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Enantioselective Scandium-Catalyzed Vinylsilane Additions: A New Approach to the Synthesis of Enantiopure β,γ -Unsaturated α -Hydroxy Acid Derivatives

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The purpose of this study is to report the enantioselective Lewis acid-promoted addition of vinylsilanes to *N*-phenylglyoxamide 2 catalyzed by the chiral Sc(III) complex **1f** (eq 1). Carbonyl addition reactions of vinylsilane nucleophiles are rare, 1 presumably due to the low intrinsic nucleophilicity associated with these organosilicon reagents. Intramolecular vinylsilane additions to iminium ions have been reported; 2 however, to our knowledge, the present examples represent the first intermolecular Lewis acid-catalyzed vinylsilane addition reactions. 3

$$R^{2} \xrightarrow{\text{SiMe}_{3}} O \xrightarrow{\text{H}} Ph \xrightarrow{\text{cat. 1f}} R^{2} OH \xrightarrow{\text{H}} N$$

$$R^{1} = \text{alkyl, aryl} \qquad 2$$

$$R^{1} \xrightarrow{\text{Ph}} O \xrightarrow{\text{N}} S \xrightarrow{\text{N}} O \xrightarrow{\text{Ph}} 1f$$

In view of our previous success in promoting the asymmetric glyoxamide-ene⁴ and Sakurai additions,⁵ the present study was initiated with a screen of potential Sc(III)—pybox ligand complexes (Table 1, eq 2). Initial investigations using 2-phenyl-substituted vinylsilane **3a**⁶ revealed that, while most Sc(III)—pybox complexes provided good enantioselectivities, norephedrine-pybox 1f was uniquely efficient in affording complete conversion at room temperature at 15 mol % catalyst loading (entries 1-6). Efforts to optimize this result led to the following observations. (1) Enantioselectivites were independent of the catalyst loading (99% ee from 15 to 1 mol % catalyst) while the yield suffered only a slight diminution (77% yield at 1 mol %). (2) Best results were obtained in CH₂Cl₂ or CHCl₃ (entries 6 and 7). Similar enantioselectivities were obtained in toluene but at the expense of yields (entry 8). (3) An increase in the reaction temperature was detrimental to enantioselectivities.

Reaction scope was evaluated by investigating a range of 2-aryl-substituted vinylsilanes containing both electron-releasing and electron-withdrawing substituents in the para position (Table 2, entries 2–5).6 Good yields and enantioselectivities (97–99%) were observed for each of the products formed.7 The corresponding additions of 2-alkyl-substituted vinylsilanes8 (entries 6 and 7) revealed that these substrates reacted equally selectively. However, in keeping with the lower reactivity of these substrates, conversions were low (<40%) at 2.5 mol % catalyst loading. Elevated catalyst loading (10 mol %) allowed product isolation in moderate yields. As isopropyl 3g and glyoxamide 2 proved to be efficient coupling partners, the reaction enantioselectivity does not appear to be effected by branching in the alkyl side chain.

In an effort to establish the reaction stereospecificity, we investigated the coupling of (Z) 2-substituted vinylsilanes. Vinylation with (Z)-phenylvinylsilane⁹ was found to afford the (E) allylic alcohol (99% ee, 89% yield), the same product that was previously formed via alkenylation with (E)-3a. We hypothesized that the

Table 1. Preliminary Screen of Vinylsilane Alkenylation

entry	ligand ^a	solvent	time (h)	ee (%) ^b	yield (%)
1	(S,S)-Phpybox (1a)	CH ₂ Cl ₂	30	-5	16
2	(R,R) -bisphpybox $(\mathbf{1b})$	CH_2Cl_2	24	88	45
3	(S,S)-t-Bupybox (1c)	CH_2Cl_2	40	-43	36
4	(S,S) -i-Prpybox $(\mathbf{1d})$	CH_2Cl_2	24	-95	65
5	(S,S)-indapybox $(1e)$	CH_2Cl_2	12	-99	68
6	(R,R)-norephedrinepybox (1f)	CH_2Cl_2	8	99	92
7	(R,R)-norephedrinepybox (1f)	$CHCl_3$	8	99	93
8	(R,R)-norephedrinepybox (1f)	toluene	12	99	53

^a Reactions were carried out with 0.1 mmol of 2 and 0.4 mmol of 3a in 1.2 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.

