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Asymmetric 1,4-Hydrosilylations of α,β-Unsaturated Esters

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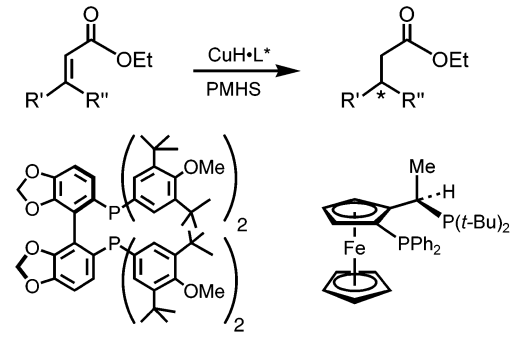
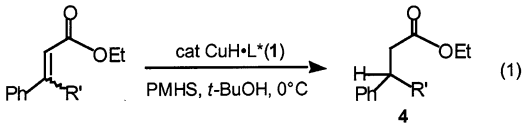
Asymmetric 1,4-hydrosilylations of conjugated carbonyl systems at the acid oxidation level are especially challenging. As amply demonstrated by the Buchwald group in their study in 1999,[1a] as well as in very recent work,[1b] enoates respond to selected nonracemically ligated CuH/PMHS reagent combinations and typically afford ee's in the 80−92% range. No other competing reductive process irrespective of the metal involved, to our knowledge, is currently known.[2] The notion that stereochemistry β- to an ester could be highly controlled in an absolute sense has obvious merit, as such products offer access to a wealth of structural arrays both acyclic and cyclic in nature.[3] In this communication, we describe methodology based on two nonracemic ligands of recent vintage (**1** and **2**) which chelate Cu(I), presumably as CuH, and lead to exceptionally reactive reagents and remarkably selective conjugate reductions of enoates as well as unsaturated lactones.



L* = (*R*)-(-)-DTBM-SEGPHOS (**1**) (*R,S*)-PPF-P(*t*-Bu)$_2$ (**2**)

Initially, β-substituted ethyl cinnamate derivatives were studied using small percentages of Stryker's reagent $[(Ph_3P)CuH]_6$[4] in the presence of excess polymethylhydrosiloxane (PMHS). Takasago's ligand, (*R*)-(−)-DTBM-SEGPHOS[5] was tested given our prior success with this system for asymmetric hydrosilylations of aryl ketones,[6a] imines,[6b] and cyclic enones.[6c] Although educt *Z*-**3** (R′ = Me; eq 1)

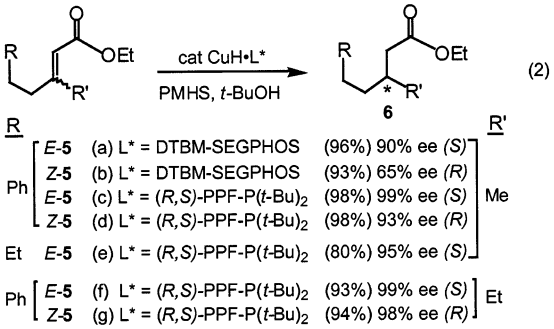


(1)

Z-**3**	(a) R' = Me	(92%) 99% ee (*S*)
E-**3**	(b) R' = Et	(90%) 95% ee (*R*)
	(c) R' = cyclopropyl	(97%) 99% ee (*R*)
	(d) R' = Me [run at rt]]	(94%) 91% ee (*R*)

afforded the corresponding product **4** with an ee of 95%, after 17 h at 0 °C the reaction had progressed only to the extent of 85%. By simply supplying 1.1 equiv of *t*-BuOH to the original reagent mix,[1b,4,6b] complete reduction could be effected within 1 h to give (*S*)-**4** in 99% ee (92% isolated yield; entry a). Geometrically isomeric cinnamate derivatives *E*-**3** (entries b−d), likewise led to similar levels of induction, albeit with products of opposite (*R*) chirality. Raising the temperature of the 1,4-addition from 0 °C to room temperature (entry d), resulted in a decrease in selectivity to 91% ee.[7a]

