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Hydroaminoalkylation of Allylsilanes and a One-Pot Procedure for the Synthesis of 1,5-Benzoazasilepines

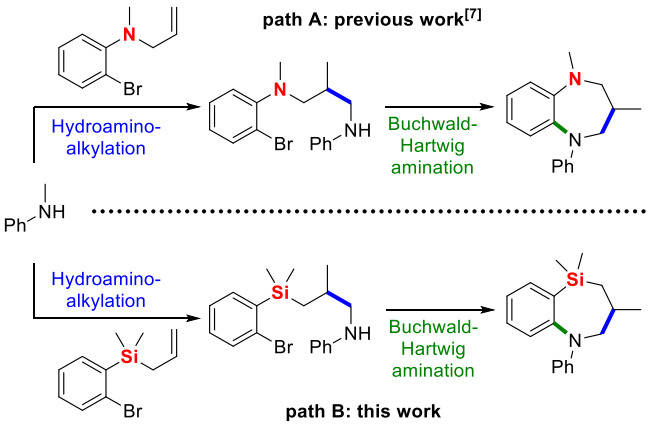
Lars H. Lühning, Julia Strehl, Marc Schmidtmann, and Sven Doye*[a]

Abstract: Allylsilanes undergo highly regioselective intermolecular alkene hydroaminoalkylation with secondary amines in the presence of a titanium mono(formamidinate) catalyst. Corresponding reactions of a suitable allyl(2-bromophenyl)silane which exclusively deliver the branched hydroaminoalkylation products combined with a subsequent Buchwald-Hartwig amination result in the development of an elegant one-pot procedure for the synthesis of literature-unknown silicon analogues of 1,5-benzodiazepines, so-called 1,5-benzoazasilepines.

Introduction

Until the early 1960´s, organosilicon compounds were widely regarded as a biologically ineffective class of chemical substances.[1] However, after this opinion had been changed through the investigation of the unusual high toxicity of silatranes by Voronkov et al.,[2] organosilicon chemistry became more and more popular in the pharmaceutical sector during the past decades.[3] While one method for the development of new drugs is the high-throughput synthesis and high-throughput screening approach, an alternative possibility is the sila-substitution (Si/C exchange) in known drug scaffolds.[3,4] The feasibility of the latter approach which was pioneered by the Tacke-group,[4a-c,e-k] has strongly been underlined by a large number of examples in which sila-substitution significantly affects the features of a drug. For example, the different geometry and bond lengths of Si-C (187 pm) and C-C bonds (154 pm) as well as the different pK_a values of silanols (p$K_{a(DMSO)}$ of Ph_3SiOH = 16.6) compared to alcohols (p$K_{a(DMSO)}$ of Ph_3COH = 17.0) are important aspects which may favor sila-substituted drugs over the corresponding carbon species.[3] In addition, silicon analogues are generally more lipophilic, which makes them less prone to hepatic metabolism. On the other hand, the increase of the lipophilicity also influences the ability to cross the blood/brain barrier.[4b] The latter effect should be even more significant when, for example, a nitrogen atom is replaced by a silicon atom. Therefore, pharmaceuticals interacting with the central nervous system, especially with the brain, may benefit from the introduction of a silicon atom into their structures. However, relatively little attention has been paid to the exchange of nitrogen with silicon in known drug scaffolds.

Benzodiazepines are able to bind to the inhibitory important GABA receptors (GABA: γ-aminobutyric acid) of the central nervous system and as a result, they show sedative, muscle relaxant, anticonvulsant, and anxiolytic effects.[5,6] Very recently, we were able to develop a new one-pot procedure for the synthesis of 1,5-benzodiazepines.[7] The corresponding reaction sequence includes an initial highly regioselective titanium-catalyzed intermolecular hydroaminoalkylation,[8,9] which takes place by the addition of an α-C(sp^3)–H bond of an *N*-methylaniline across a C–C double bond of an *N*-allyl-2-bromoaniline, and a subsequent intramolecular Buchwald-Hartwig amination (Scheme 1, path A).[10] In continuation of this study and inspired by the fact that until now, unsaturated silanes have not been used as substrates for titanium-catalyzed hydroaminoalkylation reactions, we recently decided to investigate the scope of allylsilanes as starting materials for corresponding transformations. However, in this context it must be noted that Schafer et al. already achieved the hydroaminoalkylation of allyltrimethylsilane with *N*-methylaniline in the presence of a tantalum catalyst.[11] Interestingly, by choosing allyl(2-bromophenyl)silanes as starting materials, the literature-unknown silicon analogues of 1,5-benzodiazepines, so-called 1,5-benzoazasilepines (Scheme 1, path B), should be accessible by a one-pot procedure that is similar to our 1,5-benzodiazepines synthesis. In this context, it has to be mentioned that Voronkov et al.[12] as well as Tacke et al.[13] already synthesized closely related 1,4-azasilepanes, which lack the benzo-annulation of the seven-membered ring, by using alternative strategies and very recently, a lot of effort has been spent on the development of new pathways for the enantioselective synthesis of closely related 1,5-benzothiazepines.[14] In addition, the synthesis of fully unsaturated 1-benzosilepines has also been described before.[15]



Scheme 1. One-pot procedures for the preparation of 1,5-benzodiazepines and 1,5-benzoazasilepines.

