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Synthesis of 1,3-Amino Alcohols by Hydroxy-Directed Aziridination and Aziridine Hydrosilylation

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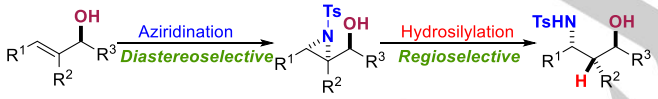
Dedicated to Prof. M. T. Reetz on the occasion of his 75th birthday

Abstract: We describe an approach to N-tosyl 1,3-amino alcohols that consists of a diastereoselective aziridination reaction of acyclic allylic alcohols and an unprecedented regioselective hydrosilylation of α-hydroxy aziridines. The products contain up to three contiguous stereocenters. Computational studies outline key-aspects of the aziridination mechanism that is more intricate and different than anticipated.

1,3-amino alcohols are important structural units in natural products,[1] pharmaceuticals,[2] ligands for catalysis,[3] and synthetic intermediates.[4] The Mannich reaction as well as additions of metalated N-sulfonyl imines to aldehydes, have, in combination with reductions of ketones or imines, been utilized for 1,3-amino alcohol synthesis.[5,6] Recently, transition metal catalyzed additions to allenes,[7] allylic aminations,[8] and C-H aminations[9] emerged as alternative methods that mostly employ tethered carbamates as substrates.

Here, we describe a complementary strategy to 1,3-amino alcohols from readily accessible allylic alcohols. It consists of a diastereoselective aziridination of acyclic allylic alcohols via the excellent Sharpless-protocol[10,11] and a regioselective hydrosilylation of the α-hydroxy N-tosyl aziridines. The products may contain three contiguous stereocenters (Scheme 1).



Scheme 1. The synthesis of 1,3-amino alcohols via diastereoselective aziridination and regioselective hydrosilylation. Ts = tosyl.

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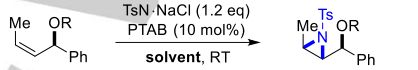
The hydrosilylation of aziridines is, to the best of our knowledge, unprecedented. The diastereoselectivity of the aziridination of allylic alcohols has only been studied with cyclic systems.[12] To investigate the aziridination of acyclic allylic alcohols, we selected **1a** as model substrate. The reaction proceeds in high yield to provide **2a** with a *syn*:*anti*-selectivity of 89:11 in CH_3CN (entry 1).[10]

Table 1. Optimization of the diastereoselective aziridination of **1a** and **1b**.



1a: R = H; **1b**: R = Me. **2a**: R = H; **2b**: R = Me.

Entry	Substrate	Solvent	Conversion (%)	Yield(%)[a]	d.r.[b]
1	**1a**	CH_3CN	100	87	89:11
2	**1a**	Toluene	36	21	85:15
3	**1a**	CH_2Cl_2	70	42	95:5
4	**1a**	CH_2Cl_2:CH_3CN (v/v 1:1)	100	82	93:7
5	**1a**	CH_2Cl_2:CH_3CN (v/v 4:1)	100	82(76[c])	95:5
6	**1b**	CH_2Cl_2:CH_3CN (v/v 4:1)	<5	-	-

Conditions: substrate (0.5 mmol), chloroamine-T (0.6 mmol), PTAB (10 mol%), solvent (2.5 mL), RT. [a] NMR yield. [b] By ^{1}H-NMR of the reaction mixture. [c] Isolated yield of the major isomer. PTAB = $PhNMe_3^+$ Br_3^-.

In CH_2Cl_2 the selectivity is substantially higher (95:5) at the expense of a lower yield (42%). A solvent mixture (CH_2Cl_2:CH_3CN = 80:20 v/v) combines the advantages of both solvents to give **2a** in high selectivity (95:5). The major isomer was isolated in 76% yield. Its relative configuration was established by X-ray crystallography.[13] The O-methylated **1b** does not lead to product formation. Thus, the free hydroxy group is essential for the reaction. Other (*Z*)-2,3-disubstituted allylic alcohols are equally suitable substrates (Table 2A).

2,3,3-trisubstituted allylic alcohols are aziridinated in excellent selectivities (>96:<4) (Table 2B) while (*E*)-2,2,3-trisubstituted allylic alcohols displayed low reactivity in CH_2Cl_2/CH_3CN. In CH_3CN, the diastereoselectivity was in the range of 81:19 to 87:13 and the major *anti*-isomers were obtained in yields around 60% (Table 2C).

