A Conjugate Reduction Pathway to Chiral Silanes Using CuH

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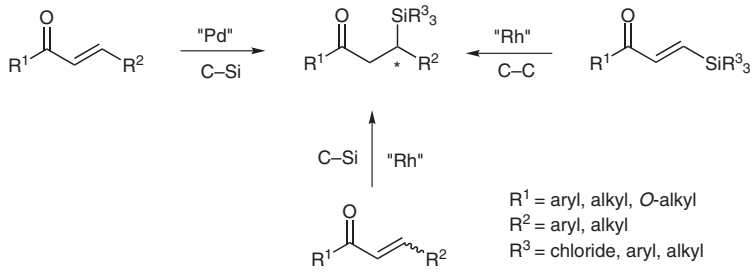
Received 28 March 2007

Dedicated to Prof. Madeleine M. Joullie on the occasion of her 80th birthday.

Abstract: Experimental details concerning asymmetric 1,4-reduction of β-silylated-β,β-disubstituted enoates catalyzed by CuH are described. High yields and enantiomeric excesses are to be expected when Solvias' JOSIPHOS bis-phosphine PPF-P(*t*-Bu)$_2$ is used as a nonracemic ligand.

Key words: chiral silanes, CuH, asymmetric conjugate reduction

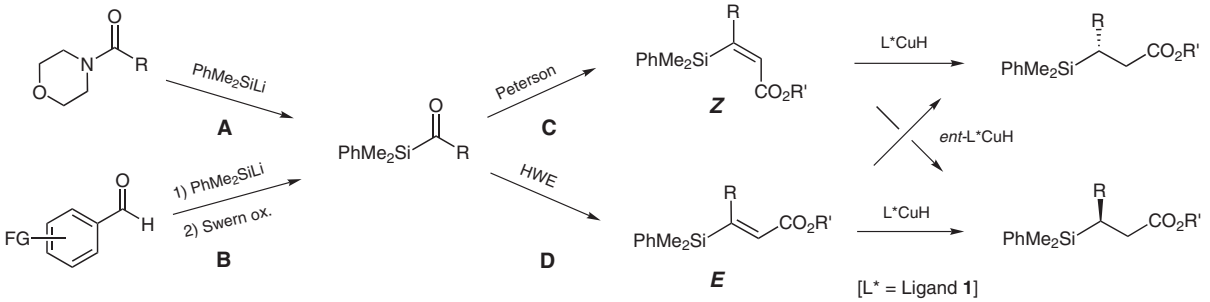


Scheme 1

Chiral organosilanes are valued intermediates in organic synthesis.[1] The Si–C bond is not only commonly used as an equivalent to the hydroxyl group using a Tamao[2]/Fleming[3] oxidation, but also provides many inroads for asymmetric C–C bond construction.[4] Due to their wide utility, a number of efforts have been dedicated to the synthesis of enantioenriched organosilanes (Scheme 1).[5]

These routes involve enantioselective C–Si[5a,c]or C–C[5b] bond formation under rhodium or palladium catalysis, respectively. Recently,[6] we disclosed a versatile method for preparing nonracemic silanes that relies on copper-catalyzed asymmetric hydrosilylations of β-silylated-β,β-disubstituted enoates (Scheme 2). Herein, we summarize this novel and potentially useful technology for synthesis of chiral organosilanes in high yields and enantioselectivities.

Acyl silane precursors to β-silylated-β,β-disubstituted enoates are easily prepared by treatment of morpholine amides with Fleming's PhMe$_2$SiLi (a deep red-colored solution in THF; path **A**, Scheme 2).[7] It is important to quench the initially formed tetrahedral intermediate at –78 °C to avoid the Brook rearrangement. β-Aryl-substituted enoates were made by 1,2-addition of PhMe$_2$SiLi to a benzaldehyde, followed by Swern oxidation (path **B**). Subsequent conversion to the corresponding educts useful for copper hydride-catalyzed asymmetric hydrosilylation



