C–H Activation

International Edition: DOI: 10.1002/anie.201500796
German Edition: DOI: 10.1002/ange.201500796

Efficient Access to Titanaaziridines by C–H Activation of *N*-Methylanilines at Ambient Temperature**

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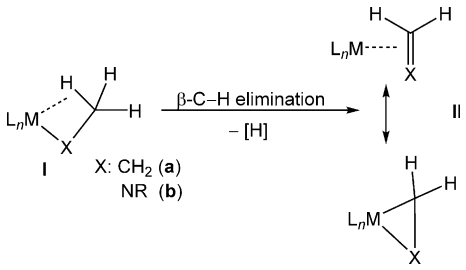
Abstract: *Titanaaziridines or η^2-imine titanium complexes are considered key intermediates of the titanium-catalyzed hydroaminoalkylation of alkenes. Herein, we present an efficient synthetic route to this class of compounds, starting from N-methylanilines and a bis(η^5:η^1-pentafulvene)titanium complex. Consecutive reactions on the η^2-methyleneaniline complexes, characterized for the first time, prove a high chemical versatility. In particular, hydroaminoalkylation products were found in reactions of the three-membered titanacycles with alkenes. For the first time, all the intermediates of the hydroaminoalkylation of alkenes were isolated and characterized.*



Scheme 1. β-C–H elimination reactions.

Knowledge of C–H activation and elimination reactions in the coordination spheres of early transition metals contributes considerably to the understanding of organometallic compounds.[1,2] For example, in this way the different behavior of ethyl derivates (**Ia**) and β-H free organometallic compounds could be understood. Whereas β-H containing metal alkyls (**Ia**) react spontaneously to alkene complexes (**IIa**), analogous reactions of metal amides (**Ib**) to metallaaziridines (**IIb**) require significantly harsher reaction conditions (Scheme 1).[1,2] In general, C–H functionalization reactions establish new efficient synthetic concepts for the formation of carbon–carbon as well as carbon–heteroatom bonds.[3–5]

First indications for C–H activation at C_{sp^3}-centers in the α-position to a nitrogen atom in titanium complexes comes from thermolysis experiments of titanium benzyl amides which take place by elimination of toluene. However, the expected formation of imine complexes (**IIb**) was not observed.[6] On the other hand, metallaaziridines could be made tangible by isotopic-labeling experiments or trapping reactions using alkenes during thermolysis experiments (140–180 °C) of d^0 metal (dialkyl)amides.[2]

Recently, titanaaziridines became of interest as intermediates of the hydroaminoalkylation of alkenes, in which the insertion of the alkene into the Ti–C bond of the titanaaziridine is supposed to be the C–C bond forming step.[7–11] Furthermore, titanaaziridines are used in a variety of further organic syntheses.[12,13] Herein, we report the synthesis of titanaaziridines under mild conditions, starting from secondary *N*-methylamines, in which the use of the sterically demanding bis(η^5:η^1-adamantylidene pentafulvene) titanium complex (**1**) proves to be exceptionally effective.[14,15] This complex is available as turquoise blue crystals from reaction of [$TiCl_3$(THF)] with magnesium in the presence of adamantylidenfulvene in 84% yield. The recently obtained X-ray structure (Figure 1) shows a significant reduction of the pentafulvene ligands, as evident by the bending (37.3°, 38.3°) of the exocyclic C–C bond out of the 5-membered ring plane, and by the elongation of the exocyclic bonds (C1–C6 1.454(3), C16–C21 1.451(3) Å, compared to C_{ipso}–C_{exo} 1.342(2) Å of the isolated ligand[16]).[12] In consequence, the complexed ligand now exhibits a reversed polarity and a significant nucleophilic character of the C_{exo} position.[14,17,18]

Whereas classic titanocene dialkylderivates, such as [$Cp_2Ti(CH_3)_2$], react with acidic compounds only at temper-