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Results and Discussion

Initially, a series of titanium[9] and tantalum catalysts,[16] that had already been identified to be active in hydroaminoalkylation reactions,[8] were used for a brief catalyst screening (Figure 1, Table 1) in which allyldimethylphenylsilane (**1a**) was tried to react with *N*-methylaniline (**2**). First of all, it was recognized that $Ti(NMe_2)_4$ as well the aminopyridinato titanium catalysts **I** and **II** do not show any catalytic activity at 140 °C (Table 1, entries 1-3), while at the same temperature, complexes **III**, **IV**, Ind_2TiMe_2 (Ind = η^5-indenyl), and $Ta(NMe_2)_5$ do catalyze the desired reaction (Table 1, entries 4, 5, 8, and 10). Among the active catalysts, titanium mono(formamidinate) complex **IV** initially synthesized by Eisen et al.[17] gave the best result which led to the formation of the desired branched hydroaminoalkylation product **3a** in excellent yield of 90 % (Table 1, entry 5). Inspired by the well-established fact, that hydroaminoalkylation reactions performed with the catalyst Ind_2TiMe_2 often give improved yields at lower temperatures,[9d] we also performed selected reactions at lower temperatures. However, while a significantly improved yield of 71 % was indeed obtained with the catalyst Ind_2TiMe_2 at 105 °C (compared to 10 % at 140 °C, Table 1, entries 8 and 9), the catalytic performance of **IV** could not be improved, neither at lower nor at higher temperatures (Table 1, entries 5-7). Interestingly, and in contrast to corresponding reactions of styrenes,[9d,k] detectable amounts of the linear hydroaminoalkylation product were not formed from allylsilane **1a** in the presence of catalysts **IV** or Ind_2TiMe_2. Although corresponding regioselectivities were also obtained with catalysts **III** or $Ta(NMe_2)_5$, the better yield of 90 % obtained with **IV** (Table 1, entry 5) led to the decision to run all further experiments with formamidinate catalyst **IV** at 140 °C.

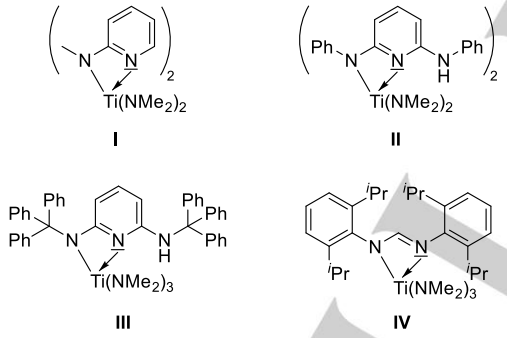
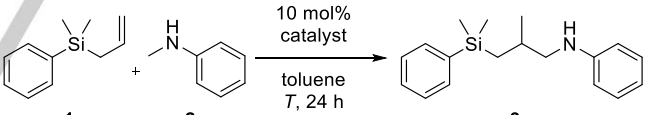


Figure 1. Titanium catalysts for hydroaminoalkylation reactions of alkenes.

To investigate the scope of the hydroaminoalkylation of allylsilanes, a large number of *ortho*-, *meta*-, and *para*-substituted *N*-methylanilines were then reacted with allyldimethylphenylsilane (**1a**), allyltrimethylsilane (**1b**), or allyltriphenylsilane (**1c**) under the conditions of Table 1, entry 5 using 10 mol% of catalyst **IV**. During this study which is summarized in Table 2, it was first recognized that the reactivity of the allylsilane is not significantly influenced by the nature of the substituents bound to the silicon center and correspondingly, all three allylsilanes **1a**-**1c** gave comparable results. On the other hand, sterically demanding *ortho*-substituted *N*-methylanilines were found to be challenging substrates and as a result, slightly reduced yields between 59 % and 74 % were obtained with *N*-methyl-*ortho*-toluidine. In addition, a successful reaction of *N*-methyl-*ortho*-chloroaniline could only be achieved with sterically less demanding allylsilane **1b** but even in this case, the product **5b** could only be isolated in a disappointing yield of 6 %. With regard to the results obtained with *meta*- and *para*-substituted *N*-methylanilines, it becomes clear that besides alkyl substitution, the presence of fluoro, chloro, and bromo substituents is also tolerated. The excellent yields in which the chloro- and bromo-substituted products **8a**-**8c**, **9a**-**9c**, **13a**-**13c**, and **14a**-**14c** (76-96 %) were formed deserve particular attention because bromo and chloro substituents offer various possibilities for further functionalization.[18] In addition, it should be mentioned that in former studies, halogenated substrates often gave poor results in hydroaminoalkylation chemistry.[9d,g,h] Since the same is true for reactions of the electron acceptor-substituted starting material *N*-methyl-*para*-trifluoromethylaniline, it was not surprising to find that under the reaction conditions, this substrate does not react at all with the allylsilanes **1a**-**1c**. However, on the other hand, the hydroaminoalkylation products **16a**-**16c** which possess a pharmacologically relevant trifluoromethoxy substituent could be isolated in excellent yields between 83 % and 87 %. This result is in good agreement with the performance of additional ether-substituted *N*-methylanilines which led to the formation of the corresponding methoxy- or phenoxy-substituted products **15a**-**15c** and **17a**-**17c** in 74-87 % yield. Finally, it was even possible to isolate the thiomethyl ether products **18a**-**18c** in good yields of 74-87 %.

