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Highly Enantioselective Syntheses of Homopropargylic Alcohols and Dihydrofurans Catalyzed by a Bis(oxazolinyl)pyridine−Scandium Triflate Complex

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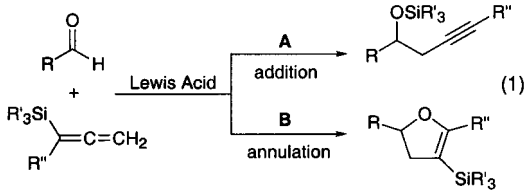
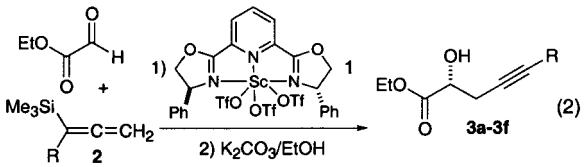
Lewis acid promoted reactions of allylsilanes and allenylsilanes provide access to important building blocks for natural product synthesis.[1] For example, trimethylsilylallenes function as propargylic anion equivalents in aldehyde addition reactions (eq 1, Path A).[2] If the silicon center is sterically congested, the normal addition pathway is suppressed and functionalized dihydrofurans are produced (eq 1, Path B).[3] Although both transformations may be promoted by stoichiometric amounts of titanium tetrachloride, enantioselective reactions of allenylsilanes have not been reported.[4] In this Communication, we describe highly enantioselective scandium triflate catalyzed addition and annulation reactions of allenylsilanes with ethyl glyoxylate.



Initial investigations revealed that [Sc(*S*,*S*)-Ph-pybox](OTf)$_3$ complex (**1**)[5] (10 mol %, CH_2Cl_2, −55 °C) promotes the addition of 1-methyl-1-(trimethylsilyl)allene (**2a**) to ethyl glyoxylate (eq 2) to afford (*R*)-**3a** in high enantioselectivity following desilylation with K_2CO_3/EtOH (98% ee, 95% yield).[6] The catalyst does not appear to be affected by small amounts of water (ca. 1 equiv) or alcohol (10 equiv), and yields were slightly improved when hexafluoro-2-propanol (HFIP) was added to the reaction mixture. This additive suppresses the formation of oligomeric byproducts, but does not influence either the catalyst activity or the reaction enantioselectivity. The scope of this reaction is summarized in Table 1. The scandium triflate complex **1** affords good enantioselectivities and yields with allenylsilanes containing either linear or branched alkyl substituents. When the less reactive 1-phenyl-1-(trimethylsilyl)allene (**2e**) was used as a substrate, it was necessary to warm the reaction mixture to 0 °C to ensure complete conversion of the allene (entry 5, 97% ee, 63% yield).

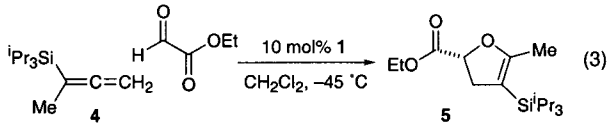
Table 1. Enantioselective Addition Reactions of Allenylsilanes 2[a]



entry	silane	R	3, (% yield)	% ee[b]
1	**2a**	Me	**3a** (95)	98
2	**2b**	^{n}Bu	**3b** (90)	94
3	**2c**	Cy	**3c** (95)	90
4	**2d**	$(CH_2)_3OTBS$	**3d** (75)	93
5[c]	**2e**	Ph	**3e** (63)	97
6	**2f**	^{i}Pr	**3f** (96)	93
7[c]	**2f**	^{i}Pr	**3f** (94)	84

[a] Unless otherwise noted, all reactions were carried out in CH_2Cl_2 for 16 h at −55 °C with 10 equiv of HFIP and 10 mol% **1**. [b] Enantiomeric excess determined by GLC using a Cyclodex-B or Gamma-TA column. [c] Reaction run at 0 °C.

As expected, [3+2] cycloaddition products are produced when the steric bulk of the silane substituents is increased.[3] Dihydrofuran **5** was isolated in excellent yield (>98%) and enantiomeric excess (89% ee) when scandium complex **1** was used as a catalyst for the reaction between 1-methyl-1-(triisopropyl)allene (**4**) and ethyl glyoxylate (10 mol % **1**, CH_2Cl_2, −45 °C, eq 3).[7] The sterically demanding silicon substituents completely altered the course of the reaction, and no addition products were observed in the ^{1}H NMR spectra of unpurified reaction mixtures. Variation in the silyl group of the allenylsilane component revealed that the *tert*-butyldiphenylsilyl functionality was optimal for this process (92% ee).



