Communication

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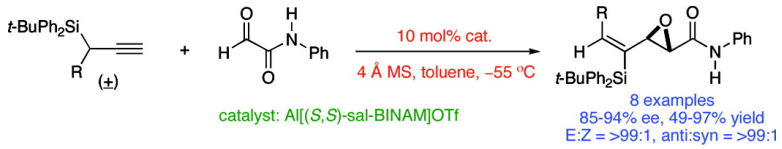

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Aluminum-Catalyzed Enantio- and Diastereoselective Carbonyl Addition of Propargylsilanes. A New Approach to Enantioenriched Vinyl Epoxides

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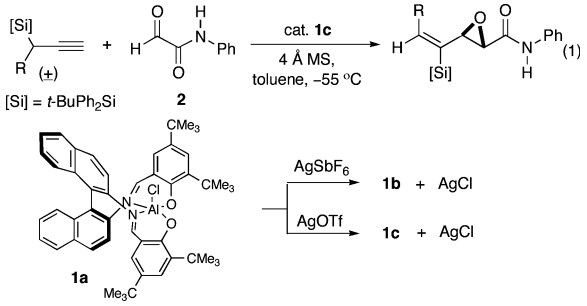
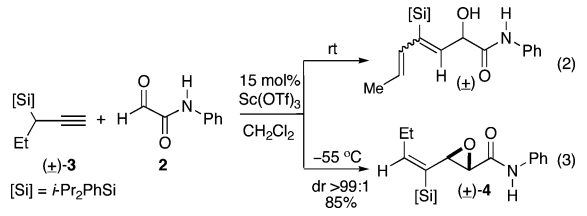
In this Communication we describe a new enantioselective process involving the carbonyl addition of propargylsilanes to *N*-phenylglyoxamide **2** that affords highly functionalized vinyl epoxides (eq 1). This reaction is catalyzed by the chiral Al(III)-sal-BINAM complex **1c**, previously utilized by us in another context.[1]



The current realm of Lewis acid-promoted propargylsilane additions to carbonyl groups[2] may be subdivided into two mechanistically distinct categories: (i) additions proceeding via a desilylation pathway;[3] (ii) additions involving a [1,2]-silyl shift.[4] Process (i) generates allenic alcohols and is most common when nonbulky silyl groups such as TMS are employed,[3] whereas the latter scenario has been shown to furnish mixtures of dienyl alcohols[5] and five-membered carbocyles.[4] The chemodiversity of these two pathways can be explained in terms of the steric bulk of the silyl species: the less encumbering silyl group favors desilylation via nucleophilic addition to silicon forming an "ate" complex; the larger silyl group discourages addition, enabling a migration to occur. Nonstereoselective examples of each of the above transformations have been reported;[2−5] however, this study not only constitutes the first intermolecular stereoselective propargylsilane-carbonyl addition reaction, but it also represents a new approach to the formation of vinyl epoxides.



In view of our previous success in promoting catalytic asymmetric Sakurai allylation[6] and vinylsilane additions to glyoxamide **2**,[7] we began to investigate the corresponding process using propargylsilanes.[8] Upon performing the addition of racemic diisopropylphenylsilane **3** to glyoxamide **2** with a catalytic amount of $Sc(OTf)_3$, in the absence of additional ligand at room temperature, a mixture of products was observed. The major product was a diastereomeric mixture of the corresponding dienyl alcohol, consistent with previous reports using stoichiometric Lewis acids and bulky silanes (eq 2).[5] However, when the analogous reaction was conducted at −55 °C, a disparate outcome was observed. Vinyl epoxide **4** was detected as a single product in 85% yield (eq 3). An X-ray crystal structure confirmed the (*E*) geometry of the olefin as well as the anti orientation of the epoxide.[9]

Scheme 1. Proposed Mechanism for Vinyl Epoxide Formation

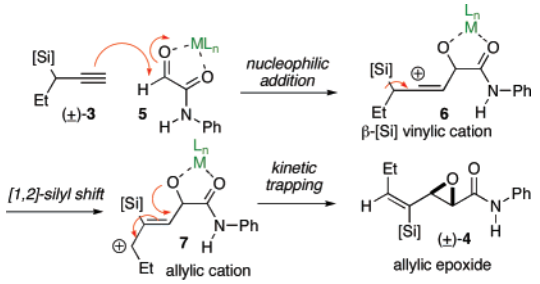
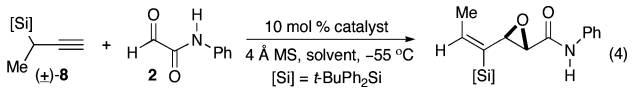