Table 1. Catalyst screening for the hydroaminoalkylation of allyldimethylphenylsilane (**1a**) with *N*-methylaniline (**2**).[a]



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

Entry	Catalyst	*T* [°C]	Yield [%][b]
1	$Ti(NMe_2)_4$	140	0
2	**I**	140	0
3	**II**	140	0
4	**III**	140	71
5	**IV**	140	90
6	**IV**	120	65
7	**IV**	160	78
8	Ind_2TiMe_2	140	10
9	Ind_2TiMe_2	105	71
10	$Ta(NMe_2)_5$	140	70

[a] Reaction conditions: allyldimethylphenylsilane (**1a**, 2.2 mmol, 388 mg), *N*-methylaniline (**2**, 2.0 mmol, 214 mg), catalyst (0.2 mmol, 10 mol%), toluene (1 mL), *T*, 24 h. [b] Isolated yield.

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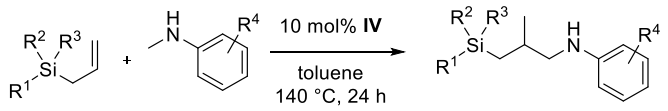
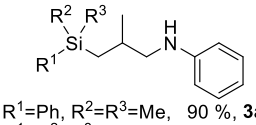
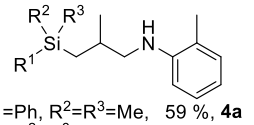
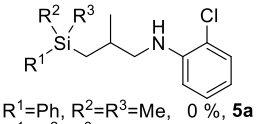
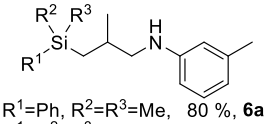
Table 2. Hydroaminoalkylation of allylsilanes with various *N*-methylanilines.[a]

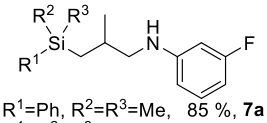


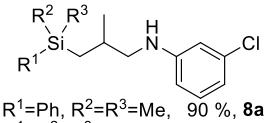

R^1=Ph, R^2=R^3=Me, 90 %, **3a**
R^1=R^2=R^3=Me, 87 %, **3b**
R^1=R^2=R^3=Ph, 84 %, **3c**

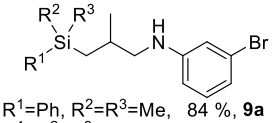

R^1=Ph, R^2=R^3=Me, 59 %, **4a**
R^1=R^2=R^3=Me, 74 %, **4b**
R^1=R^2=R^3=Ph, 66 %, **4c**

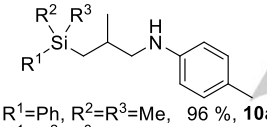

R^1=Ph, R^2=R^3=Me, 0 %, **5a**
R^1=R^2=R^3=Me, 6 %, **5b**
R^1=R^2=R^3=Ph, 0 %, **5c**

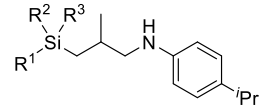

R^1=Ph, R^2=R^3=Me, 80 %, **6a**
R^1=R^2=R^3=Me, 82 %, **6b**
R^1=R^2=R^3=Ph, 82 %, **6c**

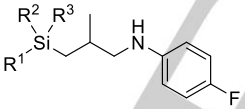

R^1=Ph, R^2=R^3=Me, 85 %, **7a**
R^1=R^2=R^3=Me, 89 %, **7b**
R^1=R^2=R^3=Ph, 91 %, **7c**

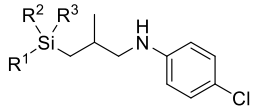

R^1=Ph, R^2=R^3=Me, 90 %, **8a**
R^1=R^2=R^3=Me, 89 %, **8b**
R^1=R^2=R^3=Ph, 87 %, **8c**

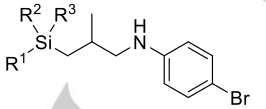

R^1=Ph, R^2=R^3=Me, 84 %, **9a**
R^1=R^2=R^3=Me, 87 %, **9b**
R^1=R^2=R^3=Ph, 92 %, **9c**

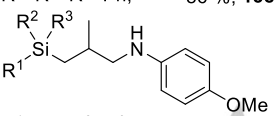

R^1=Ph, R^2=R^3=Me, 96 %, **10a**
R^1=R^2=R^3=Me, 88 %, **10b**
R^1=R^2=R^3=Ph, 93 %, **10c**

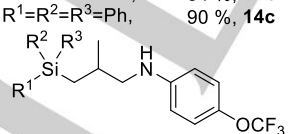

R^1=Ph, R^2=R^3=Me, 81 %, **11a**
R^1=R^2=R^3=Me, 89 %, **11b**
R^1=R^2=R^3=Ph, 83 %, **11c**

