Synthetic Methods

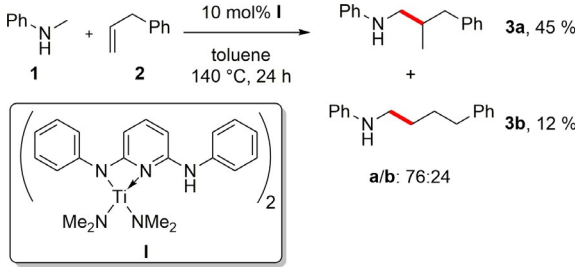
Linear Hydroaminoalkylation Products from Alkyl-Substituted Alkenes

Michael Warsitz and Sven Doye*[a]

Abstract: The regioselective conversion of alkyl-substituted alkenes into linear hydroaminoalkylation products represents a strongly desirable synthetic transformation. In particular, such conversions of *N*-methylamine derivatives are of great scientific interest, because they would give direct access to important amines with unbranched alkyl chains. Herein, we present a new one-pot procedure that includes an initial alkene hydroaminoalkylation with an α-silylated amine substrate and a subsequent protodesilylation reaction that delivers linear hydroaminoalkylation products with high selectivity from simple alkyl-substituted alkenes. For that purpose, new titanium catalysts have been developed, which are able to activate the α-C–H bond of more challenging α-silylated amine substrates. In addition, a direct relationship between the ligand structure of the new catalysts and the obtained regioselectivity is described.

The most important industrially practiced synthesis of amines from alkenes uses a two-step process that combines the hydroformylation of an alkene and a subsequent reductive amination.[1] An alternative synthetic approach for the synthesis of corresponding amines, which can, in principle, deliver the same amine products, if the same alkene substrates are used, is the catalytic hydroaminoalkylation of alkenes (Scheme 1). This 100% atom economic one-step transformation, which has particularly been studied in recent decades, allows for the addition of α-C–H bonds of primary or secondary amines across C–C double bonds.[2] Unfortunately, hydroaminoalkylation reactions mostly favor the formation of the corresponding branched products, while in contrast, linear amine products are easily accessible via the industrially applied hydroformylation/reductive amination sequence from alkyl-substituted alkenes. However, although most of the group 5 metal and titanium based catalysts[2] convert aryl- and alkyl-substituted alkenes into branched hydroaminoalkylation products with high regioselectivity, the bis(aminopyridinato) titanium catalyst **I** depicted in Scheme 1 was already found to deliver the linear isomers as the major products from styrenes[3] and vinylsilanes.[4] In this context, it should be mentioned that ruthenium-[5] and iridium[6]-catalyzed hydroaminoalkylation reactions also give linear isomers exclusively, but these reactions are limited to amine substrates that contain additional metal-binding directing groups or the use of electron-deficient alkenes. On the other hand, hydroaminoalkylation reactions of alkyl-substituted alkenes, such as allylbenzene (**2**), with *N*-methylaniline (**1**) performed in the presence of titanium catalyst **I** still lead to the formation of the branched isomer as the major product (Scheme 1). Overall, it must be stated that, up to now, no general method for the hydroaminoalkylation of simple alkyl-substituted alkenes that results in the selective formation of linear hydroaminoalkylation products is known. However, very recently, the preferred formation of linear hydroaminoalkylation products from sterically more or less demanding alkyl- or silyl-substituted alkenes with *N*-trimethylsilylbenzylamine was reported to take place in the presence of a zirconium catalyst.[7]

In order to overcome this synthetic issue, we developed a new one-pot procedure, which enables the formal conversion of *N*-methylanilines and alkyl-substituted alkenes into linear hydroaminoalkylation products. For that purpose, we considered to direct the regioselectivity towards the linear isomer by influencing the regioselectivity-determining step of the hydroaminoalkylation reaction through steric effects. As can be seen from the mechanism of the titanium-catalyzed alkene hydroaminoalkylation (Scheme 2),[8,9] the insertion of the alkene into the Ti–C bond of the catalytically active titanaaziridine, which is formed by α-C–H activation from the amine substrate and the titanium catalyst, can occur in two ways, which as a result lead to regioisomeric products. In pathway A



Scheme 1. Hydroaminoalkylation of allylbenzene (**2**) with *N*-methylaniline (**1**).

