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Double Stereodifferentiation in the Lewis Acid Promoted Crotylation of *(S)*-2-Alkoxypropanal with Chiral β-Alkyl *(E)*-Crotylsilanes

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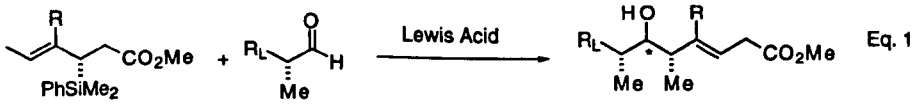
Abstract. The sense and level of 1,2-asymmetric induction have been evaluated in the Lewis acid promoted addition of *(E)*-crotylsilanes *(S)*-**1** and *(R)*-**2** to *(S)*-2-alkoxypropanal **3** and **7**. These aldehydes are substituted at the α-position with benzyloxy (OBn) to reinforce chelation and *tert*-butyldiphenylsilyloxy (TBDPSO) groups to prevent chelation with bidentate Lewis acids. The nature of the Lewis acid and the chirality of the silane reagent were found to play a pivotal role in the direction and levels of carbonyl diastereoface selectivity.

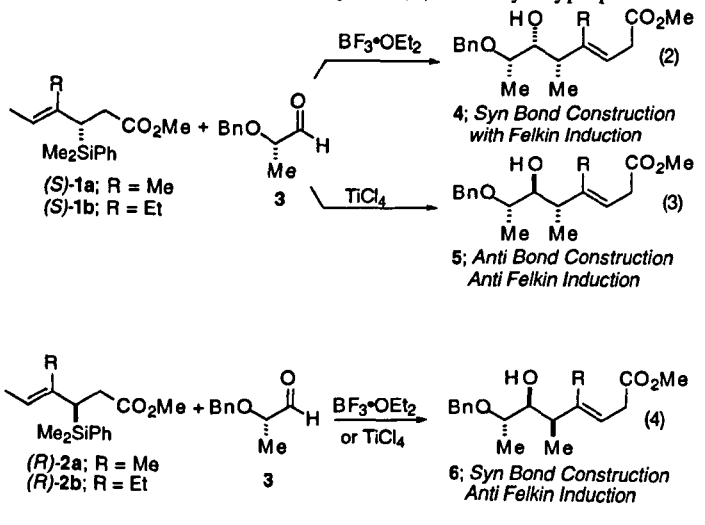
The purpose of this communication is to describe the turnover of diastereoface selection in Lewis acid promoted double stereodifferentiating crotylation reactions with chiral, hetero-substituted aldehydes.[1] Stereoselectivity is dependent on the absolute configuration of the two reaction partners, aldehyde (and its hetero-atom substituent, benzyloxy *vs* silyloxy) and crotylsilane. Concerning the stereochemical aspects of the allylmetalation processes, the development of transition state models that are able to rationalize the effect of aldehyde substituents on carbonyl diastereoface selection has been an important objective.[2] In that context, the accepted tenet suggests that in the cases of γ-substituted allylsilanes, there are two dominating stereochemical features that can influence the reaction diastereoface selectivity, and both are associated with the local chirality of the individual reaction components. For instance, with a chiral (*S, E*)-crotylsilane, the configuration of the C-SiR_3 center determines the absolute stereochemistry of the emerging center bearing the methyl group, while the chirality of the aldehydes generally controls the absolute stereochemistry of the developing hydroxyl bearing stereocenter (eq. 1). Thus, the addition to the aldehydes occurs principally by an *anti*-S_E' addition[3] while proceeding through an open transition state with an antiperiplanar or synclinal arrangement between the reaction components.



Lewis Acid Promoted Reactions with *(S)*-2-Benzyloxypropanal: Conventional wisdom suggests that the absolute configuration of the emerged hydroxyl bearing stereocenter in Lewis acid promoted crotylsilation reactions, as well as the Mukaiyama aldol, is generally controlled by the inherent diastereofacial bias of the aldehyde. We have learned that certain aldehyde-Lewis acid combinations exhibit the ability to turn over the stereoselectivity in these double stereodifferentiating reactions (Scheme 1). For example, the reaction of *(S)*-2-benzyloxypropanal **3**[4] with the β-alkyl silane reagents *(S)*-**1** under the influence of $BF_3{\cdot}OEt_2$, a monodentate Lewis acid[5], produced the *syn* homoallylic alcohols **4a** and **b** (eq. 2)[6] with excellent levels of Felkin induction.[7] It was interesting to learn that the condensation of *(S)*-**3**