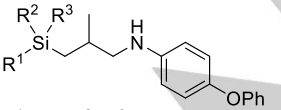

R^1=Ph, R^2=R^3=Me, 87 %, **12a**
R^1=R^2=R^3=Me, 86 %, **12b**
R^1=R^2=R^3=Ph, 94 %, **12c**

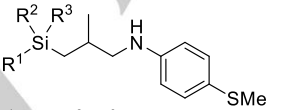

R^1=Ph, R^2=R^3=Me, 82 %, **13a**
R^1=R^2=R^3=Me, 96 %, **13b**
R^1=R^2=R^3=Ph, 86 %, **13c**


R^1=Ph, R^2=R^3=Me, 76 %, **14a**
R^1=R^2=R^3=Me, 84 %, **14b**
R^1=R^2=R^3=Ph, 90 %, **14c**


R^1=Ph, R^2=R^3=Me, 78 %, **15a**
R^1=R^2=R^3=Me, 87 %, **15b**
R^1=R^2=R^3=Ph, 82 %, **15c**


R^1=Ph, R^2=R^3=Me, 87 %, **16a**
R^1=R^2=R^3=Me, 87 %, **16b**
R^1=R^2=R^3=Ph, 83 %, **16c**

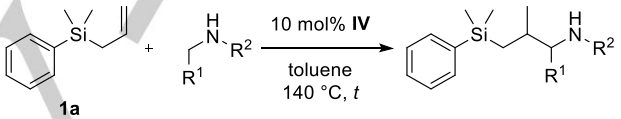

R^1=Ph, R^2=R^3=Me, 66 %, **17a**
R^1=R^2=R^3=Me, 85 %, **17b**
R^1=R^2=R^3=Ph, 74 %, **17c**


R^1=Ph, R^2=R^3=Me, 84 %, **18a**
R^1=R^2=R^3=Me, 87 %, **18b**
R^1=R^2=R^3=Ph, 74 %, **18c**

[a] Reaction conditions: silane (2.2 mmol), *N*-methylaniline (2.0 mmol), **IV** (0.2 mmol, 109 mg, 10 mol%), toluene (1 mL), 140 °C, 24 h. Yields refer to isolated yields.

Additional attempts to achieve corresponding reactions of allyldimethylphenylsilane (**1a**) with dialkylamines turned out to be successful under identical reaction conditions with *N*-methylcyclohexylamine and *N*-methylbenzylamine (Table 3). However, the generally reduced reactivity of dialkylamines in hydroaminoalkylation reactions[8,9,11,16] is in good agreement with the reduced yield of 50 % in which product **19** was obtained from **1a** and *N*-methylcyclohexylamine (Table 3, entry 1). On the other hand, a simple prolongation of the reaction time from 24 h to 48 h raised the yield to 76 % (Table 3, entry 2). The reaction of *N*-methylbenzylamine with **1a** gave access to product **20** in good yield of 70 % (Table 3, entry 3) but in this case, the alkylation of the amine took place selectively at the benzylic position and not at the usually preferred methyl group. The latter observation has been made before during closely related hydroaminoalkylation studies with this substrate.[9g,j]

Table 3. Hydroaminoalkylation of allyldimethylphenylsilane (**1a**) with dialkylamines.[a]

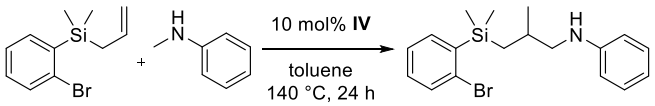


1a

Entry	*t* [h]	R^1	R^2	Yield [%][b]
1	24	H	Cy	50 (**19**)
2	48	H	Cy	76 (**19**)
3	24	Ph	Me	70 (**20**)

[a] Reaction conditions: allyldimethylphenylsilane (**1a**, 2.2 mmol, 388 mg), dialkylamine (2.0 mmol), **IV** (0.2 mmol, 109 mg, 10 mol%), toluene (1 mL), 140 °C, *t*. [b] Isolated yield.

As mentioned above, a reasonable synthetic approach towards 1,5-benzoazasilepines, which represent the silicon analogues of pharmaceutically relevant 1,5-benzodiazepines, consists of an initial hydroaminoalkylation of allyl(2-bromophenyl)silanes and a subsequent intramolecular Buchwald-Hartwig amination (Scheme 1, path b). Correspondingly, we next focused on the hydroaminoalkylation of allyl(2-bromophenyl)dimethylsilane (**21**) which to our delight, took place smoothly with *N*-methylaniline (**2**) under standard conditions to give the desired product **22** in excellent yield of 91 % (Scheme 2).



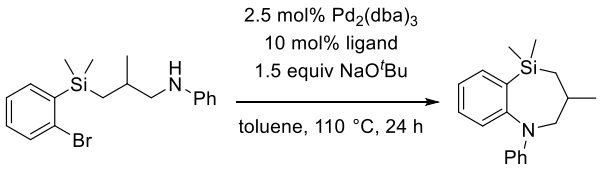
21 **2** 91 %, **22**

Scheme 2. Hydroaminoalkylation of allyl(2-bromophenyl)dimethylsilane (**21**).