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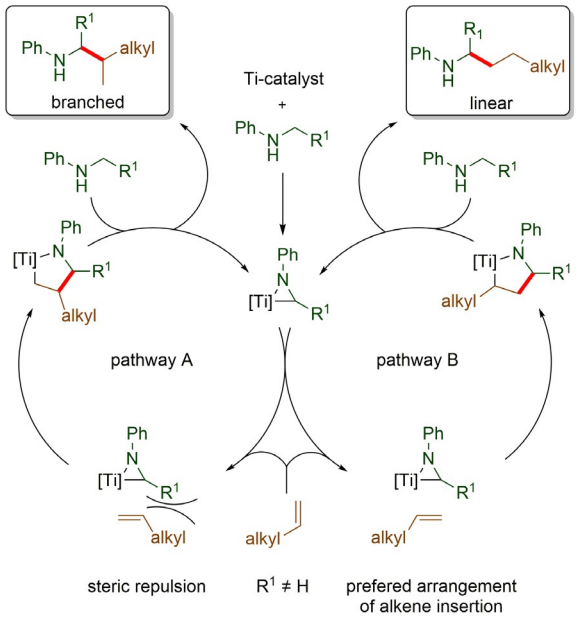
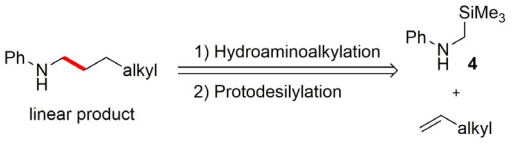
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/chem.202003223.



Scheme 2. Mechanistic details of the hydroaminoalkylation of alkyl-substituted alkenes with *N*-alkylanilines.

(Scheme 2), the alkyl-substituent of the alkene is oriented towards the substituent R^1 of the substrate amine which causes steric repulsion in the transition state if $R^1 \neq H$. After alkene insertion, the resulting titanapyrrolidine subsequently undergoes aminolysis and regeneration of the titanaaziridine with simultaneous liberation of the branched product. The catalytic cycle according to pathway B, which delivers the linear product, is analogous, but in contrast, the insertion of the alkene into the titanaaziridine is sterically not significantly hindered by the substituent R^1 of the amine, because the alkyl-substituent of the alkene is arranged in opposite direction to R^1. Due to the steric hindrance in pathway A, hydroaminoalkylation reactions of alkenes should favor pathway B, which leads to the desired linear products. However, an essential requirement for this substrate based regioselectivity is the use of amine substrates with substituents R^1 larger than a hydrogen atom, because corresponding reactions with *N*-methylaniline would not deliver the linear hydroaminoalkylation product as the major isomer. In order to solve this problem, we assumed that linear hydroaminoalkylation products could formally be obtained from alkyl-substituted alkenes and *N*-methylaniline, if the employed amine substrate possesses a removable substituent R^1, such as a trimethylsilyl group, which can be removed by a subsequent protodesilylation step after the hydroaminoalkylation reaction (Scheme 3).



Scheme 3. Retrosynthetic analysis for the formal conversion of alkyl-substituted alkenes with *N*-methylaniline to linear hydroaminoalkylation products.

