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Stereoselective Synthesis of Functionalized Pyrrolidines via a [3 + 2]-Annulation of *N*-Ts-α-Amino Aldehydes and 1,3-Bis(silyl)propenes

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The stereoselective synthesis of functionalized pyrrolidines is a topic of considerable interest, due to their great abundance in natural products[1] and wide applications as chiral ligands[2] and organocatalysts[3] in asymmetric synthesis. Consequently, significant efforts have been devoted to the development of efficient routes to substituted pyrrolidines. Recent examples include 1,3-dipolar cycloadditions of azomethine ylides to electron-deficient alkenes,[4] reduction of pyrroles,[5] intramolecular hydroaminations,[6] and annulation reactions of allyl-,[7] vinyl-,[8] and allenesilanes.[9] However, the efficient construction of polysubstituted pyrrolidines with well-defined stereochemistry and derivatizable functional groups remains a challenge in organic synthesis. The Lewis acid promoted addition of allylsilanes to aldehydes is an important method for stereoselective C−C bond formation.[10] Allylsilanes can also function as synthetic equivalents of 1,2-[7a,11] or 1,3-dipoles[7b,c,12] in annulation reactions to activated C═X π-bonds, due to the efficient $\sigma\rightarrow$p hyperconjugative stabilization of β-silyl carbocations by adjacent C−Si bonds.[10] Herein, we report an efficient procedure for stereoselective construction of densely functionalized pyrrolidines **A** by a Lewis acid promoted [3 + 2]-annulation of silanes **B** and *N*-Ts-α-amino aldehydes **C** (Scheme 1). In this approach, silane **B** functions as a 1,2-dipole equivalent, which after a stereoselective addition to **C** yields intermediate **D**. The subsequent annulation, to afford **A**, exploits the nucleophilicity of the sulfonamide nitrogen toward the β-silyl cation for cyclization. This approach provides a straightforward entry to polyhydroxylated pyrrolidines, which are common subunits in a variety of biologically active alkaloids.[1]

Initial focus was directed toward investigating the effect of different silicon substituents on the [3 + 2]-annulation. Gratifyingly, treatment of *N*-Ts-valinal (**1a**)[13] with silane **2a**[14] (SiR′$_3$ = SiMe$_3$) and BF_3·OEt_2 in CH_2Cl_2 at −78 °C afforded pyrrolidine **3a** in good yield and excellent stereoselectivity (Table 1, entry 1). Interestingly, silane **2a** functions only as a 1,2-dipole equivalent, and no 1,2-silyl migration[7b,c,12] to give piperidines was observed. Silane **2b**[15] (SiR′$_3$ = Si^{i}Pr$_3$) failed to participate in the [3 + 2]-annulation, the reason probably being increased steric hindrance (entry 2). The synthetic utility of this transformation would be greatly increased if the silyl moieties in **3** could be transformed into hydroxy groups via a Tamao−Fleming oxidation,[16] a process which requires an activating group on silicon. Alkylsilanes have been shown to be resistant toward oxidation, but in contrast, the dimethylphenylsilyl group is a known hydroxyl group synthon.[16] However, treatment of silane **2c**[17] (SiR′$_3$ = SiMe$_2$Ph) and aldehyde **1a** with BF_3·OEt_2 afforded pyrrolidine **3b** in low yield, although still as a single diastereomer (entry 3). Instead, a pyrrolidine lacking the C4 Si moiety could be isolated as the major product. To circumvent this problem, other monodentate and chelating Lewis acids were screened,[18] none of which yielded pyrrolidine **3b**. To our delight, the aluminum-based Lewis acids afforded pyrrolidine **3b** as a single diastereomer with no sign of desilylation (entries 4 and 5). Competing elimination to the corresponding diene was, however, observed,[19] and the optimal result was obtained using $MeAlCl_2$ as Lewis acid, furnishing pyrrolidine **3b** in 67% (entry 5).[20] Finally, the effect of nitrogen protecting groups was studied, but neither *N*HCbz (entry 6) nor *N*HBz (entry 7) resulted in pyrrolidine formation.

