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LIPASE MEDIATED RESOLUTION OF CHIRAL (E)-VINYLSILANES: AN IMPROVED PROCEDURE FOR THE PRODUCTION OF (*R*)- AND (*S*)-(E)-1-TRIALKYLSILYL-1-BUTEN-3-OL DERIVATIVES

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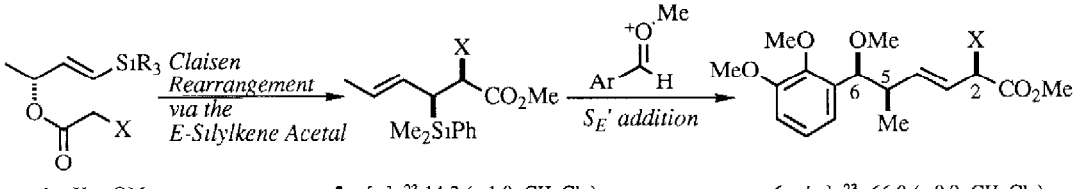
Abstract. A crude enzymic extract of *Pseudomonas* AK in pentane catalyzes the transesterification of chiral (E)-vinylsilanes **1**, resulting in the production of highly enantiomerically enriched (*R*)- and (*S*)-(E)-1-trialkylsilyl-1-buten-3-ol derivatives (***S*)-2** and (***R*)-3**. A series of related vinylsilanes and two-different lipases have been screened to identify optimal reaction conditions.

We are currently engaged in the asymmetric synthesis of certain members of the ansamycin class of anti-tumor antibiotics In this regard we have recently reported the synthesis[2] and the utility of enantiomerically pure α-chiral-β-silyl-(E)-hexenoate derivatives in highly diastereo- and enantioselective addition reactions to activated aryl acetals as illustrated with (2*S*, 3*S*)-**5** in the Scheme. Those reactions resulted in the formation of optically active hexenoic acid derivatives **6**, with high levels of 1,4- and 1,5-remote asymmetric induction [3] Our initial experiments in this area support the notion that chiral allylsilane reagents of type **5**, can exhibit high levels of topological bias for diastereoface selection in carbonyl-like addition reactions.

Scheme



4a; X = OMe — **5a**; $[\alpha]_D^{23}$ 14.2 (c 1.0, CH_2Cl_2) — **6a**; $[\alpha]_D^{23}$ -66.0 (c 0.9, CH_2Cl_2)

4b; X = Me — **5b**; $[\alpha]_D^{23}$ 10 6 (c 0 5, CH_2Cl_2) — **6b**; $[\alpha]_D^{23}$ -41 0 (c 1 0, CH_2Cl_2)

The successful employment of these reagents in asymmetric synthesis was based on the availability of optically pure (E)-vinylsilanes **4**, precursors to the optically active (E)-crotylsilanes **5**, through a well precedented Ireland ester Claisen rearrangement [4] In two recent reports from these laboratories, we have described the synthesis[5] and resolution of two related structural types· 1-trialkylsilyl-2-buten-1-ol (C1-oxygenated allylsilanes) and 1-trialkylsilyl-1-buten-3-ol derivatives (C3-oxygenated-(E)-vinylsilanes, **1**), utilizing (*R*)-O-acetyl mandelic acid as the resolving agent.[6] Although the classical resolution procedure was effective in obtaining useful quantities of both (*R*)- and (*S*)-(E)-1-trialkylsilyl-1-buten-3-ol derivatives, it required a difficult chromatography step which detracted from the overall utility of this method Hence, we sought a more efficient procedure for the rapid production of greater quantities of optically pure E-vinylsilanes

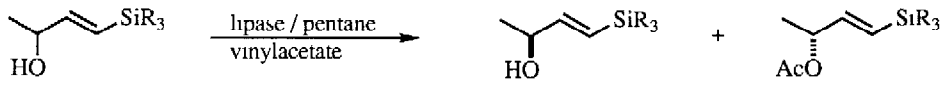
Prior to our initial report detailing the resolution of oxygenated allyl and vinylsilanes, structurally similar (E)-vinyltrimethylsilanes had been obtained in optically active form through a Katsuki/Sharpless asymmetric epoxidation.[7] In addition, a recent report by Burgess and Jennings[8] demonstrated that allylic and propargylic alcohols, which are not easily resolved by an asymmetric epoxidation,[9] are good substrates for certain lipases and effectively participate in irreversible enzyme-promoted transesterifications[10] in hydrocarbon solvents.[11]

In this letter we would like to report the results of our studies which describe a lipase[12] mediated resolution of racemic (E)-1-trialkylsilyl-1-buten-3-ol derivatives **1**, producing the optically active (E)-vinylsilanes (***S*)-2** and (***R*)-3** with excellent levels of enantiomeric purity. Three racemic (E)-vinylsilane substrates bearing different silicon groups, including trimethylsilyl (TMS), dimethylphenylsilyl (DMPS) and tert-butyldimethylsilyl (TBDMS) were investigated. The date presented in the Table indicate that the vinylsilanes can be conveniently resolved as illustrated with entries 3, 6 and 10 producing nearly optically pure (*S*)-alcohol (***S*)-2**. With regards to the size of the silicon group and its effect on turnover rate, the TMS vinylsilane reacted faster than the DMPS vinylsilane which in turn reacted faster than the TBDMS derivative; compare entries 2, 5, and 9. In contrast the porcine pancreatic lipase (Sigma) exhibited high ee's for the (*S*)-acetate, albeit longer reaction times were required; see entries 4 and 11. Resolution of the trimethyl- and dimethylphenylsilanes with the AK lipase were typically complete in 1-2 hours at ambient temperature. The sterically larger 1-tert-butyldimethylsilyl-1-buten-3-ol required heating (36 °C) to effect resolution in 2.5 hours (see entry 7).