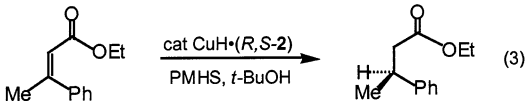
On the other hand, β,β-dialkyl-substituted enoates did not respond in the same fashion using CuH−SEGPHOS technology. Although *E*-enoate **5** (entry a; eq 2) still gave a respectable 90% ee of S-**6**,



(2)

results with the *Z*-isomer (entry b; 65% ee) clearly indicated that limitations exist with this substrate/ligand combination. Fortunately, the di-*tert*-butyl analogue (**2**) of the (*R,S*)-JOSIPHOS series of ligands, as provided in the Solvias "kit",[8] displayed outstanding facial discrimination in the dialkyl enoate cases. Indeed, *E*- and/or *Z* isomers of three substrates **5** (entries c−g) could be individually converted at 0 °C to their enantiomerically enriched derivatives **6** in high yields and ee's.[7b] The previously reported difficult case of an enoate akin to *E*-**5** (R = Et, R′ = Me; entry e) was also found to give the product (*S*)-**6** in 95% ee (vs 81% ee).[1a]

Although substrate to ligand (S/L) ratios typically on the order of 500−1000:1 were used for convenience, much lower levels of ligand can be employed. For example, reduction of 2.5 g of ester *Z*-**3** was accomplished (0 °C, 12 h) in the presence of only 2 mg of ligand *R,S*-**2** (S/L = ∼7700:1; eq 3).

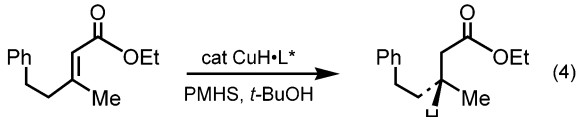


(3)

Z-**3** 2.5 g 2 mg (*R,S*)-PPF-P(*t*-Bu)$_2$ (92%) 98% ee

S/L ~7700

With availability of the enantiomeric JOSIPHOS derivative of ligand **2**, (*S,R*)-PPF-P(*t*-Bu)$_2$ (*ent*-**2**), absolute stereochemistry in the product could be controlled from either olefin geometry of the educt or ligand configuration. Thus, *E*-**5** reacts with CuH ligated by *R,S*-**2** to give S-**6** (cf. eq 2, entry c), while the *S,R* form of **2** gives *R*-**6** (eq 4).



(4)

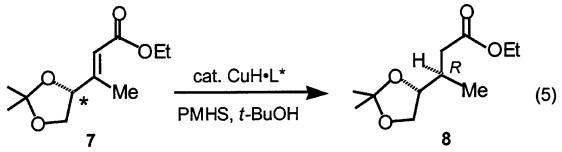
E-**5**

L* = (*S,R*)-PPF-P(*t*-Bu)$_2$ (96%) 98% ee

10.1021/ja049135l CCC: $27.50

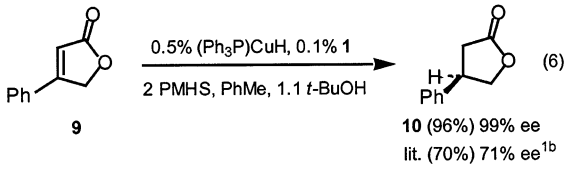
Since JOSIPHOS **2** possesses elements of central and planar chirality, it was of particular interest to ascertain the effect of an available diastereomeric version (i.e., the *R*,*R*-isomer)[8] on the level of induction. Using *E*-**3** (R′ = Me), a very modest selectivity resulted (<10% ee) along with a diminution in reaction rate (54% conversion after 24 h at room temperature).