Scheme 1

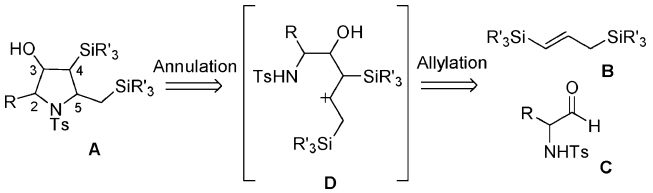
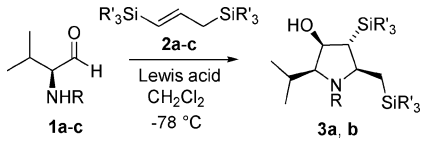


Table 1. Optimization of the [3 + 2]-Annulation[a]



entry	**1** (R)	**2** (SiR′$_3$)	Lewis acid	yield of **3** (%)[b]	dr[c]
1	**a** (Ts)	**a** (SiMe$_3$)	BF_3·OEt_2	**a** (77)	>98:2
2	**a** (Ts)	**b** (Si^{i}Pr$_3$)	BF_3·OEt_2		
3	**a** (Ts)	**c** (SiMe$_2$Ph)	BF_3·OEt_2	**b** (15)	>98:2
4	**a** (Ts)	**c** (SiMe$_2$Ph)	Me_2AlCl	**b** (25)	>98:2
5	**a** (Ts)	**c** (SiMe$_2$Ph)	$MeAlCl_2$	**b** (67)	>98:2
6	**b** (Cbz)	**c** (SiMe$_2$Ph)	$MeAlCl_2$		
7	**c** (Bz)	**c** (SiMe$_2$Ph)	$MeAlCl_2$		

[a] For experimental details, see Supporting Information. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the crude reaction mixtures.

With optimized conditions at hand, we turned our attention to the nature of the *N*-Ts-α-amino aldehydes, and **1a**,**d**−**h**[13] were selected for further investigation (Table 2). The [3 + 2]-annulation with silane **2c** proceeded with excellent levels of diastereoselection regardless of the nature of the R groups, and ^{1}H NMR analysis of the crude reaction mixtures could in each case only detect the formation of a single diastereomer. Aldehydes **1a**,**d**−**h** afforded densely functionalized pyrrolidines **3b**,**d**−**h**, substituted with a C3 hydroxyl and latent C4 hydroxyl and C5 hydroxymethyl groups, which are possible to synthetically differentiate for selective functionalization. In addition, pyrrolidines **3e**−**h** contain a C2 substituent amenable for further synthetic transformations.

X-ray crystallographic analysis of **3b** showed its relative stereochemistry to be (2*S**,3*R**,4*R**,5*R**).[21] The stereochemistry of pyrrolidines **3a**,**d**−**h** was assigned in analogy to **3b**.

We have previously demonstrated that excellent levels of chelation-controlled diastereoselection can be achieved in nucleophilic additions to α-*N*HTs aldehydes by using a monodentate Lewis acid.[22] The stereochemical outcome in such additions can be

[†] Organic Chemistry.
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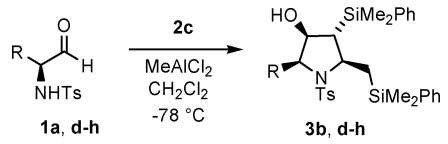
Table 2. Stereoselective [3 + 2]-Annulation of Silane **2c** and *N*-Ts-α-Amino Aldehydes **1a**,**d**−**h**[a]



entry	**1** (R)	yield of **3** (%)[b]	dr[c]
1	**a** (^{i}Pr)	**b** (67)	>98:2
2	**d** (Me)	**d** (33)[d]	>98:2
3	**e** (Ph)	**e** (69)	>98:2
4	**f** (CH_2OTBS)	**f** (57)	>98:2
5	**g** ($CH_2CH_2{=}CH_2$)	**g** (35)[d]	>98:2
6	**h** ($CH_2CH_2OTBDPS$)	**h** (61)	>98:2

[a] For experimental details, see Supporting Information. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the crude reaction mixtures. [d] Low yield due to instability of the aldehyde.

