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of Reliable Methods
for the Preparation
of Organic Compounds

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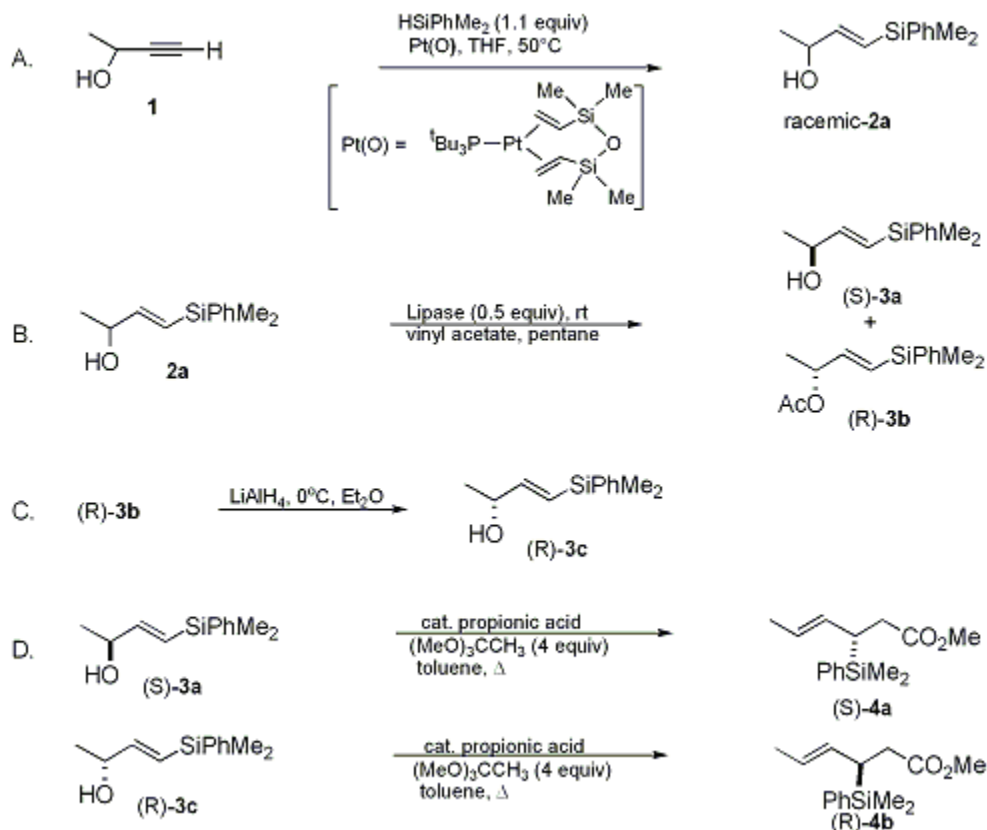
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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**SYNTHESIS OF CHIRAL (E)-CROTYLSILANES: [3R- AND 3S-]-
(4E)-METHYL 3-(DIMETHYLPHENYLSILYL)-4-HEXENOATE
[4-Hexenoic acid, 3-(dimethylphenylsilyl)-, methyl ester, [(R)-, and (S)-(E)-]-]**



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Checked by Pradeep Madan and Steven Wolff.

1. Procedure

A. (±)-1-(Dimethylphenylsilyl)-1-buten-3-ol (2a). A solution of 10.0 g (0.143 mol) of racemic 3-buten-2-ol (Note 1) dissolved in 255 mL of tetrahydrofuran (THF, Note 2) in a 1-L, round-bottomed flask equipped with a reflux condenser and nitrogen atmosphere is prepared. Dimethylphenylsilane (21.4 g, 0.157 mol) (Note 3) and a small piece of sodium metal (ca. 5 mg) (Note 4) are placed in the reaction mixture. The solution is stirred for 15 min and 12 mg (2.05×10^{-5} mol) of bis(η -divinyltetramethyldisiloxane)tri-tert-butylphosphineplatinum(0) (Note 5) is added. The reaction mixture is then heated under reflux for 12 hr. The orange solution is cooled to ambient temperature, and the solvent is removed under reduced pressure to yield a crude orange residue containing **2a**. The oil is subjected to column chromatography on silica gel (Note 6) (gradient elution 5, 10, 20, 35% EtOAc/hexanes) providing 25.4 g (123.23 mmol, 86%) of pure **2a** as a yellow oil (Note 7).

