Allylation Transition States

# Origins of Stereoselectivity in Strain-Release Allylations**

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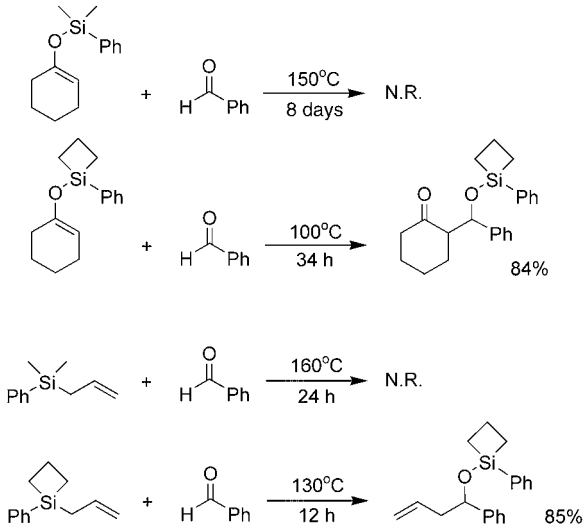
A decade ago, the research groups led by Myers and Denmark discovered independently that enol silacyclobutanes could undergo aldol-like reactions with benzaldehyde, while no reaction was observed with the corresponding acyclic enol silanes (Scheme 1).[1] Later, Utimoto et al. reported similar results for carbonyl allylations (Scheme 1).[2]




***Scheme 1.*** Reactions of acyclic and cyclic silanes reported by the research groups of Myers, Denmark, and Utimoto.[1,2] N.R. = no reaction.

The phenomenon responsible for this unusual reactivity was termed "strain-release Lewis acidity" by Denmark.[3] Scheme 2 contrasts cyclic and acyclic tetrahedral silanes.

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Supporting information (ChemDraw structures of 12 transition states for allylation of formaldehyde, relative energies of **TS1**–**4**, **TS1-e**/**a**, and **TS2-e**/**a** from calculations with different methods and basis sets, and Cartesian coordinates of **TS1**–**4**, **TS1-e**/**a**, and **TS2-e**/**a**) for this article is available on the WWW under http://www.angewandte.org from the author.

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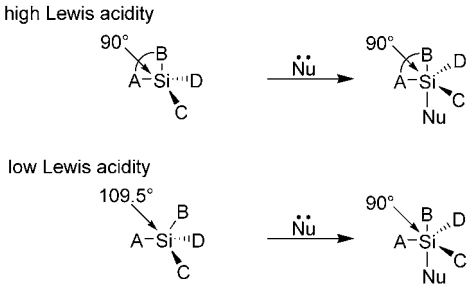
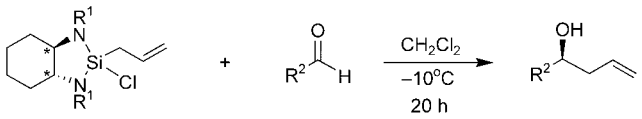



***Scheme 2.*** "Strain-release Lewis acidity" proposed by Denmark et al.[3]

The latter has relatively low Lewis acidity. However, when incorporated into a four-membered ring, a silane exhibits much higher Lewis acidity; nucleophilic attack on the strained silane produces a pentavalent, trigonal-bipyramidal silane intermediate in which the unstrained silacyclobutane spans apical and equatorial positions.

Recently, a new silane reagent has been developed for the asymmetric allylation of aldehydes based upon this concept (Scheme 3).[4] The novel *N*,*N*′-bis-4-bromobenzyldiazasilane



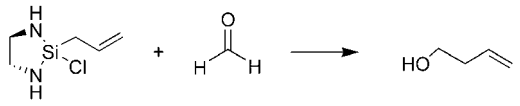

**1**: $R^1 = CH_2C_6H_4$-*p*-Br, 95–98% *ee*
**2**: $R^1 = CH_3$, 90–95% *ee*

aliphatic, aromatic, and conjugated aldehydes

***Scheme 3.*** Enantioselective aldehyde allylation by the silane reagents developed by Leighton and Kubota.[4]

reagent (*R*,*R*)-**1** is crystalline and easy to prepare. Ring-strain-release Lewis acidity still remains in such five-membered silacycles due to the long Si–N bonds and short C–N bonds. (*R*,*R*)-**1** has been used for the allylation of aliphatic, aromatic, and conjugated aldehydes. Yields range from 61 to 93%, and the enantioselectivities are always excellent (95–98% *ee*). Interestingly, without the benzyl substituents, (*R*,*R*)-**2** still gives 90–95% *ee* (Scheme 3).