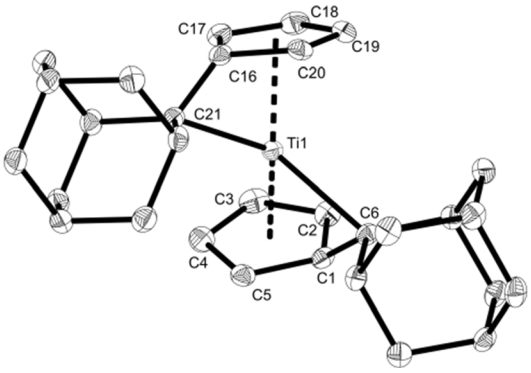


Figure 1. ORTEP representation of **1** (thermal ellipsoids set at 50% probability, hydrogen atoms are omitted for clarity). Selected bond lengths [Å]: Ti1–C6 2.310(2), Ti1–C21 2.320(2), C1–C6 1.454(3), C16–C21 1.451(3).

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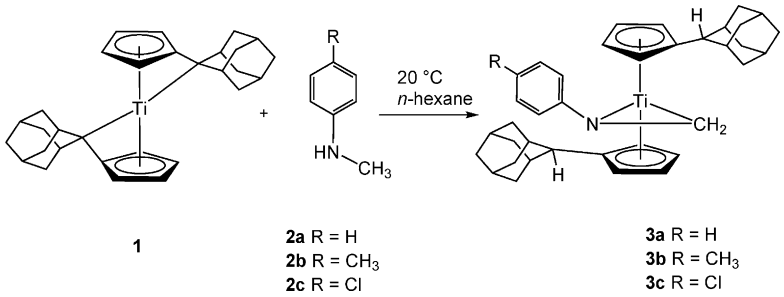
[**] We thank the Deutsche Forschungsgemeinschaft for financial support of our research (BE 1700/7-1, DO 601/7-2).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201500796.

atures above 60 °C,[19] the bis(η^5:η^1-pentafulvene)titanium complexes show no such kinetic hindrance.[18]

The reactions of compound **1** with secondary amines **2a**–**2c** in *n*-hexane at ambient temperature (Scheme 2) are accompanied by an instant color change from blue to dark red and in all cases, yellow products start to crystallize within 30 min. The analytical data confirm the spontaneous formation of the titanaaziridines **3a**–**3c** in quantitative yields.[15] The golden yellow solids show a high reactivity and decompose directly in the presence of oxygen or atmospheric moisture. However, the compounds **3a**–**3c** can be stored for months in inert conditions as solids at temperatures up to 110 °C without any indication of decomposition, and show good solubility in polar solvents.



Scheme 2. Formation of the titanaaziridines **3a**–**3c** from *N*-methylanilines.

The conversion of the methyl group of **2a**–**2c** into the methylene group of the titanaaziridines **3a**–**3c** is confirmed by NMR spectroscopic experiments including DEPT-135 and gated-decoupling as well as ^{1}H, ^{15}N correlation experiments.[15] As a result, the signals of the N-CH_2 protons are detectable in the region around of 4 ppm ($\delta = 4.02$ (**3a**), 4.02 (**3b**), 3.80 (**3c**), each (s), 2H). Furthermore, the ^{1}H NMR spectrum reveals four signals of the non-equivalent protons of C2–C5 and C17–C20 (classification according to Figure 2, **3a**, **3b**, **3c** analogous) of the enantiotopic cyclopentadienyl ligands (**3a** $\delta = 5.03$, 5.60, 6.41, 6.71).

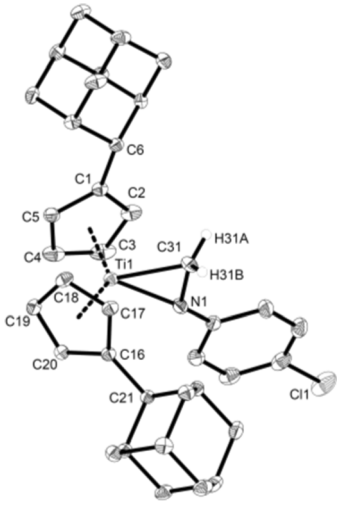


Figure 2. ORTEP representation of **3c** (thermal ellipsoids set at 50% probability, hydrogen atoms are omitted for clarity, except for H31A and H31B). Selected bond lengths [Å]: Ti1–N1 1.9692(9), Ti1–C31 2.1322(11), N1–C31 1.4070(14).

