Diastereoselective Heteroatom-Directed Conjugate Addition of Silylcuprate Reagents to Unsaturated Carbonyls. A Stereoselective Route to β-Carbonyl Siloxanes[1]

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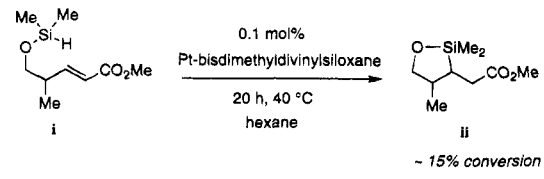
Summary: Directed conjugate addition of the silylcuprate reagent lithium bis[diphenyl(diethylamino)silyl]-cuprate ($(Ph_2(Et_2N)Si)_2CuLi$) to unsaturated esters and ketones is reported. The stereochemical course of the reaction can be controlled by the presence of an appropriately disposed internal Lewis basic functionality, affording the corresponding β-hydroxysilyl carbonyls with good to excellent levels of diastereoselection (*e.g.*, **3b** → **4b**).

The design and development of stereoselective C–Si bond-forming reactions is of value to modern organic synthesis. Because C–Si bonds often allow for the effective differentiation of diastereotopic faces of proximal prostereogenic sites, and may subsequently undergo protodesilylation[2] or oxidation[3] (C–Si → C–OH), carbosilyl units can be versatile intermediates in complex molecule synthesis. We recently employed a five-membered β-siloxy aldehyde in the assembly of the C27–C33 segment of rapamycin,[2d] where the silicon-containing carbon center proved critical in controlling stereochemistry. Our synthesis scheme for the construction of the remaining segments of rapamycin then required utilization of β-siloxy esters as templates for acyclic stereodifferentiation. However, we discovered that the initial method used by us for the installment of the C–Si bond is inadequate: whereas intramolecular hydrosilylation of allylic ethers by a homoallylic siloxyhydride proceeds efficiently,[4] similar reactions of unsaturated esters and ketones proved to be notoriously sluggish.[5] An alternative strategy that would effect stereoselective "hydrosilylation" of the latter class of substrates thus became a target for synthesis method development in our laboratories. Within this context, we herein describe the results of our studies on the stereoselective heteroatom-directed[6] conjugate addition of lithium bis[diphenyl(diethylamino)silyl]cuprate ($(Ph_2(Et_2N)Si)_2CuLi$)[7] to unsaturated carbonyls.[8] To our knowledge, this is the first report of a stereoselective *directed* addition of a cuprate to α,β-unsaturated esters and ketones.[9]

As illustrated in Table 1, when **1a,b** are treated with 3 equiv of $(Ph_2(Et_2N)Si)_2CuLi$ (prepared from the reaction of $Ph_2(Et_2N)SiLi$[10] and $CuBr{\cdot}Me_2S$ at −78 °C, **2a,b** are obtained in 95% and 45% yield, respectively. Although the elements of Si–H are added to the substrate alkene, ^1H NMR spectra indicate that **2a** and **2b** are formed as equal mixtures of diastereomers.[11] Since the inherent sense of stereoselectivity in these reactions proved unsatisfactory, we focused our attention on several earlier reports which demonstrated that carbamate units can act as directing groups in reactions that involve alkylcopper reagents.[12] In these studies formation of a Cu–N bond was shown to be largely responsible for the steering influence; several examples were reported where carbonates did not effectively deliver the silylcopper reagent (sterics proved dominant).

Consistent with previous reports, unlike ethers **1a-b**, carbamate **3a** affords **4a** in 89:11 diastereoselectivity (entry 2). However, carbonates **3b** and **3c** undergo conjugate addition in excellent yields and superior levels of diastereoselection (>95:5; single isomer detected by 300-MHz ^1H NMR).[13] As entry 2 of Table 1 illustrates (**3d** → **4d**), an acetate group, where the carbonyl oxygen is expected to be less Lewis basic than C=O of a carbamate or a carbonate, may also deliver the silylmetal



[⊗] Abstract published in *Advance ACS Abstracts,* July 15, 1994.

(1) Dedicated to our valued friend and colleague Professor Lawrence T. Scott on the occasion of his 50th birthday.

