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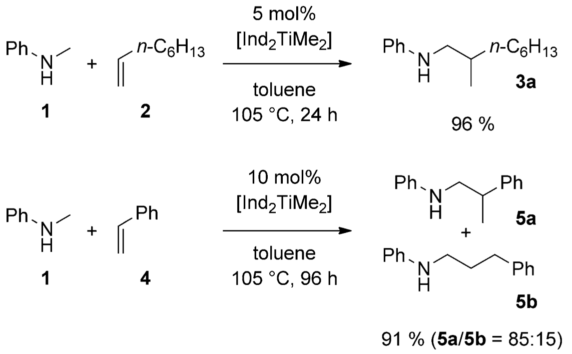
Hydroaminoalkylation

Aminopyridinato Titanium Catalysts for the Hydroaminoalkylation of Alkenes and Styrenes**

*Jaika Dörfler and Sven Doye**

Dedicated to Professor Ekkehard Winterfeldt on the occasion of his 80th Birthday

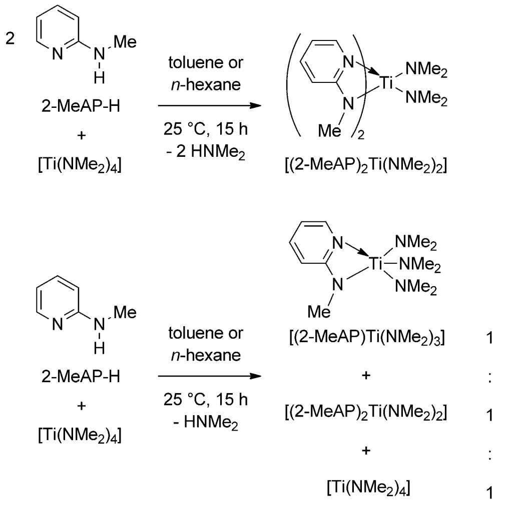
The hydroaminoalkylation of alkenes[1] is a highly atom efficient (100%) reaction that allows the addition of the α-C–H bond of an amine across a C–C double bond (Scheme 1).



Scheme 1. [Ind$_2$TiMe$_2$]-catalyzed hydroaminoalkylation.[6d]

As the formed α-alkylated amines are of great industrial importance it is not surprising that a number of hydroaminoalkylation catalysts have already been identified.[2–6] Successful hydroaminoalkylation reactions of alkenes can be achieved in the presence of ruthenium,[2] iridium,[3] Group 5 metals,[4] zirconium,[5] or titanium catalysts[6] but the use of ruthenium and iridium catalysts is limited to amine substrates possessing a directing 2-pyridinyl substituent bound to the nitrogen atom of the amine.[2,3] While in the presence of Group 5 metal catalysts or [Ind$_2$TiMe$_2$] (Ind = η^5-indenyl), the hydroaminoalkylation of 1-alkenes, such as 1-octene (**2**), with secondary amines, such as *N*-methylaniline (**1**), always gives the branched product **3a** exclusively (Scheme 1), the corresponding [Ind$_2$TiMe$_2$]-catalyzed reaction of styrene (**4**) also leads to the formation of the linear product **5b** as a side product.[6d] Unfortunately, successful [Ind$_2$TiMe$_2$]-catalyzed hydroaminoalkylation reactions could only be achieved with *N*-methylanilines and in this context, it must also be mentioned that by using Group 5 metal catalysts only a single additional example of a successful hydroaminomethylation of a styrene has been reported.[4i] In this case, the branched product was again the exclusive product of the reaction. Interestingly, linear side products could also be obtained from hydroaminoalkylation reactions of 1-alkenes performed with [Ti(NMe$_2$)$_4$][6b] or [TiBn$_4$][6c] (Bn = benzyl) as the catalysts. However, to our knowledge, up to now, no early transition-metal-catalyzed hydroaminoalkylation of an alkene or a styrene that leads to the formation of the industrially important linear product as the major product of the reaction has been reported.[7] In addition, hydroaminoalkylation reactions of styrenes with dialkylamines or *N*-alkylanilines possessing alkyl groups larger than a methyl group have never been achieved.