Scheme 2

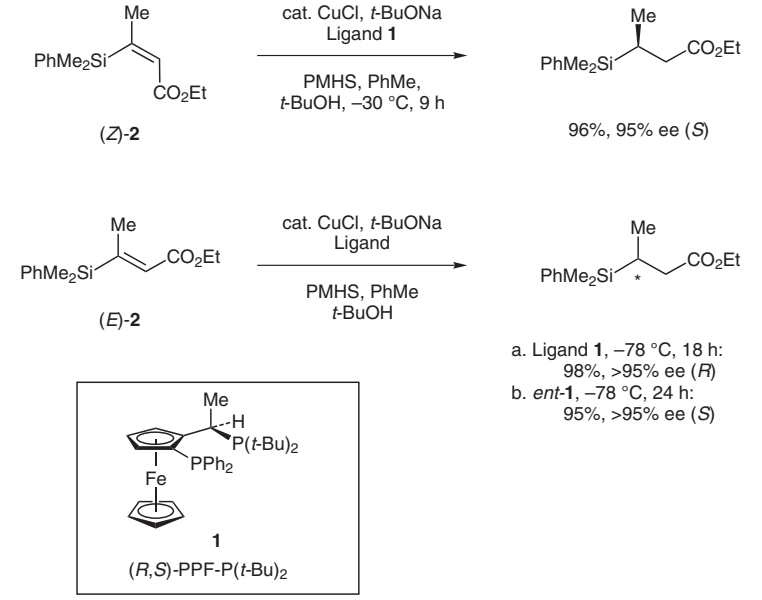
SYNTHESIS 2007, No. 20, pp 3257–3260
Advanced online publication: 30.07.2007
DOI: 10.1055/s-2007-983830; Art ID: Z08007SS

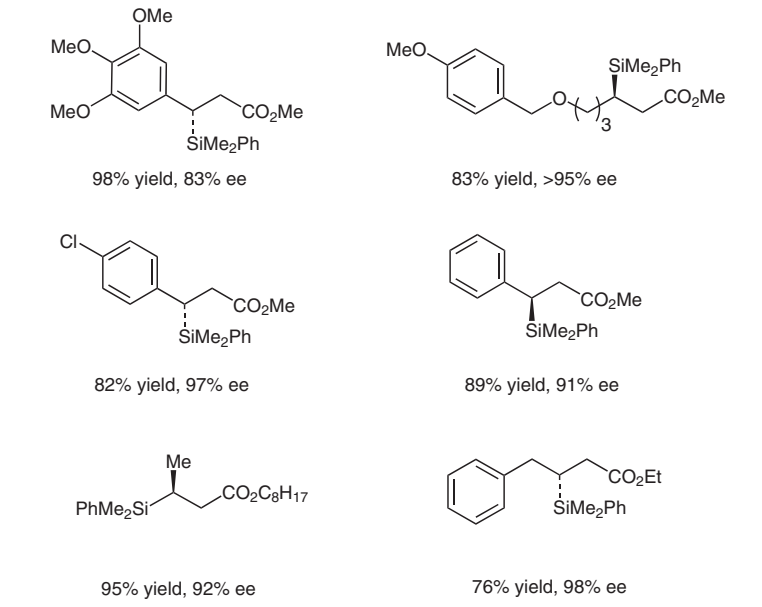
followed from either Peterson olefination (path **C**) or Horner–Wadsworth–Emmons reaction (HWE, path **D**) of intermediate acyl silanes, giving rise to *Z*- and *E*-enoates, respectively.[8] Pure geometrical isomers can be obtained by silica gel chromatographic purification affording stable materials as colorless oils.

Using 1% CuCl and 1% *t*-BuONa, active CuH can be generated in situ in the presence of polymethylhydrosiloxane (PMHS), purchased from Lancaster.[9,10] Copper can also be introduced in the form of Stryker's reagent [hexameric $(Ph_3P)CuH$],[11] although care should be exercised to ensure that commercial material is of good quality, easily done by ^1H NMR analysis in C_6D_6.[12] A third alternative is to use $Cu(OAc)_2 \cdot H_2O$ as the copper(I) source, also forming CuH upon introduction of PMHS in toluene at room temperature.[13]

Although ligand-accelerated CuH reductions are not usually sensitive to neutral water,[11] exposure to oxygen should be minimized to avoid (presumably) oxidation at the ligand to phosphine oxides. Nonracemic JOSIPHOS analogue PPF-P(*t*-Bu)$_2$ (**1**, Scheme 3),[14] supplied by Solvias,[15] was found to be particularly effective [substrate-to-ligand (S/L) ratios up to 1000:1] as the derived CuH complex at promoting asymmetric hydrosilylation of several β-silyl enoates.[16]

