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Hydroaminoalkylation of Allenes

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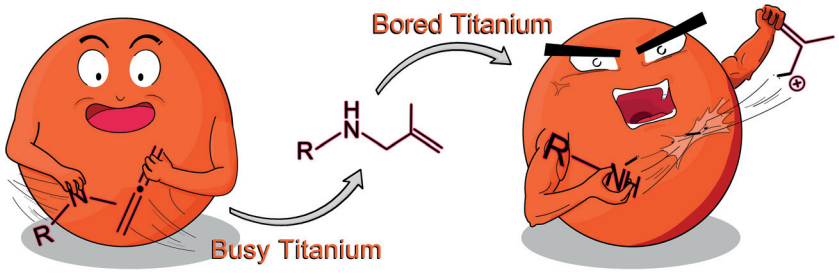

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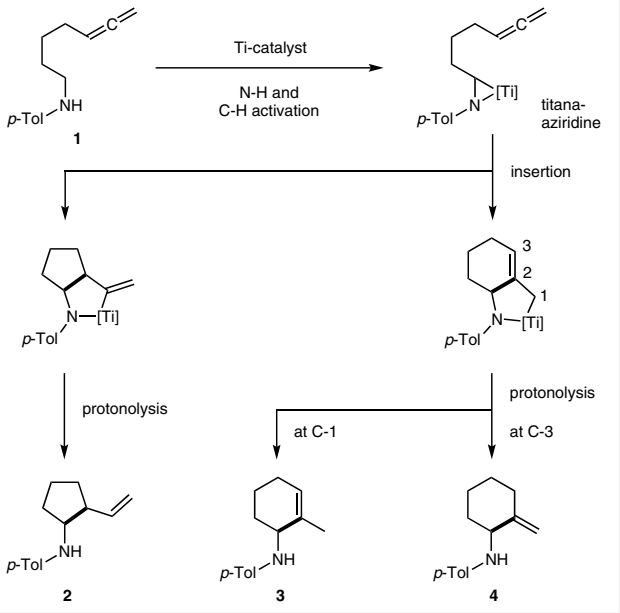
Abstract The first examples of early-transition-metal-catalyzed hydroaminoalkylation reactions of allenes are reported. Initial studies performed with secondary aminoallenes led to the identification of a suitable titanium catalyst and revealed that under the reaction conditions, the initially formed hydroaminoalkylation products undergo an unexpected titanium-catalyzed rearrangement to form the thermodynamically more stable allylamines. The assumption that this rearrangement involves a reactive allylic cation intermediate provides a simple explanation of the fact that no successful early-transition-metal-catalyzed hydroaminoalkylations of allenes have previously been reported. As a result of the generation of the corresponding cation, the titanium-catalyzed intermolecular hydroaminoalkylation of propa-1,2-diene unexpectedly gives an aminocyclopentane product formed by incorporation of two equivalents of propa-1,2-diene.

Key words allenes, amines, C–H activation, homogeneous catalysis, titanium, hydroaminoalkylation

Transition metal-catalyzed hydroaminoalkylation reactions of alkenes with secondary or tertiary amines,[1] which involve C–H bond activation at the α-carbon atom of the amine,[2] have attracted a great deal of attention during the past decade. Whereas the use of group 3 metal catalysts[3] is limited to reactions of tertiary amines, late-transition-metal catalysts[4] usually require the presence of a directing group on the nitrogen atom of the amine. On the other hand, the optimization of group 4[5] and group 5[6] metal-based catalyst systems has resulted in significant progress with regard to the scope of the alkene and amine, as well as the activity of the catalyst. However, corresponding reactions of other unsaturated substrates such as allenes or alkynes have not been reported. This is regrettable because, in particular, the conversion of allenes into allyl- or homoallylamines would offer simple possibilities for further functionalization of the remaining C–C double bond.