With key-intermediate **22** in hand, a brief ligand screening for the Buchwald-Hartwig amination was then conducted using

$Pd_2(dba)_3$ (dba = dibenzylideneacetone) as the palladium source and sodium *tert*-butoxide as a base (Table 4). Although *rac*-BINAP had already been identified to be a good ligand for the corresponding formation of 1,5-benzodiazepines,[7] the cyclization of **22** which delivered the 1,5-benzoazasilepine **23** only took place with a moderate yield of 64 % in the presence of this ligand (Table 4, entry 1). While even worse yields were obtained with the ligands JohnPhos and dppf (Table 4, entries 2 and 3), the use of the biphenyl-based ligands XPhos or RuPhos finally gave access to the desired product **23** in significantly improved yields of 82 % and 93 %, respectively (Table 4, entries 4 and 5).

Table 4. Ligand screening for the intramolecular Buchwald-Hartwig amination of hydroaminoalkylation product **22**.[a]



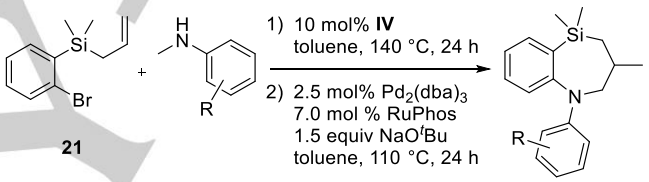
22 **23**

Entry	Ligand	Yield [%][b]
1	*rac*-BINAP	64
2	JohnPhos	36
3	dppf	53
4	XPhos	82
5	RuPhos	93

[a] Reaction conditions: silane (1.0 mmol, 362 mg), $Pd_2(dba)_3$ (0.025 mmol, 23 mg, 2.5 mol%), ligand (0.1 mmol, 10 mol%), NaO^tBu (1.5 mmol, 144 mg), toluene (3 mL), 110 °C, 24 h. [b] Isolated yield.

Because overall the best result of the intramolecular Buchwald-Hartwig amination of **22** was obtained with RuPhos, this ligand was then used for the finally planned development of a one-pot procedure for the synthesis of 1,5-benzoazasilepines from allyl(2-bromophenyl)silanes (Table 5). For that purpose, a hydroaminoalkylation reaction mixture of allylsilane **21** and *N*-methylaniline (**1**) in toluene was initially heated to 140 °C for 24 h in the presence of 10 mol% of catalyst **IV**. Afterwards, 2.5 mol% $Pd_2(dba)_3$, 7 mol% RuPhos, sodium *tert*-butoxide and additional toluene were added and the resulting reaction mixture was heated to 110 °C for additional 24 h. The yield of 83 % in which 1,5-benzoazasilepine **23** was obtained after chromatographic purification (Table 5, entry 1) again underlines the well-established fact that the Buchwald-Hartwig amination tolerates the presence of the reagents used in hydroaminoalkylation reactions.[7] However, the sensitivity of the titanium catalyst against alcohols and carbonyl compounds rules out the possibility to develop a related one-pot protocol in which both the titanium and the palladium catalyst are added to the flask at the same time. To finally investigate the scope of the one-pot procedure, we then reacted additional *ortho*-, *meta*-, and *para*-substituted *N*-methylanilines with allylsilane **21**. As expected and in good agreement with the results obtained for the hydroaminoalkylation of simple allylsilanes presented in Table 2, it was found that *para*- or *meta*-substituted *N*-methylanilines undergo smooth reaction to give the desired 1,5-benzoazasilepines in good yields between 66 % and 84 % (Table 5, entries 3-11). On the other hand, it is worth mentioning that even the sterically demanding *ortho*-methyl-substituted 1,5-benzoazasilepine **24** could be isolated in a moderate yield of 47 % (Table 5, entry 2). However, overall, the results presented in Table 5 clearly show that besides alkyl and ether substitution, the one-pot procedure also tolerates the presence of pharmacologically promising fluoro, chloro, trifluoromethyl, and thioether substituents. Finally, confirmation of the successful synthesis of the 1,5-benzoazasilepines could be achieved by a single crystal X-ray analysis of the *para*-methyl-substituted product **26** which is shown in Figure 2.[19]

Table 5. Scope of the one-pot procedure for the synthesis of 1,5-benzoazasilepines.[a]



21

Entry	R	Yield [%][b]
1	H	83 (**23**)
2	*o*-Me	47 (**24**)
3	*m*-Me	81 (**25**)
4	*p*-Me	81 (**26**)
5	*m*-F	78 (**27**)
6	*p*-F	65 (**28**)
7	*m*-Cl	70 (**29**)
8	*p*-Cl	74 (**30**)
9	*p*-OMe	66 (**31**)
10	*p*-OCF_3	84 (**32**)
11	*p*-SMe	84 (**33**)

[a] Reaction conditions: 1) silane (**23**, 2.2 mmol, 562 mg), *N*-methylaniline (2.0 mmol), **IV** (0.2 mmol, 109 mg, 10 mol%), toluene (1 mL), 140 °C, 24 h. 2) $Pd_2(dba)_3$ (0.05 mmol, 46 mg, 2.5 mol%), RuPhos (0.14 mmol, 66 mg, 7 mol%), NaO^tBu (3.0 mmol, 288 mg), toluene (5 mL), 110 °C, 24 h [b] Isolated yield.

