Titanium Catalysis

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[Ind_2TiMe_2]: A Catalyst for the Hydroaminomethylation of Alkenes and Styrenes**

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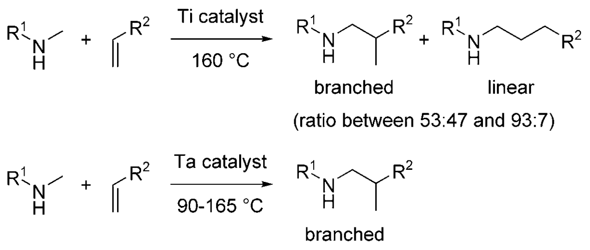
Owing to the great biological and industrial importance of nitrogen-containing molecules, much research has focused on the development of efficient methods for the synthesis of amines for a long time. Among various synthetic strategies, the hydroamination of alkenes and alkynes[1] and the hydroaminoalkylation of alkenes[2–7] must be regarded as particularly promising because both processes offer a direct and highly atom-efficient (100 %) conversion of simple starting materials into more complex molecules by C–N or C–C bond formation. During a hydroaminoalkylation reaction of an alkene, the α-C–H bond of a primary or a secondary amine undergoes an addition across a C–C double bond, which results in an alkylation of the amine in the α position to the nitrogen atom. Whilst simple tantalum catalysts[3,4] were initially used for this C–H activation process, corresponding enantioselective reactions could recently be achieved in the presence of chiral tantalum amidate complexes.[5] An additional class of suitable catalysts for hydroaminoalkylation reactions of alkenes are complexes of the Group 4 metals.[6,7] However, it must be noted that zirconium catalysts can only be used for intramolecular reactions of primary aminoalkenes,[7] whereas titanium catalysts, such as [$Ti(NMe_2)_4$] or [$TiBn_4$], catalyze intra- and intermolecular reactions,[6] and furthermore, titanium complexes show a higher catalytic activity than their zirconium counterparts. Upon inspection of intermolecular hydroaminoalkylation reactions of 1-alkenes reported in the literature, it becomes clear that the use of titanium catalysts usually results in the formation of two regioisomeric products (branched and linear; Scheme 1), whereas the branched regioisomer is formed exclusively in the presence of tantalum catalysts. Another interesting point is that efficient intermolecular hydroaminoalkylation reactions of styrenes have not been reported to date.[8] A possible explanation for this fact could be that hydroaminoalkylation reactions are usually performed under harsh reaction conditions (temperatures of 130–165 °C)[9] under which styrenes tend to undergo polymerization reactions.

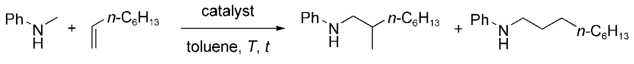


Scheme 1. Formation of regioisomers during intermolecular hydroaminomethylation reactions of alkenes performed with titanium or tantalum catalysts.

Based on the simple assumption that the regioselectivity of titanium-catalyzed intermolecular hydroaminoalkylation reactions and the results with styrenes may be improved by performing the reactions under milder conditions, we reinvestigated the catalytic performance of [$Ti(NMe_2)_4$] and [Ind_2TiMe_2] (Ind = η^5-indenyl), because with these two catalysts, the initially observed titanium-catalyzed hydroaminoalkylation reactions took place as side reactions during attempted intramolecular hydroaminations at a temperature of only 105 °C.[10]

Initial intermolecular hydroaminoalkylation reactions of 1-octene (**2**) with *N*-methylaniline (**1**) performed in toluene[11] at temperatures of 160 °C or 105 °C for 96 h in the presence of 10 mol % of [$Ti(NMe_2)_4$] or [Ind_2TiMe_2] revealed that only [Ind_2TiMe_2] is catalytically active at 105 °C (Table 1, entries 1–4). Surprisingly, it was also found that with [Ind_2TiMe_2] as the catalyst, the branched isomer **3a** is

Table 1: Intermolecular titanium-catalyzed hydroaminomethylation of 1-octene (**2**) with *N*-methylaniline (**1**).



1 **2** **3a** **3b**

Entry	Catalyst	mol %	*T* [°C]	*t* [h]	Yield **3a** + **3b** [%][a]	Selectivity **3a**/**3b**[b]
1	[$Ti(NMe_2)_4$]	10	160	96	32	93:7
2		10	105	96	< 5	n.d.
3	[Ind_2TiMe_2]	10	160	96	84	> 99:1
4		10	105	96	97	> 99:1
5		10	105	24	96	> 99:1
6		5	105	24	96	> 99:1
7		5	90	24	81	> 99:1
8		5	80	24	86	> 99:1
9		5	70	24	< 5	n.d.
10		2	105	24	90	> 99:1
11		1	105	24	6	n.d.