To provide a first proof of principle for the assumption that, in principle, allenes might be suitable substrates for hydroaminoalkylation reactions, we chose aminoallene **1** as a substrate (Scheme 1) and we achieved a successful intramolecular hydroaminoalkylation. For this purpose, we screened a variety of titanium-based catalysts (Figure 1)[5a–f] that have already been successfully applied in hydroaminoalkylation reactions of alkenes, 1,3-dienes, and styrenes. In this context, it must be noted that we expected the formation of 2-vinylcyclopentane-1-amine **2**, the cyclohex-2-en-1-amine **3**, and the 2-methylenecyclohexane-1-amine **4** (Scheme 1) as the hydroaminoalkylation products, because



Scheme 1 Possible pathways for the titanium-catalyzed intramolecular hydroaminoalkylation of aminoallene **1**

corresponding cyclization reactions of aminoalkenes are known to take place by a 5-*exo-trig* or a 6-*exo-trig* pathway.[5a,7]

From a mechanistic point of view, the key intermediate for the reaction is expected to be a titanaaziridine (Scheme 1),[2] which should be capable of inserting one of the two C–C double bonds of the allene moiety into its Ti–C bond. Insertion of the internal double bond should then deliver a five-membered ring-containing vinyltitanium species, which should finally give the 2-vinylcyclopentane-1-amine **2** after protonolysis. On the other hand, insertion of the terminal double bond should result in a six-membered ring-containing an allyltitanium intermediate. In this case, protonolysis of the allyltitanium species might take place in the 1- or 3-position[8] and, as a consequence, formation of the two six-membered cyclic products **3** and **4** should occur.

During a catalyst screening, performed with $Ti(NMe_2)_4$, $Ti(NEt_2)_4$, Ind_2TiMe_2 (Ind = η^5-indenyl), the aminopyridinato titanium complexes **I**–**III**, and the formamidinato complex **IV** (Figure 1) at temperatures between 100 °C and 170 °C, we first found that **IV**, originally a polymerization catalyst synthesized by Eisen and co-workers,[9] was the only active catalyst for the conversion of **1** into a hydroaminoalkylation product.

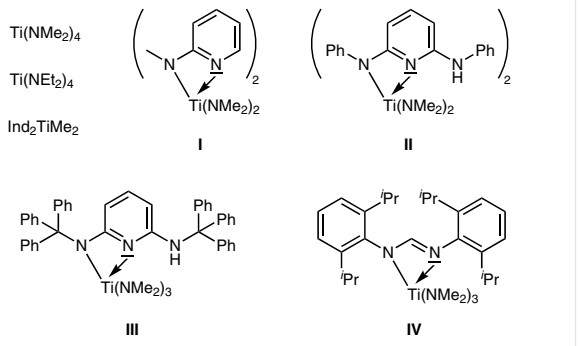
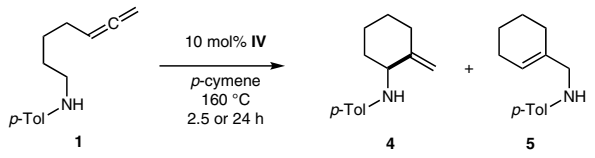


Figure 1 Titanium catalysts investigated for the intramolecular hydroaminoalkylation of aminoallene **1** (Ind = η^5-indenyl)