In addition, the structure of the titanaaziridine **3c** is confirmed by X-ray diffraction. Suitable single crystals in the shape of yellow needles were obtained directly from the very low concentrated reaction mixtures. Compound **3c** crystallizes in the monoclinic space group $P2_1/c$ with four molecules per asymmetric unit. The bond lengths of Ti1–N1 (1.9692(9) Å) and Ti1–C31 (2.1322(11) Å) confirm the expected single bonds,[20] whereas the bond length of N1–C31 (1.4070(14) Å) constitutes a significant elongation compared to the N–C bond of the imine (average 1.28 Å[21]). This elongation is analogous to that found in η^2-aldimine titanocene complexes (1.403(2) Å).[13]

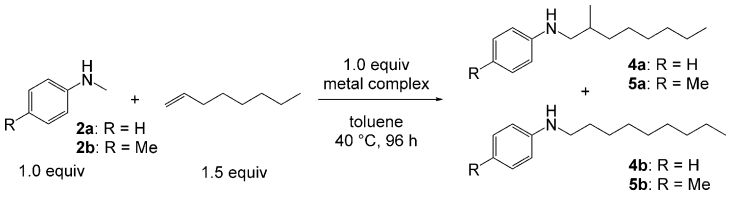
The angle sum of the bonds at the nitrogen atom (347°) matches with the deflection of the *N*-phenyl ligand from the plane of the three-membered ring (23°). According to the smallest possible substitution pattern present at the imine carbon atom, the compounds **3a**–**c** constitute three new examples of the few isolated η^2-complexes of *N*-methyleneaniline. Owing to spontaneous oligomerization or trimerization, *N*-methyleneaniline cannot be used directly as ligand.[22,23] Therefore, the generation of *N*-methyleneaniline complexes always requires alternative synthetic routes.[24,25] To our knowledge, **3c** is the first structurally characterized titanium representative of this compound class and therefore, offers an opportunity to investigate its reaction chemistry.

The hydroaminoalkylation of alkenes is of considerable interest. The reactions of **2a** or **2b** with 1.5 equivalents of 1-octene performed in the presence of the bis(pentafulvene)-titanium complex **1** lead to the formation of the hydroaminoalkylation products **4** and **5** under very mild conditions (toluene, 40 °C, 96 h) in good yields and regioselectivities (ratio **4a**/**4b** 94:6; ratio **5a**/**5b** 98:2).

Whereas classic hydroaminoalkylation catalysts, such as bis(indenyl)titaniumdimethyl,[26] do not show any reaction under analogous conditions, the direct use of the isolated titanaaziridine **3b** (as in Scheme 3 but in the absence of the amine) leads to identical yields and selectivities as the use of compound **1** (Table 1). These preparative results provide evidence that titanaaziridines are the key intermediates in hydroaminoalkylation reactions of alkenes.

The formation of a titanaazapentane derivative which is expected to take place during hydroaminoalkylation reactions of alkenes can simply be achieved by the reaction of **3b** with excess 1-hexene in the absence of any additional solvent (Scheme 4). Compound **6** is isolated, after the removal of surplus 1-hexene, in 90% yield without any by-products.[15]

The NMR spectra of **6** reveal that only one structural isomer is formed (shown in Scheme 4), with the C_4H_9-substituent in the position β to the titanium center as evident by the ^{13}C chemical shift ($\delta = 66.2$ ppm) which is characteristic of the $TiCH_2$-group.[27,28] The tertiary carbon atom (marked with a * in Scheme 4)) as a stereogenic center, which is situated in the ring structure, induces the appearance of diastereotopic signals of the metallocene (eight signals), as

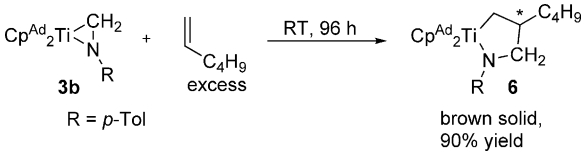


Scheme 3. Hydroaminoalkylation of 1-octene with **2a** and **2b**.

