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Chiral Silanes via Asymmetric Hydrosilylation with Catalytic CuH

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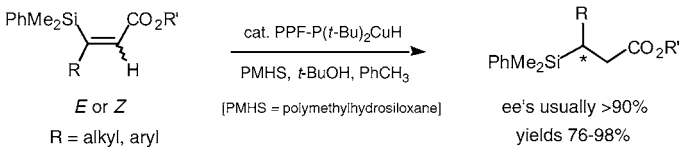
ABSTRACT



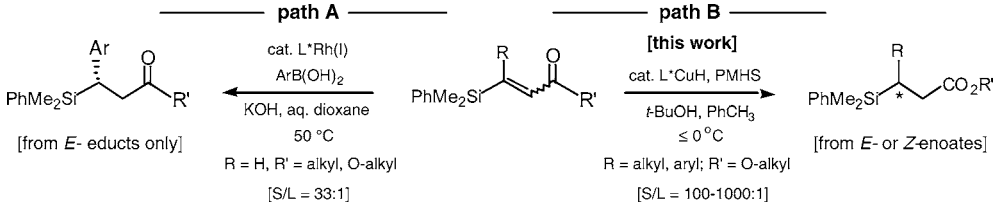
CuH-catalyzed asymmetric conjugate reduction of β-silyl-α,β-unsaturated esters has been developed. Using PMHS as a stoichiometric source of hydride and in situ generated CuH ligated by Solvias' JOSIPHOS analogue PPF−P(*t*-Bu)$_2$ leads to highly enantioselective 1,4-reductions.

Enantioenriched organosilanes are valued intermediates in organic synthesis.[1] Aside from their potential as hydroxyl surrogates via oxidation under Tamao[2]/Fleming[3] conditions, they offer many opportunities for asymmetric C−C bond formations.[4] Several routes to chiral silanes are available,[4] with the most recent involving a Rh-catalyzed 1,4-addition of arylboronic acids to, mainly, conjugated enones.[5] Hayashi's (*R,R*)-Bn-bod ligand (L* in Scheme 1, path A) was found to give excellent levels of stereoinduction associated with arylated ketones.[5] In this report, we describe an alternative strategy that allows for the conversion of a broad array of β-silylated-β,β-disubstituted enoates to chiral silanes using nonracemically ligated CuH (Scheme 1, path B; PMHS = polymethylhydrosiloxane).

Starting materials as pure geometrical isomers were readily prepared by chromatographic purification following standard Horner−Wadsworth−Emmons (HWE) or Peterson olefinations[6] of precursor acyl silanes (Scheme 2). Fleming's $PhMe_2SiLi$[7] was used to convert a morpholino amide to the correspondinig acyl silane. HWE on educts **1** (R = alkyl) preferentially afforded *E*-enoates (*E*-**2**), whereas an α-trimethylsilyl ester anion led to the isomeric *Z*-species *Z*-**3**. Aryl-substituted educts required 1,2-addition of $PhMe_2SiLi$ to the benzaldehyde and then Swern oxidation to acyl silanes (**1**, R = aromatic).

Asymmetric hydrosilylations of β-silyl enoates *E*-**2** and *Z*-**3** were conducted with in situ derived CuH, generated using 1% CuCl and 1% NaO^{t}Bu (Method A) or $(Ph_3P)CuH$ (Method B) in the presence of PMHS.[8] Solutions contained 1% of a nonracemic ligand, which initially was Takasago's *R*-(−)-DTBM-SEGPHOS (**4**, Figure 1).[9] This combination, leading to kinetically reactive yet thermodynamically stable DTBM-SEGPHOS·CuH,[10] has been shown previously to be extremely selective toward cinnamate-type β,β-disubstituted

Scheme 1



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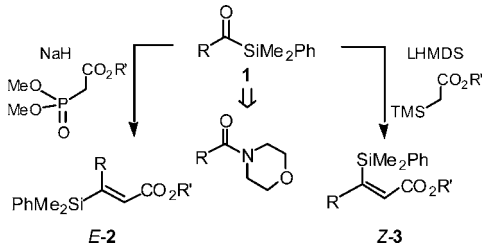
Scheme 2



enoates.[11] However, reactions with four different β-silylated enoates (Table 1, entries 1−4) indicated that this ligand was not particularly discriminating under these modified circumstances. Fortunately, as also observed in our previous study,[11] the JOSIPHOS analogue PPF−P(*t*-Bu)$_2$ (**5**, Figure 1), supplied by Solvias,[12] was very effective as the CuH complex in delivering hydride to the β-site.