with the *(R)*-silanes **2a** and **b**, a combination of reactants thought to be mismatched cases, high levels of diastereoselectivity were observed under the influence of $BF_3{\cdot}OEt_2$ affording *syn* homoallylic alcohol **6a** and **b** (eq. 4). Consistent with our earlier experiements, this silane reagent-Lewis acid combination exclusively produced *syn* homoallylic alcohols. These experiments indicate that the *(R)*-silanes are capable of overriding the inherent chirality associated with the aldehydes affording the *syn* disposed crotylsilation product. On the other hand, reactions with *(S)*-2-benzyloxypropanal **3** and the β alkyl *(S)*-silanes under the influence of a bidentate Lewis acid ($TiCl_4$) produced *anti* homoallylic alcohols **5a** and **b** (eq. 3) with high levels of *anti*-Felkin induction. In contrast, the reactions of *(S)*-2-benzyloxypropanal and *(R)*-silanes **2** promoted by $TiCl_4$, produced *syn* homoallylic alcohols **6** (eq. 4). Presumably, the reactions proceed through a Cram chelate transition state model.[8,9] An important result associated with this set of experiments is that the stereochemistry of the emerging hydroxyl group appears to be influenced by chirality of aldehydes while the absolute stereochemical relationships are dictated by the configuration of the C-SiR_3 bond.

Scheme 1. Diasteroface Selectivity with *(S)*-2-Benzyloxypropanal.



X; R	Diast. Syn / Anti	% Yield
4a; Me	> 30 : 1	64[a]
4b; Et	> 30 : 1	51[a]
5a; Me	> 1 : 30	51[b]
5b; Et	> 1 : 30	87[b]

a. Run with 1.5 equiv $BF_3{\cdot}OEt_2$
b. Run with1.0 equiv $TiCl_4$

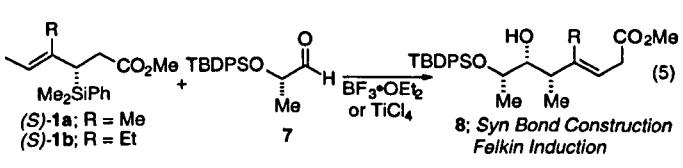
X; R	Diast. Syn / Anti	% Yield
6a; Me	> 30 : 1	64[a]
6b; Et	> 30 : 1	69[a]
6a; Me	20 : 1	64[b]
6b; Et	10 : 1	71[b]

a. Run with1.5 equiv $BF_3{\cdot}OEt_2$
b. Run with 1.0 equiv $TiCl_4$

Lewis Acid Promoted Reactions with *(S)*-2-(*tert*-Butyldiphenylsilyloxy)propanal. In contrast to the benzyloxy substituted aldehyde case (Scheme 1), the reaction of *(S)*-2-(*tert*-butyldiphenylsilyloxy)propanal **7** wth the silane reagents *(S)*-**1** under the influence of $BF_3{\cdot}OEt_2$ or $TiCl_4$ produced the *syn* homoallylic alcohols **8** (eq. 5) with excellent levels of Felkin induction. In these examples, the bulky silicon group prevents the Lewis acid from chelate formation with the aldehyde.[10] In a similar manner, the reaction of *(S)*-aldehyde **7** and the *(R)*-silane reagents **2** under the influence of $BF_3{\cdot}OEt_2$ or $TiCl_4$ produced the *syn* homoallylic alcohols **9a** and **b** (eq. 6). Again the reactions display a tendency for the formation of *syn* diastereomers although the $TiCl_4$ promoted reactions exhibit lower selectivity. For the cases examined in this study, there is a consistent predisposition for Felkin induction in the reactions of the *(S)*-silanes in the presence of $BF_3{\cdot}OEt_2$ or $TiCl_4$ and, for the *(R)*-silanes, *anti*-Felkin induction predominates. These experiments indicate that the chirality of the *(R)*-silane reagents is capable

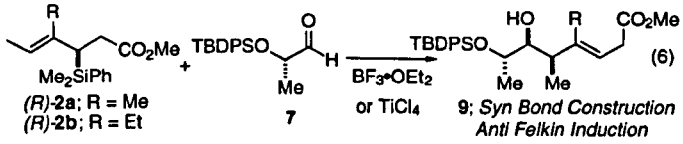
of overriding the inherent chirality associated with aldehyde **7** affording the *syn* disposed crotylsilation products with *anti*-Felkin induction for the cases examined. The other important observation made in this set of experiments is the consistent formation of the *syn* homoallylic alcohols and the absolute stereochemical relationships being dictated by the configuration of the C-SiR_3 bond.

Scheme II. Diastereoface Selectivity with *(S)*-2-(*tert*-butyldiphenylsilyloxy)propanal.