(2) (a) Hudrlik, P. F.; Hudrlik, A. M.; Kulkarni, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 6809–6811. (b) Stork, G.; Sofia, M. *J. Am. Chem. Soc.* **1986**, *108*, 6826–6828. (c) Koot, W.-J.; Ginkel, R.; Kranenburg, M.; Hiemstra, H.; Louwrier, S.; Moolenaar, M. J.; Speckamp, W. N. *Tetrahedron Lett.* **1991**, *32*, 401–404. (d) Hale, M. R.; Hoveyda, A. H. *J. Org. Chem.* **1992**, *57*, 1643–1645. (e) Stork, G.; Chan, T. Y.; Breault, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 7578–7579.

(3) Tamao, K.; Nakajima, T.; Sumiya, R.; Arai, H.; Higuchi, N.; Ito, Y. *Organometallics* **1983**, *2*, 1694–1696.

(4) (a) Tamao, K.; Nakajima, T.; Sumiya, R.; Arai, H.; Higuchi, N.; Ito, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6090–6093. (b) Tamao, K.; Tohma, T.; Inui, N.; Nakayama, O.; Ito, Y. *Tetrahedron Lett.* **1990**, *31*, 7333–7336. (c) Reference 2d. (d) Curtis, N. R.; Holmes, A. B. *Tetrahedron Lett.* **1992**, *33*, 675–678.

(5) As shown below, intramolecular hydrosilylation of **i** proceeds to <20% conversion (20 h, 40 °C). Recently, Bosnich and co-workers reported an intramolecular hydrosilylation of an unsaturated ester (90%, 18 h); however, in the latter instance the alkoxysilyl hydride is positioned at the allylic position rather than the homoallylic position: Bergens, S. H.; Noheda, P.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1992**, *114*, 2121–2128.

(6) For a recent review of substrate-directable chemical reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370.

(7) Tamao, K.; Kawachi, A.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 3989–3990.

(8) For nondirected conjugate addition of (trialkylsilyl)copper reagents to unsaturated carbonyls, see: (a) Ager, D. J.; Fleming, I.; Patel, K. S. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2520–2526. (b) Bernhard, W.; Fleming, I.; Waterson, D. *J. Chem. Soc., Chem. Commun.* **1984**, 28–29. (c) Bernhard, W.; Fleming, I.; Waterson, D. *J. Chem. Soc., Chem. Commun.* **1984**, 28–29. (d) Fleming, I.; Henning, R.; Plaut, H. *J. Chem. Soc., Chem. Commun.* **1984**, 29–31.

(9) For a study on the influence of an internal Lewis base on the rate of an alkylcuprate conjugate addition, see: Christenson, B.; Hallnemo, G.; Ullenius, C. *Chem. Scr.* **1987**, *27*, 511–512. See Section VII C of ref 6 for a discussion on directed conjugate addition reactions.

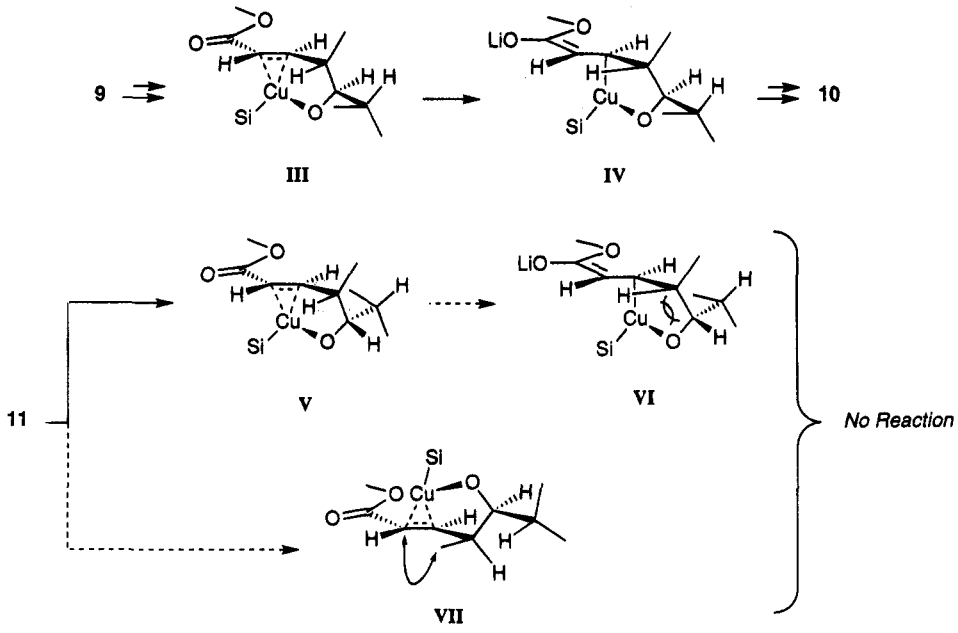
(10) Treatment of **1a** with $Ph_2(Et_2N)SiLi$ (in the absence of Cu salts) resulted in the near complete recovery of the starting material (after H_2O quench).