However, instead of the expected formation of a mixture of **2**, **3**, and **4**, we surprisingly obtained the 2-methylenecyclohexane-1-amine **4** and the allylic amine **5** (Table 1) in ratios that depended on the reaction conditions. After a comprehensive optimization study (6–10 mol% **IV**, [**1**]= 0.025–0.625 mol/L in benzene, toluene, or *p*-cymene, reaction time: 2–24 h), it was finally possible to isolate the hydroaminoalkylation product **4** in 50% yield from a reaction mixture that had been stirred for 2.5 h at 160 °C in *p*-cymene with a catalyst loading of 10 mol% of **IV** (Table 1, entry 1).[10] Whereas in this case the allylamine side product **5** was obtained in only 5% yield, a corresponding experiment involving heating to 160 °C for 24 h gave **5** in 35% yield and **4** in only 4% yield (entry 2). Both results were in good agreement with the ratios of **4** and **5** determined by GC analysis of the crude reaction mixtures after 2.5 hours (**4**/**5** = 91:9) and 24 hours (**4**/**5** = 23:77). The products **4** and **5** could easily be identified by NMR analysis. For example, the presence of the exomethylene group of **4** was strongly supported by two singlet signals in the ^{1}H NMR spectrum (δ = 4.77 and 4.84 ppm) and a corresponding signal for an olefinic CH_2 group in the ^{13}C NMR spectrum (δ = 106.7 ppm). In addition, the C–H group at position α to the N-atom of **4** is consistent with a ^{1}H NMR signal at δ = 3.71 ppm (dd) with an integral of one proton and a ^{13}C NMR signal for a C–H group at δ = 57.1 ppm. In contrast, the ^{1}H NMR and ^{13}C NMR spectra of **5** showed signals for a CH_2 group adjacent to the N atom (δ = 3.50 ppm, s, 2 H; δ = 51.0 ppm, CH_2), and only one olefinic C–H group (δ = 5.58–5.60 ppm, m, 1 H; δ = 122.9 ppm, CH).[11]

Table 1 Intramolecular Hydroaminoalkylation of Aminoallene **1** at 160 °C in the Presence of Catalyst **IV**[a]



Entry	Time (h)	Ratio[b] **4**/**5**	Yield[c] (%) of **4**	Yield[c] (%) of **5**
1	2.5	91:9[d]	50	5
2	24	23:77[d]	4	35

[a] Reaction conditions: aminoallene (**1**, 0.5 mmol), **IV** (0.05 mmol, 10 mol%), *p*-cymene (15 mL), 160 °C.
[b] Determined by GC analysis before chromatography.
[c] Isolated yield.
[d] According to GC analysis, the conversion of substrate **1** was close to quantitative. This strongly suggests that significant decomposition of the allene and/or the products occurs under the reaction conditions.

With sufficient quantities of **4** in hand, we were also able to confirm its exomethylene-group-containing structure by single-crystal X-ray analysis (Figure 2).[12]

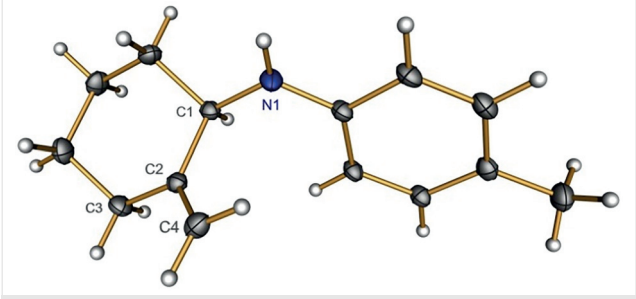
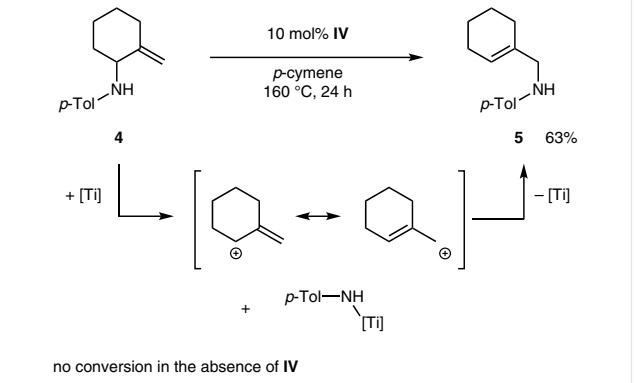


Figure 2 Single-crystal X-ray structure of **4**;[12] ellipsoid representation at the 50% probability level. Selected bond lengths [Å] and angles [°]: C1–C2 = 1.5185(8), C2–C3 = 1.5059(8), C2–C4 = 1.3337(8), C1–C2–C3 = 113.61(5), C1–C2–C4 = 123.57(6), C3–C2–C4 = 122.76(6).