B. (3S)-1-(Dimethylphenylsilyl)-1-buten-3-ol (3a) and (3R)-1-(dimethylphenylsilyl)-1-buten-3-ol acetate (3b). A 400-mL pentane solution of 20.0 g (97.08 mmol) of the racemic secondary allylic alcohol **2a** in a 500-mL, round-bottomed flask is prepared. A crude preparation of 10.0 g of lipase Amano AK (Note 8) is added along with 24.8 mL (269.1 mmol) of freshly distilled vinyl acetate (Note 9). The heterogeneous mixture is stirred vigorously at 25°C for 4 hr (Note 10) before being filtered through a sintered glass funnel to recover the enzyme extract. The extract is washed with ether (Et₂O) (2

× 20 mL). The solvent is removed under reduced pressure and the products are purified by column chromatography on silica gel: gradient elution 4% EtOAc/hexanes affords 11.56 g of acetate (R)-**3b** (46.59 mmol, 48%), and gradient elution 20->35% EtOAc/hexanes affords 9.3 g of alcohol (S)-**3a** (45.12 mmol, 46%), as faint yellow oils (Note 6), (Note 11) and (Note 12).

C. (3R)-1-(Dimethylphenylsilyl)-1-buten-3-ol (**3c**). Acetate (R)-**3b** (9.0 g, 36.27 mmol) is dissolved under a nitrogen atmosphere in a cooled (0°C), 1-L, round-bottomed flask containing 120 mL of anhydrous Et₂O (Note 13). To this stirred mixture is slowly added over 10 min 1.81 g (47.79 mmol, 1.3 eq) of lithium aluminum hydride (LiAlH₄). After 15 min, aqueous 5% hydrochloric acid is added dropwise until bubbling ceases (Note 13). The resulting suspension is further diluted with a total volume of 100 mL of the acidic solution. The layers are separated, and the aqueous layer is extracted with 100 mL of Et₂O. The combined organic extracts are washed with an aqueous saturated solution of sodium chloride and dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum, to yield 6.27 g (30.42 mmol, 83%) of the (R)-alcohol **3c**. No additional purification is performed (Note 14).

D. (3S, 4E)-Methyl 3-(dimethylphenylsilyl)-4-hexenoate (**4a**). A stirred solution of 6.0 g (29.11 mmol) of alcohol **3a** and 60 mL of dry toluene in a 200-mL flask equipped with a reflux condenser is treated with 15 mL (116.89 mmol) of trimethyl orthoacetate and 0.15 mL (2.01 mmol, 0.07 equiv) of propionic acid (Note 15). The reaction mixture is heated under reflux for 48 hr and then allowed to cool to room temperature. Solvents and volatile material are removed under reduced pressure to leave the crude (E)-crotylsilane **4a** as a yellow oil. The crude residue is chromatographed on silica gel (gradient elution 5% EtOAc/hexanes). The eluant (Note 6) affords 6.58 g (25.1 mmol, 86%) of pure **4a** as a faint yellow, viscous oil (Note 6), (Note 16) and (Note 17).