Table 1: Hydroaminoalkylation reactions.[a]

N-Methylaniline (R)	Titanium complex	Yield **a** [%][b]	Selectivity **a**/**b**[c]
H (**2a**)	**1**	78	94:6 (**4a**:**4b**)
CH_3 (**2b**)	**1**	80	98:2 (**5a**:**5b**)
without amine	**3b**	81	97:3 (**5a**:**5b**)
CH_3 (**2b**)	[Ind_2TiMe_2]	0	–

[a] Reactions (40 °C, toluene, 96 h) of 1-octene with *N*-methylanilines (**2a**, **2b**) in the presence of **1**, in comparison to the reaction of **3b** with 1-octene and **2b** with 1-octene in the presence of [$(Ind)_2TiMe_2$]. [b] Yield of isolated major product (**a**). [c] GC-analysis prior to column chromatography.



Scheme 4. Reaction of **3b** with 1-hexene.

well as the splitting of the signals for the methylene ring protons Ti-CH_2- (each 1H, m, $\delta = 1.13$; 2.62) respectively N-CH_2 (each 1H, m, $\delta = 2.89$, 3.22).[15] In addition, the ^{15}N NMR signal is shifted upfield upon ring expansion from the three-membered ring to the five-membered ring (**3b** $\delta = 220$ ppm, **6** $\delta =$ 191 ppm). The molecular ion of **6** (m/z 650) can be detected by LIFDI-MS experiments.

The ring-expansion reactions of **3a**–**3c** with alkynes, carbonyl compounds, and nitriles were studied completely. All the reactions can be performed at ambient temperatures with regioselective formation of the five-membered titanacycles **7**–**9**, nearly all of them characterized by X-ray diffraction analysis. As typical examples only the compounds **7a**, **8d** and **9a** are discussed (Scheme 5).[15]

The reaction of **3b** with phenylacetylene leads to the formation of the titanaazacyclopentene **7a** under regioselective insertion of the terminal alkyne. In this case the phenyl substituent is located β to the titanium atom. Zirconiaaziridines [29–31] and intermediary formed titanaaziridines[32] react with inverse regioselectivities. The molecular structure of **7a** is shown in Figure 3. The bond length of Ti1–N1 (2.0340(7) Å) as well as the bond length of Ti1–C33 (2.1165(9) Å) are typical of single bonds. The titanium atom is in a tetrahedrally distorted coordination environment surrounded by the cyclopentadienyl ligands (Ct-Ti-Ct 133.3°; Ct = centroid) and the newly formed bidentate ligand (N1-Ti1-C33