We started our investigation with a few control reactions to check, whether the α-TMS-substituted *N*-methylaniline **4** (Scheme 3) is a suitable substrate for hydroaminoalkylation reactions. For that purpose, we reacted *N*-((trimethylsilyl)methyl)aniline (**4**) with allylbenzene (**2**) in the presence of the selected titanium complexes **I**,[3] **II**,[10,11] or **III**[12] (Figure 1), that have already been identified to be active hydroaminoalkylation catalysts. As expected, the corresponding reactions performed with **I**, **II**, or **III** delivered the hydroaminoalkylation products **5a** and **5b** with a promising regioselectivity of up to 18:82 in favor of the linear isomer **5b** (Table 1, entries 1–3), but only disappointing combined yields (≤34%) were obtained. Due to the fact, that the α-C–H activation at methylene groups is quite more challenging when compared to methyl groups, a more active hydroaminoalkylation catalyst is required for successful reac-

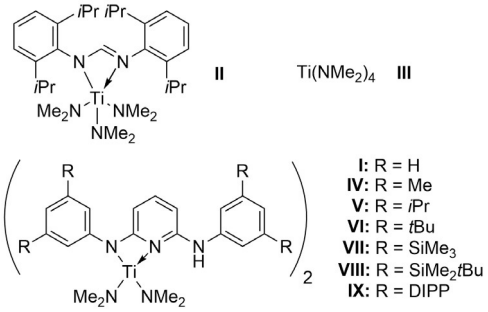
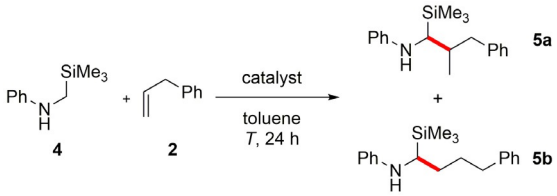


Figure 1. Selected titanium catalysts for the hydroaminoalkylation of alkenes. DIPP = 2,6-diisopropylphenyl.

Table 1. Catalyst screening for the hydroaminoalkylation of allylbenzene (**2**) with *N*-((trimethylsilyl)methyl)aniline (**4**).[a]



Entry	Catalyst	Catalyst loading [mol%]	*T* [°C]	Yield **a**+**b** [%][b]	Sel. **5a**/**5b**[c]
1	**I**	10	140	8	18:82
2	**II**	10	160	traces	24:76
3	**III**	10	160	34	18:82
4	**IV**	10	140	24	24:76
5	**V**	10	140	65	16:84
6	**VI**	10	140	81	13:87
7	**VII**	10	140	81	12:88
8	**VIII**	10	140	89	7:93
9	**IX**	10	140	78	13:87
10	**VIII**	5	140	85	7:93
11	**VIII**	2.5	140	24	7:93

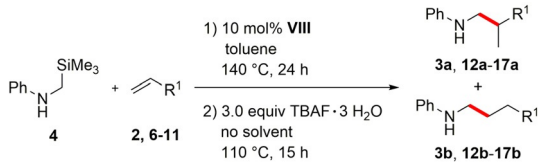
[a] Reaction conditions: *N*-((trimethylsilyl)methyl)aniline (**4**, 179 mg, 1.00 mmol), allylbenzene (**2**, 177 mg, 1.50 mmol), catalyst (0.10 mmol, 10 mol% or 0.05 mmol, 5 mol% or 0.025 mmol, 2.5 mol%), toluene (1.0 mL), *T*, 24 h. [b] Isolated Yield of **5a**+**5b**. [c] Product ratios were determined by GC analysis prior to flash chromatography.