Conclusions

In summary, we have presented the first examples of titanium-catalyzed hydroaminoalkylation reactions of allylsilanes. Although a number of different titanium complexes were found to be competent catalysts for this challenging transformation, best results were obtained with a titanium mono(formamidinate) catalyst initially synthesized by the Eisen group. Based on the finding that allylsilanes are exclusively converted to branched hydroaminoalkylation products, it was also possible to develop a one-pot procedure for the synthesis of 1,5-benzoazasilepines. The corresponding reaction sequence includes an initial hydroaminoalkylation of an allyl(2-bromophenyl)silane and a subsequent intramolecular Buchwald-Hartwig amination. Finally, it is worth mentioning that very recently, we found that vinyl silanes can also be used for closely related synthetic procedures. However, the corresponding results will be published separately in due course.[20]

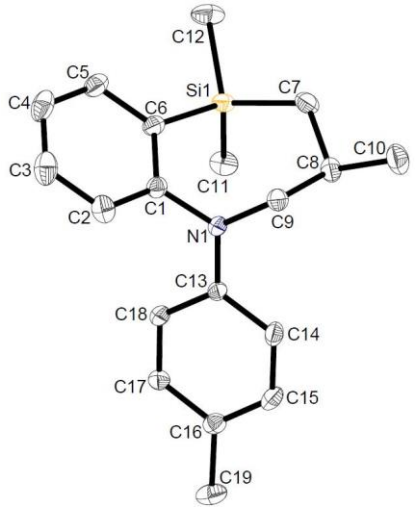


Figure 2. Single crystal X-ray structure of 1,5-benzoazasilepine **26**,[19] ellipsoid representation at the 50 % probability level, hydrogen atoms are omitted for clarity. Selected bond length [Å] and angles [°]: Si1-C12 1.872 (2), Si1-C11 1.858 (3), Si1-C6 1.857 (2), Si1-C7 1.874 (2), C7-C8 1.540 (3), C8-C9 1.527 (3), C8-C10 1.523 (3), N1-C1 1.426 (3), N1-C9 1.464 (3), C12-Si1-C11 109.53 (15), C11-Si1-C7 111.16 (13), C12-Si1-C7 107.87 (11), C5-C6-Si1 123.41 (16), C1-C6-Si1 119.55 (15), C6-Si1-C7 109.87 (10), C13-N1-C9 121.15 (16), C13-N1-C1 121.23 (16), C1-N1-C9 116.96 (17), C1-N1-C9 116.96(17), C7-C8-C9 112.23 (17), C7-C8-C10 110.60 (18), C9-C8-C10 110.51 (19).

Experimental Section

General: Unless otherwise noted, all reactions were performed under an inert atmosphere of nitrogen in oven-dried Schlenk tubes (Duran glassware, 100 mL, ø = 30 mm) equipped with Teflon® stopcocks and magnetic stirring bars (15 × 4.5 mm). Toluene was purified by distillation from sodium wire and degassed. Catalyst **IV**,[17] the *N*-methylanilines, and the allylsilanes were synthesized according to literature procedures.[21] Prior to use, all substrates were distilled or recrystallized and degassed. Catalyst **IV**, the *N*-allylsilanes, the *N*-methylanilines, and toluene were stored in a nitrogen-filled glove box (M. Braun, Unilab). All other chemicals were purchased from commercial sources and were used without further purification. For flash chromatography, silica gel from GRACE Davison (particle size 0.037-0.063 mm) was used. Light petroleum ether (b.p. 40-60 °C, PE), *tert*-butyl methyl ether (MTBE), CH_2Cl_2, and EtOAc used for flash chromatography were distilled prior to use. For thin layer chromatography, silica on TLC aluminum foils with fluorescent indicator 254 nm from Fluka were used. The substances were detected with UV light or iodine. All products that have already been reported in the literature were identified by comparison of the obtained ^{1}H NMR and ^{13}C NMR spectra with those reported in the literature. New compounds were additionally characterized by infrared (IR) spectroscopy, GC-MS, high resolution mass spectrometry (HRMS) and ^{29}Si NMR spectroscopy. NMR spectra were recorded on the following spectrometers: Bruker Fourier 300, Bruker Avance DRX 500, or Bruker Avance III, 500 MHz. All ^{1}H NMR spectra are reported in δ units (ppm) relative to the signal of $CDCl_3$ at 7.26 ppm. *J* values are given in Hz. All ^{13}C NMR spectra are reported in δ units (ppm) relative to the central line of the triplet for $CDCl_3$ at 77.0 ppm. ^{29}Si NMR spectra are reported in δ units (ppm) relative to the external standard Me_2SiHCl (δ = 11.1 ppm) in relation to $SiMe_4$ (δ = 0.0 ppm). Infrared spectra were recorded on a Bruker Vector 22 spectrometer or a Bruker Tensor 27 spectrometer (ATR). GC-MS analyses were performed on a Thermo Finnigan Focus gas chromatograph equipped with a DSQ mass detector and Agilent DB-5 column (length: 30 m, inner diameter: 0.32 mm, film thickness: 0.25 µm (94%-methyl)-(5%-phenyl)-(1%-vinyl)polysiloxan). GC analyses were performed on a Shimadzu GC-2010 gas chromatograph equipped with a flame ionization detector. High resolution mass spectra (HRMS) were recorded on a Waters Q-TOF Premier spectrometer in EI or ESI mode (ESI+, TOF).