The mechanism and stereoselectivity of asymmetric aldehyde allylations employing the strain-release-activated silane reagents has been studied with computational methods. Optimizations in the gas-phase and frequency calculations were carried out using HF/6-31G* and B3LYP/6-31G* as implemented in Gaussian 98.[5] These give very similar geometries. Single-point energies were computed at HF, B3LYP, and MP2 levels employing the 6-31G* and 6-311++G** basis sets.[6] Calculations using MP2/6-311++G**//HF/6-31G* give reaction barriers ($\Delta E_a^{\ddagger}$, $\Delta E_b^{\ddagger}$) and stereoselectivity ($\Delta\Delta E_{ab}^{\ddagger}$) that agree with the experimental results. B3LYP gives qualitatively similar results but underestimates the stereoselectivity.



***Scheme 4.*** The simplified computational model.

A simplified model used for the initial computational mechanistic studies is shown in Scheme 4. An achiral backbone was used but held in the gauche conformation present in the actual (*R*,*R*) reagent. This means if the two equatorial H atoms were replaced with other substituents, the two backbone C atoms would have *R* chirality. No constraint was applied in the transition-state optimizations. Formaldehyde was used as the model aldehyde. Calculations indicate that the neutral trigonal-bipyramidal silane intermediates, with formaldehyde at either apical or equatorial position, are not energy minima. Optimizations at HF, B3LYP, and MP2 levels lead to dissociation to the reactants. Thus, the reaction occurs in a single concerted step.

With the diazasilane ring spanning one apical and one equatorial position, there are 12 possible chairlike transition states for the model reaction, including four with apical aldehyde, four with apical allyl, and four with apical chlorine.[6] Boatlike transition states were calculated to be 10 kcal mol$^{-1}$ higher in energy. Experimentally, the *cis*-crotyl version of the diazasilane reagent gives the *syn* product, and the *trans*-crotyl diazasilane reagent gives *anti*.[7]

The calculations show that only the four transition states with apical aldehyde, **TS1**–**TS4**, are true saddle points (Figure 1). This places electronegative atoms, N and O, in

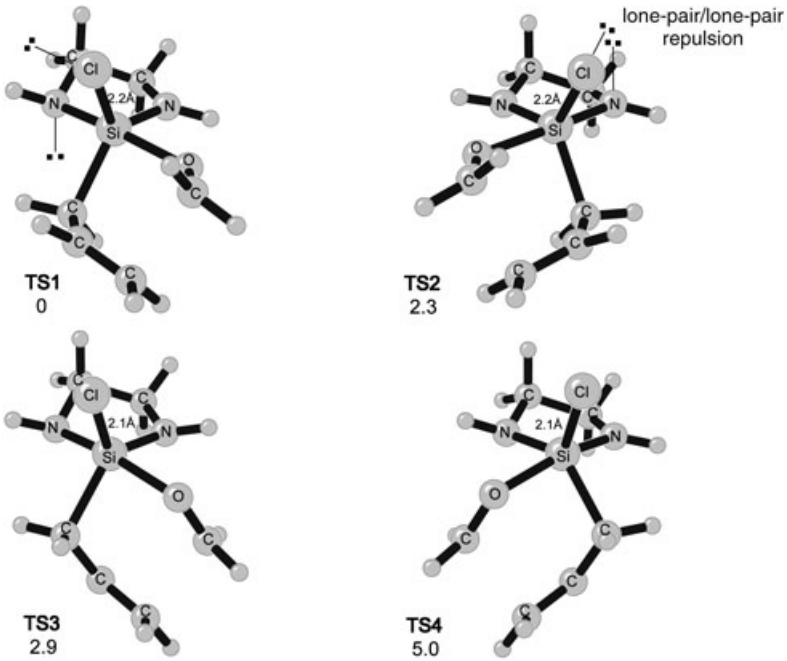



***Figure 1.*** Transition-state geometries from HF/6-31G* optimizations and relative energies [kcal mol$^{-1}$] from MP2/6-311++G** single-point energy calculations for a simplified model (Scheme 4). Nonlabeled atoms are hydrogen; the Si–Cl distances are given in Å.

apical positions. **TS1** is the lowest energy transition state. IRC calculations performed on **TS1** confirm that **TS1** is a transition state for formaldehyde allylation. The activation barrier is only 11.8 kcal mol$^{-1}$. This agrees with the ease of reaction even at reduced temperatures (−10 °C).[4] The reagent with a six-membered diazasilane ring does not react even at 50 °C.[8] Our calculations show that when the diazasilane ring is six-membered instead of five-membered, the reaction barrier increases to 22.9 kcal mol$^{-1}$. With the five-membered-ring reagent, the transition state achieves an N-Si-N angle of 89°, while this becomes 98° for the transition state with the six-membered ring; the substantial strain lowers the activation barrier by 11.1 kcal mol$^{-1}$.

