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Strained Silacycles in Organic Synthesis: A New Reagent for the Enantioselective Allylation of Aldehydes

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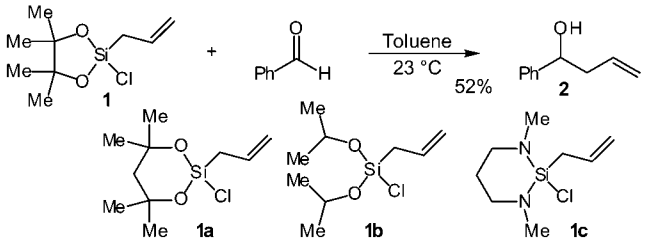
The asymmetric allylation of aldehydes remains one of the most important and fundamental carbonyl addition reactions for the synthesis of optically active chiral building blocks. Many moderately to highly enantioselective chiral reagents[1] and catalytic systems[2] have been developed, yet a general solution that meets every condition for true convenience—easily and inexpensively prepared *and* stable/storable reagent/catalyst, no toxic reagents/byproducts, and easy separation/purification of the homoallylic alcohol products—remains elusive. We now report significant progress toward this goal in the form of a new reagent that meets all of these criteria, while providing good to excellent enantioselectivities for a range of aliphatic aldehydes.

Ample precedent[3] and prior experience[4] alerted us to the fact that silicon, when constrained in a four- or five-membered ring, exhibits substantial Lewis acidity that may be harnessed for uncatalyzed aldol and allylation reactions. This led to the proposal that allyltrichlorosilane might simply be treated with various 1,2-diols, 1,2-amino alcohols, and 1,2-diamines, to give *active allylation reagents without need for any additional catalysts or reagents*. If so, the rapid evaluation of chiral diols, amino alcohols, and diamines could ensue. Conceptually, this would represent an interesting class of chiral auxiliary—one that induces not only chirality but also reactivity.

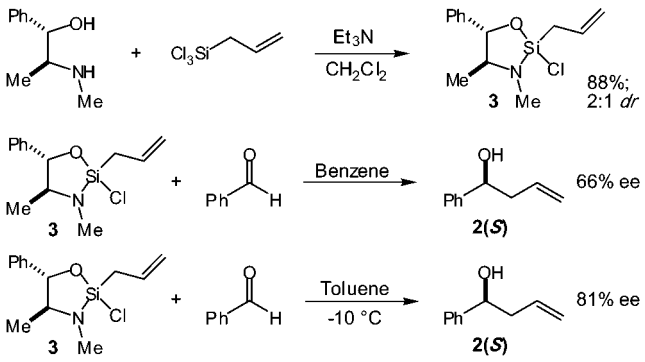
To evaluate this hypothesis, allyltrichlorosilane was treated with pinacol and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in CH_2Cl_2 to provide allylsilane **1** in 72% yield. Gratifyingly, when **1** was treated with benzaldehyde in toluene at room temperature, a smooth uncatalyzed allylation took place to afford alcohol **2** in an unoptimized 52% yield (Scheme 1). In related studies involving the use of diisopropyltartrate as the diol component, Wang[5] employed Lewis bases for activation, and Kira[6] proposed that the ester groups themselves provide activation by acting as a Lewis base for silicon. The present work clearly establishes that Lewis base activation of this type is not necessary.[7] Indeed, that ring strain is at least partially responsible for the reactivity of allylsilane **1** is supported by the fact that related allylsilanes **1a**, **1b**, and **1c** do not react with benzaldehyde even at 50 °C.

Screening of chiral, nonracemic 1,2-diols, 1,2-amino alcohols. and 1,2-diamines commenced. and amino alcohols were chosen for initial study due to the diverse array of inexpensive amino alcohols that are readily available. Indeed, both enantiomers of pseudoephedrine are available and inexpensive, and we began our investigation with this amino alcohol. Reaction of (*1S*,*2S*)-pseudoephedrine with allyltrichlorosilane and Et_3N in CH_2Cl_2 allowed the isolation of allylsilane **3** (as a 2:1 mixture of diastereomers) in 88% yield (Scheme 2). Reaction of **3** with benzaldehyde in benzene at room

Scheme 1



Scheme 2



temperature gave alcohol **2(*S*)** with 66% enantiomeric excess (ee). Optimization of the reaction variables (solvent, concentration, and temperature) led to an increase in selectivity to 81% ee. Toluene proved the best solvent among those screened (THF, DMF, EtOAc, CH_2Cl_2, hexane, *t*-BuOMe, Et_2O, CH_3CN, benzene), while 0.2−0.4 M silane concentration provided the best results. Lower temperatures did provide higher enantioselectivity, as expected, but only to about −10 °C. Below this temperature the ee decreased, suggesting a complex mechanism.

A survey of several different aldehydes (Table 1) revealed that while reagent **3** is only moderately effective with aromatic and conjugated aldehydes (entries 1 and 2), it is generally effective for a range of aliphatic aldehydes (entries 3−8). Thus, dihydrocinnamaldehyde may be allylated in 84% yield and 88% ee (entry 3), isovaleraldehyde in 79% yield and 87% ee (entry 4), and cyclohexanecarboxaldehyde in 70% yield and 87% ee (entry 5). Pivaldehyde is allylated with superior enantioselectivity (96% ee, 80% yield, entry 6), and benzyloxyacetaldehyde and *tert*-butyldimethylsilyloxyacetaldehyde proceed in 85% and 71% yield and 88% and 89% ee respectively (entries 7 and 8), demonstrating tolerance for potentially Lewis basic functionality.