To expand the substrate scope of the hydroaminoalkylation of alkenes, we recently performed a number of corresponding transformations with *N*-methylated aminoheteroaromatics as substrates in the presence of the precatalyst [Ti(NMe$_2$)$_4$]. During these unsuccessful attempts we observed that the addition of 2-(methylamino)pyridine (2-MeAP-H) to a bright yellow solution of the alkene and the precatalyst [Ti(NMe$_2$)$_4$] in toluene results in a significant color change to dark red which suggests a fast formation of titanium complexes with 2-aminopyridinato ligands,[8] such as [(2-MeAP)$_2$Ti(NMe$_2$)$_2$] or [(2-MeAP)Ti(NMe$_2$)$_3$] (Scheme 2). In this context, it must be noted that Kempe has already synthesized the complex [(2-MeAP)$_2$Ti(NMe$_2$)$_2$] by amine



Scheme 2. Detection of in situ generated 2-aminopyridinato titanium complexes by ^{1}H NMR spectroscopy.[10]

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[*] J. Dörfler, Prof. S. Doye
Institut für Reine und Angewandte Chemie, Universität Oldenburg
Carl-von-Ossietzky-Strasse 9-11, 26111 Oldenburg (Germany)
E-mail: doye@uni-oldenburg.de

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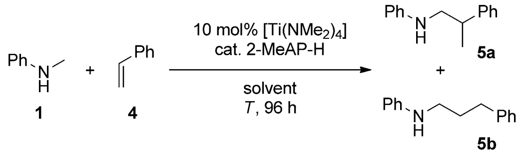
elimination from [Ti(NMe$_2$)$_4$] and 2 equivalents of 2-MeAP-H.[9] In agreement with Kempe's result, we were able to detect by ^{1}H NMR spectroscopy that stirring of a 1:2 mixture of [Ti(NMe$_2$)$_4$] und 2-MeAP-H in toluene or *n*-hexane at room temperature results in the selective formation of the complex [(2-MeAP)$_2$Ti(NMe$_2$)$_2$] (Scheme 2).[10] In contrast, an analogous experiment performed with a 1:1 mixture of [Ti(NMe$_2$)$_4$] und 2-MeAP-H did not give the expected complex [(2-MeAP)Ti(NMe$_2$)$_3$] selectively. In this case, a statistical mixture of [(2-MeAP)Ti(NMe$_2$)$_3$], [(2-MeAP)$_2$Ti(NMe$_2$)$_2$], and the precursor [Ti(NMe$_2$)$_4$] in a ratio of approximately 1:1:1 was formed.

Because 2-aminopyridinato Ti-complexes have never been used as catalysts for hydroaminoalkylation reactions of alkenes, we investigated whether the in situ generated complexes are able to catalyze the hydroaminoalkylation of styrene (**4**) with *N*-methylaniline (**1**). For that purpose, mixtures of [Ti(NMe$_2$)$_4$] (10 mol %) and 2-MeAP-H (10 or 20 mol %) in toluene were stirred at 25 °C for 15 h and after addition of *N*-methylaniline and styrene, the mixtures were heated to 105 °C for 96 h (Table 1, entries 2 and 3). Fortunately and in contrast to a corresponding reaction performed in the absence of 2-MeAP-H (Table 1, entry 1), it was possible to isolate the desired products **5a** and **5b** in combined yields of 55 and 10 %. Particularly important is that these two experiments represent the first examples of a hydroaminoalkylation performed with *N*-methylaniline in which the linear product **5b** is formed in larger quantities than the branched product **5a**. A brief optimization study then revealed that a simple elevation of the reaction temperature to 140 °C and a change of the solvent to *n*-hexane significantly improve the combined yields to 79 and 76 % (Table 1, entries 8 and 9). In this context, it is of note that the result obtained with a mixture of 10 mol % [Ti(NMe$_2$)$_4$] and 20 mol % 2-MeAP-H is almost identical to the result of a control experiment performed with 10 mol % [(2-MeAP)$_2$Ti(NMe$_2$)$_2$][9] which was synthesized according to Kempe's procedure (Table 1, entry 9).[11]