2. Notes

1. 3-Butyn-2-ol, 99%, is purchased from Aldrich Chemical Company, Inc.
2. Tetrahydrofuran is freshly distilled from sodium and benzophenone.
3. Dimethylphenylsilane is purchased from United Chemical Technologies, Inc (formerly Hüls Petrarch Inc.).
4. In the Pt(0)-catalyzed hydrosilylation, the addition of a catalytic amount of Na(0) appears to be necessary to achieve high levels of regioselectivity (cf., 1,1- vs 1,2-disubstituted vinylsilane). Without the inclusion of Na(0), the reaction yields a minor regioisomer, (±)-2-(dimethylphenylsilyl)-1-buten-3-ol, **2b**, in a ratio of 10-15:1. The checkers found that the reaction was considerably faster and higher-yielding with 60 mg of the catalyst, bis(η-divinyltetramethyldisiloxane)tri-tert-butylphosphineplatinum(0).
5. The platinum catalyst is prepared according to the procedure of Chandra and Lo.² Chloroplatinic acid, H₂PtCl₆, (5.0 g, 12.22 mmol) and 0.6 mL of water are added to 61.71 mL (268.84 mmol) of 1,3-divinyltetramethyldisiloxane. The heterogeneous solution is heated to 55°C in an oil bath for 4 hr. The now homogeneous solution is cooled to room temperature and 5.0 g of sodium bicarbonate is added. The solid is filtered, and the resulting yellow solution is treated with 3.33 mL (13.44 mmol) of tri-tert-butylphosphine[(tert-Bu)₃P]. The catalyst precipitates as 4.8 g (67%) of a white solid that is filtered and washed with 1,3-divinyltetramethyldisiloxane (25 mL), and dried under vacuum. The checkers found that the mixture remained heterogeneous after 4 hr. Heating was continued for 18 hr.
6. Flash chromatography is performed on E. Merck silica gel 230-400 mesh: 250 g of silica gel is loaded on a 16- × 2-in size column using a minimum amount of hexanes as loading solvent.
7. The hydrosilylation product **2a** is sufficiently pure for use as starting material in procedure B. The spectral properties are as follows: ¹H NMR (400 MHz, CDCl₃) δ: 0.38 (s, 6 H), 1.30 (d, 3 H, J = 6.5), 4.34 (m, 1 H), 5.99 (dd, 1 H, J = 1.3, 18.7), 6.22 (dd, 1 H, J = 4.9, 18.7), 7.28-7.56 (m, 5 H); ¹³C NMR (67.5 MHz) δ: -2.7(2C), 22.8, 70.4, 125.9, 126.6, 127.6, 128.9, 133.8, 151.3; IR (neat) cm⁻¹: 3380, 3080, 2960, 1730, 1620, 1430, 1250, 1110, 860; CIHRMS M + NH₄⁺ (calcd for C₁₂H₂₂NOSi): 224.1470, (found): 224.1416.
8. The amount of enzyme extract is roughly calculated to be 0.5 wt equiv. The crude enzyme preparation may be purchased from Amano Enzyme U.S.A. Co., Ltd., Rt. 2, Box 1475, Troy, VA 22974.
9. A marked increase in reaction rate is noted when vinyl acetate is freshly distilled.

10. Reaction progress is monitored by ^1H NMR (CDCl_3); 0.5-mL of sample is withdrawn periodically (at 30-min intervals after 3 hr), filtered through a cotton plug, and the solvent is removed under reduced pressure. The integration ratio of proton 4.34 (m, 1 H) (S)-**3a**, and 5.38 (m, 1 H) (R)-**3b** is measured and the reaction is terminated when the integration ratio is 1:1.

11. The enantiomeric purity of vinylsilane (S)-**3a** and (R)-**3c** are determined to be >95% ee by ^1H -NMR (400 MHz) on the derived mandelate ester, obtained by a DCC-promoted coupling to (R)-O-acetylmandelic acid, and absolute stereochemical assignment is accomplished by ^1H NMR analysis of the derived (R)-O-acetylmandelate esters. For details of this procedure see the published method of Trost.^{3,4,5}