(11) The ^1H NMR spectrum of the unpurified reaction mixture indicates equal amounts of diethylamino and hydroxysilyl products. After silica gel chromatography, the hydroxysilyl product (*e.g.*, **1a**) is obtained exclusively.

(12) (a) Gallina, C.; Ciattini, P. G. *J. Am. Chem. Soc.* **1979**, *101*, 1035–1036. (b) Goering, H. L.; Singleton, V. D. *J. Am. Chem. Soc.* **1976**, *98*, 7854–7855. (c) Goering, H. L.; Kantner, S. S.; Tseng, C. C. *J. Org. Chem.* **1983**, *48*, 715–721. (d) Fleming, I.; Thomas, A. P. *J. Chem. Soc., Chem. Commun.* **1986**, 1456–1457.

0022-3263/94/1959-4370$04.50/0

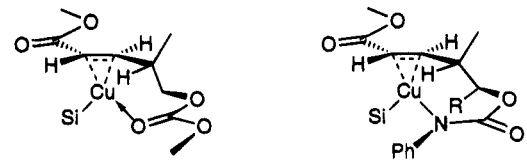
Scheme 1



reagent. Entry 3 of Table 1 illustrates that the reaction of keto carbonate **5** is somewhat less selective than that of ester **3b**, and, as entry 4 exhibits, when the stereogenic site is further removed from the reacting π face, a slight diminution in diastereocontrol is detected (cf. **7** vs **3b**).

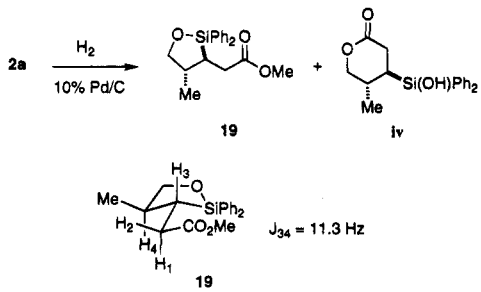
Reaction of anti homoallylic alcohol **11** affords the derived siloxane **10** in >95:5 diastereoselectivity directly from treatment with the silylcuprate (entry 5 of Table 1).[14] In contrast, syn homoallylic alcohol **9**, under identical conditions, is recovered unchanged. This difference in reactivity indicates that local chirality might play a critical role in determining the overall efficiency of the addition process and is likely connected to the interaction of the internal Lewis basic alkoxy group with the silyl-copper reagent. In accord with this paradigm, when syn and anti silyl ethers **12** and **14** are subjected to the above conditions, where little heteroatom–Cu association is feasible, reactions proceed smoothly in both instances to afford β-(hydroxysilyl) esters **13** and **15** in good yield and with excellent stereocontrol (>95:5).[15]

The stereochemical outcome of substrates **3-7** may be rationalized by the intermediacy of complexes **I** and **IIa** (below). The lower level of stereoselectivity observed with

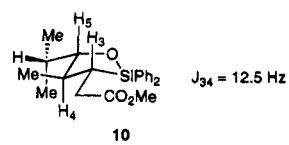


the carbamate vs carbonate derivatives might be because internal chelation, as shown in **IIa** (based on studies of Goering),[12b] would require the directing unit to adopt a high energy (anti) conformer.[16] In support of this mechanistic picture, in contrast to **3a**, the phenylcarbamate