[a] Reaction conditions: amine (2.0 mmol), alkene (3.0 mmol), catalyst, toluene (1 mL), *T*, *t*. Yields refer to the total yield of isolated product (**3a** + **3b**). [b] GC analysis prior to chromatography under conditions where a ratio of 99.5:0.5 could be detected. n.d. = not determined.

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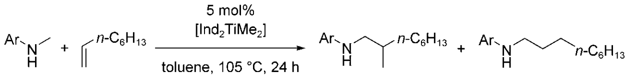
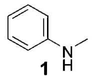
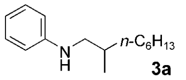
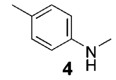
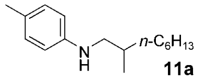
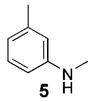
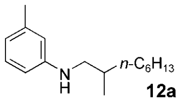
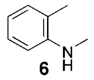
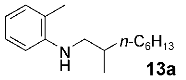
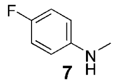
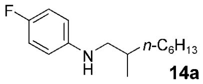
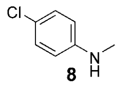
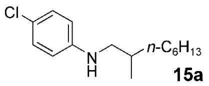
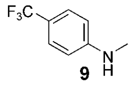
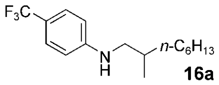
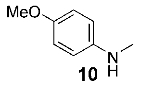
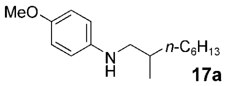
formed with a regioselectivity of better than 99:1 at both 160 °C and at 105 °C. These promising results inspired us to perform a number of additional experiments with reduced reaction time, temperature, and catalyst loading, which led to the finding that the product **3a** is still formed in 86 % yield and with unchanged regioselectivity when the reaction is performed for 24 h with 5 mol % [Ind$_2$TiMe$_2$] at a temperature of only 80 °C (Table 1, entry 8). To the best of our knowledge, a corresponding metal-catalyzed hydroaminoalkylation of an alkene has never been reported to occur at such a low temperature.[9] However, a subsequent experiment performed at 70 °C revealed that the reaction no longer takes place at this temperature. On the other hand, it was possible to reduce the catalyst loading to only 2 mol % in a corresponding experiment performed at 105 °C. After a reaction time of 24 h, **3a** was still obtained in 90 % yield (Table 1, entry 10). Although almost identical results (96 %) were obtained in corresponding experiments with 5 mol % and 10 mol % [Ind$_2$TiMe$_2$], a further reduction of the catalyst loading to 1 mol % resulted in low conversion and a yield of only 6 % (Table 1, entry 11). In general, all the reactions took place smoothly, and we were not able to detect the formation of any side products by GC.

With these results in hand, we then tried to react a number of amines with 1-octene (**1**) under the convenient conditions that are shown in Table 1, entry 6 (5 mol % [Ind$_2$TiMe$_2$], 105 °C, 24 h). However, at an early stage of this investigation, it became clear that successful reactions can only be achieved with *N*-methylanilines (Table 2). No conversion was observed with primary amines, dialkylamines, and *N*-ethyl- or *N*-propylanilines[12] under the chosen reaction conditions. Among the various *N*-methylanilines investigated, best results were obtained with substrates that possess methyl or fluoro substituents on the benzene ring. In these cases, yields of at least 84 % and regioselectivities of more than 99:1 in favor of the branched product were always achieved. However, an *ortho*-methyl substituent of the aniline is not tolerated, and similar behavior was found for a strong electron acceptor (CF$_3$) and an electron donor (OMe) in the *para* position. In contrast, the *para*-chloro-substituted *N*-methylaniline **8** underwent a slow reaction under the chosen reaction conditions, which finally gave access to the branched product **15a** in 16 % yield (Table 2, entry 6). This yield could easily be improved to 43 % by performing the reaction with an increased catalyst loading of 10 mol % and a reaction time of 96 h. Interestingly an identical observation was made during the reaction between styrene (**18**) and *N*-methylaniline (**1**; Table 3, entries 1–3). Although a corresponding reaction performed at 105 °C for 24 h in the presence of 5 mol % [Ind$_2$TiMe$_2$] gave a yield of only 13 %, a simple extension of the reaction time to 96 h led to an increased yield of 71 %. An additional increase in yield to 91 % could be achieved by increasing the catalyst loading to 10 mol %. With regard to the reactions performed with 1-octene (**2**), the regioselectivity of the hydroaminoalkylation of styrene (**18**) slightly drops to only 85:15 in favor of the branched product **30a**. Again, the reactions took place smoothly, and it was not possible to detect any side products in the crude reaction mixtures. In all cases, only the desired hydroaminomethylation products **30a** and **30b** were detected by GC together with unconsumed styrene (**18**). Overall, this reaction is the first example of an efficient metal-catalyzed hydroaminomethylation of a styrene. Additional transformations of the styrenes **19–25** with *N*-methylaniline (**1**, Table 3, entries 4–10) performed under identical reaction conditions revealed that many styrenes undergo successful hydroaminomethylation reactions in the presence of [Ind$_2$TiMe$_2$]. Only the reactions of the *ortho*-*ortho*-disubstituted styrene **23** and the CF$_3$-substituted styrene **25** gave yields of less than 5 %. In contrast, the *para*-alkyl-, *para*-aryl-, and *para*-methoxy-substituted styrenes **19–21** and **24** underwent successful hydroaminomethylation reactions with high yields (95–99 %) and regioselectivities of 82:18 or more in favor of the respective branched product (Table 3, entries 4–6, 9). Even the *ortho*-methyl-substituted styrene **22** gave the desired products **34a** and **34b** with a regioselectivity of 75:25 in 94 % yield (Table 3, entry 7). If this regioselectivity is compared with the regioselectivity observed with the comparable *ortho*-unsubstituted substrate