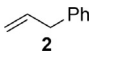
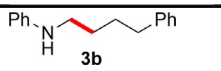
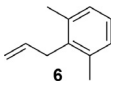
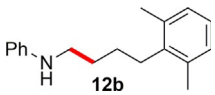
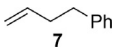
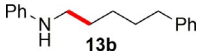
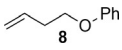
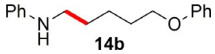
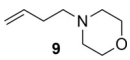
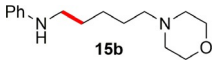
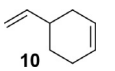
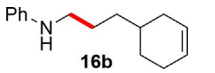
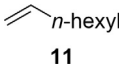
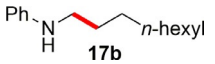
tions with amine **4**. To optimize the reaction with regard to the unsatisfying yield, we modified the 2,6-bis(phenylamino)pyridinato ligand of catalyst **I** and investigated how various substituents at the phenyl rings of the ligand influence the activity and selectivity of the catalyst. During the investigation of corresponding titanium catalysts we found that substituents at the *meta*-positions (Figure 1, complexes **IV**–**IX**) improve the outcome of the reaction massively (Table 1, entries 4–9) while substituents at the *para*- or *ortho*-position do not offer significant advantages. We assume that the new catalysts **IV**–**IX** are structural analogues of the structurally fully characterized complex **I**[3] which is clearly supported by a comparison of the ^{1}H and ^{13}C NMR data of **IV**–**IX** with those of **I** (for details see the Supporting Information). A comparison of the catalysts **IV**–**VIII** in the reaction of *N*-((trimethylsilyl)methyl)aniline (**4**) with allylbenzene (**2**) showed that the obtained yields as well as the regioselectivities significantly increase with increasing size of the *meta*-substituents of the catalysts. Unfortunately, at the moment, neither this finding nor the positive effect of the *meta*-substitution can be understood. However, the best result could be achieved in the presence of the TBDMS-substituted catalyst **VIII** which delivered the products **5a** and **5b** in 89% yield and an excellent regioselectivity of 7:93 in favor of the linear isomer **5b** (Table 1, entry 8). Additional attempts to reduce the catalyst loading were carried out with 5 mol% and 2.5 mol% **VIII** (Table 1, entries 10 and 11). However, in both cases, the isolated yields of the corresponding products decreased, which led to the decision to run all following reactions with a catalyst loading of 10 mol%.

With an optimized catalyst in hand, we then investigated the scope of the hydroaminoalkylation of various alkyl-substituted alkenes with amine **4** (Table 2). For that purpose, we additionally combined the hydroaminoalkylation reaction with a subsequent protodesilylation step into a simple one-pot process to get direct access to the desired desilylated amine products. During our optimization, we found 3.0 equivalents of TBAF trihydrate and 15 h stirring at 110 °C without any solvent to be the best conditions for the protodesilylation reaction (for further details see the Supporting Information). In this context, it must be mentioned that for a successful outcome of the desilylation reaction, it is essential that the solvent is removed after the hydroaminoalkylation step and that the vessel remains open during the protodesilylation, so that the emerging trimethylsilyl fluoride can escape; otherwise the conversion will remain poor. First, we performed the one-pot process with allylbenzene (**2**) and in good agreement with the result of the catalyst screening (Table 1, entry 8) the desired linear product **3b** could be isolated in good yield of 71% and excellent regioselectivity of 7:93 in favor of the linear isomer (Table 2, entry 1). Performing the corresponding reaction sequence with the sterically more demanding dimethyl-substituted allylbenzene derivative **6** delivered the linear product **12b** exclusively in nearly the same yield (Table 2, entry 2). By employing the sterically less hindered homoallylbenzene (**7**), a reduced regioselectivity of 18:82 resulted in a decreased yield of 55% of the linear product **13b** (Table 2, entry 3). In comparison, the functionalized alkenes **8** and **9** bearing a phenoxy or morpholine substituent at the homoallylic position instead of the phenyl group, showed an enhanced regioselectivity of 10:90 with good yields of 60–61% of the linear products **14b** and **15b** (Table 2, entries 4 and 5). In the case of 4-vinylcyclohexene (**10**), the regioselectivity enhanced to 3:97 but unfortunately, the linear isomer **16b** could only be isolated in 47% yield (Table 2, entry 6), probably caused by the more difficult insertion of the sterically more hindered alkene into the titanaaziridine. In contrast, the less hindered substrate 1-octene (**11**) delivered the products **17a** and **17b** as a mixture in better yield (65%) but with a reduced regioselectivity of only 19:81 (Table 2, entry 7). Finally, it should be noted that in all cases, the desilylation of the initial hydroaminoalkylation products occurred with 100% conversion. In contrast, the *tert*-butyldimethylsilyl substituents of the ligand of catalyst **VIII** did not undergo desilylation reaction under the applied conditions. This finding could be of high interest for large scale reactions because it offers the possibility of recycling the ligand.