(13) Stereochemical identity: treatment of the 1:1 diastereomeric mixture of **2a** and **2b** with H_2 in the presence of 10% Pd(C) affords **19** and **iii** each with >95% diastereomeric purity (separable by silica gel). The stereochemical assignment is supported by ^{1}H NMR coupling constant analysis. In **19**, H_3 appears as a doublet of triplets (J = 11.3, 2.7 Hz), indicating two large (180° H–C–C–H dihedral angle) couplings with H_1 and H_4. Reaction of **4a-4d** with DIBAL-H (for **4a**, **4b** and **4d**) and H_2 (for **4c**) affords **19** with >95% selectivity (<5% **iii**). For further discussion on stereochemical assignment, see refs 14 and 15.



(14) The stereochemical identity of siloxane **10** was established through coupling constant analysis and NOESY experiments. For example, as shown below, H_3 and H_4 are antiperiplanar as indicated by the 12.5-Hz coupling constant between these two protons; irradiation of H_3 results in enhancement of H_5.



(15) The stereochemical outcome of the conjugate reactions with **13** and **15** may be readily accounted for through Felkin–Anh transition-state models ($Me_2CH(OSiR_3)$ = large group, Me = medium group, and H = small group). Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science* **1986**, *231*, 1108–1117 and references cited therein. The stereochemical identity of **13** and **15** was ascertained through analysis of the ^{1}H NMR spectra of the derived lactones, which were synthesized from reaction of the silyl ethers with 48% HF (CH_3CN, 25 °C).

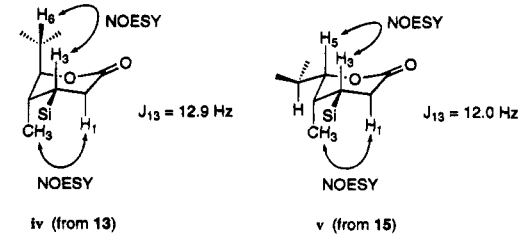
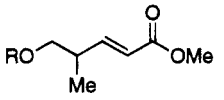
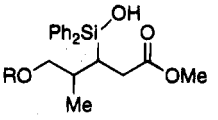
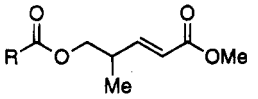
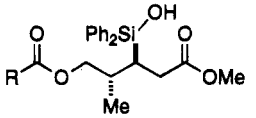
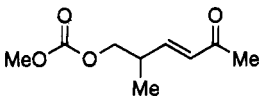
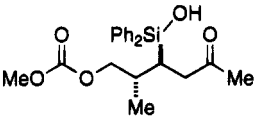
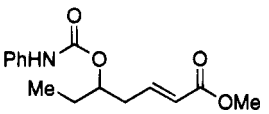
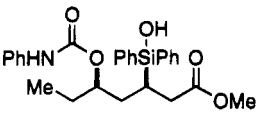
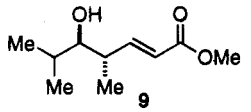
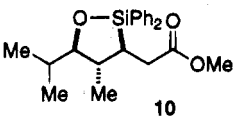
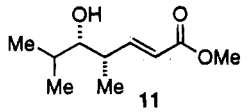
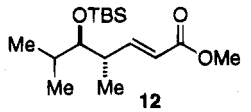
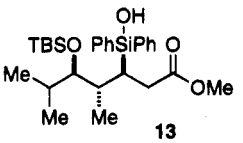
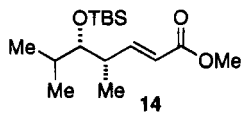
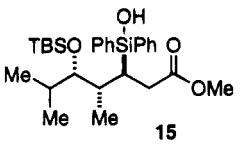


Table 1. Diastereocontrol in Conjugate Addition of $(Ph_2(Et_2N)Si)_2CuLi$ to Unsaturated Carbonyls[a]

entry	substrate	product		selectivity[b]	yield (%)[c]
1	 **1**	 **2**	a R=Bn b R=TBS	50 : 50 50 : 50	95 45
2	 **3**	 **4**	a R=NHPh b R=OMe c R=OBn d R=Me	89 : 11 >95 : 5 >95 : 5 90 : 10	77 80 85 65
3	 **5**	 **6**		88 : 12	86
4	 **7**	 **8**		85 : 15	80
5	 **9**	 **10**		>95 : 5	55
6	 **11**	NO REACTION			
7	 **12**	 **13**		>95 : 5	66
8	 **14**	 **15**		>95 : 5	72