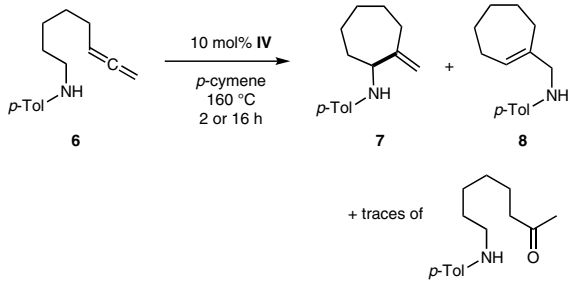
Because the dependency of the product ratio on the reaction time suggests a rearrangement of the initially formed hydroaminoalkylation product **4** (the disubstituted exocyclic alkene) into the thermodynamically more stable allylamine **5** (a trisubstituted endocyclic alkene) under the reaction conditions, we investigated the conversion of **4** into **5** (Scheme 2). For this purpose, we initially heated a solution of **4** in *p*-cymene to 160 °C for six hours in the absence of the titanium catalyst to rule out the possibility of a simple thermal rearrangement. Because, in this case, the formation of **5** could not be detected by GC analysis, the experiment was repeated in the presence of 7 mol% of catalyst **IV** and, not surprisingly, after six hours the product ratio **4**/**5** was found to be 14:86. With this result in hand, we then conducted a final experiment on a preparative scale (10 mol% **IV**, 24 h), from which allylamine **5** was isolated in 63% yield. From a mechanistic point of view, it seems to be reasonable that the rearrangement of **4** to **5** involves the generation of an allylic cation intermediate in a process that is initiated by the presence of the Lewis acidic titanium catalyst (Scheme 2). This might also explain why no successful hydroaminoalkylations of allenes have been previously reported; the expected products can generally be converted into reactive allylic cations and, correspondingly, a strong likelihood of unwanted side reactions is to be expected in these cases. In this context, it is worth mentioning that, to the best of our knowledge, the corresponding Lewis acid-catalyzed rearrangement of allylamines have not been previously reported.[13] The fact that we were unable to identify suitable reaction conditions for the hydroaminoalkylation of aminoallene **1** to give the expected product **4** selectively provides a clear indication that the rearrangement of **4** to **5** occurs at the temperatures that are required for the hydroaminoalkylation of **1** in the presence of catalyst **IV**. Consequently, future research needs to focus on the identification of more-active hydroaminoalkylation catalysts that are active at lower temperatures, thereby avoiding the isomerization side reaction.



Scheme 2 Rearrangement of the hydroaminoalkylation product **4** and a possible mechanistic pathway

The assumption that the hydroaminoalkylation products obtainable from allenes are generally labile under the reaction conditions was subsequently confirmed by two cyclization experiments performed with the 1-aminoocta-6,7-diene **6** at 160 °C in the presence of 10 mol% of **IV** (Table 2). During these experiments, we found again that after a relatively short reaction time of two hours, the desired hydroaminoalkylation product **7** was the major product of the reaction (Table 2, entry 1) whereas the rearranged allylamine **8** dominated after 16 hours (entry 2). From a preparative point of view, the well-established fact that formation of seven-membered rings is difficult to achieve can be regarded as a simple explanation for the isolation of **7** and **8** in poor yields of only 5 and 10%, respectively. In addition, it should also be mentioned that separation of **7** and **8** was only possible on an analytical scale for characterization purposes.[11] Interestingly, traces of 8-(*p*-tolylamino)octan-2-one were also isolated from the reaction mixtures, suggesting that an unexpected intramolecular allene hydroamination[14] with the secondary amine[15] moiety, initially leading to the formation of a moisture-sensitive eight-membered cyclic enamine, takes place as a side reaction.

