$\sigma-\pi$ Chelation-Controlled Stereoselective Hydrosilylation of Ketones

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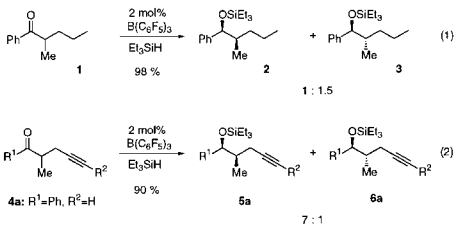
Since Cram's pioneering work on chelation control in Grignard-type addition to chiral alkoxy carbonyl substrates,[1] a number of studies on related subjects have appeared.[2] Among them, the Lewis acid-mediated chelation control is one of the most fundamental and practically important concepts in modern organic chemistry.[3] The concept of chelation control has been applicable to carbonyl compounds bearing heteroatom-containing functionalities such as an alkoxy group in appropriate proximity ($\sigma-\sigma$ *chelation*). To the best of our knowledge, there is no example of the chelation-controlled stereoselective reaction of carbonyl compounds through $\sigma-\pi$ *chelation*. Recently, we reported that the chelation controlled regio- and chemoselective reaction which proceeds via the coordination of π*-electrons of triple bonds* to Lewis acids.[4] Now, we wish to report the first example for the stereoselective reactions which are controlled by the $\sigma-\pi$ *chelation* (Scheme 1).

We examined the stereoselective hydrosilylation of various ketones using $R_3SiH-B(C_6F_5)_3$ as a reducing agent.[5] The reaction of 2-methyl-1-phenyl-pentan-1-one **1** with Et_3SiH in the presence of catalytic amounts of $B(C_6F_5)_3$ proceeded smoothly to give a mixture of the hydrosilylated products **2** and **3** in 98% yield (eq 1). Slightly predominant formation of the *anti*-product **3** over *syn*-product **2** was observed; the ratio of **2**:**3** was 1:1.5. We next examined the hydrosilylation of 2-methyl-1-phenyl-pent-4-yn-1-one **4a** (R^1 = Ph, R^2 = H) under the same reaction conditions as above. Interestingly, the *syn*-product **5a** was afforded as the major product (**5a**:**6a** = 7:1) (eq 2). This result prompted us to examine the hydrosilylation of **4a** and related ketones **4b**−**4h** to clarify the generality of this unusual diastereoselectivity. The results are summarized in Table 1.



The predominant formation of the *syn*-product was also observed in the reaction of **4a** with other silanes such as Ph_2MeSiH (entry 2). The reactions of **4b**−**d**, bearing Me, Ph, and TMS groups at the terminal position of alkyne, respectively, also gave *syn*-selectivities (entries 3−5). Not only aromatic ketones but also aliphatic ketones **4e**, **4f**, and **4h** produced *syn*-products selectively (entries 6, 7, and 9). Interestingly, stereoselectivities increased from 4.4:1 (R^1 = Et) to >30:1 (R^1 = ^{t}Bu) as the substituents at R^1 position became bulkier. These results clearly indicate that the *syn* diastereoselectivity is widely observed in the $B(C_6F_5)_3$-catalyzed reduction of **4** with hydrosilanes.

Scheme 1

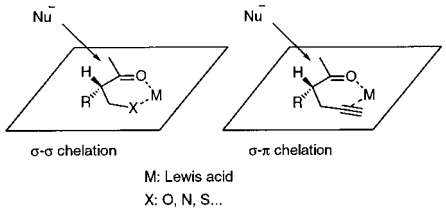
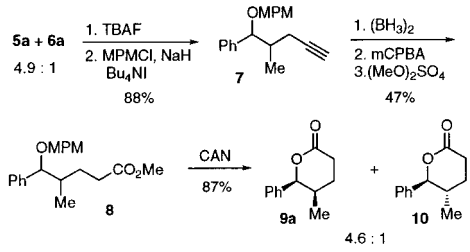