General Procedure for the Hydroaminoalkylation of Allylsilanes, as Exemplified by the Reaction of Allyldimethylphenylsilane (1a) with *N*-Methylaniline (2): An oven-dried Schlenk tube equipped with a Teflon stopcock and a magnetic stirring bar was transferred into a nitrogen-filled glovebox and charged with catalyst **IV** (109 mg, 0.2 mmol, 10 mol%) and toluene (0.5 mL). Afterwards, *N*-methylaniline (**2**, 214 mg, 2.0 mmol), allyldimethylphenylsilane (**1a**, 388 mg, 2.2 mmol), and toluene (0.5 mL) were added and the mixture was heated to 140 °C for 24 hours. After the reaction mixture had been cooled to room temperature, the crude product was purified by flash chromatography (SiO_2, PE/MTBE, 40:1) to give *N*-(2-methyl-3-(dimethyl(phenyl)silyl)propyl)aniline (**3a**, 509 mg, 1.80 mmol, 90 %) as a colorless oil. R_f = 0.17 (SiO_2, PE/MTBE, 40:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.57-7.47 (m, 2 H), 7.38-7.32 (m, 3 H), 7.16-7.09 (m, 2 H), 6.65 (tt, *J* = 0.9 Hz, *J* = 7.3 Hz, 1 H), 6.50 (dd, *J* = 0.9 Hz, *J* = 8.4 Hz, 2 H), 3.65 (br. s, 1 H), 2.96 (dd, *J* = 6.0 Hz, *J* = 12.3 Hz, 1 H), *2*.84 (dd, *J* = 7.2 Hz, *J* = 12.3 Hz, 1 H), 1.95-1.84 (m, 1 H), 0.99 (dd, *J* = 4.6 Hz, *J* = 14.8 Hz, 1 H), 0.96 (d, *J* = 6.6 Hz, 3 H), 0.70 (dd, *J* = 8.9 Hz, *J* = 14.8 Hz, 1 H), 0.31 (s, 6 H) ppm. ^{13}C{^{1}H} NMR (125 MHz, DEPT, $CDCl_3$): δ = 148.4 (C), 139.5 (C), 133.5 (CH), 129.2 (CH), 128.9 (CH), 127.8 (CH), 116.9 (CH), 112.6 (CH), 53.1 (CH_2), 29.5 (CH), 21.9 (CH_2), 21.0 (CH_3), −1.9 (CH_3), −2.3 (CH_3) ppm. ^{29}Si{^{1}H} NMR (99.4 MHz, INEPT, $CDCl_3$): δ = −3.6 ppm. GC/MS (EI, 70 eV): *m*/*z* (%) = 283 (3) $[M]^+$, 135 (33) $[C_8H_{11}Si]^+$, 106 (100) $[C_7H_8N]^+$, 77 (10) $[C_6H_5]^+$. HRMS (EI): calcd. ($C_{18}H_{25}NSi$) 283.1751, found 283.1750 $[M]^+$. IR (ATR, neat): λ^{-1} = 3417, 3066, 2955, 1602, 1505, 1427, 1320, 1249, 1179, 1111, 829, 791, 746, 690 cm^{-1}.

General Procedure for the One-Pot Synthesis of 1,5-Benzoazasilepines, as Exemplified by the Synthesis of Product 26: An oven-dried Schlenk tube equipped with a Teflon stopcock and a magnetic stirring bar was transferred into a nitrogen-filled glovebox and charged with catalyst **IV** (109 mg, 0.2 mmol, 10 mol%) and toluene (0.5 mL). Afterwards, 4,*N*-dimethylaniline (242 mg, 2.0 mmol), allyl(2-bromophenyl)dimethylsilane (**21**, 562 mg, 2.2 mmol), and toluene (0.5 mL) were added. After the mixture had been heated to 140 °C for 24 hours, the Schlenk tube was cooled to room temperature and transferred back into a nitrogen-filled glovebox. Then $Pd_2(dba)_3$ (46 mg, 0.05 mmol, 2.5 mol%), RuPhos (66 mg, 0.1 mmol, 7 mol%), NaO^{t}Bu (288 mg, 3.0