Table 2 Intramolecular Hydroaminoalkylation of Aminoallene **6**[a]

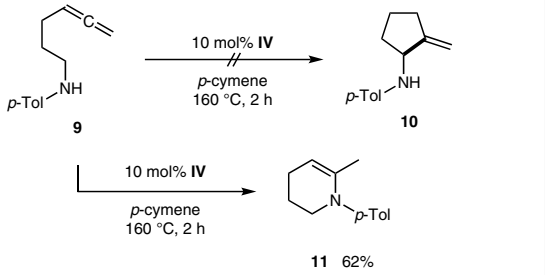


Entry	Time (h)	Ratio[b] **7**/**8**	Yield[c] (%) of **7** + **8**
1	2	74:26[d]	5
2	16	13:87[d]	10

[a] Reaction conditions: aminoallene (**6**, 0.5 mmol), **IV** (0.05 mmol, 10 mol%), *p*-cymene (15 mL), 160 °C.
[b] Determined by GC analysis before chromatography.
[c] Isolated yield.
[d] According to GC analysis, conversion of substrate **6** is close to quantitative. This strongly suggests that significant decomposition of the allene and/or the products occurs under the reaction conditions.

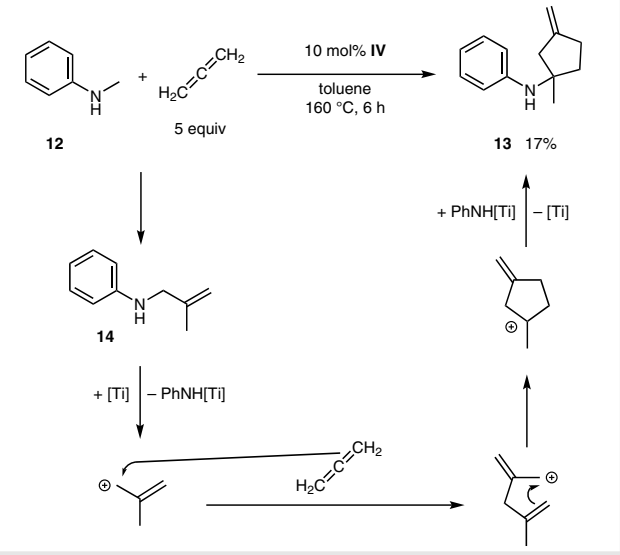
In contrast to the 1-aminoocta-6,7-diene **6**, the 1-aminohexa-4,5-diene **9** (Scheme 3) was expected to undergo smooth intramolecular hydroaminoalkylation to form the relatively unstrained 2-methylenecyclopentane-1-amine **10** as the product. However, surprisingly, a reaction performed with **9** at 160 °C in the presence of 10 mol% of **IV** selectively delivered a 62% isolated yield of the six-membered-ring-containing enamine **11** (Scheme 3) as a result of an unexpected intramolecular allene hydroamination. In this context, it must be mentioned that hydroamination re-

actions of unsaturated substrates with secondary amines catalyzed by neutral group 4 metal complexes have rarely been reported.[15]



Scheme 3 Unexpected intramolecular hydroamination of aminoallene **9**

Finally, we then applied the reaction conditions that successfully facilitated the intramolecular allene hydroaminoalkylation to an intermolecular reaction between *N*-methylaniline (**12**) and propa-1,2-diene (Scheme 4), used as a solution in toluene.[16] Obviously, in this case, the initial hydroaminoalkylation product **14** immediately undergoes the previously discussed formation of an allylic cation that reacts with a second equivalent of propa-1,2-diene to give the interesting aminocyclopentane **13** as the final product of the reaction. In this context, it is worth mentioning that the low yield of only 17% obtained in this preliminary study is not caused by insufficient catalytic activity, since a 100% conversion of **12** was observed by GC analysis under the applied reaction conditions. The major problem was the formation of an abundance of side products that were observed by GC analysis, but could not be identified.