12. The spectral properties are as follows: (S)-**3a**: ^1H NMR (400 MHz, CDCl_3) δ : 0.38 (s, 6 H), 1.30 (d, 3 H, $J = 6.5$), 4.34 (m, 1 H), 5.99 (dd, 1 H, $J = 1.3, 18.7$), 6.22 (dd, 1 H, $J = 4.9, 18.7$), 7.28-7.56 (m, 5 H); ^{13}C NMR (67.5 MHz) δ : -2.7 (2C), 22.8, 70.4, 125.9, 126.6, 127.6, 128.9, 133.8, 151.3; IR (neat) cm^{-1} : 3380, 3080, 2960, 1730, 1620, 1430, 1250, 1110, 860; CIMS (NH_3), m/e (relative intensity): 224 ($\text{M}+\text{NH}_4^+$, 100), 206 (M, 44); CIHRMS (NH_3), m/e $\text{M}+\text{NH}_4^+$ (calcd for $\text{C}_{12}\text{H}_{22}\text{NOSi}$): 224.1470, (found): 224.1416; $[\alpha]_{\text{D}}^{23} +4.3^\circ$ (CHCl_3 , c 0.8); (R)-**3b**: ^1H NMR (400 MHz, CDCl_3) δ : 0.37 (s, 6 H), 1.32 (d, 3 H, $J = 6.5$), 2.08 (s, 3 H), 5.38 (m, 1 H), 5.9 (dd, 1 H, $J = 1.33, 18.8$), 6.1 (dd, 1 H, $J = 4.64, 18.8$), 7.3-7.5 (m, 5 H); ^{13}C NMR δ : -2.7 (2C), 19.8, 21.3, 72.1, 127.7, 127.8, 128.0, 129.0, 133.8, 146.6, 170.2; IR (neat) cm^{-1} : 3040, 2950, 1740, 1430, 1570, 1240, 1110, 1040, 830, 740; CIMS (NH_3), m/e (relative intensity) 209 (33), 179 (24), 171 (68), 135 (100), 117 (97); CIHRMS (NH_3), m/e M^+ (calcd for $\text{C}_{14}\text{H}_{20}\text{O}_2\text{Si}$): 248.1233, (found): 248.1299; $[\alpha]_{\text{D}}^{23} +58.3^\circ$ (CHCl_3 , c 0.5).

13. Ether is freshly distilled from sodium and benzophenone. Lithium aluminum hydride is purchased from Aldrich Chemical Company, Inc., and used as supplied.

14. The specific rotation of alcohol (R)-**3c** obtained from LiAlH_4 reduction of acetate (R)-**3b** is $[\alpha]_{\text{D}}^{23} -3.8^\circ$ (CHCl_3 , c 0.8).

15. Toluene is freshly distilled from calcium hydride. Trimethyl orthoacetate, 99%, and propionic acid, 99%, are purchased from Aldrich Chemical Company, Inc., and used as supplied.

16. The determination of enantiomeric excess (96% ee) of the Claisen rearrangement products **4a** and **4b** is accomplished by a Mosher ^1H NMR analysis of the (R)-O-acetylmandelate esters that are derived from the primary alcohols. For example, **4a** is reduced with LiAlH_4 (1.0 equiv/THF/0°C) followed by esterification of the resulting primary alcohol with (R)-O-acetylmandelic acid (DCC, 1.5 equiv/cat. DMAP/ CH_2Cl_2) to afford the mandelate ester in 91% yield (two steps).^{3,4,5}