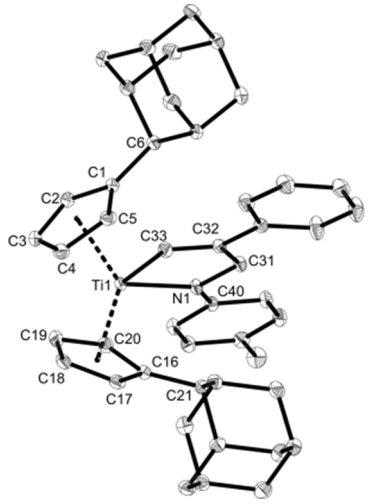
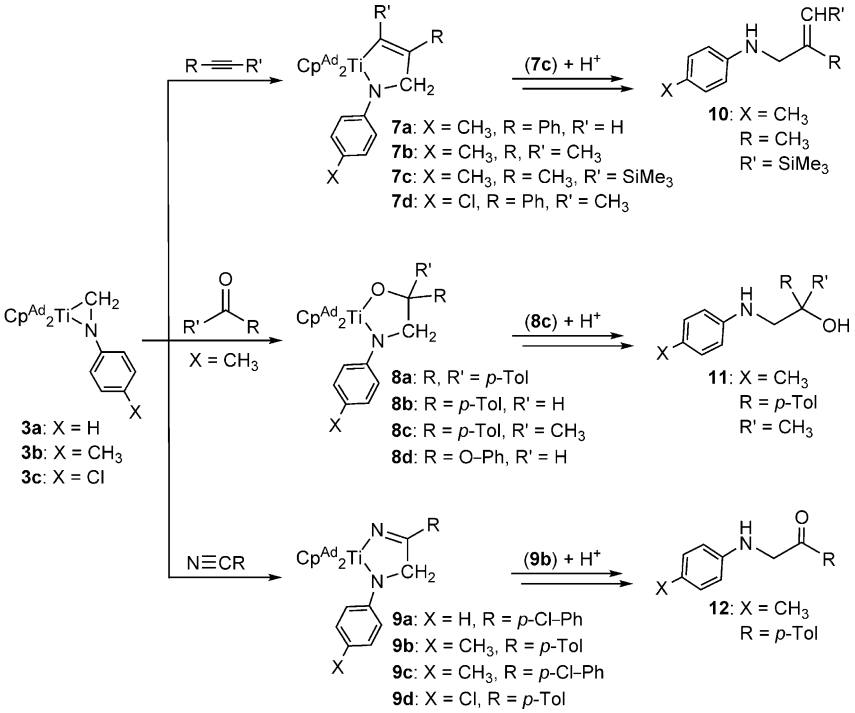


Figure 3. ORTEP representation of **7a** (thermal ellipsoids set at 50% probability, hydrogen atoms are omitted for clarity). Selected bond lengths [Å] and angles [°]: Ti1–N1 2.0340(7), Ti1–C33 2.1165(9), N1–C31 1.4596(11), C31–C32 1.5053(12), C32–C33 1.3480(12); N1-Ti1-C33 80.59(3).



Scheme 5. Ring-expansion reactions of **3a**–**3c**.

80.59(3)°). The newly formed C–C bond C31–C32 (1.5053(12) Å) is a single bond.

Both the ^{1}H and the ^{13}C NMR spectra are consistent with the X-ray structure. Thus there are four signals for the enantiotopic cyclopentadienyl ligands ($\delta = 5.34$, 5.98, 6.03, 6.43 ppm) and the distinctive singlet for the N-CH_2-protons ($\delta = 4.31$ ppm). The assignment of the Ti–C_{sp^2} atom can be made by the significant downfield chemical shift ($\delta =$ 191.2 ppm), and the assignment of the *N*-methylene group ($\delta = 58.9$) by ^{1}H,^{13}C-correlation spectra and DEPT-135 experiments. The ^{15}N NMR signal observed at $\delta = 173$ ppm is within the expected upfield range. Furthermore, the molecular ion of **7a** can be detected in LIFDI-MS experiments. The additional analytical data of **7a**–**7d** are summarized in the Supporting Information.[15]

The reactions of **3b** with carbonyl compounds lead to the formation of the titanaoxazolidines **8a**–**8d**. The titanaoxazolidine **8d** is obtained after reaction with phenyl formate as a red solid in 70% yield. The X-ray structure is shown in Figure 4. The five-membered ring is not planar, a result of the

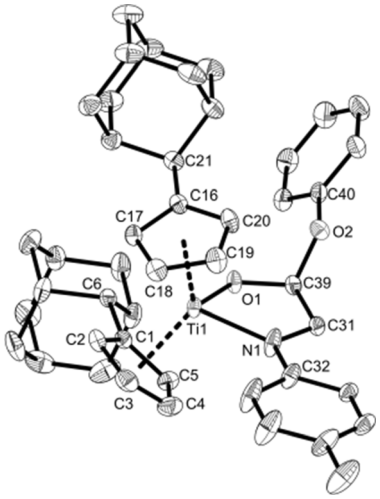


Figure 4. ORTEP representation of **8d** (thermal ellipsoids set at 50% probability, hydrogen atoms are omitted for clarity). Selected bond lengths [Å] and angles [°]: Ti1–N1 2.0438(11), Ti1–O1 1.9046(9), O1–C39 1.3760(14), N1–C31 1.4494(16), C31–C39 1.5224(17); O1-Ti1-N1 81.52(4).