[a] Reaction conditions: 2.0–3.0 equiv of $(Ph_2(Et_2N)Si)_2CuLi$ at −78 °C for 3 h (see supplementary material for details). [b] Diastereomeric ratios were determined through analysis of the 300-MHz ^1H NMR spectra of the reaction mixture. [c] Isolated yields of purified products after silica gel chromatography.

derived from anti homoallylic alcohol **9**, undergoes conjugate addition with only 3:1 diastereoselectivity: the directing group presumably does not serve effectively in this case, since the requisite Cu–alkene complex **IIb** would carry unfavorable steric interactions. That carbamate and carbonate units interact with the transition metal through different contact points is supported by the observation that whereas ether **1b** reacts twice as fast as carbamate **3a**,[20] treatment of a 1:1 mixture of carbonate **3b** and **1b** with 1 equiv of silylcopper reagent affords *only* **4b** (50%; <5% **2b**).[17]

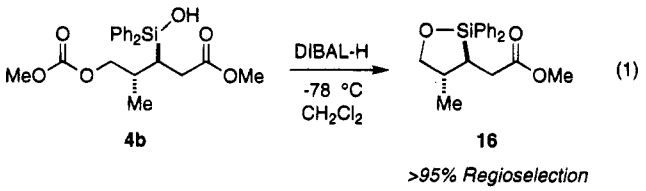
In the case of **9** and **11**, if we assume that reactions involve initial formation of the derived copper alkoxide,[18] alcohol **9** would afford copper–olefin complex **III** (Scheme 1). Stereoselective formation of the C–Cu bond (**III** → **IV**) may then be followed by the reductive elimination of alkylsilane to afford eventually siloxane **10**. It is plausible that with syn homoallylic alcohol **11**, the intermediacy of complex **V** does not lead to the generation of **VI**, since shifting of the bound copper toward the β alkene

(16) (a) Wang, X.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 1870–1872. (b) Wiberg, K. B.; Laidig, K. E. *J. Am. Chem. Soc.* **1988**, *110*, 1872–1874.

(17) The reason why, in contrast to our work, in studies reported previously carbonates are inferior directing groups is not clear at present, but may be linked to the variation in the positioning of the Lewis basic sites (allylic in other work and homoallylic in this article). It is possible that there is a strict geometric requirement for effective Cu–carbonate or Cu–carbamate association (effective metal–heteroatom interaction only from the homoallylic site for Cu–carbonate). These and related mechanistic issues are the subject of ongoing studies. For other examples, where a longer tether between the directing group and the reactive site is required for effective stereochemical control, see: (a) Corey, E. J.; Niwa, H.; Falk, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 1586–1587. (b) Nagata, R.; Saito, I. *Synlett* **1990**, 291–300. (c) Rebek, J.; McCready, R. *J. Am. Chem. Soc.* **1980**, *102*, 5602–5605.

carbon results in severe steric strain. The alternative complex **VII**, where the α Me substituent adopts the inside position, suffers from an unfavorable interaction between the α carbon and the allylic methyl substituent.[19] The suggested mechanistic paradigm is predicated on the principle that an alkene site, once associated with a copper complex, is no longer prone to *inter*molecular attack by another silylcopper reagent (otherwise a nonstereoselective addition should occur in the case of **11**). The above proposal is tenable, since preassociation of a second transition metal in an intermolecular manner, a process that is presumably required for conjugate addition, should be disfavored by chelation of the first copper complex; intramolecular olefin–copper interaction, particularly in the case of **V**, where there are no significant steric interactions, should be preferred over an intermolecular mode of chelation.[20]