To further investigate how the alkyl-substituent of the amine substrate influences the regioselectivity of the reaction, we performed additional hydroaminoalkylation reactions of allylbenzene (**2**) and 2-allyl-1,3-dimethylbenzene (**6**) with various secondary amines (Table 3). First of all, corresponding reactions

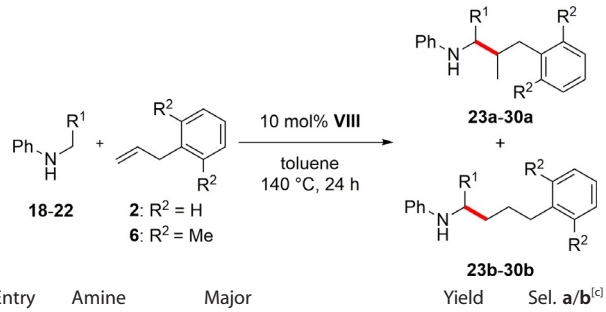
Table 2. One-pot procedure for the formal conversion of *N*-methylaniline with various alkyl-substituted alkenes into linear hydroaminoalkylation products.[a]

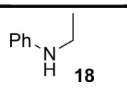
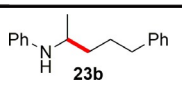
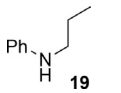
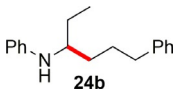
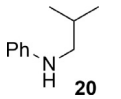
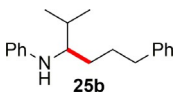
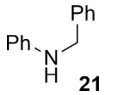
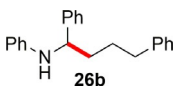
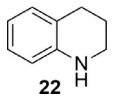
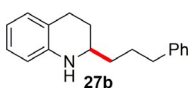
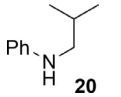
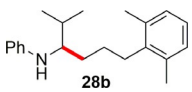
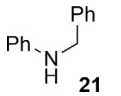
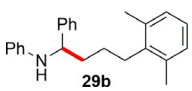
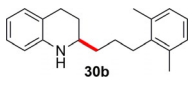


Entry	Alkene substrate	Major product	Yield [%][b] a	Yield [%][b] b	Sel. a/b[c]
1	 **2**	 **3b**	7	71	7:93
2	 **6**	 **12b**	–	68	0:100
3	 **7**	 **13b**	11	55	18:82
4	 **8**	 **14b**	5	60	10:90
5[d]	 **9**	 **15b**	7	61	10:90
6	 **10**	 **16b**	–	47	3:97
7	 *n*-hexyl **11**	 *n*-hexyl **17b**	65 (**a**+**b**)		19:81

[a] Reaction conditions: 1) *N*-((trimethylsilyl)methyl)aniline (**4**, 179 mg, 1.00 mmol), alkene (1.50 mmol), **VIII** (157 mg, 0.10 mmol, 10 mol%), toluene (1.0 mL), 140 °C, 24 h; 2) TBAF·3 H_2O (947 mg, 3.00 mmol), no solvent, 110 °C, 15 h. [b] Isolated yields. [c] Product ratios were determined by GC analysis prior to flash chromatography. [d] Pure **15a** and pure **15b** were obtained in 5% and 47% yield, respectively. Additionally, a mixture of **15a** and **15b** (**15a**/**15b** = 11:89) was obtained in 16% yield.