Table 1: Hydroaminoalkylation of styrene (**4**) with *N*-methylaniline (**1**).[10]



Entry	2-MeAP-H [mol %]	Solvent	*T* [°C]	Yield **5a** + **5b** [%][a]	Selectivity **5a**/**5b**[b]
1	–	toluene	105	–	–
2	10	toluene	105	55	39:61
3	20	toluene	105	10	23:77
4	–	toluene	140	11	39:61
5	10	toluene	140	78	46:54
6	20	toluene	140	41	34:66
7	–	*n*-hexane	140	6	42:58
8	10	*n*-hexane	140	79	32:68
9	20	*n*-hexane	140	76[c]	34:66

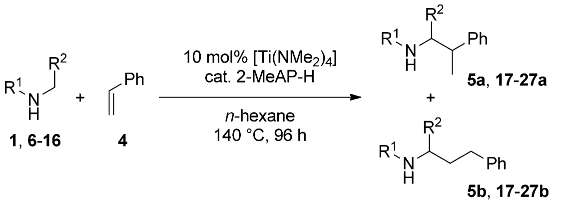
[a] Reaction conditions: *N*-methylaniline (**1**, 2.0 mmol), styrene (**4**, 3.0 mmol), [Ti(NMe$_2$)$_4$] (0.2 mmol, 10 mol %), 2-MeAP-H (0.2 mmol, 10 mol % or 0.4 mmol, 20 mol %), solvent (1.0 mL), *T*, 96 h. Yields refer to the total yield of isolated product (**5a** + **5b**). [b] GC analysis prior to chromatography. [c] A control experiment performed with 10 mol % [(2-MeAP)$_2$Ti(NMe$_2$)$_2$] gave a comparable result (76 %, **5a**/**5b** = 33:67).

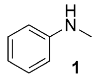
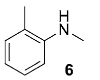
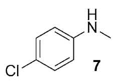
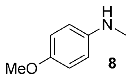
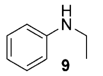
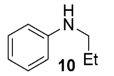
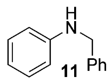
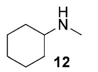
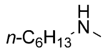
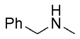
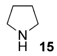
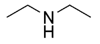
A comparison of the results obtained with 10 and 20 mol % 2-MeAP-H in Table 1 leads to the conclusion that the use of 20 mol % 2-MeAP-H mostly results in a better regioselectivity in favor of the linear product **5b** but a reduced overall yield of the reaction. In addition, it becomes clear that with increasing temperature, the regioselectivity of the reaction decreases while the yield increases. Under optimized conditions (Table 1, entry 8), it was finally possible to obtain the products **5a** and **5b** in 79 % combined yield with a regioselectivity of 32:68 in favor of the linear product **5b**. The control experiments performed in the absence of 2-MeAP-H which are also presented in Table 1 (entries 1,4,7) impressively show that in comparison with [Ti(NMe$_2$)$_4$], the in situ generated 2-aminopyridinato titanium catalysts have a significantly improved catalytic activity.