For the synthesis of the desired 1,3-amino alcohols a general method for the reduction of the aziridines at the C2 is required. It must be regioselective and has to occur at tertiary carbons. Moreover, the reduction must provide a stereochemically uniform

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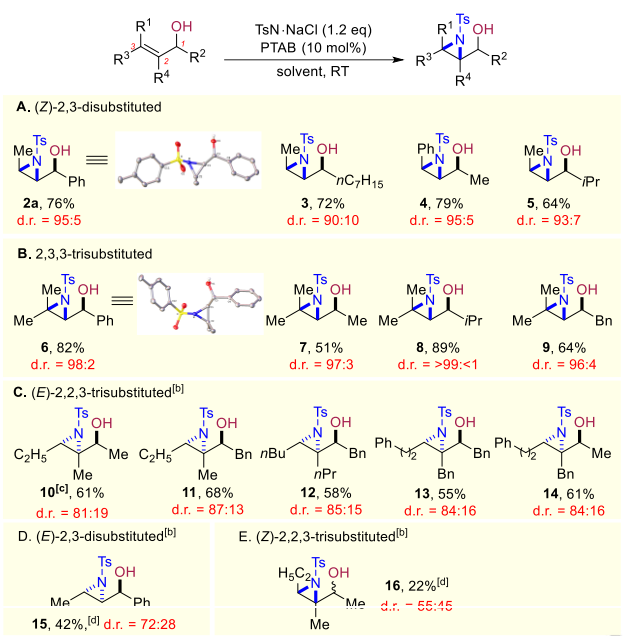
product and should work with primary, secondary, and tertiary alcohols in the aziridine substrates.

Table 2. Diastereoselective aziridination of acyclic allylic alcohols.[a]



[a] Isolated yields of the major isomers. d.r. by ^{1}H-NMR of the crude reaction mixture. Conditions: allylic alcohol (0.5 mmol), chloramine-T (0.6 mmol), PTAB (10 mol%), CH_2Cl_2/CH_3CN (2.0/0.5 mL), RT. [b] CH_3CN (2.5 mL). [c] *anti*-configuration by x-ray of the minor diastereomer **10'**. [d] Combined yields of both isomers.

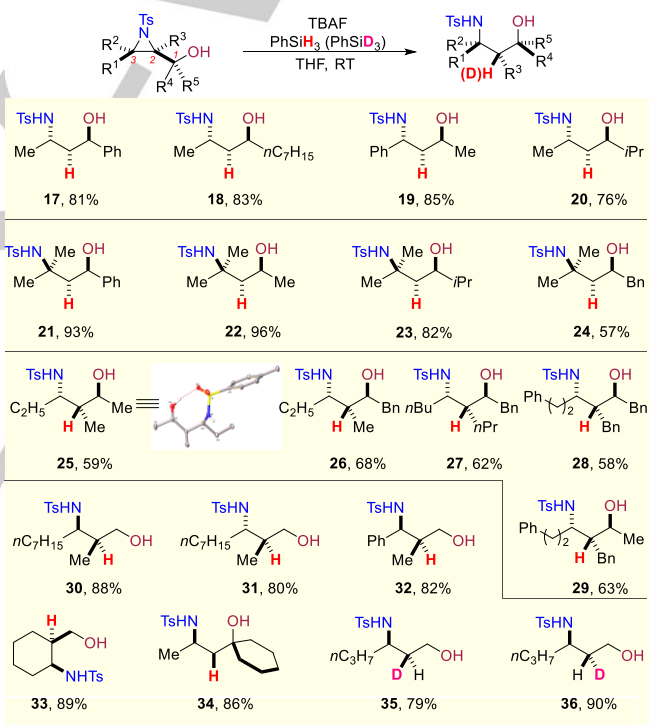
The methods employing $LiAlH_4$[14] or Red-Al[14] are unsuitable because reduction at tertiary C-atoms is not possible and secondary or tertiary alcohols fail to act as directing groups.

Hydrosilylation reactions of epoxides are useful methods for the preparation of alcohols as shown in recent years.[15] Our fluoride mediated hydroxy-directed synthesis of 1,3-diols from Sharpless epoxides is attractive for our purposes, because it provides the 1,3-diols with a completely regioselective ring-opening at C2 under inversion of configuration even at tertiary carbon centers.[15b,d] Gratifyingly, it also provides the 1,3-amino alcohols as single isomers from α–hydroxy aziridines (Table 3).