Several (*tert*-butyldiphenylsilyl)allenes were prepared and employed in the annulation reaction (Table 2). Alkyl-substituted allenes provided the corresponding dihydrofurans in good yields (63−91%) and enantioselectivities (91−94% ee). To demonstrate the practicality of the catalyzed [3+2] annulation, the reaction between **6a** and ethyl glyoxylate was performed with 3.5 mmol of **6a** and 5 mol % of readily available catalyst **1** to produce 1.2 g of **7a** (94% ee, 91% yield, entry 2). The phenyl-substituted allenylsilane **6g** was poorly nucleophilic, and **7g** was isolated in low yield (entry 9). An X-ray crystal structure of **7g** confirmed the connectivity of the products while the absolute configuration of **7a** was determined by crystallographic analysis of the (*S*)-α-methylbenzylamide derivative (see Supporting Information).

The dihydrofurans and homopropargylic alcohols described in this study afford useful chiral synthons. The vinylsilane functionality in dihydrofurans **7** is nucleophilic, and can be acylated

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(5) (*S*,*S*)-Ph-pybox = [(*S*)-(*R**,*R**)]-2,6-bis(4,5-dihydro-4-phenyl-2-oxazolyl)-pyridine. Both enantiomers of this ligand, as well as scandium(III) triflate, are commercially available.

(6) The absolute stereochemistry of product **3b** was established by hydrogenation with Pd/C to produce ethyl (*R*)-2-hydroxynonanoate and comparison of the spectral data and optical rotation of this material with that reported in the literature. The remaining adducts are assigned the indicated configuration by analogy. See Supporting Information.

(7) Other catalysts were either less active or less selective: Cu((S,S)-tBu-box)(SbF6)$_2$, 21% ee, −78 °C; Cu((*S*,*S*)-tBu-box)(OTf)$_2$, 45% ee, 0 °C; Cu((*S*,*S*)-Ph-pybox)(SbF6)$_2$, 80% ee, −78 °C to room temperature, (incomplete reaction). See: (a) Evans, D. A.; Johnson, J. S. *Acc. Chem. Res.* **2000**, *33*, 325−335. (b) Evans, D. A.; Rovis, T.; Johnson, J. S. *Pure Appl. Chem.* **1999**, *71*, 1407−1415.

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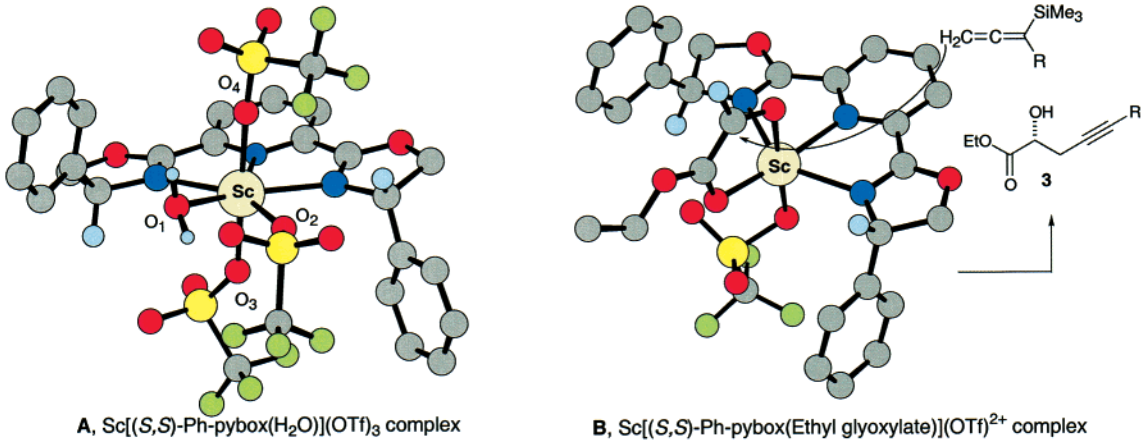
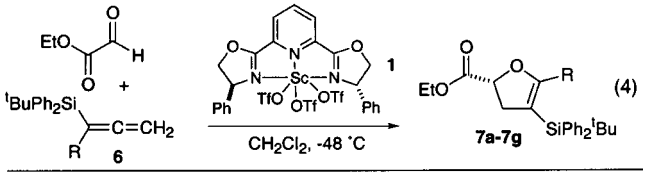


Figure 1. (a) Selected bond lengths (Å) for **1·H$_2$O**: Sc−O1 2.071; Sc−O2 2.138; Sc−O3 2.071; Sc−O4 2.080. (b) Model of the [Sc(*S*,*S*)-Ph-pybox-(OTf)(ethyl glyoxylate)] complex.