Table 2: Intermolecular hydroaminomethylation of 1-octene (**2**) with *N*-methylanilines.

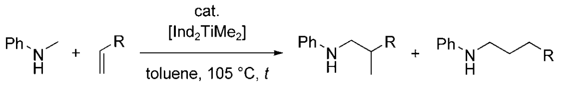


1, **4-10** **2** **3a**, **11-17a** **3b**, **11-17b**

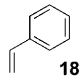
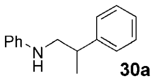
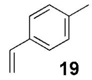
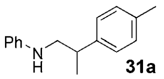
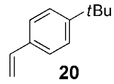
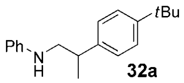
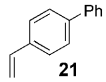
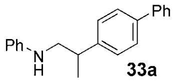
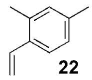
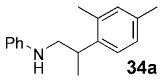
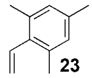
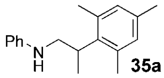
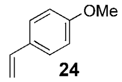
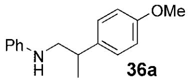
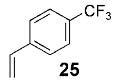
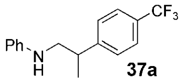
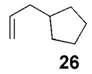
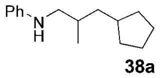
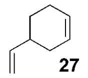
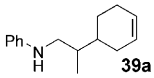
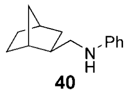
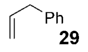
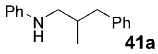
Entry	Amine	Branched product	Yield **a + b** [%][a]	Selectivity **a/b**[b]
1	 **1**	 **3a**	96	> 99:1
2	 **4**	 **11a**	95	> 99:1
3	 **5**	 **12a**	84	> 99:1
4	 **6**	 **13a**	< 5	n.d.
5	 **7**	 **14a**	96	> 99:1
6	 **8**	 **15a**	16[c]	> 99:1
7	 **9**	 **16a**	< 5	n.d.
8	 **10**	 **17a**	< 5	n.d.

[a] Reaction conditions: amine (2.0 mmol), alkene (3.0 mmol), [Ind$_2$TiMe$_2$] (0.1 mmol, 5 mol %), toluene (1 mL), 105 °C, 24 h. Yields refer to the total yield of isolated product (**a** + **b**). [b] GC analysis prior to chromatography under conditions where a ratio of 99.5:0.5 could be detected. n.d. = not determined. [c] A yield of 43 % was obtained with 10 mol % [Ind$_2$TiMe$_2$] after a reaction time of 96 h.

Table 3: Intermolecular hydroaminomethylation of alkenes with *N*-methylaniline (**1**).