A variety of β-silyl unsaturated esters were smoothly reduced under mild conditions in good yields and high ee (Scheme 3). As expected from prior observations,[16] the presence of *t*-BuOH was crucial in these cases, noticeably accelerating the reduction. Thus, using 1.1 equivalents of *t*-BuOH, reduction of **2** was complete within 24 hours at –78 °C, while without *t*-BuOH seven days at room tem-





Scheme 3

perature were needed to reach full conversion. In general, the nature of olefin geometry (*E* vs *Z*) does not affect the rate of reduction, or the level of enantioselectivity. When a stereodefined nonracemic ligand such as **1** is used with either *E*- or *Z*-isomer, complementary chirality in the 1,4-adduct is obtained. Likewise, using the enantiomeric ligand (such as *ent*-**1**) on an enoate of defined olefin geometry can dictate complimentary chirality in the product. By comparison with known products derived from initial saponification and then imide derivatization with a nonracemic oxazolidinone,[17] the sense of chirality and levels of induction (observed as dr) could be ascertained with confidence.

In summary, the combination of catalytic CuH and Solvias' nonracemic (*R*,*S*)- or (*S*,*R*)-PPF-P(*t*-Bu)$_2$ together with stoichiometric silane (PMHS) effects asymmetric conjugate reduction of β-silylated-β,β-disubstituted enoates. This method can be applied to a wide range of substrates (β-aryl- and β-alkyl-β-silyl enoates) that are readily prepared in either *E*- or *Z*-form. Absolute stereochemistry in the products is controlled by substrate geometry or ligand axial chirality. Good yields and high ee's of the resulting nonracemic silanes are typical, and turnover numbers range from 100 to 1000.

Reactions were performed in oven-dried glassware under argon containing a Teflon coated stir bar and dry septum. THF and toluene were freshly distilled from Na/benzophenone ketyl prior to use. All commercially available reagents were distilled either from CaH_2 or molecular sieves under an inert atmosphere before use. PMHS can be used directly from the bottle, purchased from Lancaster, and should be stored under an inert atmosphere. (*R*,*S*)-PPF-P(*t*-Bu)$_2$ and (*S*,*R*)-PPF-P(*t*-Bu)$_2$ were generously supplied by Solvias. Column chromatography was performed using Davisil Grade 633 Type 60A silica gel. TLC analyses were performed on commercial Kieselgel 60 F254 silica gel plates. NMR spectra were obtained on Varian Inova systems using $CDCl_3$ as solvent, with proton and carbon resonances at 400 MHz and 100 MHz, respectively. Mass spectral data were acquired on a VF Autospec or an analytical VG-70-250 HF instrument.

Morpholine Amides from Acid Chlorides; General Procedure

The acid chloride (1 equiv) was added to a flask containing CH_2Cl_2 (enough to make a 1.0 M solution of the acid chloride). The flask was cooled to 0 °C, and morpholine (3 equiv) was added dropwise via syringe. The reaction was allowed to warm to r.t. and stirred for 30 min at which time it was diluted with EtOAc (5 mL), then washed with 1 M HCl (5 mL), sat. aq $NaHCO_3$ (5 mL), and brine (5 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting amides were used without further purification.

Acyl Silanes from Morpholine Amides; General Procedure (Scheme 2, Path A)

The morpholine amide (2 mmol) was added to a flame-dried 50 mL round-bottomed flask under dry N_2. To this amide, THF (3 mL) was added, and the solution was then cooled to –78 °C. Dimethylphenylsilyllithium (1.0 M solution in THF, 3 mL) was added dropwise via a syringe, and the reaction was allowed to stir for 1.5 h, after which time it was quenched at –78 °C (to prevent decomposition) by the addition of sat. aq NH_4Cl (4 mL). The resulting mixture was allowed to warm to r.t. and then stirred for an additional 30 min. The mixture was then partitioned between H_2O (5 mL) and Et_2O (5 mL), the phases separated, and the aqueous layer extracted with Et_2O (2 × 5 mL). The combined organics were washed with H_2O (2 × 20 mL) and brine (1 × 20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography using silica gel yielding pure acylsilane as clear oils.