The actual reagent, (*R*,*R*)-**2**, has substituents at both nitrogen atoms as well as a cyclohexane ring fused to the ethylene backbone (Scheme 3). Recalculations of **TS1** and **TS2** (Figure 1) for the actual reagent with acetaldehyde gave the four transition states in Figure 2. Equatorial substitution

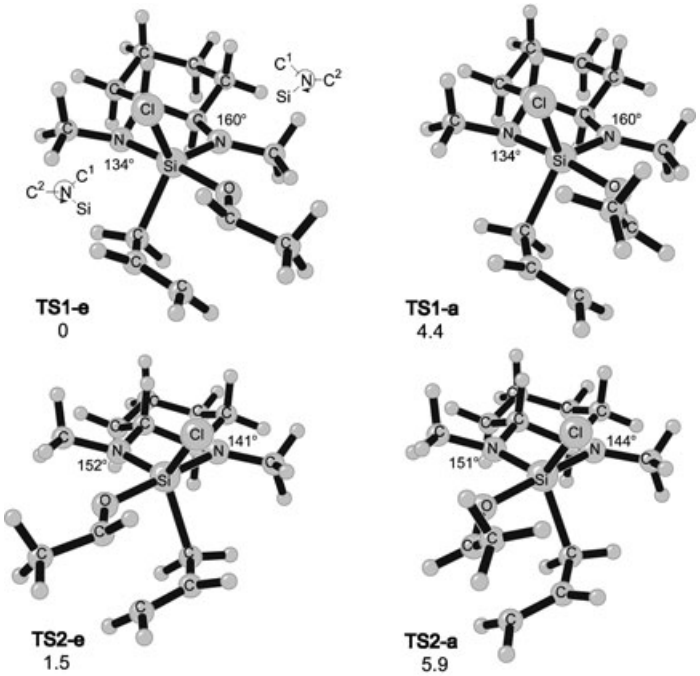



***Figure 2.*** Transition-state geometries from HF/6-31G* optimizations and relative energies [kcal mol$^{-1}$] from MP2/6-311++G** single-point energy calculations for the reaction of (*R*,*R*)-**2** with acetaldehyde. Nonlabeled atoms are hydrogen; $C^1$-N-$C^2$-Si improper torsions are given in degrees.

(**TS1-e** and **TS2-e**) is more favored than axial substitution (**TS1-a** and **TS2-a**) by 4.4 kcal mol$^{-1}$, typical for the Zimmerman–Traxler-type chair six-membered ring. **TS2-e** is higher in energy than **TS1-e** by 1.5 kcal mol$^{-1}$, similar to the energy difference for the simplified model (Figure 1). The pyramidalization of nitrogen atoms was measured as the $C^1$-N-$C^2$-Si improper torsions (120° for a perfect pyramidal $NH_3$ or 180° for a planar nonpyramidal N). Figure 2 shows that pyramidalization is greater at the apical N atom than equatorial.

The origins of stereoselectivity can be explained using the simple models in Figure 1. **TS3** and **TS4** are higher in energy than **TS1** and **TS2** due to the unfavorable electron repulsion between the formaldehyde oxygen atom and the chlorine atom in **TS3** and **TS4**, and the favorable arrangement of an oxygen lone-pair *anti* to the Si–Cl bond in **TS1** and **TS2**. This is essentially an anomeric effect, which is demonstrated by the 0.1 Å longer Si–Cl bond in **TS1** and **TS2**.[9] **TS1** is the lowest energy transition state because the apical N (directly opposite the aldehyde) is pyramidalized to have its lone pair facing downward and minimize N lone-pair and Cl lone-pair repulsion. In **TS2**, the apical N (directly opposite the aldehyde) is also pyramidalized, but its lone pair is directed upward, and therefore there is unfavorable N lone-pair and Cl lone-pair repulsion in **TS2**. To verify this reasoning, we replaced chlorine with a methyl group and found that no selectivity is predicted. The importance of nitrogen pyramidalization was already noted by Denmark and Fu in the development of their 2,2′-bispyrrolidine-based bisphosphoramide catalysts for aldehyde allylations.[10] Asymmetric allylation controlled by nitrogen pyramidalization was also employed by Williams and co-workers for the development of the C28–C41 fragment in the total synthesis of phorboxazole A.[11]

In summary, the transition states for the stereoselective strain-release allylations have been located. The model based on these transition states suggests the components important for the stereoselectivity of diazasilane reagents: 1) attack of aldehyde oxygen on an apical position of the Si center (*anti* to an N); 2) an antiperiplanar arrangement of an O lone-pair and the Si–Cl bond in the chair transition state; 3) location of the chlorine with the lone pair *anti* to the lone-pair of apical N. Studies of acylhydrazone allylations by Leighton's oxazasilane reagents are in progress.[12]

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