**Synthetic Methods**

**Linear Hydroaminoalkylation Products from Alkyl-Substituted Alkenes**

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**Abstract:** The regioselective conversion of alkyl-substituted alkenes into linear hydroaminoalkylation products represents a strongly desirable synthetic transformation. In particular, such conversions of N-methylaniline 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 titanaziridine, 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...
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)methylaniline (4) with allylbenzene (2) in the presence of the selected titanium complexes I, II, or III (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-
tions with amine 4. To optimize the reaction with regard to the unsatisfying yield, we modified the 2,6-bis(phenylamino)pyridi-nato ligand of catalyst I and investigated how various substitu-
ents at the phenyl rings of the ligand influence the activity and selectivity of the catalyst. During the investigation of cor-
responding 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 [3] which is clearly supported by a comparison of the 1H and 13C 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]amino]benzene (4) with allyl-
benzene (2) showed that the obtained yields as well as the re-
gioselectivities significantly increased 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 reac-
tions with a catalyst loading of 10 mol%.

With an optimized catalyst in hand, we then investigated the scope of the hydroaminoalkylation of various alkyl-substi-
tuted alkenes with amine 4 (Table 2). For that purpose, we ad-
ditionally combined the hydroaminoalkylation reaction with a subsequent protodesilylation step into a simple one-pot pro-
cess to get direct access to the desired desilylated amine pro-
ducts. 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 successfull outcome of the de-
silylation reaction, it is essential that the solvent is removed after the hydroaminoalkylation step and that the vessel re-
mains 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 allyl-
benzene 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 regio-
selectivity of 18:82 resulted in a decreased yield of 55% of the linear product 13b (Table 2, entry 3). In comparison, the func-
tionalized alkenes 8 and 9 bearing a phenoxo or morpholine

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

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

[a] Reaction conditions: 1) N-([(trimethylsilyl)methyl]amino]benzene (4, 179 mg, 1.00 mmol), alkene (1.50 mmol), VIII (157 mg, 0.10 mmol, 10 mol%), tolu-
ene (1.0 mL), 140 °C, 24 h; 2) TBAF·3H2O (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.
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-methyl-aniline 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 amines 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.

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Conflict of interest

The authors declare no conflict of interest.

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