We next turned our attention towards hydroaminoalkylation reactions of styrene (**4**) with various other amines (Table 2). All corresponding reactions were performed in sealed Schlenk tubes at 140 °C for 96 h with *n*-hexane as the solvent and the catalysts were generated in situ from 10 mol % [Ti(NMe$_2$)$_4$] and 10 or 20 mol % 2-MeAP-H. During these studies, it was recognized that the hydroaminoalkylation of styrene (**4**) can not only be achieved with *N*-methylanilines (Table 2, entries 1–8) but also with *N*-ethyl-, *N*-propyl-, and *N*-benzylaniline (Table 2, entries 9–14) as well as with dialkylamines (Table 2, entries 15–24). A comparison of the regioselectivities observed with the *N*-alkylanilines **1**, **9**, **10**, and **11** reveals that the regioselectivity in favor of the linear product increases with increasing size of the *N*-alkyl substituent. Correspondingly, the best selectivities of $\geq$ 91:9 in favor of the linear product were observed with *N*-propyl- (**10**) and *N*-benzylaniline (**11**). In these cases, moderate to good yields of 48 % and 85 % could be achieved (Table 2, entries 11 and 13). In contrast to the strong influence of the *N*-alkyl substituent on the regioselectivity of the reaction, *ortho*-substitution or donor- and acceptor substituents on the benzene ring of the *N*-methylanilines are less important for the regioselectivity but on the other hand, strongly influence the reactivity of the amine (Table 2, entries 1–8). Particularly interesting is the fact that for the first time, hydroaminoalkylation reactions of styrene (**4**) could also be achieved with dialkylamines (Table 2, entries 15–24). As observed before with the *N*-alkylanilines, preferred formation of the linear product (up to 93:7) took place in all cases and at least some reactions gave good yields (up to 71 %). However, it must be mentioned that prior to isolation, the products obtained from dialkylamines were converted into *para*-toluenesulfonamides. Interestingly, reactions of the unsymmetrically substituted amines *N*-methylcyclohexylamine (**12**) and *N*-methylhexylamine (**13**) took place at the methyl group of the amine selectively while the alkylation of *N*-methylbenzylamine (**14**) only occurred in the benzyl position. These findings are in good agreement with results described by Schafer et al.[4e]

Finally, analogous hydroaminoalkylation reactions using *N*-methylaniline (**1**) were performed with various other

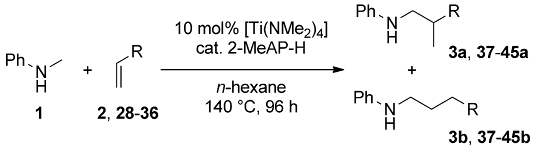
Table 2: Hydroaminoalkylation of styrene (**4**).[10]

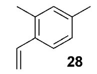
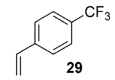
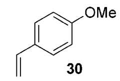
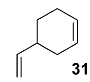
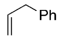
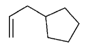
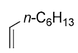
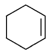
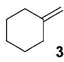


Entry	Amine	2-MeAP-H [mol %]	Yield **a**+**b** [%][a]	Selectivity **a**/**b**[b]
1	 **1**	10	79 (**5a/b**)	32:68
2		20	76 (**5a/b**)	34:66
3	 **6**	10	31 (**17a/b**)[c]	32:68
4		20	4 (**17a/b**)	33:67
5	 **7**	10	31 (**18a/b**)	43:57
6		20	2 (**18a/b**)	30:70
7	 **8**	10	50 (**19a/b**)	35:65
8		20	15 (**19a/b**)	25:75
9	 **9**	10	61 (**20a/b**)	21:79
10		20	32 (**20a/b**)[d]	21:79
11	 **10**	10	48 (**21a/b**)	9:91
12		20	4 (**21a/b**)	1:99
13	 **11**	10	85 (**22a/b**)	8:92
14		20	30 (**22a/b**)	7:93
15	 **12**	10	71 (**23a/b**)[e,f]	42:58
16		20	60 (**23a/b**)[e,f,g]	27:73
17	 **13**	10	22 (**24a/b**)[e,f]	20:80
18		20	5 (**24a/b**)[e,f]	12:88
19	 **14**	10	69 (**25a/b**)[e,h]	7:93
20		20	40 (**25a/b**)[e,h]	35:65
21	 **15**	10	5 (**26a/b**)[e]	12:88
22		20	17 (**26a/b**)[e]	12:88
23	 **16**	10	26 (**27a/b**)[e]	15:85
24		20	8 (**27a/b**)[e]	12:88

