Communications to the Editor

Stereoselective Synthesis of Functonalized Dihydropyrans via a Formal [4+2]-Annulation of Chiral Crotylsilanes

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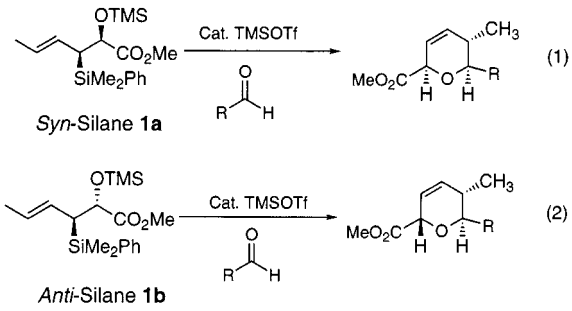
As a consequence of their frequent occurrence in natural products with useful biological activities,[1] numerous methods have been devised for the synthesis of functionalized pyran ring systems.[2] Methods available for the asymmetric synthesis of hydropyrans include hetero Diels−Alder cycloaddition,[3] S_N2 cyclization,[4] dioxanone Claisen rearrangement,[5] and ring closing metathesis.[6] Another useful approach to these oxygen heterocycles utilizes vinylsilane-terminated cyclization of oxocarbenium ions.[7] In a related development in this area, the preparation of tetrahydropyrans by C−C bond construction using Prins cyclization has emerged as a useful approach.[8] Although these methods are capable of achieving useful levels of diastereoselectivity for the synthesis of *cis*-2,6-substituted pyrans, there are few reported methods concerning the synthesis of the complementary trans-2,6-substituted isomers.[6b,8]

Methodologies that provide ready access to enantiomerically enriched *cis*-2,6- and *trans*-2,6-dihydropyrans would make a useful contribution to this area. In this communication we describe a new use of the illustrated silanes in a highly diastero- and enantioselective process for the preparation of functionalized dihydropyrans. These experiments underscore the important role of the silicon-bearing center as a dominant stereocontrol element in these heterocyclizations (eq 1 and 2). Also, since both enantiomers of silanes **1a** and **1b** are available,[9] four possible *cis*-2,6- and *trans*-2,6-dihydropyrans can be prepared.

This study was initiated with the notion that chiral silanes of **1** would show similar characteristics for the intramolecular crotylation reactions as we have previously documented in an intermolecular process.[10] In initial experiments, silanes **1a** and **1b** and aldehydes were found to cyclize to 2,5,6-trisubstituted



dihydropyrans in the presence of a catalytic amount of TMSOTf (0.1 equiv) in CH_2Cl_2 (0.3 M, 0 °C).[11] However, significant amounts of protodesilylation products were also observed. Performing the reaction at lower temperature and at a decreased concentration provided the best results (CH_2Cl_2, 0.05 M, −20 °C). Importantly, the annulation proceeded with high levels of enantioselectivity, providing optically active dihydropyrans in up to 98% ee by a direct coupling−cyclization of the silanes with a wide range of aldehydes.[12] Accordingly, the relative stereochemical relation of the individual silane diastereomers was evaluated for the effect of silane configuration on diastereoselection. Of the cases examined, the level of diastereoselectivity is independent of which silane isomer is used. However, there appears to be a correlation between aldehyde structure and reaction diastereoselectivity. Conjugated aldehydes generally gave higher selectivity (Table 1, entries 4 and 7−9), while selectivity from alkyl aldehydes was somewhat lower (Table 1, entries 1−3).

Considering that TMSOTf is a highly reactive and reliable O-silylating agent, we anticipated that the in situ formation of a α-silyl group on silane **1c** could also lead to the desired dihydropyran via trapping of the same oxocarbenium ion. Experiments using silane **1c** effectively cyclized to dihydropyrans in the presence of 1 equiv of TMSOTf (Table 1, entries 10−12). Similar levels of diastereoselectivity were achieved.

Although vinylsilanes have been employed to promote cyclizations in the synthesis of oxygen- and nitrogen-containing six-membered rings, the possibility of accessing a Cope rearrangement pathway can compromise the reaction diastereoselectivity.[8,13] In the present case, both diastereomers **1a** and **1b** afford good to

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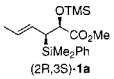
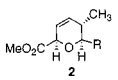
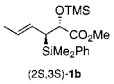
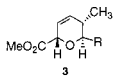
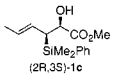
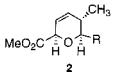
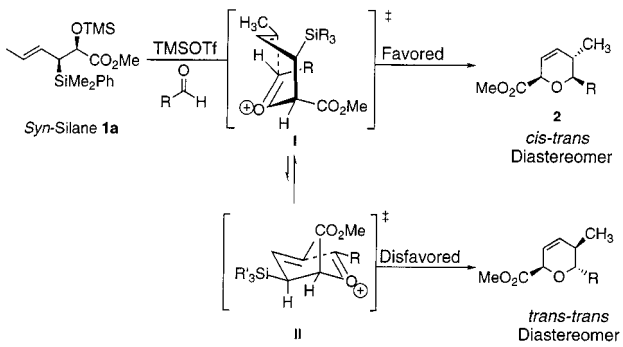
Table 1. Asymmetric Synthesis of Substituted Dihydropyrans via Chiral Silanes

