When esters 1a,b were irradiated in the presence of ephedrine (runs 12-16), not only were the observed de very close to the ee obtained by irradiation of an achiral ester such as isopropyl 2,4-dimethyl-2-pentenoate 1f^{5b} (run 23) but also the configuration of the new asymmetric center could be deduced from the model proposed to rationalize enantioselectivities.5b When bulky esters 1c-e were irradiated, the protonation, either with (+)- or (-)ephedrine, occurs on the less hindered side. When the configuration of the new asymmetric center was expected to be the same, that is, either from the protonation of the less crowded face of the chiral dienol or as determined from the model developed for the enantioselective photodeconjugation of achiral esters in the presence of aminoalcohols (runs 18, 19, and 22), the de was similar to those observed in the absence of chiral additives. By contrast, where mismatched interactions were expected (runs 17, 20, and 21), the observed diastereoselectivities were considerably lowered.

High Diastereofacial Selectivity in Nucleophilic Additions to Chiral Acylsilanes¹

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Asymmetric induction in nucleophilic additions to chiral aldehydes and ketones is a topic of great interest, and chiral aldehydes have been used more conveniently for the construction of many useful chiral synthons in natural product syntheses.² However, when the α -chiral carbonyl compounds have no ability to coordinate with metals, the 1,2-asymmetric induction is generally modest, and some more elegant approaches have been advanced recently.^{2,3} In our case, it became necessary to explore more effective construction of syn moiety in the total synthesis of a new macrolide, rhizoxin.4

In this communication, we report that α -chiral acylsilanes show exceptional diastereofacial preferences in nucleophilic additions followed by stereospecific protiodesilylation with F⁻ anion to afford Cram-type isomers 7.

The important observation and explanation by Cherest, Felkin, and Prudent that asymmetric induction increases markedly in the series of compounds 1 (R^1 = Me, Et, *i*-Pr, and *t*-Bu) as the size of R increases⁵ suggests to us to start with an aldehyde equivalent having a bulky group R¹ (Scheme I), and, chiral acylsilanes⁶ were selected to be one of the most ideal chiral carbonyl compounds because of the following three characteristic points; (1) the trimethyl silyl group may be bulky⁷ enough to cause strong sterScheme I



Scheme II



(major conformer)







eodifferentiation between A and B (Scheme II), (2) the silvl group can be stereospecifically replaced with hydrogen after nucleophilic additions, and (3) the acylsilanes and α -hydroxysilanes are both considered to be easy to handle and stable (Scheme III). Thus, α -chiral acylsilane 4 (R² = Ph)⁸ was treated with *n*-BuLi in THF at -78 °C for 5 min, affording a mixture of α -hydroxysilanes⁹ 5 and 6. The diastereomer ratio was estimated to be >100:1.¹⁰ Subsequent treatment of the crude α -hydroxysilanes with TBAF $(n-\mathrm{Bu}_4\mathrm{N}^+\mathrm{F}^-)^{11,12}$ in DMF at room temperature gave the known desilylated products 7 and 8 in a ratio of >100:1.^{13,14} For comparison, the syn and anti isomers 7 and 8 were obtained from the reaction of 10 ($R^2 = Ph$) and *n*-BuLi in a ratio of 5:1.¹⁵ On the

(9) α -Hydroxysilanes were prepared and well characterized in the study of Brook rearrangement, see: Brook, A. G. Acc. Chem. Res. 1974, 7, 77 and references cited therein

(10) The ratio was determined by 400 MHz ¹H NMR analysis of the reaction mixture.

(11) TBAF (n-Bu₄N⁺F⁻·3H₂O, purchased from Aldrich) was used. TBAF (1 M solution in THF, Aldrich) was also effective. In THF, the reaction proceeded more slowly.

(12) During the present methology was developed as an essential part for the total synthesis of a new macrolide, rhizoxin, a high stereoselective addition of nucleophiles to 2-(phenylthio)-3-phenyl-1-(trimethylsilyl)-1-propanone, see: Reich, H. J.; Holton, R. C.; Borkowsky, S. L. J. Org. Chem. **1987**, 52, 314. This prompted us to publish our own results.⁴

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⁽¹⁾ Dedicated to Prof. E. J. Corey of Harvard University on the occasion of his 60th birthday.