The substitution pattern at the alcohol does not affect the outcome of the reaction and ring-opening reaction at tertiary C-centers proceeds smoothly. This allows the preparation of 1,3-amino alcohols with three contiguous stereocenters that are of high synthetic value and difficult to access otherwise. The deuteration experiments provide the diastereomeric products **35** and **36** stereospecifically. This is in line with an S_N2 mechanism and rules out Meinwald [16] and semipinacol rearrangements[17]. Therefore, the reaction constitutes an example of an S_N2-reaction at tertiary C-atoms.[18]

In order to understand the selectivities in the formation of the α-hydroxy aziridines, we studied the aziridination of **1a** computationally employing an established multilevel ansatz[19]. All geometries are optimized with the global hybrid PBEh-3c[20] in combination with the implicit solvent model COSMO. PBEh-3c yields reliable structures and offers good thermochemical properties. Reaction pathways and initial guesses on the transition states were prepared by employing the GSM[21] method together with the robust and fast tight-binding quantum chemical method GFN-xTB.[22] The resulting reaction paths were refined with GSM at the PBEh-3c/DCOSMO-RS DFT-level. Free energies are calculated on the optimized DFT geometries as the sum of the electronic energy, thermo statistical and solvation contributions to the free energy. The highest level electronic energy is obtained with a hybrid density functional in a large basis set, including a dispersion correction PW6B95-D3/QZ.[23] Thermostatistical contributions are included at the level of geometry optimization and COSMO-RS[24] is applied as solvation correction to free energy. Free barriers of activation are then obtained as the difference between the free energy of the transition state and the corresponding substrates. All ΔG values were computed at 298.15 K and 1 bar pressure in the solvents $CHCl_3$, CH_2Cl_2 and CH_3CN.

Table 3. Regioselective hydrosilylations of α-hydroxyaziridines.[a]



[a] Conditions: aziridine (0.5 mmol), $PhSiH_3$ (2.0 eq), TBAF (0.6 mmol), THF (2.0 mL), RT. TBAF = *n*-Bu_4NF. THF = tetrahydrofuran.

In olefin brominations, a π-complex of Br_2 and the olefin is initially formed that can fragment to give a bromonium ion. Alternatively, in the presence of bromide, the π-complex can directly react via attack of nucleophile to yield the 1,2-addition product.[25a-c] For PTAB catalyzed aziridinations a bromonium ion was postulated as key-intermediate in the catalytic cycle.[10,12] Therefore, we started our computational investigation with $\mathbf{1a}_{Br}$ and $\mathbf{1a'}_{Br}$ (Scheme 2). However, all reactions of $\mathbf{1a}_{Br}$ and $\mathbf{1a'}_{Br}$ with $TsNCl^-$ proceed barrierless (see SI for details). Thus, the diastereoselectivity of the PTAB catalyzed aziridination of **1a** cannot be accounted for with bromonium ions as intermediates.

Experimental studies on brominations have shown that the formation of bromonium ions only occurs in the absence of

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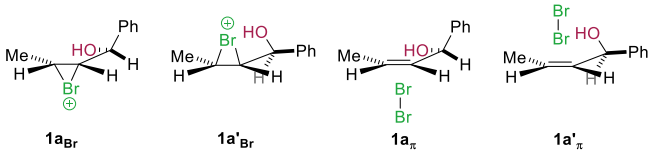
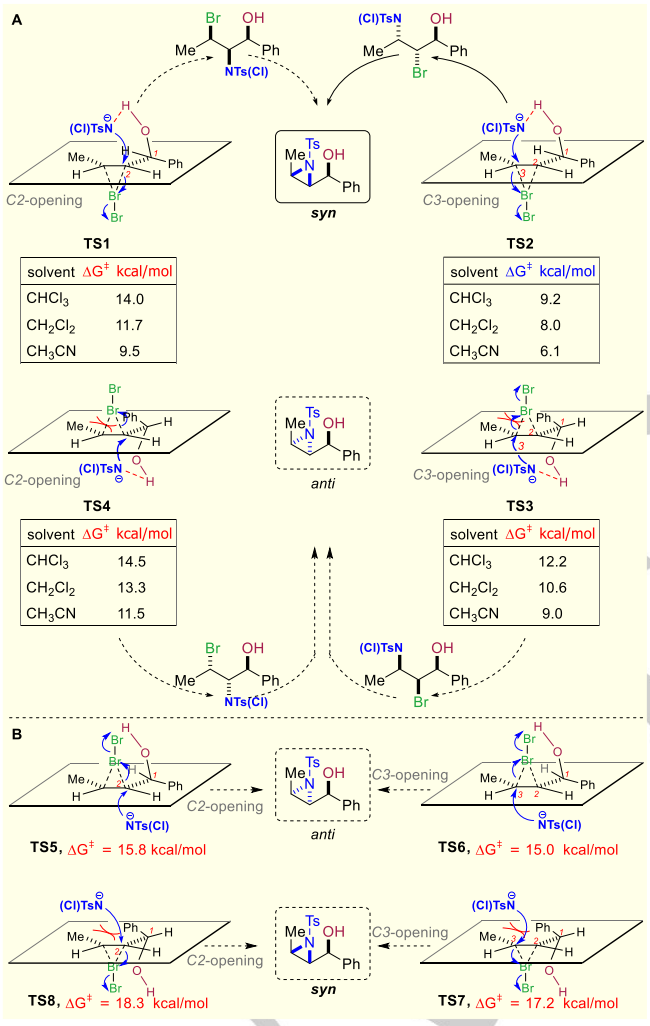
nucleophiles and requires a protic solvent or excess Br_2 to facilitate ionization of the π-complex.[25a-c]