As outlined in Table 1, several *Z*- (entries 1−3) and *E*- (entries 4−9) β-silyl enoates bearing *either* β-aryl (entries 2, 7, and 8) *or* β-alkyl (entries 1, 3−6, and 9) substituents were smoothly reduced in high chemical yields. In general, we have observed that these substrates are less prone toward reduction than are nonsilylated enoates,[11] requiring longer reaction times and higher ligand loadings typically run at 0.5 M in toluene. Thus, care needs be exercised to maintain an inert atmosphere, as adventitious oxygen can destroy the catalyst over time. Facial selectivity of the CuH complex derived from (*R*,*S*)-PPF−P(*t*-Bu)$_2$, with a substrate-to-ligand (S/L) ratio of 100:1, afforded product esters with >90% ee in most cases. A higher substrate-to-ligand ratio, e.g., 1000:1, is also possible, although in the one case studied (entry 1c) the reduction required a longer time (36 vs 9 h) to reach completion at both a higher temperature (−20 vs −30 °C)

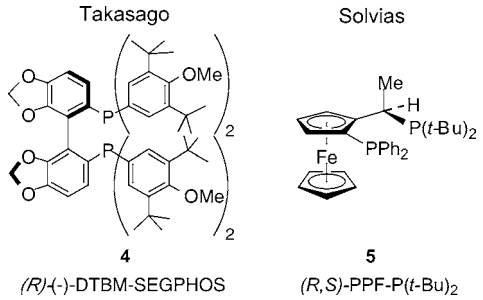


Figure 1. Nonracemic ligands used in this study.

and a higher concentration (0.7 vs 0.5 M). Although overall reaction efficiency was maintained (90% isolated yield), the somewhat higher temperature caused a modest drop in ee (92% vs 95% ee). The presence of *t*-BuOH to assist with catalyst turnover is important as well.[13] In the absence of this additive, a reaction time of 5 h at −30 °C (entry 4c) took 7 days at room temperature to reach completion. Only in the case of an especially electron-rich cinnamate **6** (entry 7) did the ee drop, perhaps because of the higher temperature required to drive the reaction to completion within a 24 h time period. The *E*- vs *Z*- nature of the enoate did not affect the rate of hydrosilylation (entry 1 vs 4) at related temperatures. Although methyl esters appear to be better choices for otherwise slow-reacting substrates, both ethyl and even a far more lipophilic ester (e.g., *n*-octyl, entry 3) react at similar rates and in good ee's (compare entries 1 and 3). Treatment of an *E*-enoate with enantiomeric [(*S*,*R*)-PPF−P(*t*-Bu)$_2$]CuH (entry 4b) gave the *S*-product in an equally selective event (vs entry 4a).

The enantiomeric excesses and absolute stereochemistry of each product (other than that for Table 1, entry 9) were determined by conversion to the known imide derivatives **8** using a commercially available lactam in the form of its lithium salt, **7** (Scheme 3). Fleming had shown years ago that de's of imides **8** could be easily established by NMR, and assignments of absolute stereochemistry can be made on the basis of known chemical shifts.[14] Thus, initial saponification of product esters was followed by conversion