X; R	Diast. Syn / Anti	% Yield
8a; Me	> 30 : 1	64[a]
8b; Et	> 30 : 1	36[a]
8a; Me	> 30 : 1	78[b]
8b; Et	> 30 : 1	72[b]

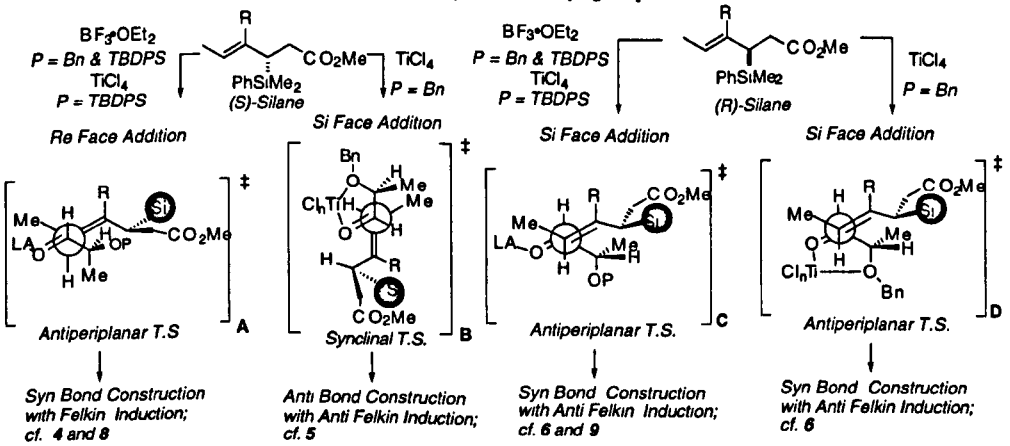
a. Run with1.2 equiv BF_3•OEt_2
b. Run with1.0 equiv $TiCl_4$



X; R	Diast. Syn / Anti	% Yield
9a; Me	> 30 : 1	64[a]
9b; Et	> 30 : 1	79[a]
9a; Me	3 : 1	79[b]
9b; Et	2 : 1	88[b]

a. Run with1.2 equiv BF_3•OEt_2
b. Run with1.0 equiv $TiCl_4$

Open Transition State Models. The open transition state model for 1,2-asymmetric induction in the crotylation[11] reactions with aldehydes has been widely adopted. In view of those models, two related steric models **A** and **C** are employed to account for the turnover in aldehydes face selectivity (*syn*-1,2-induction → *anti*-1,2-induction) of the BF_3•OEt_2 promoted crotylation reactions. For crotylation products **4** and **8** and **6** and **9** transition structure (TS) **A** and **C** orients the reacting π-bonds at 180° to each other (antiperiplanar arrangement). In TS **A**, the *(S)*-silane approaches the *re* face of the aldehyde where aldehyde adopts the preferred Felkin rotamer. In TS **C**, the *(R)*-silane approaches the *si* face of the aldehydes **3** or **7** shown adopting a Cornforth conformation.[12] In this case, the aldehyde adopts the *anti*-Felkin rotamer with the large OP group eclipsing the carbonyl group.



The TS's **B** and **D** (illustrated with the chelated aldehyde **3**) are postulated to account for the formation of *anti* homoallylic alcohols **5** and *syn* homoallylic alcohols **6** and **9** respectively, where the aldehyde adopts a Cram chelate conformer. In this case, both *(S)*-silane **1** and *(R)*-silane **2** approach the *si* face of the aldehyde. However, TS **B** orients the reacting π-bonds at 45° to each other (synclinal arrangement).

In summary, the β-substituted (*E*)-crotylsilane reagents exhibit excellent levels of 1,2-asymmetric induction in the Lewis acid promoted additions to *(S)*-2-benzyloxy- and *(S)*-2-(*tert*-butyldiphenylsilyloxy)propanal producing *syn* and *anti* disposed homoallylic alcohols. The open transition state models for 1,2-asymmetric induction shown above adequately account for the diastereoface selectivity in the presence or absence of internal chelation with the chiral, heterosubstituted aldehydes. Our continued exploration of these reagents to further develop their utility in double stereodifferentiating reactions will be reported in due course.

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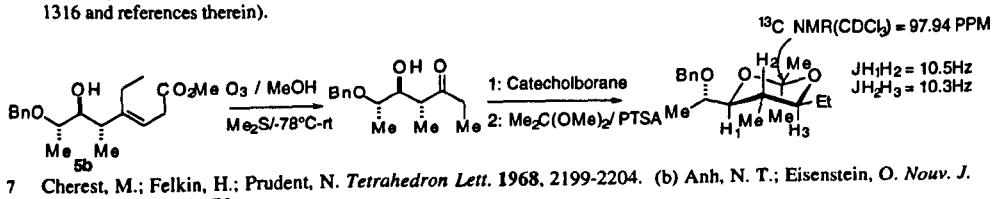
5 All reactions were performed in CH_2Cl_2 (0.5 M), at a reaction temperature of -78°C, (BF_3•OEt_2 → 24h, $TiCl_4$→12h).

6 The relative stereochemistry of all crotylation products was assigned through the measurement of ^{1}H-NMR three bond coupling constants and ^{13}C-NMR chemical shift correlation of the corresponding six-member acetonides and is illustrated for **5b** (*cf.* Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511-5184. Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099). The absolute stereochemistry of the homoallylic alcohol products was assigned based on *anti*-S_E' addition, (*cf.* Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293-1316 and references therein).



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