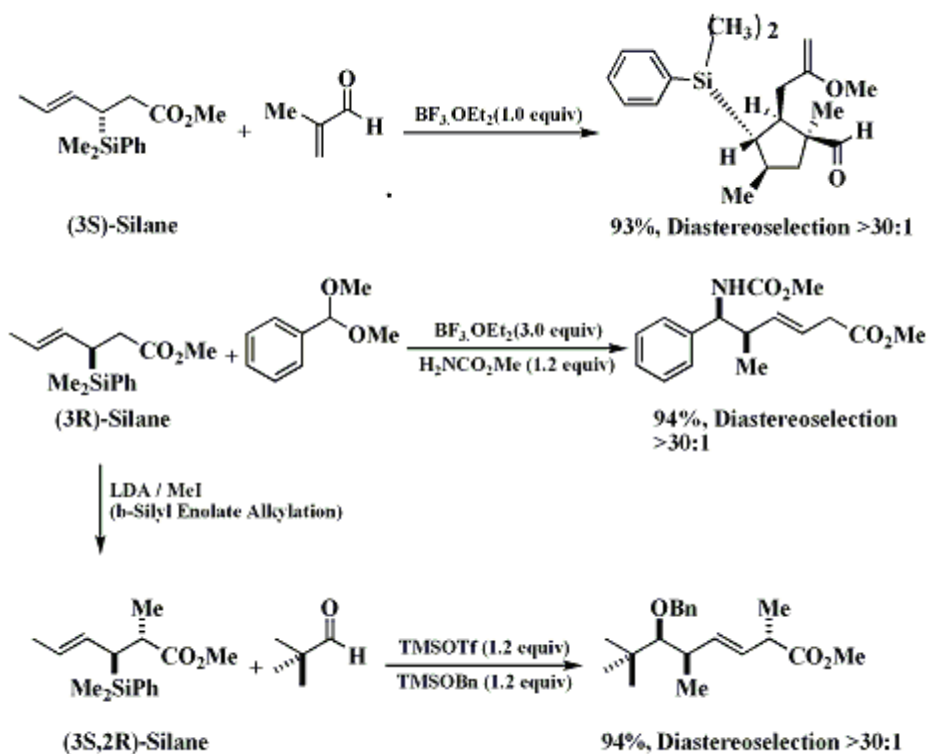
17. The spectral properties are as follows: ^1H NMR (400 MHz, CDCl_3) δ : 0.28 (s, 6 H), 1.64 (d, 3 H, $J = 4.7$), 2.20 (m, 1 H), 2.27 (dd, 1 H, $J = <1.0, 14.5$), 2.33 (dd, 1 H, $J = 6.3, 14.5$), 3.57 (s, 3 H), 5.28 (m, 2 H), 7.35-7.49 (m, 5 H); ^{13}C NMR (67.5 MHz) δ : -5.5, -4.5, 18.1, 28.7, 34.3, 51.4, 123.8, 127.7, 129.1, 129.8, 133.9, 136.8, 173.9; CIMS (NH_3), m/e (relative intensity) 280 ($\text{M}+\text{NH}_4^+$, 48), 263 (M^+ , 39), 184 (100), 151 (40); CIHRMS (NH_3), m/e $\text{M}+\text{NH}_4^+$ (calcd for $\text{C}_{15}\text{H}_{26}\text{NO}_2\text{Si}$): 280.1733, (found): 280.1734; $[\alpha]_{\text{D}}^{23} -11.4^\circ$ (CHCl_3 , c 0.5) and $[\alpha]_{\text{D}}^{23} -15.4^\circ$ (CH_2Cl_2 , c 1.4) for [(R)-**4b**] derived from Claisen rearrangement of (R)-**3c**. For (S)-**4a** $[\alpha]_{\text{D}}^{23} +11.9^\circ$ (CHCl_3 , c 0.5) and $[\alpha]_{\text{D}}^{23} +15.9^\circ$ (CH_2Cl_2 , c 1.6).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Functionalized chiral (E)-crotylsilanes **4a** and **4b** and related silane reagents have recently been used as carbon nucleophiles in highly diastereo- and enantioselective crotylation reactions.⁶ Of particular interest are enantioselective transformations, including an asymmetric [3 + 2] cyclopentane annulation through a conjugate addition and subsequent cyclization. The condensation between the chiral silane reagent and in situ generated N-acylimines affords the homoallylic N-acylamines⁷ and functionalized homoallylic ether formation via a three-component, in situ generation and trapping the derived oxonium ion.^{8,9} A subsequent silyl group-directed alkylation of the derived lithium enolate produces a silane reagent bearing functionalization α to the methyl ester which has been employed in the in situ asymmetric crotylsilation producing homoallylic ethers.¹⁰ Equations 1 - 3 illustrate representative examples of the Lewis acid-promoted enantioselective transformations of the silane reagent.