Table 2. Alkenylation with 2-Substituted Vinylsilanes

entry	R ^a	cat. load (mol %)	time (h)	ee (%) ^b	yield (%)	mp (°C)
1	Ph (3a)	2.5	8	99 ^c	92 ^c	91
2	4-Me-Ph (3b)	2.5	6	98	89	113
3	4-OMe-Ph (3c)	2.5	4	97	87	139
4	4-F-Ph (3d)	2.5	7	99	83	145
5	4-CF ₃ -Ph (3e)	2.5	8	98	86	164
6	<i>n</i> -Bu (3f)	10	24	98	63	85
7	<i>i</i> -Pr (3g)	10	24	99	55	65

^a Reactions of aromatic vinylsilanes (entries 1−5) were carried out with 0.1 mmol of 2 and 4.0 equiv of 3 in 1.2 mL of CH₂Cl₂. Analogous reactions of aliphatic vinysilanes (entries 6 and 7) were carried out with 8.0 equiv of 3 in 0.5 mL of CH₂Cl₂. Unreacted silanes were recovered and reused. ^b Enantiomeric excesses were determined by HPLC using Chiracel AD-H column. ^c Absolute stereochemistry was determined by Mosher's ester analysis. Remaining product configurations were assigned by analogy.

observed stereoconvergence, leading to the thermodynamic product, occurred because the benzylic carbocation was stable enough to allow bond rotation which reduces the extent of hyperconjugative stabilization from the β -Si substituent. To test this hypothesis, we evaluated the stereoselectivity of (Z)-2-n-butylvinylsilane 4^9 in additions to glyoxamide 2 (eq 4). In this case, we only detected the presence of a single product which was subsequently isolated and characterized as the (Z) allylic alcohol 5 (albeit poor yield associated with a low conversion), in accordance with the stereospecificity generally observed in electrophilic additions of vinylsilanes. 10 It is noteworthy that the couplings of (E)- and (Z)-2-n-butylvinylsilanes (3f and 4) constitute a complementary route to the two allylic alcohol geometrical isomers. Interestingly, reactions using the (Z)-silanes were observed to take longer times than the corresponding additions using (E)-silanes: a competition experiment

Table 3. Alkenylation with 2,2-Disubstituted Vinylsilanes

entry	R ¹	R ²	product ^a	ee (%) b	yield (%)	mp (°C)
1°	Ph	Me (6a)	Ph H O Ph	98	92	106
2 ^c	Ph	<i>n</i> -Bu (6b)	Ph OH H	99	99	94
3 ^d	Me	Me (6c)	Me OH H	98	64	80
4 ^d	i-Pent	Me (6d)	Pent Me OH H	98	59	92
5 ^d	<i>t</i> -Bu	Me (6e)	t-Bu Me OH H	98	55	115

^a Reactions were carried out with 0.1 mmol of 2 and 0.2 mmol of 6 in 1.2 mL of solvent. b Enantiomeric excesses were determined by HPLC using a Chiracel AD-H column. ^c Reactions were run at 2.5 mol % catalyst loading. d Reations were run at 5.0 mol % catalyst loading in the presence of 3.5 mol % 2,6-di-tert-butylpyridine.

starting with 1:1 ratio of (E)-3a and its (Z) isomer showed that at 40% conversion, the ratio of the remaining silanes was 1:3 (E):(Z).

The addition of of 2,2-disubstituted vinylsilanes¹¹ has also been explored (Table 3, eq 5). In line with the significant increase in electron density of the olefin, the reactions were, in all instances, complete within a few hours (<5 h) at room temperature. With aryl-substituted 6a and 6b, the expected allylic alcohol products were observed in high yields and enantioselectivities at 2.5 mol % catalyst loading (entries 1 and 2).12 With 2,2-dialkyl substituted vinylsilanes (6c-6e), the desired alkenylation products were isolated under optimized conditions using a catalytic amount of 2,6ditertbutylpyridine as an external additive (entries 3-5). In the absence of the added base, partial product isomerization into the corresponding homoallylic alcohols was observed.¹³ The resulting mixtures proved to be only partially separable (eq 6).

To investigate the cause of these isomerizations, a mixture of 7 and 8 was redissolved in CDCl₃. Reanalysis of this mixture by ¹H NMR spectroscopy after several hours at room temperature revealed that its composition had not changed. However, addition of 2.5 mol % of either 1f or Sc(OTf)3 or TfOH to this solution effected slow isomerization to give a new mixture of isomers containing >95% of 7, suggesting the intervention of an in situ acid-promoted isomerization process.¹⁴ In addition, internally substituted vinylsilane 9 also proved to be a good coupling partner to give 10 (eq 7). In this instance, we also detected in the unpurified reaction mixture (<15% in total) of the regioisomeric homoallylic alcohol products derived from the corresponding glyoxamide-ene process.⁴