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Table I.	Diastereomer	Ratios in	the	Reactions	of	Nucleophiles	with	α -Chiral	Acyl	silane
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entry	R ² (4)	Nu-M ^a	conditions ^b	yield ^c % (5 + 6)	α -hydroxysilane ratio ^d 5:6	yield ^e % (7 + 8)	product ratio ^f 7:8
1	Ph	n-Bu-Li	A	92	>100:1	89	>100:18
2	Ph	Me-Li	Α	96	>40:1	76	>40:1
3	Ph	allyl-TMS	В	68	>100:1	56	>10018
4	Ph	allyl-MgBr	Α	96	11:1	85	11:18
5	1-cyclohexenyl	n-Bu-Li	А	56	>30:1	40	>30:1
6	1-cyclohexenyl	Me-Li	Α	69	>100:1	69	>100:1
7	1-cyclohexenyl	allyl-TMS	В	50	>30:1	40	>301
8	1-cyclohexenyl	allyl–MgBr	А	69	11:1	39	11:1
9	cyclohexyl	n-BuLi	А	98	15:1	80	15:1
10	cyclohexyl	Me-Li	А	77	21:1	61	21:1
11	cyclohexyl	allyl-TMS	В	96	>100:1	79	>100:1
12	cyclohexyl	allyl–MgBr	А	93	3.5:1	75	3.5:1

^{*a*}Nucleophiles (2 equiv) were used. ^{*b*}A: THF, -78 °C, 5 min; B: CH₂Cl₂, TiCl₄ (1 equiv), -78 °C, 5 min. ^{*c*}Isolated yield. ^{*d*}Determined by 400 MHz ¹H NMR. ^{*e*}Isolated yield from 4. ^{*f*}Determined by 400 MHz ¹H NMR. ^{*s*}Determined by GLC analysis.

Table II. Diastereomer Ratios in the Reactions of Nucleophiles with α -Chiral Aldehydes

entry	R ² (10)	Nu-M ^a	condi- tions ^b	yield ^c % (7 + 8)	product ratio ^d 7:8
1	Ph	n-Bu-Li	A	91	5:1e
2	Ph	Me-Li	Α	91	4:1
3	Ph	allyl-TMS	В	90	2:1 ^f
4	Ph	allyl-MgBr	Α	92	$1.7:1^{f}$
5	1-cyclohexenyl	n-Bu-Li	Α	40	16:1
6	1-cyclohexenyl	Me-Li	Α	49	1.9:1
7	1-cyclohexenyl	allyl-TMS	В	61	1:1
8	1-cyclohexenyl	allyl-MgBr	Α	54	2.5:1
9	cyclohexyl	n-Bu-Li	Α	96	3.5:1
10	cyclohexyl	Me-Li	Α	75	2:1
11	cyclohexyl	allyl-TMS	В	84	1.5:1
12	cyclohexyl	allyl-MgBr	A	59	2:1

^aNucleophiles (2 equiv) were used. ^bA: THF, -78 °C, 5 min; B: CH₂Cl₂, TiCl₄ (1 equiv), -78 °C, 5 min. ^cIsolated yield. ^dDetermined by 400 MHz ¹H NMR. ^eReference 3c. ^fDetermined by GLC analysis.

other hand, the diastereomers 5 and 6 were also prepared in a ratio of 1:>50 from the reaction of 1 ($R^1 = n$ -Bu) and TMSLi,¹⁶ and then treatment of the mixture with TBAF afforded 7 and 8 in a ratio of 1:>50.¹⁴ The protiodesilylation mentioned above was assumed to proceed with complete retention (>99%).¹³ This supposition was verified by single-crystal X-ray analysis of the 3,5-dinitrobenzoate derivative of the major diastereomer of α -hydroxysilanes prepared from 4 and allyltrimethylsilane by the present methodology (entry 3, Table I),^{17,18} which indeed showed it to be 9. The extension of these reactions using various α -chiral silanes and nucleophiles was performed, representative results are shown in Table I, and direct nucleophilic additions to aldehydes 10 are also shown for comparison in Table II.



The results clearly showed that acylsilanes with a phenyl group at the α -position to the carbonyl group afford syn products with highly remarkable selectivity not accessible by simple addition to chiral aldehydes, and those with the cyclohexenyl and cyclohexyl groups showed less selectivity but generally much better than that of direct additions to aldehydes. Our results can be accommodated within the general framework of Felkin's model for 1,2-asymmetric induction. However, steric effects alone cannot explain the results, and an electronic effect (σ^* -orbital energies) is considered to contribute equally to the stereodifferentiation.¹⁷⁻¹⁹

Thus, the utility of acylsilanes as aldehyde equivalents and the highly stereospecific protiodesilylation of α -hydroxysilanes with F⁻ enable us to construct syn isomers or Cram-type isomers,²⁰ and, considering that α -hydroxysilanes are also accessible by other methods,²¹ the overall stereocontrolling methods via α -hydroxysilanes in acyclic systems are quite effective and are now applied toward the total synthesis of rhizoxin.

