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Double Stereodifferentiating Crotylation Reactions with α-Amino Aldehydes: Asymmetric Synthesis of Vicinal Amino Alcohol Synthons

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Abstract: The sense and level of 1,2-asymmetric induction have been evaluated in the BF_3•OEt_2 promoted addition of *(E)*- crotylsilanes *(R)*-**1** and *(S)*-**1** to α-amino aldehydes **2a** through **2d**. The sense of carbonyl diastereoface selectivity was shown to be dependent of the chirality of the silane reagent.
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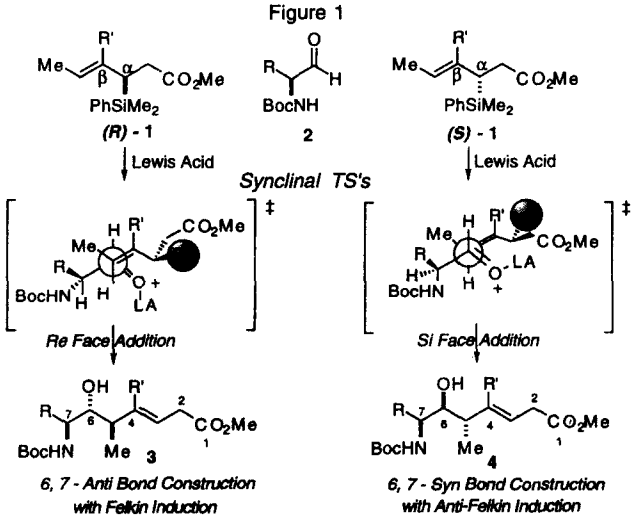
Stereochemically well-defined vicinal amino alcohols and their synthetic equivalents are valuable intermediates and building blocks for the asymmetric synthesis of biologically active natural products.[1] Recent literature has documented the use of amino sugars and polyhydroxylated alkaloids as selective inhibitors of glycosidases and implicated their potential for the treatment of carbohydrate dependent metabolic disorders.[2,3] Moreover these structure-types have been used as scaffolds and incorporated into chiral ligands for use in asymmetric catalytic processes.[4] Therefore, new stereoselective routes to vicinal amino alcohols and their synthetic equivalents would be useful contributions to the field. In earlier reports we have described double stereodifferentiation in the Lewis acid promoted addition reactions of *(E)*-crotylsilanes with *(S)*-2-alkoxypropanal,[5] and evaluated a new approach for the synthesis of polypropionate-derived natural products.[6] In this communication, we report that the Lewis acid promoted double stereodifferentiating crotylation reactions of chiral *(E)*-crotylsilanes[7] *(R)*-**1** or *(S)*-**1** with α-amino aldehydes **2**[8] provide amino alcohols with useful levels of selectivity. The aldehydes, readily available from naturally occurring L-amino acids, when condensed with chiral silanes afford *anti*- and *syn*-vicinal amino alcohols **3** and **4** (Figure 1).

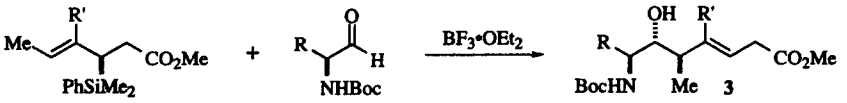
Figure 1



We have previously demonstrated during the stereochemical course of the condensation reactions of *(E)*-crotylsilanes with aldehydes, the configuration of the C-SiR_3 center determines the absolute configuration of the center bearing the methyl group, while the chirality of the aldehyde controls the absolute stereochemistry of the oxygen bearing stereocenter.[6] However, in the case of crotylation reactions with α-amino aldehydes, although the chirality of the aldehyde still exerts considerable influence on

the stereochemical outcome, which is reflected in the level of diastereoselectivity of the addition products, the absolute configuration of both the methyl and hydroxyl groups bearing stereocenters are dependent on the absolute configuration of the C-SiR_3 center in silane reagents.

Table 1. Reactions of *(R, E)*-Crotylsilanes with α-Amino Aldehydes[a]

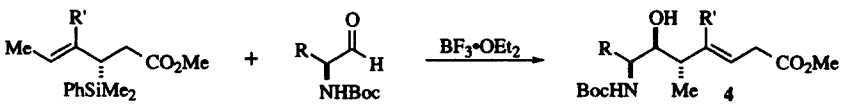


Entry	Crotylsilanes (R')		Amino Aldehydes (R)		Diast. *Anti / Syn*[b]	% Yield [c]
1	(R)-**1a**	H	**2a**	$PhCH_2$	**3a** 2:1	78
2	(R)-**1b**	Me	**2a**	$PhCH_2$	**3a'** 1:1	83
3	(R)-**1a**	H	**2b**	$TBDPSOCH_2$	**3b** 30:1	94
4	(R)-**1a**	H	**2c**	CH_3	**3c** 30:1	77
5	(R)-**1a**	H	**2d**	Me_2CHCH_2	**3d** 5:1	74

[a] All reactions were carried out in CH_2Cl_2 (0.25 M) using 2.0 equivalents of BF_3•OEt_2. [b] Ratios were determined by ^{1}H-NMR analysis on the crude reaction mixtures. [c] Yields were based on mixtures of diastereomers isolated by chromatography on SiO_2.