presence of two C_{sp^3} centers in this moiety. The ^{1}H NMR spectrum reveals eight signals for the diastereotopic protons of the cyclopentadienyl ligands and a significant splitting of the N-CH_2 protons ($\delta = 4.27$, 4.45 ppm each 1H). In addition, with LIFDI-MS experiments, the molecular ion, as well as the cleavage of the phenoxy group can be detected. Compound **8d** is readily soluble in polar solvents and the solid decomposes at 132 °C.

The insertion products **9a**–**9d** are formed by reactions of the titanaaziridines **3a**–**3c** with benzonitriles. Consequently, the reaction of **3a** with *p*-chlorobenzonitrile generates the titanaimidazoline **9a** as red crystals in 91% yield. In this case, the X-ray structure (Figure 5) shows that the five-membered ring is almost planar, owing to the presence of the C_{sp^2} center of the imine moiety. In the ^{1}H NMR spectrum, the four signals

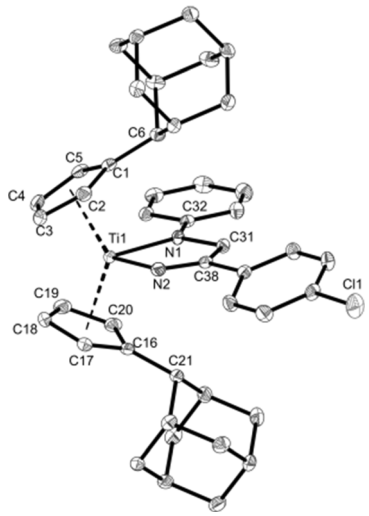


Figure 5. ORTEP representation of **9a** (thermal ellipsoids set at 50% probability, hydrogen atoms are omitted for clarity). Selected bond lengths [Å] and angles [°]: Ti1–N1 2.0895(12), Ti1–N2 1.9412(12), N1-C31 1.4603(17), N2–C38 1.2716(18), C31–C38 1.510(2); N2-Ti1-N1 79.64(5).

typical of the cyclopentadienyl ligands ($\delta = 5.73$, 5.82, 6.25, 6.43 ppm), and one well defined singlet of the N-CH_2 protons ($\delta = 5.03$ ppm) are observed. Furthermore, the molecular ion (*m*/*z* 689) can be detected in LIFDI-MS experiments. Compound **9a** is moderately soluble in polar solvents and decomposes in the solid state at 163 °C. Analogous properties were found for **9b**–**9d**.[15]

Hydrolysis of compounds **7c**, **8c**, and **9b** gives the β-functionalized secondary amines **10**–**12** which can be isolated in good yields after subsequent purification (Scheme 5). As a result of its imine moiety, hydrolysis of **9b** delivers the expected substituted ketone **12**.

Overall, our results clearly demonstrate the suitability of **1** as a powerful stoichiometric reagent for the formation of titanaaziridines (**3**) by N–H and C–H activation of secondary amines under mild conditions. The reactions of **3** with alkynes, carbonyl compounds, or nitriles emphasize the potential applications of the η^2-imine complexes **3**. The experimental access to **6**, and the formation of products **4** and **5** provide experimental evidence for the reaction mechanism of the hydroaminoalkylation of alkenes. All the reactions presented herein were carried out at room temperature and the generation of the five-membered titanacycles **6**–**9** took place with impressive regioselectivities.

Keywords: alkene titanium · amine · C–H activation · titanaaziridine

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 4383–4387
Angew. Chem. **2015**, *127*, 4458–4462

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Received: February 27, 2015