$$Me \xrightarrow{\text{SiMe}_3} O \xrightarrow{\text{H}} O = \frac{10 \text{ mol } \% \text{ cat. 1f}}{4 \text{ Å MS}} O = \frac{10 \text{ mol } \% \text{ cat. 1f}}{10 \text{ mol } \% \text{ cat. 1f}} O = \frac{10 \text{ mol } \% \text{ cat. 1f}}{10 \text{ mol } \% \text{ cat. 1f}} O = \frac{10 \text{ mol } \% \text{ cat. 1f}}{10 \text{ mol } \% \text{ cat. 1f}} O = \frac{10 \text{ mol } \% \text{ cat. 1f}}{10 \text{ mol } \% \text{ cat. 1f}} O = \frac{10 \text{ mol } \% \text{ cat. 1f}}{10 \text{ mol } \% \text{ cat. 1f}} O = \frac{10 \text{ mol } \% \text{ cat. 1f}}{10 \text{ mol } \% \text{ cat. 1f}} O = \frac{10 \text{ mol } \% \text{ cat. 1f}}{10 \text{ mol } \% \text{ cat. 1f}} O = \frac{10 \text{ mol } \% \text{ cat. 1f}}{10 \text{ mol } \% \text{ cat. 1f}} O = \frac{10 \text{ mol } \% \text{ cat. 1f}}{10 \text{ mol } \% \text{ cat. 1f}} O = \frac{10 \text{ mol } \% \text{ cat. 1f}}{10 \text{ mol } \% \text{ cat. 1f}} O = \frac{10 \text{ mol } \% \text{ cat. 1f}}{10 \text{ mol } \% \text{ cat. 1f}} O = \frac{10 \text{ mol } \% \text{ cat. 1f}}{10 \text{ mol } \% \text{ cat. 1f}} O = \frac{10 \text{ mol } \% \text{ cat. 1f}}{10 \text{ mol } \% \text{ cat. 1f}} O = \frac{10 \text{ mol } \% \text{ cat. 1f}}{10 \text{ mol } \% \text{ cat. 1f}} O = \frac{10 \text{ mol } \% \text{ cat. 1f}}{10 \text{ mol } \% \text{ cat. 1f}} O = \frac{10 \text{ mol } \% \text{ cat. 1f}}{10 \text{ mol } \% \text{ cat. 1f}} O = \frac{10 \text{ mol } \% \text{ cat. 1f}}{10 \text{ mol } \% \text{ cat. 1f}} O = \frac{10 \text{ mol } \% \text{ cat. 1f}}{10 \text{ mol } \% \text{ cat. 1f}} O = \frac{10 \text{ mol } \% \text{ cat. 1f}}{10 \text{ mol } \% \text{ cat. 1f}} O = \frac{10 \text{ mol } \% \text{ cat. 1f}}{10 \text{ mol } \% \text{ cat. 1f}} O = \frac{10 \text{ mol } \% \text{ cat. 1f}}{10 \text{ mol } \% \text{ cat. 1f}} O = \frac{10 \text{ mol } \% \text{ cat. 1f}}{10 \text{ mol } \% \text{ cat. 1f}} O = \frac{10 \text{ mol } \% \text{ cat. 1f}}{10 \text{ mol } \% \text{ cat. 1f}} O = \frac{10 \text{ mol } \% \text{ cat. 1f}}{10 \text{ mol } \% \text{ cat. 1f}} O = \frac{10 \text{ mol } \% \text{ cat. 1f}}{10 \text{ mol } \% \text{ cat. 1f}} O = \frac{10 \text{ mol } \% \text{ cat. 1f}}{10 \text{ mol } \% \text{ cat. 1f}} O = \frac{10 \text{ mol } \% \text{ cat. 1f}}{10 \text{ mol } \% \text{ cat. 1f}} O = \frac{10 \text{ mol } \% \text{ cat. 1f}}{10 \text{ mol } \% \text{ cat. 1f}} O = \frac{10 \text{ mol } \% \text{ cat. 1f}}{10 \text{ mol } \% \text{ cat. 1f}} O = \frac{10 \text{ mol } \% \text{ cat. 1f}}{10 \text{ mol } \% \text{ cat. 1f}} O = \frac{10 \text{ mol } \% \text{ cat. 1f}}{10 \text{ mol } \% \text{ cat. 1f}} O = \frac{10 \text{ mol } \% \text{ cat. 1f}}{10 \text{ mol } \% \text{ cat. 1f}} O = \frac{10 \text{ mol } \% \text{ cat. 1f}}{10 \text{ mol } \% \text{ cat$$

As an extension to the present study, we have also found that enantioenriched propargylic alcohols such as 12 may be obtained via an analogous Sc(III)-pybox-catalyzed addition between 2 and (trimethylsilyl)phenylacetylene (11) (eq 8). Further studies on these alkynylation processes are ongoing.

In summary, we have developed the first Lewis acid-catalyzed enantioselective alkenylation using air- and moisture-stable trimethylvinylsilanes under mild conditions. All products (except 5) are highly crystalline solids, ideally suited for industrial process chemistry. Care was taken to analyze the enantiopurities of the unpurified products prior to recrystallization. The N-phenylcarboxamides employed in this study are easily activated for either hydrolysis or transesterification.¹⁵

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Supporting Information Available: Experimental details, characterization data, HPLC enantiomer analysis, and ¹H and ¹³C 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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- Using catalyst 1a, similar results were obtained: -96% ee and 82% yield in addition of **6a**; -99% ee and 98% yield in addition of **6b**. (13) Under standard conditions, 60-75% of the corresponding isomerized
- products were observed in the crude reaction mixture by ¹H NMR.
- Întegration of the vinylic protons from both isomers vs an internal standard indicated that an isomerization, and not a selective decomposition of one of the isomers, was occurring.
- See ref 5 above and references therein.

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