Scheme 2. Bromonium ions **1a**$_{Br}$ and **1a'**$_{Br}$ and π-Complexes **1a**$_{\pi}$ and **1a'**$_{\pi}$ from **1a**.



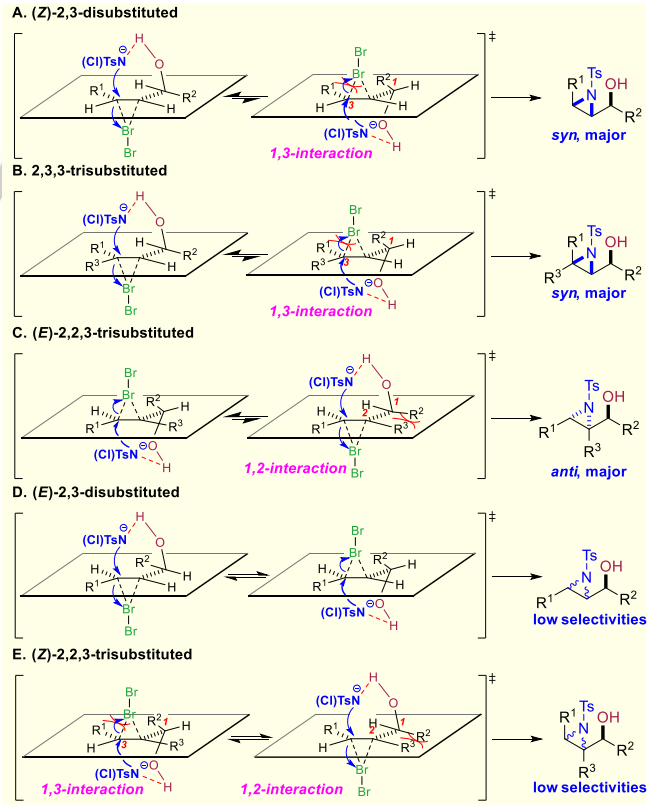
Scheme 3. A) Transition states for the aziridination of **1a** with hydrogen bonding. B) Transition states for the aziridination of **1a** without hydrogen bonding in $CHCl_3$.

Therefore, we investigated π-complexes as intermediates in the aziridination. They have been proposed and discussed in the PTAB catalyzed ring-opening of vinylcyclopropanes.[25e] **1a**$_{\pi}$ and **1a'**$_{\pi}$ are almost identical in stability with **1a'**$_{\pi}$ being favored by 0.3, 0.7, and 0.8 kcal mol^{-1} ($CHCl_3$, CH_2Cl_2, CH_3CN). The activation barriers for the ring-opening of **1a**$_{\pi}$ and **1a'**$_{\pi}$ with $TsNCl^-$ were calculated next. **TS2** and **TS3** that feature hydrogen bonding of $TsNCl^-$ are lower in energy than **TS1** and **TS4** because 1,3-attack is more favorable than 1,2-attack (Scheme 3A). More polar solvents lead to lower barriers for the nucleophilic attack. This can be rationalized by less repulsive values for $\Delta\delta G_{solv}$ (see SI for details). The trends for the reaction barriers are not affected.