Table 1. $\sigma-\pi$ Chelation-Controlled Hydrosilylation of **4**[a]

entry	substrate **4** R^1	substrate **4** R^2		R_3SiH	yield of **5** and **6** (%)[b]	ratio *syn*-**5**:*anti*-**6**
1	Ph	H	**4a**	Et_3SiH	90	7.0:1
2	Ph	H	**4a**	Ph_2MeSiH	99	6.8:1
3	Ph	Me	**4b**	Et_3SiH	quant	5.0:1
4	Ph	Ph	**4c**	Et_3SiH	quant	3.0:1
5	Ph	TMS	**4d**	Et_3SiH	quant	7.7:1
6	Et	H	**4e**	Et_3SiH	quant	4.4:1
7	*c*-C_6H_{11}	H	**4f**	Et_3SiH	93	5.0:1
8	*o*-MePh	H	**4g**	Et_3SiH	94	15:1
9	*t*Bu	H	**4h**	Et_3SiH	quant	>30:1

[a] Reaction was performed with R_3SiH (1 equiv) and $B(C_6F_5)_3$ (2 mol %) in toluene at 0 °C within 1 h. [b] Isolated yield.

Scheme 2



The stereostructures of **5a** and **6a** were unambiguously determined by converting **5a** and **6a** to **9a** and **10**, respectively, as shown in Scheme 2. The treatment of a mixture of **5a** and **6a** (4.9:1) with TBAF, followed by the protection of the resulting alcohols by MPMCl under basic condition gave **7** in 88% yield. The alkynyl part of **7** was converted to a carboxylic acid by hydroboration−oxidative workup, which was subsequently esterified to give **8** in 47% yield. Deprotection of the MPM group of **8** by CAN gave a mixture of the lactones **9a** and **10** in a ratio of 4.6:1 in 87% yield. The ^{1}H NMR spectrum of **9a** was identical to that of the known compound.[6] The stereostructure of **5h**, which was obtained from the aliphatic ketone **4h**, was also determined by converting **5h** to *cis*-6-*tert*-butyl-5-methyl-tetrahydro-pyran-2-one (**9b**) via similar routes. The stereostructures of **5b**−**g** and **6b**−**g** were assigned by their ^{1}H NMR spectra on the analogy of those of **5a**, **6a**, and **5h**.

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(2) (a) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191−1223. (b) *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000.

(3) (a) *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, 2000; Vols. 1−2. (b) *Lewis Acid Reagents*; Yamamoto, H., Ed.; Oxford University Press: New York, 1999. (c) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095−1120. (d) Santelli, M.; Pons, J. M. *Lewis Acids and Selectivity in Organic Synthesis*; CRC Press: Boca Raton, FL,1996. (e) Shambayati, S.; Schreiber, S. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 283−324. (f) Yamaguchi, M. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 325−353.

(4) Asao, N.; Asano, T.; Ohishi, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4817−4818.

(5) Piers and co-workers found that $B(C_6F_5)_3$-catalyzed hydrosilylation of carbonyl functions, such as aldehydes, ketones and esters, proceeded very smoothly to give the corresponding reduced compounds in high yields. (a) Parks, D. J.; Piers, W. E. *J. Am. Chem. Soc.* **1996**, *118*, 9440−9441. (b) Parks, D. J.; Blackwell, J. M.; Piers, W. E. *J. Org. Chem.* **2000**, *65*, 3090−3098.

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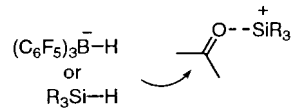
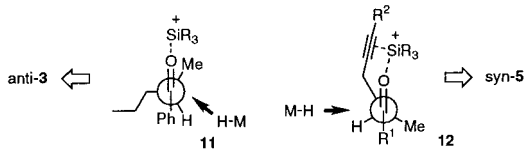


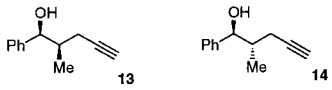
Figure 1.