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Registry No. 1 ($\mathbf{R}' = n$ -Bu), 103189-52-2; **4** ($\mathbf{R}^2 = Ph$), 114634-03-6; 4 ($R^2 = 1$ -cyclohexenyl), 114634-04-7; 4 ($R^2 = cyclohexyl$), 114634-05-8; 5 ($R^2 = Ph$; Nu = *n*-Bu), 114634-06-9; 5 ($R^2 = Ph$; Nu = Me), 114634-07-0; 5 ($R^2 = Ph$; Nu = allyl), 114634-08-1; 5 ($R^2 = 1$ -cyclohexyl; Nu = n-Bu), 114634-09-2; 5 (R² = 1-cyclohexyl; Nu = Me), 114634-10-5; 5 ($R^2 = 1$ -cyclohexyl; Nu = allyl), 114634-11-6; 5 ($R^2 =$ cyclohexyl; Nu = n-Bu), 114634-12-7; 5 ($R^2 =$ cyclohexyl; Nu = Me), 114634-13-8; 5 (R^2 = cyclohexyl; Nu = allyl), 114634-14-9; 6 (R^2 = Ph; $Nu = allyl), 114634-17-2; 6 (R^2 = 1-cyclohexenyl; Nu = allyl),$ 114634-18-3; **6** (\mathbb{R}^2 = cyclohexyl; Nu = allyl), 114634-19-4; **6** (\mathbb{R}^2 = cyclohexyl; Nu = *n*-Bu), 114634-22-9; **6** (\mathbb{R}^2 = Ph; Nu = *n*-Bu), 114634-24-1; 7 ($R^2 = Ph$; Nu = *n*-Bu), 56844-72-5; 7 ($R^2 = Ph$; Nu = Me), 40960-66-5; 7 ($R^2 = Ph$; Nu = allyl), 74333-47-4; 7 ($R^2 = 1$ -cyclohexenyl; Nu = *n*-Bu), 114222-04-7; 7 ($R^2 = 1$ -cyclohexenyl; Nu = Me), 114222-00-3; 7 ($R^2 = 1$ -cyclohexenyl; Nu = allyl), 114634-15-0; $\begin{aligned} &\text{Me}, 114222\text{-}00\text{-}3, 7 (\text{R}^2 = 1\text{-}\text{cyclonexchyl}, 1\text{-}\text{u} = 4\text{-}\text{hyl}), 11403\text{-}13\text{-}0, \\ &\text{7} (\text{R}^2 = \text{cyclohexyl}; \text{Nu} = n\text{-}\text{Bu}), 114222\text{-}08\text{-}1; 7 (\text{R}^2 = \text{cyclohexyl}; \text{Nu} = \text{Me}), 114222\text{-}06\text{-}9; 7 (\text{R}^2 = \text{cyclohexyl}; \text{Nu} = \text{allyl}), 114634\text{-}16\text{-}1; \\ &\text{R}^2 = \text{Ph}; \text{Nu} = \text{allyl}), 74333\text{-}46\text{-}3; \\ &\text{R}^2 = \text{Ph}; \text{Nu} = \text{allyl}), 74333\text{-}46\text{-}3; \\ &\text{R}^2 = 1\text{-}\text{cyclohexenyl}; \text{Nu} = \text{allyl}), \end{aligned}$ 114634-20-7; 8 (R^2 = cyclohexyl; Nu = allyl), 114634-21-8; 8 (R^2 = cyclohexyl; Nu = *n*-Bu), 114222-09-2; 8 (R^2 = Ph; Nu = *n*-Bu), 56844-77-0; 8 ($R^2 = Ph$; Nu = Me), 56907-39-2; 8 ($R^2 = 1$ -cyclohexenyl; Nu = n-Bu), 114222-05-8; 8 ($R^2 = 1$ -cyclohexenyl; Nu = Me), 114222-01-4; 8 (R^2 = cyclohexyl; Nu = Me), 114222-07-0; 9, 114634-23-0; 10 ($R^2 = Ph$), 34713-70-7; 10 ($R^2 = 1$ -cyclohexenyl), 114221-81-7; 10 (R^2 = cyclohexyl), 97859-57-9; allyltrimethylsilane, 762-72-1.

Supplementary Material Available: Structural and physical data for all new compounds, X-ray data for 9, and the structure of rhizoxin (15 pages). Ordering information is given on any current masthead page.

⁽¹⁶⁾ Still, W. C. J. Org. Chem. 1976, 41, 3063.

⁽¹⁷⁾ The crystalline benzoate 9 was prepared from 8 (see: entry 3, Table I) by four-step reactions (allyltrimethylsilane/TiCl₄, BH₃·SMe₂, H₂O₂-Na-OH, and 3,5-dinitrobenzoylchloride/Py) in a good overall yield and purified by recrystallization from methanol, mp 104-105 °C. (18) The important effect of σ^* -orbital energies in diastereoface differ-

⁽¹⁸⁾ The important effect of σ^* -orbital energies in diastereoface differentiation in additions to α -chiral aldehydes is persuasively well discussed by Heathcock and Lodge in ref 2.

⁽¹⁹⁾ A preliminary study showed that the diastereoselectivity in the cases of 4 ($R^2 = n$ -alkyl) and β -chiral acylsilanes was not high.

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