1 **18-29** **30-41a** **30-41b**

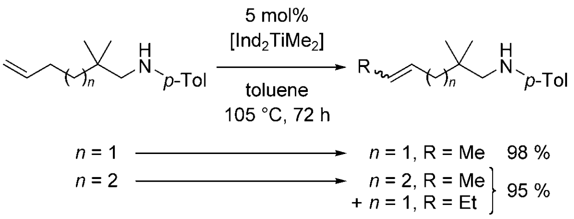
Entry	Alkene	mol %	*t* [h]	Branched product	Yield **a**+**b** [%][a]	Selectivity **a**/**b**[b]
1	 **18**	5	24	 **30a**	13	85:15
2		5	96		71	85:15
3		10	96		91	85:15
4	 **19**	10	96	 **31a**	99	90:10
5	 **20**	10	96	 **32a**	97	87:13
6	 **21**	10	96	 **33a**	97	82:18
7	 **22**	10	96	 **34a**	94	75:25
8	 **23**	10	96	 **35a**	<5	n.d.
9	 **24**	10	96	 **36a**	95	92:8
10	 **25**	10	96	 **37a**	<5	n.d.
11	 **26**	10	96	 **38a**	93	>99:1
12	 **27**	10	96	 **39a**	92[c]	>99:1
13	 **28**	10	96	 **40**	12	n.d.
14	 **29**	10	96	 **41a**	40	92:8

[a] Reaction conditions: amine (2.0 mmol), alkene (3.0 mmol), [Ind$_2$TiMe$_2$], toluene (1 mL), 105 °C, *t*. Yields refer to the total yield of isolated product (**a**+**b**). [b] GC analysis prior to chromatography under conditions where a ratio of 99.5:0.5 could be detected. n.d. = not determined. [c] Two diastereomers in a ratio of 85:15.

19 (90:10), it becomes clear that an increasing steric demand of the aryl ring of the styrene supports the formation of the linear product. However, the finding that the regioselectivities of hydroaminomethylation reactions of the *para*-substituted styrenes **19**–**21** and **24** also vary significantly (from 92:8 to 82:18) clearly indicates that not only pure steric effects but also electronic factors influence the regioselectivity of the reaction.

Although successful transformations of α- and β-methylstyrene and indene could not be achieved under analogous conditions, corresponding reactions of the 1-alkenes **26** and **27** gave the desired branched products **38a** and **39a** with excellent yields of 93 % and 92 %, respectively (Table 3, entries 11, 12). In particular, the regioselectivity of more than 99:1 observed with alkene **27** that can be seen as a "tetrahydrostyrene" is worthy of attention because this result is much better than the selectivity observed (85:15) with the corresponding styrene **18**. From these data, one can draw the conclusion that electronic reasons are responsible for the decreased regioselectivity observed with styrenes. Experiments performed with norbornene (**28**) and allylbenzene (**29**) clearly indicated that better yields (83 % and 94 %) have already been reported for these substrates.[6]

Further attempted intramolecular reactions of secondary aminoalkenes performed at 105 °C in the presence of the catalyst [Ind$_2$TiMe$_2$] (Scheme 2) did not give access to the desired cyclopentyl- or cyclohexylamines. Instead of a hydroaminoalkylation reaction, an isomerization of the C–C double bond, which is probably caused by a competing C–H bond activation in the allylic position, always occurred.



Scheme 2. Double-bond migration during attempted intramolecular hydroaminoalkylation reactions performed in the presence of [Ind$_2$TiMe$_2$].

In summary, it was shown for the first time that efficient metal-catalyzed hydroaminomethylation reactions of styrenes can be achieved in the presence of titanium catalysts. Furthermore, [Ind$_2$TiMe$_2$] was identified as a catalyst that is catalytically active at temperatures as low as 80 °C. With this catalyst, 1-alkenes react with *N*-methylanilines to give the corresponding branched hydroaminomethylation products with very high regioselectivity.

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[8] The general feasibility of a titanium-catalyzed hydroaminoalkylation of styrene has already been demonstrated using [$TiBn_4$] as the catalyst; see Ref. [6b].

[9] With [$\{Cl_3Ta(NMePh)_2\}_2$] as the catalyst, a successful hydroaminoalkylation (1-ocetene + *N*-methylaniline) could be achieved at a temperature of only 90 °C; see Ref. [4b].

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[11] For the corresponding reaction between allylbenzene and *N*-methylaniline, comparable yields are obtained in various solvents, such as toluene, xylenes, 1,4-dioxane, *n*-heptane or diphenyl ether: N. Bruns, BSc Thesis, Universität Oldenburg, **2009**.

[12] A possible explanation for the fact that, among the substance class of *N*-alkylamines, only *N*-methylamines undergo successful reactions could be that a sterically more demanding *N*-alkyl substituent prevents alkene insertion into the carbon–titanium bond of a titanaaziridine, which is assumed to be the catalytically active species. For plausible suggestions regarding the mechanism of the hydroaminoalkylation reaction, see Refs [4–7].