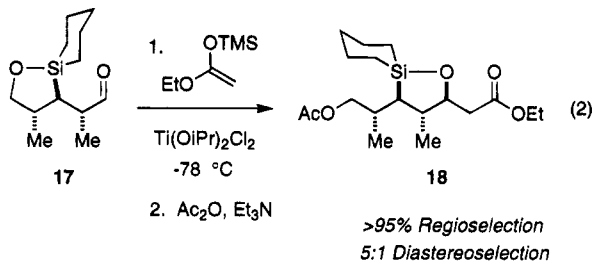
Since any functionalization procedure which converts the carbonyl group to a hydroxyl unit in β-siloxycarbonyls may also be accompanied by silyl transfer, few observations with regard to the regiochemical preferences of β-hydroxysiloxanes merit mention. In general, when there is a choice between two possible siloxane regioisomers, the ring structure with the larger number of substituents is favored (barring any overwhelming steric effects). For example, as shown in eq 1, treatment of **4b**



(1)

4b **16**

>95% Regioselection



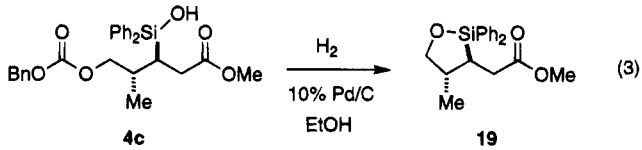
(2)

17 **18**

>95% Regioselection
5:1 Diastereoselection

with DIBAL-H and subsequent acylation affords **16** as a single regioisomer (>95:5, 70% yield; initial alcohol product is a 90:10 mixture of regioisomers). As another example, Lewis acid-catalyzed aldol condensation/acylation of **17** affords **18** (eq 2)[21] with >95:5 regioselectivity (5:1 diastereoselection, 60% overall yield).[22] Although hydroxysiloxanes certainly do appear to undergo silyl transfer, once the more favorable isomer is obtained, subsequent functionalization may be carried out without any adventitious rearrangement. For instance, the reduction product from eq 1 can be oxidized (Swern) and subjected to Horner–Emmons olefination conditions with high regioselectivity (>95:5, 60% overall yield) without complications arising from isomerization of the unsymmetrical siloxy alcohol. The reason for the above regiochemical trends is not clear; however, such tendencies can be relied upon and be incorporated in a synthesis plan with a reasonably high confidence level.

A useful attribute of the stereoselective silylcuprate conjugate addition strategy is that the silylcopper reagent contains a labile group (*i.e.*, the Et_2N ligand), so that formation of a siloxane ring can be achieved subsequently. In contrast to reaction of **9**, with homoallylic alcohols that serve as precursors to **1-8**, subjection of the starting materials to the above reaction conditions only results in complete decomposition. Nonetheless, β-silylcarbonyl adducts such as **4c** can be readily converted to the corresponding siloxane; the example shown in eq 3 is illustrative.



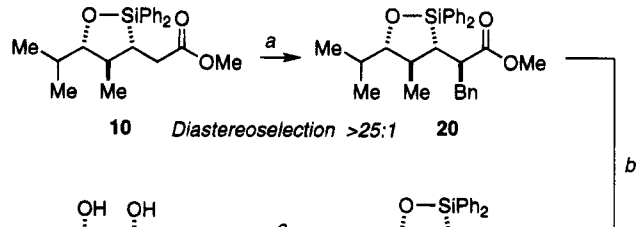
(3)

4c **19**

70% yield
(60% overall from **2c**)

That cyclic siloxanes (*e.g.*, **10**) can be prepared by the above methods is important, since silyl hydroxide products (*e.g.*, **4c**) appear to be less suitable to further functionalization. As an example, as illustrated in Scheme 2, deprotonation, followed by alkylation of the

Scheme 2[a]



[a] Key: (a) $Li(SiMe_3)_2N$, $PhCH_2Br$, −78 → 0 °C; 65%; (b) DIBAL-H, CH_2Cl_2, −78 °C; 70%; (c) H_2O_2, KF, $KHCO_3$, THF, MeOH; 70%.

(18) Bertz, S. H.; Smith, R. A. J. *J. Am. Chem. Soc.* **1989**, *111*, 8276–8277. For an X-ray crystalographic study of a copper complex of an unsaturated carbonyl compound, see: Andersson, S.; Hakansson, M.; Jagner, S.; Nilsson, M.; Ullenius, C.; Urso, F. *Acta Chem. Scand.* **1986**, *A40*, 58–62.