Scheme 3

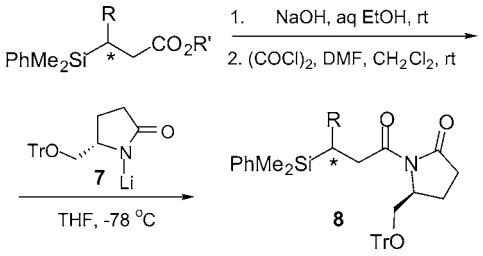


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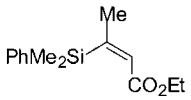
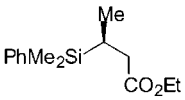
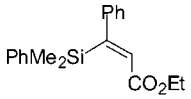
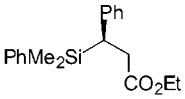
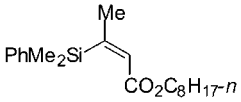
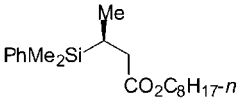
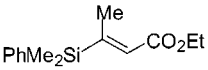
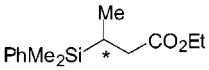
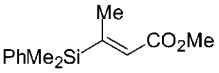
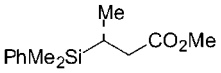
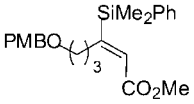
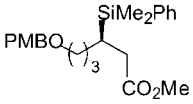
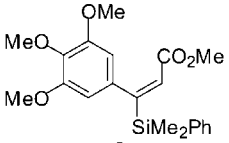
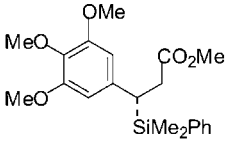
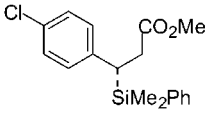
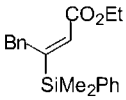
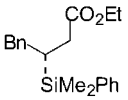
Table 1. Representative Examples of Asymmetric Hydrosilylations of β-Silyl Enoates[a]

entry	substrate	ligand	temp (°C)	time (h)	product[b]	yield (%)[c]	ee (%)[d]
1 (a)[e]		**5**	-30	9		96	95 *(S)*
1 (b)[f]		**4**	-30	7.5		97	24 *(S)*
1 (c)[e]		**5**	-20	36		90	92 *(S)*[g]
2 (a)[e]		**5**	-30	15		89	91 *(R)*
2 (b)[f]		**4**	-20	48		90	20 *(R)*
3 (a)[e]		**5**	-30	9.5		95	92 *(S)*
3 (b)[f]		**4**	-30	7		92	15 *(S)*
4 (a)[e]		**5**	-78	18		98	>95 *(R)*
4 (b)[e]		*ent*-**5**	-78	24		95	>95 *(S)*
4 (c)[f]		**4**	-30	5		98	83 *(R)*
5[e]		**5**	-60	12		97	>95 *(R)*
6[e]		**5**	-30	24		83	>95 *(R)*
7[e]	 **6**	**5**	0	24		98	83 (82) *(S)*[h]
8[e]		**5**	-30	24		82	>95 (97.3) *(S)*[h]
9[e]		**5**	0	24		76	98.5 *(R)*[h]

[a] Reactions were run with a S/L ratio of 100:1 with 1.1 equiv of *t*-BuOH present and at 0.5 M in toluene. The enoates used were geometrically pure materials. [b] Fully characterized. [c] Isolated, chromatographically purified material. [d] Unless noted otherwise, based on conversion of each product to its chiral imide derivatives; see text. [e] Method A (see text). [f] Method B (see text). [g] S/L = 1000:1. [h] By chiral HPLC.

to their acid chlorides. Reaction with the preformed salt **7** gave imides **8**. To confirm the method, use of a racemic β-silyl ester (e.g., Table 1, product in entry 1) led to a 1:1 mix of diastereomers, with the spectral data on each isomer being in perfect agreement with that of Fleming on these exact compounds.[14] Chiral HPLC analyses were also performed on the products illustrated in entries 7−9, which gave more precise enantiomeric excesses on baseline-resolved enantiomers.

In summary, it has been shown that CuH, when complexed by Solvias' nonracemic ligand PPF−P(t-Bu)$_2$, can effect asymmetric hydrosilylation of both β-aryl and β-alkyl β-silyl enoates in very high enantiomeric excesses. Turnover numbers of $\geq$100 are demonstrated for these highly hindered substrates, and reaction conditions are quite mild ($\leq$0 °C) and neutral. Both enantiomers of the ligand are readily available, providing access to either stereochemistry of the resulting chiral silanes. Finally, use of enoates as substrates provides a broad range of subsequent opportunities for functional group interconversions of the product β-silyl esters,[15] where the absolute configuration of the newly installed residue on silicon should remain intact.

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Supporting Information Available: Procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) For representative uses of chiral silanes, see: (a) Panek, J. S.; Wrona, I. E.; Gabarda, A. E.; Evano, G. *J. Am. Chem. Soc.* **2005**, *127*, 15026. (b) Panek, J. S.; Kesavan, S.; Su, Q.; Shao, J.; Porco, J. A., Jr. *Org. Lett*. **2005**, *7*, 4435.