(*Z*)-β-Silyl Enoates from Acyl Silanes; General Peterson Olefination Procedure (Scheme 2, Path C)

To a THF (3 mL) solution of 1,1,1,3,3,3-hexamethyldisilazane (194 mg, 1.2 mmol) was added a hexane solution of *n*-BuLi (l.6 M, 0.75 mL, 1.2 mmol) at 0 °C and the mixture was stirred for 20 min. After cooling to –78 °C, ethyl (trimethylsilyl)acetate (192 mg, 1.2 mmol) in THF (1 mL) was added, and stirring was continued for 15 min. A THF (1 mL) solution of acylsilane (1 mmol) was added, and the mixture was stirred at the same temperature for 1 h. The cooling bath was removed, and the mixture was allowed to warm to r.t. Sat. aq NH_4Cl (10 mL) was added, and the organic materials were extracted with Et_2O (2 × 15 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue, which consisted of both *E*- and *Z*-isomers, was purified by flash column chromatography using silica gel yielding pure *Z*-enoate.

(*E*)-β-Silyl Enoates from Acyl Silanes; General HWE Procedure (Scheme 2, Path D)

To a mineral oil dispersion of NaH (2 mmol) was added a THF (2 mL) solution of triethyl phosphonoacetate (2.0 mmol) at r.t. with stirring. After 30 min, acylsilane (2.0 mmol) was added dropwise and the mixture was stirred overnight. The mixture was quenched with deionized H_2O (5 mL) and diluted with Et_2O (5 mL). The aqueous phase was further extracted with Et_2O (2 × 5 mL). The combined organics were washed with $NaHCO_3$ (2 × 20 mL), brine (1 × 20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue, which consisted of both *E*- and *Z*-isomers, was purified by flash column chromatography using silica gel yielding pure *E*-enoate.

Catalytic Asymmetric CuH Hydrosilylation of β-Silyl Enoates; Ethyl (*S*)-3-(Dimethylphenylsilyl)butanoate; Typical Procedure (Scheme 3)

To a 50 mL round-bottomed flask, flame dried and purged with argon, was added CuCl (1.5 mg, 0.015 mmol), (*R*,*S*)-PPF-P(*t*-Bu)$_2$ (2.7 mg, 0.005 mmol), and *t*-BuONa (1.4 mg, 0.015 mmol). Toluene (1 mL) was added and the solution was stirred at 0 °C for 30 min, followed by the addition of *t*-BuOH (52 μL, 0.55 mmol). The solution was cooled to –30 °C before the addition of PMHS (65 μL, 1.0 mmol), and was further stirred at –30 °C for 10 min. *Z*-Enoate **2** (124 mg, 0.50 mmol) was added via a syringe. The mixture was stirred at –30 °C until complete by TLC (9 h; Et_2O–hexanes, 1:9). The reaction was quenched with sat. aq $NaHCO_3$ (5 mL) and diluted with Et_2O (5 mL). The aqueous layer was extracted with Et_2O (5 × 5 mL) and the organic layer was washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. The residue was purified by flash chromatography (Et_2O–hexanes, 1:10) to afford the title product (120 mg, 96%) as a clear oil. The de was determined by ^{1}H NMR spectrum of the corresponding imide derivative to be 95%;[17] R_f = 0.36 (Et_2O–hexanes, 1:9).

IR (neat): 3070, 2956, 1734, 1428, 1368, 1208 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.29 (s, 6 H), 0.98 (d, *J* = 7.4 Hz, 3 H), 1.24 (t, *J* = 7.1 Hz, 3 H), 1.45 (m, 1 H), 2.05 (dd, *J* = 15.2, 11.4 Hz, 1 H), 2.38 (dd, *J* = 15.2, 4.0 Hz, 1 H), 4.09 (q, *J* = 7.1 Hz, 2 H), 7.33–7.40 (m, 3 H), 7.47–7.54 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.14, –4.84, 14.44, 14.63, 16.66, 37.04, 60.37, 127.96, 129.26, 134.11, 137.49, 174.14.

MS-EI: *m*/*z* (%) = 250 (5.4, [M$^+$]), 235 (23), 205 (16), 145 (27), 135 (100).

HRMS-EI: *m/z* calcd for $C_{14}H_{22}O_2Si$ [M^+]: 250.1389; found: 250.1390.

Acknowledgment

We sincerely thank the NSF CHE 05-50232 for financial support, and Solvias for supplying PPF-P(*t*-Bu)$_2$ (Dr. H.-U. Blaser and Dr. M. Thomen).

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