Reagent **3** offers several advantages in terms of practicality and convenience: (1) reagent **3** (and its enantiomer) may be prepared in bulk quantities in a single step from commercially available and inexpensive materials. (2) reagent **3** is stable and may be stored

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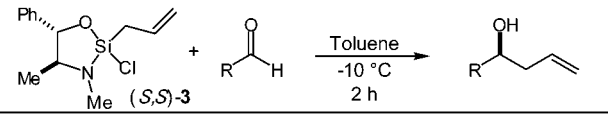
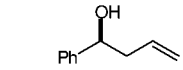
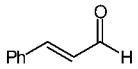
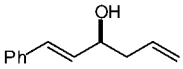
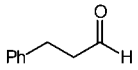
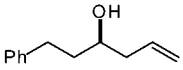
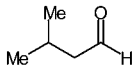
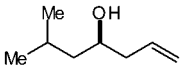
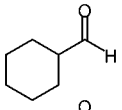
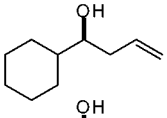
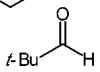
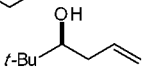
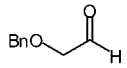
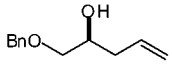
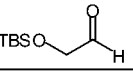
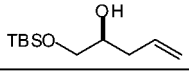
Table 1. Enantioselective Allylation of Aldehydes with (*S,S*)-**3**



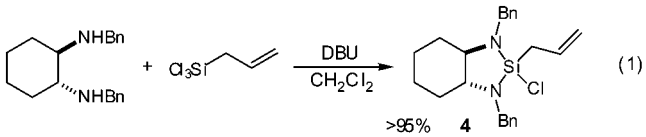
entry[a]	aldehyde	product	yield(%)[b]	ee(%)[c]
1[d]			80	81
2[d]			59	78
3			84	88
4			79[e]	87
5			70	87
6[d]			80[e]	96
7			85	88
8			71	89

[a] Reactions run with silane **3** (1.5 mmol) and aldehyde (1.0 mmol) in toluene (5 mL) at −10 °C for 2 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis or by the Mosher ester method. [d] Reaction time = 24 h. [e] Due to product volatility, an alternative workup and purification was employed. See the Supporting Information.

for long periods of time (several weeks, at least) obviating the need to freshly prepare **3** for each use. (3) The workup and purification consist of the addition of 1 N HCl and EtOAc, separation of the layers, and concentration, to give the homoallylic alcohol product in typically >90% purity.

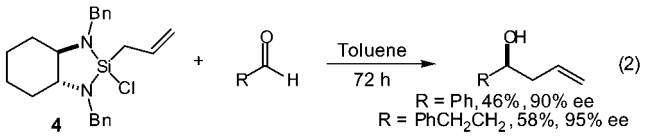
Mechanistically, we envision that complexation of the aldehyde to the silane to give a trigonal bipyramidal intermediate is followed by allyl transfer. Whether the two diastereomers of reagent **3** react identically or differently remains an open question as a complexation−pseudorotation−decomplexation sequence could lead to interconversion. Experiments designed to elucidate this issue are in progress.[8]

Finally, we note that 1,2-diamines also may serve as effective auxiliaries. Reaction of (*1R,2R*)-*N,N*′-dibenzylcyclohexane-1,2-diamine[9] with allyltrichlorosilane and DBU in CH_2Cl_2, and filtration of the resulting ammonium salts gave allylsilane **4** in >95% yield and sufficient purity (>95%) for use in allylation reactions (eq 1).



(1)

Treatment of **4** with benzaldehyde in benzene resulted in a slow allylation to give alcohol **2(*S*)** in 46% yield and 90% ee, and under identical conditions dihydrocinnamaldehyde could be allylated in 58% yield and 95% ee (eq 2).



(2)

While optimization will be required for greater reaction efficiency, these results establish that diamines may allow for the highly enantioselective allylation of a broad range of aldehydes.

We have described the development of a new chiral reagent for the enantioselective allylation of aliphatic aldehydes. While the search for other auxiliaries that give higher selectivities will continue, and the performance of reagent **3** with more complex (chiral) aldehydes remains to be investigated, the convenience and practicality associated with reagent **3** recommend it for immediate use with simple aliphatic aldehydes. In addition, it has been shown that simply by constraining silicon in a five-membered ring with 1,2-diols, 1,2-diamines and 1,2-amino alcohols, sufficient Lewis acidity for uncatalyzed aldehyde allylation reactions obtains. The use of this discovery for the development of other reactions should prove possible and will be reported in due course.[10]

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Supporting Information Available: Experimental procedures, characterization data, and stereochemical proofs (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) For a discussion of this type of Lewis base activation and lead references, see: Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2000**, *122*, 12021.

(8) Preliminary attempts to separate the diastereomers or to obtain a mixture with a ratio different than 2:1 have failed.

(9) Denmark, S. E.; Stadler, H.; Dorow, R. L.; Kim, J. H. *J. Org. Chem.* **1991**, *56*, 5063.

(10) We have preliminarily examined crotylation reactions in this context and found the enantioselectivities to be moderately lower. Details of our attempts to optimize these reactions will be reported as indicated.

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