The influence of an existing stereocenter at the γ-carbon in an enoate, as in educt **7**, has also been examined given the inherently strong facial preference associated with ligand **2** toward β,β-disubstituted enoates. Energetically dissimilar conformations might create opportunities for a "matched/mismatched" situation manifested in the observed de's. By contrast, the innate bias of this CuH−ligand system could overshadow such internal preferences (i.e., exerting reagent, rather than substrate control). In the event, treatment of optically pure **7** with catalytic CuH complexed by ligand *R*,*S*-**2** led to a 99:1 ratio of diastereomers favoring **8** via *si* face attack (eq 5). The enantiomeric CuH complex using *S*,*R*-**2**,

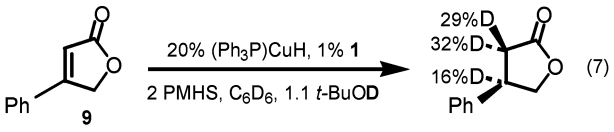


however, afforded only a −40% de (70% conversion) of the diastereomeric product (i.e., the 3*S* isomer) under identical conditions (0 °C, 36 h), suggesting that facial delivery of hydride onto **7** as drawn from the *re* face, while favored (70:30), is a mismatched situation.

α,β-Unsaturated lactones, represented by **9** and studied previously in a related context,[1b] appear to be especially prone toward this type of asymmetric 1,4-hydrosilylation (eq 6). Thus, educt **9** could be converted to butyrolactone **10** in high yield at 0 °C in 3 h under the influence of minimal DTBM-SEGPHOS (1000:1 S/L) in 99% ee.



Last, the rate-accelerating role of the alcohol[1,4b] in this sequence was briefly investigated. In the absence of this additive, silyl ketene acetal derivatives are initially formed.[6a] Reduction of unsaturated lactone **9** (cf. eq 6) in benzene-d_6 at room temperature was analyzed directly by proton NMR, the spectrum from which showed only lactone **10**. A second experiment using *t*-BuOD followed by careful integration of the three proton signals at the α- and β-sites revealed that most of the deuterium was incorporated as expected at the α-position (eq 7).[10] Thus, since no exchange occurs between PMHS and *t*-BuOD, it would seem that the rate enhancement may well be due to more rapid quenching of a copper enolate by alcohol than by the silane.



In summary, ligands in the SEGPHOS and JOSIPHOS families of nonracemic bis-phosphines, when complexed with CuH, have been found to exert remarkably high degrees of facial selectivity in 1,4-reductions of β,β-disubstituted enoates. Levels of product ester ee's and chemical yields routinely in excess of 95% are observed employing high S/L ratios and are independent of substitution pattern in the substrate. These results suggest that this new technology is not only operationally straightforward but is also of considerable generality.

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

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(7) (a) Product *R*-**4** (R′ = Me) was saponified to the known, commercially available acid (Fluka). (b) Product *S*-**6**, R = Et, is known; Norsikian, S.; Marek, I.; Klein, S.; Poisson, J. F.; Normant, J. F. *Chem. Eur. J.* **1999**, *5*, 2055.
(8) *R*,*S*-2, *S*,*R*-2, and *R*,*R*-2 are all available from Solvias, Inc.; cf. Blaser, H.-U.; Brieden, W.; Pugin, B.; Spindler, F.; Studer, M.; Togni, A. *Top. Catal.* **2002**, *19*, 3.
(9) Product **8** was deprotected and cyclized to the corresponding γ-lactone with mild acid (1% H_2SO_4/dioxane).The resulting *cis*-disubstitued butyrolactone, indicative of the *R*-stereochemistry at the β-site, was readily confirmed by NMR (cf. Supporting Information).
(10) It is likely that CuH (20 mol % present) and *t*-BuOH (1.1 equiv) undergo facile H/D-exhange at room temperature, which accounts for the (16%) deuterium incorporation at the β-site. If copper hydride remains deuterated given excess *t*-BuOD and thus accounts for 20 mol % of the deuterium present, the maximum level of D incorporation is 90% (1.1 equiv *t*-BuOD = 110% D available − 20% in the form of CuD). Thus, 77% (29% + 32% + 16% D incorporation, based on NMR integrations) of this 90%, or 85.5% deuteration has occurred.

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