Scheme 4 Intermolecular hydroaminoalkylation of propa-1,2-diene with *N*-methylaniline (**12**), and a mechanistic explanation for the formation of product **13**

In summary, we have presented the first examples of early-transition-metal-catalyzed hydroaminoalkylation reactions of allenes. The studies performed with secondary aminoallenes revealed that, under the reaction conditions, the initially formed products undergo an unexpected rearrangement to the thermodynamically more stable allylamine products. The assumption that this rearrangement involves the generation of a reactive allylic cation intermediate, which can generally initiate unwanted side reactions, might serve as a simple explanation for the fact that no successful early-transition-metal-catalyzed hydroaminoalkylations of allenes have previously been reported in the literature. As a result of the formation of a corresponding cation, the first successful intermolecular hydroaminoalkylation of propa-1,2-diene finally resulted in the isolation of an unexpected aminocyclopentane derivative formed by incorporation of two equivalents of propa-1,2-diene.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611790.

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(10) **4-Methyl-*N*-(2-methylenecyclohexyl)aniline (4)**

In a glovebox under N_2, amine **1** (101 mg, 0.5 mmol) and catalyst **IV** (27 mg, 0.05 mmol, 10 mol%) were dissolved in *p*-cymene (15 mL) in a 25 mL ampoule equipped with magnetic stirrer bar. The ampoule was then sealed and heated at 160 °C for 2.5 h. The product was purified by chromatography [silica gel (250 g, length = 1 m, diam. = 20 mm), PE–Et_2O (20:1, R_f = 0.36)] to give **4** as a colorless liquid [yield: 50 mg (0.25 mmol, 50%)], together with the byproduct *N*-(cyclohex-1-en-1-ylmethyl)-4-methylaniline [**5**; yield: 5 mg (0.02 mmol, 5%)] as a yellow oil. Crystals of **4** were obtained by slow evaporation of a solution in hexane.

4

Colorless liquid [yield: 50 mg (0.25 mmol, 50%)]; mp: = 59 °C. IR (ATR) λ^{-1} 3410, 2936, 2854, 1612, 1519, 1441, 1398, 1315, 1302, 1259, 1180, 1156, 1140, 1123, 1108, 1086, 908, 804 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.38-1.46 (m, 2 H), 1.55–1.63 (m, 1 H), 1.79 (dq, *J* = 16.9, 4.0 Hz, 1 H), 1.88 (dq, *J* = 16.9, 4.1 Hz, 1 H), 2.03–2.13 (m, 2 H), 2.25 (s, 3 H), 2.44 (dt, *J* = 13.3, 3.8 Hz, 1 H), 3.71 (dd, *J* = 10.3, 4.3 Hz, 1 H), 3.75 (br. s, 1 H), 4.77 (s, 1 H), 4.84 (s, 1 H), 6.54 (d, *J* = 8.3 Hz, 2 H), 6.98 (d, *J* = 8.1 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$, DEPT): δ = 20.5 (CH_3), 25.4 (CH_2), 28.4 (CH_2), 34.5 (CH_2), 35.7 (CH_2), 57.1 (CH), 106.7 (CH_2), 113.6 (CH), 126.5 (C), 129.7 (CH), 145.3 (C), 149.6 (C). MS (EI, 70 eV): *m/z* (%) = 201 (100) $[M]^+$, 172 (15), 133 (15), 107 (61), 91 (11). HRMS (EI, 70 eV): *m/z* $[M^+]$ calcd. for $C_{14}H_{19}N$: 201.1512; found: 201.1511.

(11) For details, see the Supporting Information.

(12) CCDC 1871667 contains the supplementary crystallographic data for compound **4**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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