[a] Reaction conditions: amine (2.0 mmol), styrene (**4**, 3.0 mmol), [Ti(NMe$_2$)$_4$] (0.2 mmol, 10 mol %), 2-MeAP-H (0.2 mmol, 10 mol % or 0.4 mmol, 20 mol %), *n*-hexane (1.0 mL), 140 °C, 96 h. Yields refer to the total yield of isolated product (**a**+**b**). The reaction conditions were not separately optimized for each substrate. [b] GC analysis prior to chromatography. [c] In addition, double alkylation of the amine occurred in the α-position to the nitrogen atom in 5 % yield. [d] A control experiment performed with 10 mol % [(2-MeAP)$_2$Ti(NMe$_2$)$_2$] gave a comparable result (33 %, **20a**/**20b** = 20:80). [e] The products were isolated after derivatization as the corresponding *para*-toluenesulfonamides. [f] The reaction took place at the methyl group of the amine exclusively. [g] A control experiment performed with 10 mol % [(2-MeAP)$_2$Ti(NMe$_2$)$_2$] gave a comparable result (57 %, **23a**/**23b** = 25:75). [h] The reaction took place at the benzyl position of the amine exclusively.

Table 3: Hydroaminoalkylation of various alkenes.[10]



Entry	Alkene	2-MeAP-H [mol %]	Yield **a**+**b** [%][a]	Selectivity **a**/**b**[b]
1	 **28**	10	49 (**37a/b**)	44:56
2		20	43 (**37a/b**)	45:55
3	 **29**	10	31 (**38a/b**)	19:81
4		20	9 (**38a/b**)	4:96
5	 **30**	10	– (**39a/b**)	–
6		20	– (**39a/b**)	–
7	 **31**	10	69 (**40a/b**)	89:11
8		20	21 (**40a/b**)	93:7
9	 **32**	10	91 (**41a/b**)	90:10
10		20	15 (**41a/b**)	81:19
11	 **33**	10	85 (**42a/b**)	93:7
12		20	30 (**42a/b**)	93:7
13	 **2**	10	99 (**3a/b**)	97:3
14		20	90 (**3a/b**)	94:6
15	 **34**	10	70 (**43**)[c]	–
16		20	91 (**43**)	–
17	 **35**	10	– (**44**)	–
18		20	– (**44**)	–
19	 **36**	10	16 (**45a**)	>99:1
20		20	6 (**45a**)	>99:1

[a] Reaction conditions: *N*-methylaniline (**1**, 2.0 mmol), alkene (3.0 mmol), [Ti(NMe$_2$)$_4$] (0.2 mmol, 10 mol %), 2-MeAP-H (0.2 mmol, 10 mol % or 0.4 mmol, 20 mol %), *n*-hexane (1.0 mL), 140 °C, 96 h. Yields refer to the total yield of isolated product (**a**+**b**). The reaction conditions were not separately optimized for each substrate. [b] GC analysis prior to chromatography. [c] In addition, double alkylation of the amine occurred in the α-position to the nitrogen atom in 26 % yield.

styrenes and alkenes (Table 3). As can be seen from the results of the experiments performed with the electronically and sterically modified styrenes **28**–**30** (Table 3, entries 1–6), the yield of the hydroaminoalkylation reaction strongly depends on the electronic and steric properties of the styrene substrate. Whereas the electron-donating *para*-methoxy group of the styrene **30** totally prevents the hydroaminoalkylation reaction, the electron-withdrawing *para*-CF$_3$ group of **29** seems to result in a preferred formation of the linear product **38b**. In contrast to the reactions of styrenes, all experiments performed with 1-alkenes (Table 3, entries 7–14) delivered the branched products in large excess and good to very good yields could always be achieved. Of the disubstituted alkenes investigated (**34**–**36**), only norbornene (**34**) gave a satisfactory result (91 % yield).

In summary, our studies have shown that 2-aminopyridinato titanium complexes generated in situ from [Ti(NMe$_2$)$_4$] and 2-(methylamino)pyridine are efficient catalysts for the hydroaminoalkylation of alkenes and styrenes. With these catalysts, it is possible for the first time to achieve transition-metal-catalyzed hydroaminoalkylation reactions of styrenes with dialkylamines or *N*-alkylanilines bearing alkyl groups larger than a methyl group. Particularly noteworthy is that the industrially important linear hydroaminoalkylation products can be obtained as the major products of the reactions.

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Keywords: alkenes · amines · aminopyridines · C–H activation · titanium

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[10] For experimental details, see the Supporting Information.

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