Although both enzymes that we examined for the (E)-vinylsilane resolution were effective, the *Pseudomonas* lipase exhibited exceedingly better reaction rates than the porcine pancreatic lipase. In addition, the *Pseudomonas* lipase showed negligible loss of catalytic activity even after being recycled five times. In our efforts to optimize reaction conditions other solvents, including isooctane, chloroform, and methylene chloride, were screened and were found to be less effective in the resolution reaction. We also recommend the use of freshly distilled vinylacetate since it has been shown to enhance the over all reaction rate. For the cases examined, the inclusion of 4Å molecular sieves did not appear to show any effect on either the reaction rate or enantioselectivity with these structure types.[8] Assignment of absolute stereochemistry as well as determination of enantiomeric excess (ee) was accomplished by the careful ^{1}H NMR analysis and chemical shift correlation of the corresponding (*R*)-O-acetyl mandelic acids[6,13] according to the method of Trost and coworkers.[14] The E values[8,15] were calculated for each entry in the Table and found to be excellent (E >20), with the exception of entries 1, 2, 4 and 7 (E = 10 - 20).

A general procedure for the lipase resolution of racemic (E)-1-dimethylphenylsilyl-1-buten-3-ol is as follows: To a pentane solution of the racemic alcohol **1** (10 g, 48.54 mmol, 0.2 **M**), was added a crude preparation of the *Pseudomonas* lipase (5 g, 0.5 wt. equiv) and freshly distilled vinyl acetate (242.7 mmol, 22.4 mL, 5.0 equiv). The heterogeneous mixture was vigorously stirred at ambient temperature for 2 hours before the reaction mixture was filtered through a sintered glass funnel to recover the enzyme extract. The pentane was removed under reduced pressure and the products purified by flash chromatography on SiO_2 (100% pet. ether → 10% EtOAc-pet. ether, gradient elution) afforded acetate (***R*)-3** (5.65 g, 47% chemical yield, 80% ee) and the alcohol (***S*)-2** (4.40 g, 44 % chemical yield, >95% ee) as colorless oils (see entry 9 in the Table).

Table. Lipase Mediated Resolutions of (E)-Vinylsilanes



racemic 1

				(*S*)-2		(*R*)-3
entry	vinylsilane[R_3Si]	lipase (wt eq)[a]	time(hr)/temp(°C)	%conv.[b,c]	yield%, ee%[d]	yield%, ee%[d]
1.	Me_3Si	AK, 0.5	0.25 / 23	25	63, <5	23, 80
2.	Me_3Si	AK, 0 5	0.5 / 23	40	29, 55	34, 84
3.	Me_3Si	AK, 0.5	24 / 36	50	34.2, >95	34.5, 80
4	Me_3Si	ppl, 1.0	120 / 36	50	30, 47	35, 90
5	$^tBuMe_2Si$	AK, 0.5	2 / 23	25	74, 29	25, >95
6	$^tBuMe_2Si$	AK, 0 5	13 / 23	52	36, >95	39, 64
7.	$^tBuMe_2Si$	AK, 1 0	2 5 / 36	48	49, 65	30, 80
8.	Me_2PhSi	AK, 0 5	1 0 / 23	35	43, 38	30, >95
9.	Me_2PhSi	AK, 0 5	2 0 / 23	52	44, >95	47, 80
10.	Me_2PhSi	AK, 0 5	22 / 36	50	50, >95	36, 82
11	Me_2PhSi	ppl, 1 0	96 / 36	33	66, <5	30, 90

(a) AK = *Pseudomonas* AK (Amano Int Enzyme), ppl = porcine pancreatic lipase (Sigma). (b) determined by ^1H NMR operating at a signal to noise ratio of 200:1 (c) All products exhibited the expected ^1H NMR, ^{13}C NMR, IR and MS characteristics. (d) Determined from the ratio of the (R)-O-acetyl mandelate esters [Whitesell, J K , Reynolds, D. *J Org. Chem* **1983**, *48*, 3548]

In summary, given the utility of vinylsilanes in organic synthesis, the lipase promoted transesterification offers an efficient and convenient procedure for the production of nearly enantiomerically pure (R)- and (S)-(E)-1-trialkylsilyl-1-buten-3-ol derivatives, one that easily competes with the asymmetric epoxidation method[7] both from an operational and economic view point.

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References and Notes

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12 The *Pseudomonas* AK lipase was purchased from the Amano International Enzyme (Philadelphia, PA) at price of approximately $ 1.00/gram

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15 The E value is a term used to describe the enantiomeric ratio and is dependent on the ratio of specificity constants [V/K], where V and K denote the maximal velocities and Michaelis constants of the fast and slow-reacting enantiomers The analysis allows for a quantitative measurement of the level of discrimination between the two competing enantiomeric vinylsilanes by the lipase enzyme. For a detailed treatment of this analysis see: Chen, C.-S., Fujimoto, Y.; Girdaukas, G.; Sih, C. J *J Am Chem. Soc* **1982**, *104*, 7294.

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