The stereochemical features of these reactions are illustrated using the single rotamer models in Figure 1, where synclinal transition state models are depicted for the silanes **1** and the amino aldehydes **2**. The results of this study concerning the double asymmetric induction in the BF_3•OEt_2 promoted reactions with **2** are summarized in Tables 1 and 2. Table 1 illustrates that, in the reactions of α-amino aldehydes with (*R*)-**1**, the *syn* vicinal amino alcohols were favorably produced, presumably through Felkin induction; whereas Table 2 illustrates that, in the reactions of α-amino aldehydes with (*S*)-**1**, the *anti* vicinal amino alcohols were favorably produced. It is worth pointing out that although the condensation reactions of the α-amino aldehydes with both crotylsilane (*R*)-**1** and crotylsilane (*S*)-**1** afforded high yields, the reaction partners of (*R*)-**1** and aldehydes **2** provided considerably higher levels of diastereoselectivity. A trend of diastereoselectivity with allylsilanes has emerged which is consistent with a stereospecific *anti* S_E' pathway as originally documented by Fleming[9] and Kumada[10] and which has been confirmed by Nakai[11a] and Marshall[11b] as well as our laboratory.[12] Although in most cases, the diastereoselectivities of addition products are moderate to good, entry 2 in Tables 1 and 2 illustrates that the β-methyl silane reagents **1** are too reactive toward amino aldehyde **2a** to induce carbonyl π-facial selectivity.

Table 2. Reactions of *(S, E)*-Crotylsilanes with α-Amino Aldehydes[a]

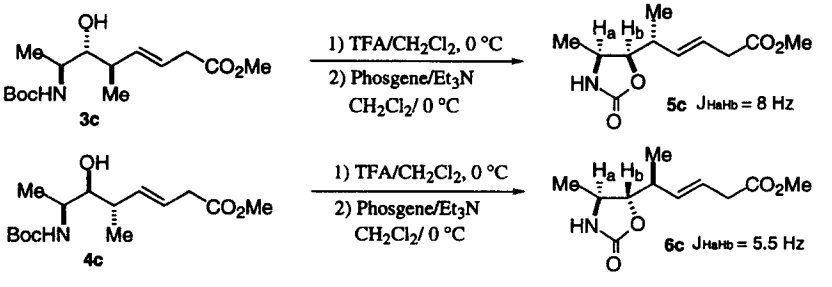


Entry	Crotylsilanes (R')		Amino Aldehydes (R)		Diast. *Syn / Anti* [b]	% Yield [c]
1	(S)-**1a**	H	**2a**	$PhCH_2$	**4a** 5:1	73
2	(S)-**1b**	Me	**2a**	$PhCH_2$	**4a'** 1:1	86
3	(S)-**1a**	H	**2b**	$TBDPSOCH_2$	**4b** 1.5:1	81
4	(S)-**1a**	H	**2c**	CH_3	**4c** 3:1	46
5	(S)-**1a**	H	**2d**	Me_2CHCH_2	**4d** 4:1	61

[a] All reactions were carried out in CH_2Cl_2 (0.25 M) using 2.0 equivalents of BF_3•OEt_2. [b] Ratios were determined by ^{1}H-NMR analysis on the crude reaction mixtures. [c] Yields were based on mixtures of diastereomers isolated by chromatography on SiO_2.

The configurational assignment for the vicinal amino alcohols was accomplished by ^{1}H-NMR analysis and was based on the measurement of well established values of vicinal coupling constants for oxazolidinones.[13] In that regard, addition products **3c** and **4c** were converted to the illustrated oxazolidinones **5c** and **6c** in a two-step sequence (Figure 2): first, the Boc-protecting group was removed with trifluoroacetic acid (TFA/CH_2Cl_2, 1/4 v/v, 0 °C); then, without purification, the crude product was cyclized using phosgene ($COCl_2$, Et_3N, CH_2Cl_2, 0 °C, 0.5 h) to afford the desired oxazolidinone. The three-bond coupling constants of the vicinally related protons (H_a and H_b) were obtained by homo-nuclear decoupling experiments. The stereochemistry of the remaining crotylation products was assigned by analogy with **5c** and **6c**.

Figure 2



In conclusion, the application of asymmetric crotylsilane bond construction methodology in the double stereodifferentiating crotylation reactions with α-amino aldehydes expands the scope of these reagents to include the asymmetric synthesis of stereochemically defined vicinal amino alcohol synthons. Further studies concerning the utility of these amino alcohols in natural product synthesis will be reported in due course.

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