13] for titanium atoms together with the corresponding SDD pseudopotentials. Stationary points were verified as ground or transition states by calculating the number of imaginary harmonic vibrational frequencies at the same level of theory. Thermochemical data are derived from the same frequency calculation data. To assess the influence of a larger basis set, additional calculations were performed with the triple-zeta basis set 6-311+G(d,p) for the ligand atoms.[14] A self-consistent reaction field approach by using the default settings (PCM) with solvent explicitly set to toluene was used to model the effect of solvent.[15]

Acknowledgements

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[19] One major argument for the simple insertion mechanism proposed by Stubbert and Marks is the fact that "blocked" "constrained geometry" complexes of type $[ZrCl\{\eta^5\text{-}(C_5Me_4)\text{-}SiMe_2\text{-}N\mathit{t}Bu\}(NMe_2)]$ catalyze the intramolecular hydroamination of alkenes. The authors assumed that due to the strong Zr–Cl bond, corresponding catalysts cannot form an imido species because only one equivalent of dimethylamine can be removed protonolytically by the reacting aminoalkene to give a $ZrCl\{\eta^5\text{-}(C_5Me_4)\text{-}SiMe_2\text{-}N\mathit{t}Bu\}$–amido species as the catalytically active species. However, very recently, we have shown that even complexes of the type $[TiCl_2\{\eta^5\text{-}(C_5H_4)\text{-}SiMe_2\text{-}N\mathit{t}Bu\}]$ catalyze hydroamination reactions of alkynes with primary amines (K. Gräbe, S. Doye, *Eur. J. Org. Chem.* **2008**, 4815–4823). A possible explanation that is supported by in situ ^{29}Si NMR spectroscopic studies could be that under the reaction conditions, the bidentate $\{\eta^5\text{-}(C_5H_4)\text{-}SiMe_2\text{-}N\mathit{t}Bu\}$–ligand system is destroyed and/or protonolytically removed from the Ti center by the reacting amine. Consequently, the formation of metal–imido species from the corresponding Ti and Zr complexes must be regarded as feasible even if they contain one or two Ti–Cl or Zr–Cl bonds.
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