entry	RCHO	(E)-crotylsilane	major diastereomer[a]	yield%[b]	dr C2,C6-syn/anti[c]
		 (2R,3S)-**1a**	 **2**		
1	*i*-PrCHO	**1a**	**2a**	86%	9:1
2	*n*-BuCHO	**1a**	**2b**	88%	15:1
3	$C_6H_{11}CHO$	**1a**	**2c**	85%	15:1
4	PhCHO	**1a**	**2d**	85%	25:1
		 (2S,3S)-**1b**	 **3**		
5	*n*-BuCHO	**1b**	**3a**	88%	1:11
6	$C_6H_{11}CHO$	**1b**	**3b**	85%	1:10
7	PhCHO	**1b**	**3c**	87%	<1:30
8	$C_2H_5CHC(CH_3)CHO$	**1b**	**3d**	85%	<1:30
9	(trans) $PhCHC(CH_3)CHO$	**1b**	**3e**	78%	<1:30
		 (2R,3S)-**1c**	 **2**		
10	*n*-BuCHO	**1c**	**2b**	83%	9:1
11	$C_6H_{11}CHO$	**1c**	**2c**	85%	15:1
12	PhCHO	**1c**	**2d**	87%	25:1

[a] Stereochemistry assigned by NOE experiments. [b] All yields are based on pure materials isolated by chromatography on SiO_2. [c] The ratio of products was determined by ^1H NMR (400 MHz), operating at an S/N ratio of >200:1.

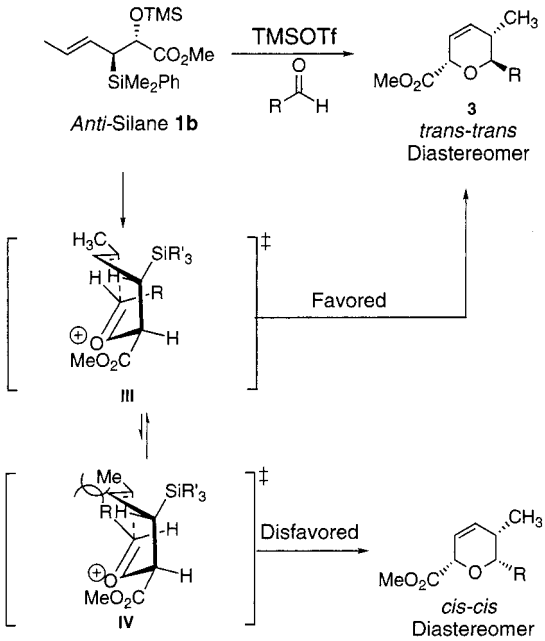
Scheme 1



excellent diastereoselectivity (Table 1). The cyclization of *syn*-**1a** produced the *cis*-2,6-*trans*-5,6-trisubstituted dihydropyrans with trans-2,6-trans-5,6-trisubstituted dihydropyrans as minor diastereomers; meanwhile the cyclization of *anti*-**1b** provided *trans*-2,6-*trans*-5,6-trisubstituted dihydropyrans as the major isomers with all cis dihydropyrans as minor products.

Results from these experiments demonstrate that the configuration of the silane reagent controls the stereochemical course of the cyclization, which can be rationalized through an *anti*-S_E' mode of addition.[14] As illustrated in a key mechanistic feature of our hypothesis (Scheme 1), for effective $\sigma-$p overlap in the cyclization step of **1a**, we suggest a pseudoaxial orientation for the silyl group is favored in a boatlike transition state.[14b,15] As a result, for the two equilibrating conformers of oxocarbenium ion

Scheme 2



I and **II**, cyclization of **I** proceeds faster than that of conformer **II** leading to the *cis*−*trans* dihydropyran **2**.

Since **1b** provides the *trans-trans* dihydropyran, the observed selectivity may be rationalized through cyclization of conformer **III** (Scheme 2), which positions the silyl group and the neighboring ester group in *anti* orientation to each other. Because the silyl group possesses considerable size, this pathway may be favored from both steric and electronic considerations. Accordingly, the minor all *cis* isomer can be rationalized with the boatlike transition state **IV**, which reverses oxocarbenium ion π-face selectivity. In this arrangement a severe, nonbonding destabilizing interaction is created between the aldehyde substituent and the vinyl methyl group. The higher level of diastereoselectivity obtained with conjugated aldehydes can be attributed to the stabilization of oxycarbenium ions through an electron-delocalizing resonance effect, which may imply that the process of cyclization is under thermodynamic control.

Using chiralsilane reagents, we have developed an efficient method to synthesize stereochemically well-defined *cis*-2,6- and the complementary *trans*-2,6-dihydropyrans. In principle, tetrahydropyrans containing up to five stereocenters can be assembled after functionalization of the double bond.

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Supporting Information Available: General experimental procedures including spectroscopic and analytical data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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