(19) If the α carbon were to preserve its sp^2-hybridization upon coordination to copper, positioning of the Me group at the inside position would not be very costly (Broeker, J. L.; Hoffmann, R. W.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5006–5017 and references cited therein). However, reported spectroscopic data on cuprate–olefin complexes support the notion that upon association with the transition metal, significant rehybridization (to sp^3) may occur at both alkene carbons. See: (a) Hallnemo, G.; Olsson, T.; Ullenius, C. *J. Organomet. Chem.* **1985**, *282*, 133–144. (b) Christenson, B.; Olsson, T.; Ullenius, C. *Tetrahedron* **1989**, *45*, 523–534.

(20) A related experimental evidence in support of this proposal is that **3a**, although less reactive than **1a** (by a factor of ~2, as determined by direct competition experiments), undergoes silylcopper conjugate addition more selectively (compare entries 1 and 2 in Table 1). It thus follows that the copper–alkene complex, wherein the transition metal is covalently bound to the carbamate group (Cu–N bond), forms rapidly and renders the alkene unreactive toward intermolecular attack (otherwise carbamate reaction would also be nonselective). That is, in the reaction of **3a**, the derived copper–olefin complex may be less reactive than **1a**, but the corresponding transfer of cuprate (and the silane) occurs with higher stereocontrol. For an example of a substrate-directed process which is slower but more selective than the related nondirected reaction, see: (a) Henbest, H. B. *Proc. Chem. Soc.* **1963**, 159–165. (b) Chamberlain, P.; Roberts, M. L.; Whitham, G. H. *J. Chem. Soc. B* **1970**, 1374–1381.

(21) Select ^1H NMR data for siloxane **18** ($CDCl_3$): δ 4.46 (dt, 1H, *J* = 9.3, 5.2 Hz, C*H*OSi), 4.17 (m, 2H, $CO_2CH_2CH_3$), 4.05 (dd, 1H, *J* = 10.7, 5.7 Hz, CH_2OAc), 3.80 (t, *J* = 10.7 Hz, CH_2OAc), 2.06 (s, 3H, $COCH_3$), 1.05 (d, 3H, *J* = 7.3 Hz, $CHCH_3$), 0.95 (d, 3H, *J* = 7.3 Hz, $CHCH_3$).

(22) The aldol product is isolated as a 1:1 mixture of regioisomers; acylation (Et_3N, DMAP, Ac_2O) completes the silyl transfer. Other examples of isomerization to the more substituted siloxane indicate that preferable formation of **18** is not due the more rapid formation of the primary vs the secondary acetate. See the dihydroxylation process reported in ref 2d.

β-siloxy ester **10** proceeds smoothly to afford **20** with >95:5 diastereoselectivity (65% after silica gel chromatography). In contrast, attempted functionalization of the corresponding silyl hydroxides (*e.g.*, **4b**) in a similar manner led to <5% conversion. Reduction of **20** provides **21** as a single stereoisomer with <5% rearrangement to the less substituted siloxane. Subsequent oxidation of the C—Si bond of **21** affords anti-anti propionate **22** with >95% diastereoselection.[23]

In summary, the conjugate addition of the silylcopper reagent $(Ph_2(Et_2N)Si)_2CuLi$ to unsaturated carbonyl systems can be carried out with high levels of diastereoselection in the presence of a suitable directing group to afford β-(hydroxysilyl) esters and ketones in good yield; the resulting products may serve as useful templates for stereoselective transformations without adventitious silyl transfer. Additional studies on the mechanism and synthetic applications of siloxanes continue in these laboratories.

(23) The stereochemical identity of the alkylation product (**10** → **20**) is based on analogy with a number of previously reported alkylations of β-silyl ketones and esters. See: (a) Reference 7. (b) Chow, H.-F.; Fleming, I. *Tetrahedron Lett.* **1985**, *26*, 397–400. (c) Reference 8b-d.

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Supplementary Material Available: Experimental procedures and spectral and analytical data for all reaction products and ^1H NMR spectra for **4a**, **4b**, **6**, **18**, **19**, and **22** (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.