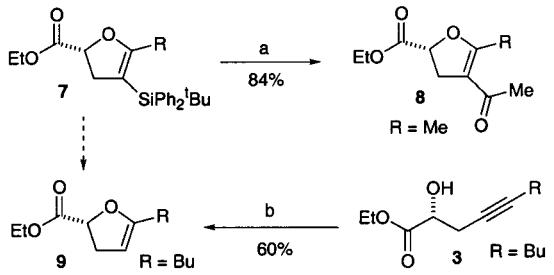
Table 2. Enantioselective Annulation Reactions of Allenylsilanes **6**



entry	silane	R	% 1	time (h)	Yield (%)	ee[a]
1	**6a**	Me	10	20	**7a** (91)	92
2	**6a**	Me	5	60	**7a** (91)	94
3	**6a**	Me	1	60	**7a** (56)	92
4	**6b**	Et	10	65	**7b** (81)	91
5	**6c**	Pr	10	60	**7c** (86)	93
6	**6d**	^{n}Bu	10	40	**7d** (89)	92
7	**6e**	^{n}Pent	10	40	**7e** (81)	92
8	**6f**	^{c}Hex	10	48	**7f** (63)	93
9[b]	**6g**	Ph	10	48	**7g** (32)	85

[a] Enantiomeric excess determined by HPLC using a Chiracel OD-H Column. [b] Reaction run at −20 °C.

Scheme 1[a]



[a] Key: (a) $AlCl_3$, $ClC(O)CH_3$, CH_2Cl_2, 0 °C; (b) $Pd(OAc)_2$, HOAc, CH_2Cl_2, 25 °C.

in a Friedel−Crafts reaction with acetyl chloride to produce *β*-alkoxyenone **8** (Scheme 1). Although all attempts to prepare dihydrofurans **9** from the protodesilylation of **7** resulted in decomposition of the starting material, these heterocycles can be synthesized by a 5-*endo*-dig cycloisomerization of the homopropargylic alcohols **3**.[8]

An X-ray crystallographic study of the metal−ligand complex has been used to gain insight into the structure of the catalyst and the origin of selectivity in these transformations.[9] Suitable crystals were grown by slow diffusion of pentane into a CH_2Cl_2 solution of (*S*,*S*)-Ph-pybox and $Sc(OTf)_3$. The structure of **1·H$_2$O** is shown in Figure 1a. The metal features a pentagonal bipyramidal geometry with the three triflate ligands bound to the metal center. A water molecule, presumably adsorbed during crystallization, is located in the equatorial plane defined by the tridentate ligand. The equatorial triflate ligand is found 2.14 Å from the metal center, while the two apical triflate ligands have Sc−O bond lengths of 2.07 and 2.08 Å, respectively.

The stereochemical course of the allenylsilane addition and annulation reactions can be rationalized by the model[10] shown in Figure 1b. In this representation, two of the triflates are dissociated from the metal center and the aldehyde functionality is bound in the apical position. Addition of the allenylsilane from the *re* face is favored as the *si* face is effectively shielded by a phenyl group of the bis(oxazolinyl)pyridine ligand. It should be noted that binding of the aldehyde in a single position (i.e. axial instead of equatorial) during addition of the allenylsilane to the coordinated glyoxylate is required to explain the high selectivities observed in the catalyzed reactions. Binding of the aldehyde in the apical position in the addition transition state can be explained by the greater trans influence of the pyridine ligand relative to the triflate ligand.[11] This should result in stronger activation of the aldehyde when it is bound in the apical rather than the equatorial position in the metal complex. Steric factors might also be important in the location of the aldehyde in the transition state, as approach of the allenylsilane in a synclinal fashion from either face appears to be hindered by the ligand when the aldehyde is bound in the equatorial position.

Further studies of the utility of bis(oxazolinyl)pyridine scandium complexes in organic synthesis are in progress.

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

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(10) This model was created from the crystal structure of **1·H$_2$O** by the following procedure: The coordinates for **1·H$_2$O** were input into Chem 3D Pro (Version 5.0); the two vicinal triflates and the bound water were removed, and ethyl glyoxylate was docked onto the scandium center. The ligand−Sc bond lengths were then held constant, and the molecular energy of the structure was minimized.

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