Table 3. Hydroaminoalkylation of allylbenzene (**2**) and 2-allyl-1,3-dimethylbenzene (**6**) with various secondary amines.[a]

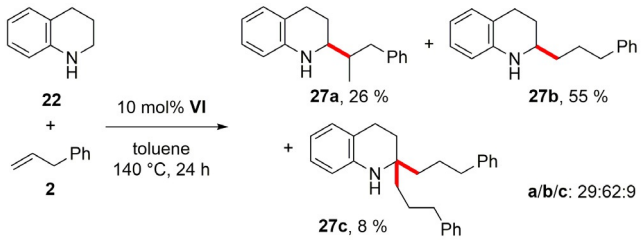


Entry	Amine substrate	Major product	Yield [%][b] a	Yield [%][b] b	Sel. a/b[c]
1	 **18**	 **23b**	3	18	18:82
2	 **19**	 **24b**	52 (a+b)		10:90
3	 **20**	 **25b**	66 (a+b)		4:96
4	 **21**	 **26b**	40	59	34:66
5	 **22**	 **27b**	8	13	41:59
6	 **20**	 **28b**	0	79	0:100
7	 **21**	 **29b**	19	69	20:80
8			9	17	38:62
9[d]	**22**	**30b**	18	60	23:77

[a] Reaction conditions: amine (1.00 mmol), alkene (1.50 mmol), **VIII** (157 mg, 0.10 mmol, 10 mol%), toluene (1.0 mL), 140 °C, 24 h. [b] Isolated yields. [c] Product ratios were determined by GC analysis prior to flash chromatography. [d] **VI** (111 mg, 0.10 mmol, 10 mol%) was used as the catalyst.

of allylbenzene (**2**) with *N*-ethylaniline (**18**), *N*-propylaniline (**19**), and *N*-isobutylaniline (**20**) revealed that as expected, the regioselectivity is shifted towards the linear isomers **23b**, **24b**, and **25b** (up to 4:96) with increasing size of the alkyl substituent of the amine and interestingly, the isolated yields (21–66%) also increase with increasing size of the substituent (Table 3, entries 1–3). Although an additional reaction with *N*-benzylaniline (**21**) gave access to the linear product **26b** in good isolated yield of 59%, only a surprisingly modest regioselectivity of 34:66 towards the linear isomer was observed in this case (Table 3, entry 4). 1,2,3,4-Tetrahydroquinoline (**22**) as an example for a bicyclic amine gave the linear product **27b** only in disappointing isolated yield of 13% and again a poor regioselectivity of only 41:59 towards the linear product was observed (Table 3, entry 5). Interestingly, by employing **VI** as the catalyst (Scheme 4), an improved yield of 55% of **27b** and a better regioselectivity of 29:71 (**a**/**b**+**c**) in favor for the linear isomers was obtained. Surprisingly, the dihydroaminoalkylation product **27c** could also be isolated in 8% yield in this case. To the best of our knowledge, this reaction represents the first example of an alkene hydroaminoalkylation, in which the α-C–H activation takes place at a tertiary carbon atom. Finally, amines **20**–**22** were reacted with the sterically more demanding 2-allyl-1,3-dimethylbenzene (**6**) and as expected, better regioselectivities of up to 0:100 towards the linear isomer as well as good yields could be observed (Table 3, entries 6–8). The corresponding reaction of **22** was also performed with catalyst **VI** which again gave improved results (Table 3, entry 9), but in this case, no dihydroaminoalkylation product was observed. The latter fact can easily be explained by the increased steric bulk of alkene **6** compared to **2**.

In summary, we have presented a new one-pot procedure which for the first time, allows formally converting *N*-methylaniline with alkyl-substituted alkenes regioselectively into linear hydroaminoalkylation products. For that purpose, several new titanium complexes were developed, which proved to be highly active catalysts for the hydroaminoalkylation of alkenes with sterically challenging amine substrates. In addition, a clear relationship between the catalyst structure and the regioselectivity was determined, which could be crucial for future ligand design.



Scheme 4. Hydroaminoalkylation of allylbenzene (**2**) with 1,2,3,4-tetrahydroquinoline (**22**) performed with catalyst **VI**.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkenes · amines · hydroaminoalkylation · titanium

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