Table 1. Preliminary Catalyst Screen of Propargylsilane Addition



entry	catalyst[a]	solvent	ee (%)[b]	yield (%)
1	Sc[(*S*,*S*)−Phpybox](OTf)$_3$ (**9a**)	CH_2Cl_2	−7	70
2	Sc[(*R*,*R*)−bisPhpybox](OTf)$_3$ (**9b**)	CH_2Cl_2	53	79
3	Sc[(*S*,*S*)−*t*-Bupybox](OTf)$_3$ (**9c**)	CH_2Cl_2	−9	82
4	Sc[(*S*,*S*)−indapybox](OTf)$_3$ (**9d**)	CH_2Cl_2	−38	89
5	Sc[(*R*,*R*)−norephedrinepybox](OTf)$_3$ (**9e**)	CH_2Cl_2	−57	94
6	Sc[(*R*,*R*)−norephedrinepybox](OTf)$_3$ (**9e**)	toluene	−78	21
7	Sc[(*R*,*R*)−norephedrinepybox](OTf)$_3$ (**9e**)	3:1 CH_2Cl_2:toluene	70	88
8	Al[(*S*)−sal-BINAM]OTf (**1c**)	toluene	86	90
9	Al[(*S*)−sal-BINAM]SbF_6 (**1b**)	toluene	92	86
10	Al[(*S*)−sal-BINAM]SbF_6 (**1b**)	CH_2Cl_2	76	96

[a] Reactions were carried out with 0.1 mmol of **2** and 0.15 mmol of (±)-**8** in 1.0 mL of solvent. The unreacted silane could be recovered and reused without loss of selectivity. [b] Enantiomeric excesses were determined by HPLC using Chiracel AD-H column.

A plausible mechanism for this new transformation would commence with nucleophilic addition of **3** to Lewis acid-activated electrophile **5**, generating vinylic carbocation **6**.[10] A [1,2]-silyl shift then occurs to furnish more stable allylic cation **7** which is kinetically trapped to afford vinyl epoxide **4** (Scheme 1).

Our ensuing efforts were focused toward transforming this reaction into its catalytic asymmetric analogue (Table 1, eq 4). Variation of the silyl group within the nucleophile revealed that the *tert*-butyldiphenylsilyl moiety afforded optimal diastereoselectivity in this process. The initial screen of a range of potential Sc(III)pybox complexes using propargylsilane **8** suggested that norephedrinepybox **9e** provided the highest enantioselectivity (entries 1−5). Subsequent evaluation of a series of metal triflates showed that only the strongest Lewis acids, Sc(III)-, Sn(II)-, and

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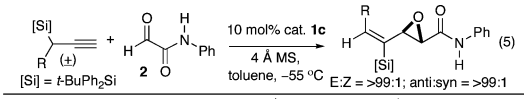
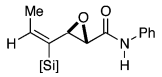
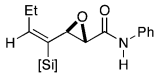
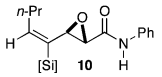
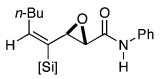
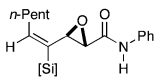
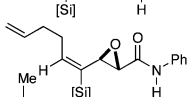
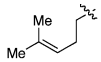
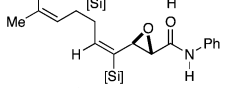
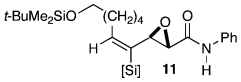
Table 2. Substrate Scope of Propargylsilane Additions



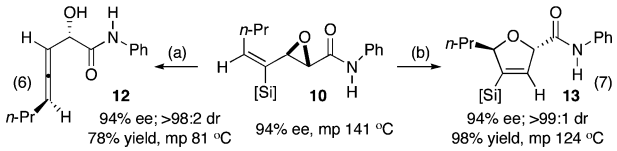
entry	R[a]	product[d]	ee (%)[b]	yield (%)	mp (°C)
1	Me[c]		92	86	145
2	Et		90	70	136
3	*n*-Pr	 **10**	94	77	141
4	*n*-Bu		92	97	143
5	*n*-Pent		90	73	118
6			94	49	132
7			85	83	105
8		 **11**	91	76	–

[a] Reactions were carried out with 1.5 equiv of propargylsilanes in 0.2 M toluene (from 0.1 *to* 2.0 mmol scales of **2**). [b] Enantiomeric excesses were determined by HPLC using Chiracel AD-H column. The data represent the ee's of unpurified products prior to recrystallization. [c] Results with catalyst **1b**. [d] Absolute stereochemistry determined by Mosher's ester analysis of the derivatized product **12** and the rest assigned by analogy.