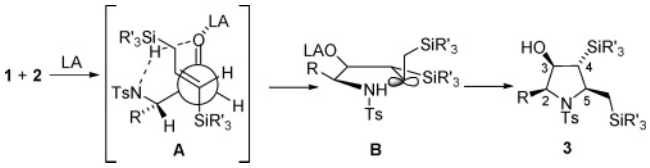


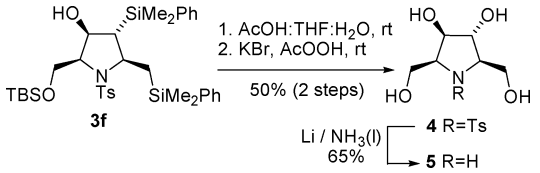
Figure 1. Rationalization of the stereoselectivity.

rationalized by invoking a hydrogen bond between the *N*HTs and C=O moieties followed by nucleophilic attack on the sterically least hindered C=O *Si* face, which also accounts for the *cis* C2−C3 relative stereochemistry in pyrrolidine **3b** (Figure 1). It has previously been argued that, in Lewis acid promoted additions of crotylstannanes to aldehydes, *syn*-synclinal arrangements are the lowest energy pathways when employing monodentate Lewis acids, due to favorable HOMO−LUMO interactions.[23] In line with this, it is proposed that silanes **2** react through *syn*-synclinal TS **A** to avoid steric interactions with the carbonyl-complexed Lewis acid,[12c] which then accounts for the observed C4-stereoselectivity. The transiently formed β-silylcation **B** is then intramolecularly trapped by the *N*HTs moiety. It should be noted that the observed C5 stereochemistry indicates that the nucleophilic attack is faster than C4−C5 bond rotation.

The pyrrolidine structural motif is a common subunit in a variety of polyhydroxylated alkaloids,[1] which are of great importance due to their potential chemotherapeutic utilities, such as anti-HIV and anticancer agents. To demonstrate the applicability of the developed [3 + 2]-annulation methodology to the synthesis of this important class of compounds, we report a straightforward synthesis of DGDP (**5**),[24] which is a potent inhibitor of glucosidases as well a substructure in more complex pyrrolizidine alkaloids (Scheme 2). Desilylation of pyrrolidine **3f** followed by a stereospecific Tamao−Fleming oxidation[16] yielded pyrrolidine **4**, which after detosylation afforded DGDP in only three steps from **3f**.

In conclusion, we have developed an efficient approach to pyrrolidines, containing four contiguous stereocenters by a highly stereoselective [3 + 2]-annulation of 1,3-bis(silyl)propenes, which functions as a 1,2-dipole equivalent, and *N*-Ts-α-amino aldehydes. The application of this methodology in the total synthesis of

Scheme 2



polyhydroxylated alkaloids is underway in our laboratory and will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral data characterizations of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Aldehydes **1a**,**d**−**f**,**h** were prepared from the corresponding enantiopure α-amino alcohols under conditions known to prevent racemization; see: Ocejo, M.; Vicario, J. L.; Badia, D.; Carrillo, L.; Reyes, E. *Synlett* **2005**, 2110−2112. Aldehydes **1b**,**c**,**g** were prepared from racemic α-amino alcohols by the same method.
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(18) Lewis acids: BCl_3, TMSOTf, $TiCl_4$, $SnCl_4$, $Sc(OTf)_3$.
(19) The ratio of **3b**:diene was approximately 4:1.
(20) The enantiomeric excess of **3b** was >97% according to chiral HPLC analysis (Chiracel OD-H hexane:^{i}PrOH 99:1, 1 mL/min).
(21) The crystals were prepared from *rac*-**3b**; see Supporting Information.
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