mmol), and toluene (5 mL) were added. After heating the mixture to 110 °C for additional 24 hours, the crude product was purified by flash chromatography (SiO_2, PE) to give 1,5-benzoazasilepine **26** (480 mg, 1.62 mmol, 81 %) as a colorless solid. R_f = 0.28 (SiO_2, PE). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.56 (dd, J = 1.5 Hz, J = 7.3 Hz, 1 H), 7.36 (dt, J = 1.5 Hz, J = 7.6 Hz, 1 H), 7.24 (dt, J = 0.9 Hz, J = 7.3 Hz, 1 H), 7.16 (d, J = 7.9 Hz, 1 H), 6.98 (d, J = 8.4 Hz, 2 H), 6.55-6.46 (m, 2 H), 3.83 (td, J = 2.0 Hz, J = 2.0 Hz, J = 14.3 Hz, 1 H), 2.82 (dd, J = 11.1 Hz, J = 14.3 Hz, 1 H), 1.04 (d, J = 6.8 Hz, 3 H), 0.95-0.83 (m, 1 H), 0.49 (dd, J = 12.0 Hz, J = 14.3 Hz, 1 H), 0.30 (s, 3 H), 0.00 (s, 3 H) ppm. ^{13}C{^{1}H} NMR (125 MHz, JMOD, $CDCl_3$): δ = 154.0 (C), 145.8 (C), 139.8 (C), 135.1 (CH), 130.6 (CH), 129.4 (CH), 127.4 (CH), 125.7 (C), 125.6 (CH), 113.2 (CH), 59.1 (CH_2), 30.0 (CH), 24.2 (CH_2), 22.8 (CH_3), 20.3 (CH_3), −2.6 (CH_3), −2.7 (CH_3) ppm. ^{29}Si{^{1}H} NMR (99.4 MHz, $CDCl_3$): δ = −4.5 ppm. GC/MS (EI, 70 eV): m/z (%) = 295 (93) $[M]^+$, 280 (59) $[C_{18}H_{22}NSi]^+$, 118 (35) $[C_8H_8N]^+$, 91 (53) $[C_7H_7]^+$. HRMS (EI): calcd. ($C_{19}H_{25}NSi$) 295.1751, found 295.1748 $[M]^+$. IR (ATR, neat): λ^{-1} = 3064, 3009, 2948, 2917, 2882, 1617, 1584, 1561, 1511, 1467, 1437, 1369, 1347, 1319, 1286, 1252, 1208, 1188, 1164, 1127, 1085, 1026, 867, 825, 790, 740, 704, 670, 632 cm^{-1}. Colorless crystals suitable for single-crystal X-ray analysis[18] were obtained by crystallization from CH_2Cl_2 at room temperature.

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Keywords: amination • amines • palladium • silanes • titanium

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[19] Compound **26**: Colorless crystals, dimensions 0.380 × 0.180 × 0.080 mm³, orthorhombic space group $Pca2_1$, unit cell dimensions a = 25.9786(6) Å, b = 10.6771(2) Å, c = 12.2213(3) Å, V = 3389.90(13) Å³, Z = 8, ρ = 1.158 Mg/m³, Θ_{max} = 32.029°, μ = 0.133 mm^{-1}, radiation Mo$K_{\alpha1}$, λ = 0.71073 Å, ϕ and ω-scans with Bruker KAPPA APEX-II CCD at T = 100(2) K, 122891 reflections measured, 11800 unique [R_{int} = 0.0510], 10371 observed [$I>2\sigma(I)$], an absorption correction was performed based on symmetry related measurements with SADABS (G. M. Sheldrick, University of Göttingen, Germany, 2014), T_{min} = 0.9192, T_{max} = 1.0000, the structure was solved by direct methods with SHELXS and refined against F^2 employing a full-matrix least-squares algorithm with SHELXL (G. M. Sheldrick, Acta Crystallogr. Sect. C 2015, 71, 3-8), the structure has been refined as a racemic twin (0.68 : 0.32), two molecules are present in the asymmetric unit, both of them showing whole molecules disorder (0.92 : 0.08), the minor sites were restraint to be equal to the major sites using the SAME instruction within SHELXL, 557 parameters refined, 115 restraints, non H atoms of the major sites were refined anisotropically, those of the minor sites isotropically, hydrogen atoms of the major sites were located from the difference Fourier maps but subsequently fixed to geometric positions using appropriate riding models, final residual values R_1 = 0.0404, wR_2 = 0.1017 for observed reflections and R_1 = 0.0499, wR_2 = 0.1086 for all reflections, goodness of fit 1.049, largest diff. peak, hole 0.455 and -0.210 e Å^{-3}. CCDC 1511412 contains the supplementary crystallographic data for compound **26**. 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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[21] For experimental details, see the Supporting Information.

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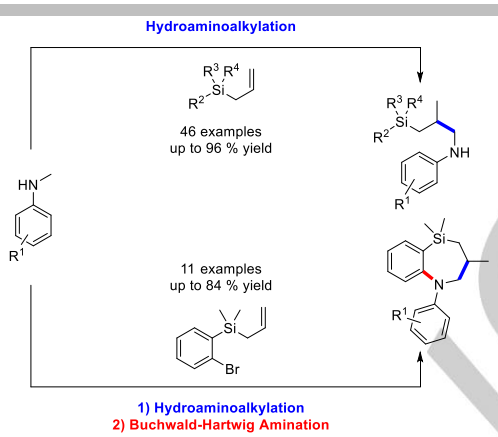
Allylsilanes undergo highly regioselective intermolecular hydroaminoalkylation reactions in the presence of a titanium mono(formamidinate) catalyst. In addition, a one-pot procedure that combines an initial hydroaminoalkylation reaction with a subsequent Buchwald-Hartwig amination directly converts an allyl(2-bromophenyl)silane into 1,5-benzoazasilepines.



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Hydroaminoalkylation of Allylsilanes and a One-Pot Procedure for the Synthesis of 1,5-Benzoazasilepines