Al(III)-pybox complexes afforded any reactivity.[11] However, Sc(III) was superior both in terms of reaction selectivity and yield. A solvent survey using catalyst **9e** indicated that the product ee and the reaction conversion showed opposite dependences on solvent polarity (entries 5−7). Further screening of other reaction parameters and additives did not lead to an acceptable level of enantioselection. Accordingly, we examined the potential of an alternative ligand scaffold. We chose the chiral Al(III)-sal-BINAM catalysts **1a**−**c** that we have characterized crystallographically.[1] Initial results were encouraging (entries 8−10), and a general system was discovered which afforded high yields and enantioselectivities using catalyst **1c** (Table 2, eq 5). Two points are noteworthy: (i) **1a** was inactive; however, catalysts **1b** and **1c** both displayed similar enantioselectivity, but the former diminished reaction conversion by 3-fold across a range of substrates.[12] (ii) Catalyst **1c** specifically needed in-situ preparation from **1a** with AgOTf.[13] Importantly, the new reaction was shown to be applicable to propargylsilanes bearing both saturated and unsaturated functions (Table 2, entries 1−7). As this methodology is a non-oxidative process, the epoxide function was established with complete regioselectivity, even in oxirane products formally derived from triolefinic substrates (entries 6 and 7). In addition, the presence of remote polar substituents was also tolerated (entry 8).

The derivatization of products initially afforded poor regioselectivity using standard carbanion additions. The bulky vinylsilicon function also emerged unscathed upon exposure to a range of protodesilylation conditions.[14] However, we were able to develop two useful isomerization processes without loss of enantiomeric purity (Scheme 2). For example, **10** was successfully converted into the corresponding allenic alcohol **12** upon treatment with NaN_3 (eq 6).[15] Intermediate O-silylated allenic alcohol was observed in >98:2 dr, and **12** was subsequently isolated after silyl deprotection.[16] By means of a corollary, the reaction of NaSCN with **10** afforded the identical product **12**, albeit in lower yield associated with incomplete conversion and a lower diastereoselectivity (93:7 dr). Treatment of **10** with I_2 also transpired to be an effective strategy to furnish dihydrofuran **13** as a single diastereomer (eq 7).[17]

Scheme 2. Transformations of Vinyl Epoxide **10**[a]



[a] Reagents and conditions: (a) NaN_3, DMF, 70 °C; TBAF, THF, room temp; (b) I_2, CH_2Cl_2, room temp.

In conclusion, we have developed the first enantioselective carbonyl addition of propargylsilanes. This reaction proceeds with high enantioselectivity and excellent diastereoselectivity, to give vinyl epoxides representing a new paradigm in propargylsilane-carbonyl additions. All products (except silylether **11**) are highly crystalline solids and may be converted to the corresponding allenic alcohols and dihydrofuran derivatives.

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Supporting Information Available: Experimental details, characterization data, HPLC enantiomer analysis, and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Evans, D. A.; Aye, Y. *J. Am. Chem. Soc.* **2006**, *128*, 11034.
(8) All propargylsilanes in this study were synthesized from commercially available prop-2-ynol in three steps (see Supporting Information).
(9) See cif files in Supporting Information.
(10) Smadja, W. *Chem. Rev.* **1983**, *83*, 263.
(11) Sn(II)- and Al(III)[(*R*,*R*)-norephedrinepybox](OTf)$_3$ returned 66% ee, 15% yield (at 0 °C), and 14% ee, 5% yield, respectively.
(12) Results using catalyst **1b**: 90% ee, 19% yield (R = Et); 91% ee, 13% yield (R = *n*-pent).
(13) The use of analogous triflate catalyst pre-prepared by the reaction of **1a** with Me_2AlOTf led to decomposition pathways.
(14) Vinyl epoxide was recovered intact under the following conditions: TBAF, THF (reflux), AcOH (neat, up to 100 °C), HF•pyridine (room temp).
(15) Allene geometry determined by Ag(I)-mediated stereospecific conversion to dihydrofuran and subsequent ^{2D}NOESY analysis. VanBrunt, M. P.; Standaert, R. F. *Org. Lett.* **2000**, *2*, 705.
(16) We ascribed this unprecedented rearrangement to the steric bulk of the [Si] hindering nucleophilic attack at the epoxide, instead promoting formation of an "ate" complex. The hypervalent silyl species then dissociates, with the $\sigma_{C-[Si]}$ attacking the lowest energy acceptor orbital (σ^*_{C-O}) to unveil the allenic alkoxide. The preferred antiperiplanar alignment between C−[Si] and C−O was thought to give rise to the observed stereochemical outcome. The azido silane thus generated then acts as a source of eletrophilic [Si] to give *O*-*t*-$BuPh_2Si$ **12**.
(17) With Br_2, bromination of the phenyl rings was observed instead.

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