For all solvents, **TS2** is favored over **TS3** isomer by 2.6-3.0 kcal mol^{-1}. Thus, the formation of the preferred isomer is correctly predicted (d.r. of **2a**: 95:5 experimentally and 99:1 computationally). The repulsive 1,3-interaction between the phenyl and the methyl group in **TS3** seems responsible for the difference in stability. The absence of hydrogen bonding leads to substantially disfavored **TS5**-**TS8** (Scheme 3B). This is because of the lack of the attractive interaction between the hydroxy group and $TsNCl^-$ ion and a repulsion between the hydroxy group and the π-complexed Br_2.

Compared to Br_2, the corresponding H-bonded transition states with BrNTs(Cl), an oxidant formed from Br_2 and $TsNCl^-$, are higher in energy by 4 – 9 kcal mol^{-1} due to increased steric interactions (see SI for details).

As with Br_2, with BrCl the reaction proceeds via hydrogen bonded $TsNCl^-$ with a transition state similar to **TS2** being most favorable. The differences between the transition state energies and, thus, the computed diastereoselectivity of the addition to the olefin (99:1) are similar to the reactions with Br_2 but all barriers are lower by about 2 kcal mol^{-1} than for Br_2. Therefore, the 1,2-addition is faster with BrCl. This is due to the positive partial charge on Br (see SI for details).



Scheme 4. Transition state models for the aziridination of allylic alcohols.

The preference of the opening of the π-complex at the 2-position, hydrogen bonding of $TsNCl^-$, and minimization of steric interactions in the transition states, can be used for a model for the aziridinations of other substrates (Scheme 4).

2,3,3-trisubstituted olefins behave like (*Z*)-2,3-disubtituted olefins. The additional alkyl group is pointing into empty space and the relative stability of the two transition states is only governed by the 1,3-interaction (Scheme 4B). Therefore, the *syn*-isomer is the main product of aziridination. In (*E*)-2,2,3-trisubtituted olefins (Scheme 4C), the situation is different due to the absence of a substituent (*Z*) to the hydroxy-substituted carbon. Opening to the *syn*-isomer is disfavored due to the repulsive 1,2-interaction shown and the *anti*-product is formed preferentially. The selectivity observed experimentally is lower than in the two types above and, thus, the 1,2-interaction seems to be weaker than the 1,3-interaction.

Finally, the low selectivities for (*E*)-2,3-disubstituted and (*Z*)-2,2,3-trisubstituted can also be deduced from the transition state models. In the former case, there are no destabilizing interactions in both transition states and, thus, aziridination occurs with low selectivity. In the latter case, in both transition states repulsive interactions are operating and the aziridination proceeds without selectivity and is noticeably slower than for the other substitution patterns.

In summary, we have developed a novel method for the synthesis of N-tosylated 1,3-amino alcohols from allylic alcohols in a two-step procedure. In the first step, α-hydroxy N-tosylated aziridines are obtained from acyclic allylic alcohols with unprecedented diastereoselectivity via the PTAB catalyzed aziridination. The computational analysis of the addition reveals that π-complexes of Br_2 or BrCl are intermediates in the aziridination and not the previously proposed bromonium ions. Hydrogen bonding of $TsNCl^-$ by the hydroxy group is essential. The diastereoselectivity of olefin addition is controlled by the steric interactions between the substituents of the allylic alcohol in the transition states of attack on the π-complex. The unprecedented hydroxy directed hydrosilylation of the aziridines yields N-tosylated 1,3-amino alcohols via an S_N2-mechanism even at tertiary C-atoms. The products may contain three contiguous stereocenters. Such compounds are of high synthetic value and difficult to prepare otherwise.

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Keywords: 1,3-amino alcohol • aziridination • diastereoselectivity • hydrosilylation • reaction mechanism

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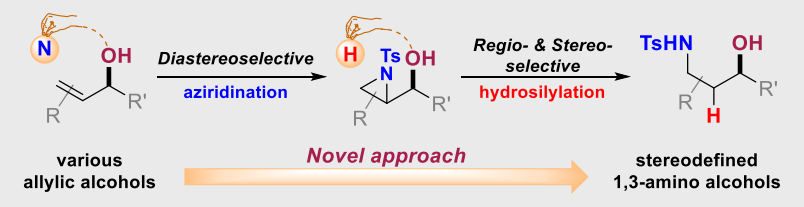

We describe an approach to N-tosylated 1,3-amino alcohols via a diastereoselective aziridination of acyclic allylic alcohols and a novel regioselective hydrosilylation of α-hydroxy aziridines via S_N2 even at tertiary C-atoms. Our computational studies show that the previously proposed bromonium ions are not involved in the aziridination but π-complexes of the olefins with Br_2 or BrCl.

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