The three-step procedure described for the preparation of the illustrated crotylsilanes is initiated with the hydrosilylation of rac-3-butyn-2-ol. This procedure is significantly improved with respect to the positional selectivity of the hydrosilylation resulting in exclusive formation of the racemic (*E*)-vinylsilane, and as a result the present procedure is much more amenable to scale-up than those previously described in the literature.^{11 12} The enzymatic resolution of the racemic secondary allylic alcohol (vinylsilane) has also been reported using commercially available lipase extracts. The use of a Johnson ortho ester Claisen rearrangement affords the (*E*)-crotylsilanes **4** in nearly enantiomerically pure form.

References and Notes

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**Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)**

(3R)-(4E)-Methyl 3-(dimethylphenylsilyl)-4-hexenoate:
4-Hexenoic acid,3-(dimethylphenylsilyl)-, methyl ester, [R-(E)]- (12); (136174-52-2)

(3S)-(4E)-Methyl 3-(dimethylphenylsilyl)-4-hexenoate:
4-Hexenoic acid,3-(dimethylphenylsilyl)-, methyl ester, [S-(E)]- (12); (136314-66-4)

(±)-1-(Dimethylphenylsilyl)-1-buten-3-ol:
3-Buten-2-ol, 1-(dimethylphenylsilyl)-, (E)-(±)- (12); (137120-08-2)

3-Butyn-2-ol:
3-Butyn-2-ol, (±)- (10); (65337-13-5)

Dimethylphenylsilane:
Silane, dimethylphenyl- (8,9); (766-77-8)

Sodium (8,9); (7440-23-5)

Bis(η-divinyltetramethyldisiloxane)tri-tert-butylphosphineplatinum(0):
Platinum, [1,3-bis(η²-ethenyl)-1,1,3,3-tetramethyldisiloxane][tris(1,1-dimethylethyl)phosphine]- (11);
(104602-18-8)

(3S)-1-(Dimethylphenylsilyl)-1-buten-3-ol:
3-Buten-2-ol, 4-(dimethylphenylsilyl)-, [S-(E)]- (12); (133398-24-0)

(3R)-1-(Dimethylphenylsilyl)-1-buten-3-ol acetate:
3-Buten-2-ol,4-(dimethylphenylsilyl)-, acetate, [R-(E)]- (12); (129921-47-7)

Vinyl acetate:
Acetic acid vinyl ester (8);
Acetic acid ethenyl ester (9); (108-05-4)

(3R)-1-(Dimethylphenylsilyl)-1-buten-3-ol:
3-Buten-2-ol, 1-(dimethylphenylsilyl)-, [R-(E)]- (12); (133398-25-1)

Trimethyl orthoacetate:
Orthoacetic acid, trimethyl ester (8);
Ethane, 1,1,1-trimethoxy- (9); (1445-45-0)

Propionic acid (8);
Propanoic acid (9); (79-09-4)

1,3-Divinyltetramethyldisiloxane:
Disiloxane, 1,1,3,3-tetramethyl-1,3-divinyl- (8);
Disiloxane, 1,3-diethenyl-1,1,3,3-tetramethyl- (9); (2627-95-4)

Chloroplatinic acid hexahydrate:
Platinate (2-), hexahydro-, dihydrogen (8);
Platinate (2-), hexachloro-, dihydrogen, (OC-6-11)- (9); (16941-12-1)

Tri-tert-butylphosphine:

Phosphine, tri-tert-butyl- (8);
Phosphine, tris(1,1-dimethylethyl)- (9); (13716-12-6)

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