The difference of the diastereoselectivities between eqs 1 and 2 clearly shows that the acetylenic bond of **4** exerts a crucial role upon the observed *syn*-selectivity. Piers et al. proposed the interesting silane activation mechanism in the $B(C_6F_5)_3$-catalyzed hydrosilylation of aldehydes and ketones; the ordinary mechanism, in which the carbonyl oxygen of the electrophiles coordinates to $B(C_6F_5)_3$ and thus carbonyl substrates are activated, is not operative in the $B(C_6F_5)_3$-catalyzed reduction.[5] Their extensive mechanistic studies clarify that $B(C_6F_5)_3$ activates the silane via hydride abstraction to form the incipient silylium species which enhances the electrophilicity of the carbonyl group, facilitating the reduction by $[HB(C_6F_5)_3]^-$ or R_3SiH (Figure 1).

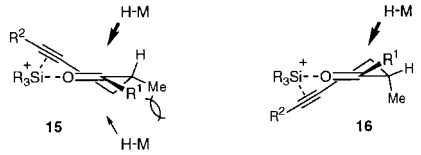
Most probably, a silylium species is generated here also, and the $\sigma-\pi$ coordination of this species is operative in the reaction of **4**. The *anti* diastereoselectivity in the reaction of **1** can be accounted for by the ordinary Felkin−Anh model. The propyl group at the α-position is regarded as the largest group and the Me as the medium size (model **11**). Accordingly, *anti*-**3** is produced with slight preference, and the observed low stereoselectivity is due to the small steric difference between propyl and methyl group at the α-position. On the contrary, in the reaction of **4**, the reduction would proceed through the $\sigma-\pi$ chelation of R_3Si^+ (model **12**): the hydride attack takes place from the less hindered side to produce the *syn*-isomer **5**.



If the ordinary Felkin−Anh model is involved also in the case of **4**, the *anti*-diastereomer **6** should be produced predominantly, since a propargyl group is sterically larger than a Me group.[7] Indeed, the *anti*-selectivity was observed with slight predominance when the reduction of **4a** was carried out using DIBAL-H, in which the ratio of **13**:**14** was 49:51.

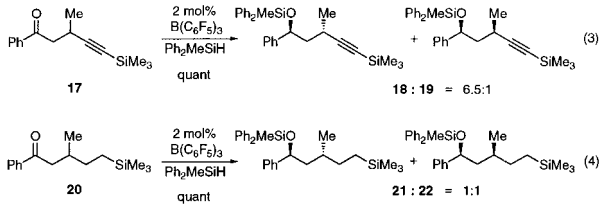


The stereoselectivities decreased as the substituents R^2 of **4** became bulky (entries 1, 3, and 4). Presumably, a bulky R^2 group would make it difficult to form strong $\sigma-\pi$ chelation in **12**. Higher selectivity obtained in the case of **4d** may be explained by the well-known β-silyl effect, which would make the chelation stronger.[8] The proposed chelation model also can explain the reason the *syn*-selectivity was obtained very predominantly or exclusively in the reaction of **4g** and **4h** having bulky R^1 groups

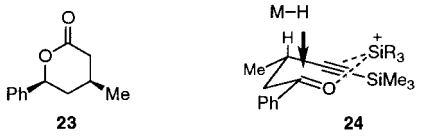


(entries 8−9). There is a possibility that hydride may attack from the bottom side of carbonyl group in the conformer **15**, which produces the *anti*-isomer **6**. On the other hand, the axially oriented methyl group prevents the hydride attack from the bottom side in the conformer **16**. The conformer **16** is more favored with the bulkier R^1 group because of the increased steric repulsion between R^1 and Me in **15**.[9]

The 1,2-asymmetric induction via the $\sigma-\pi$ chelation control could be extended to the 1,3-system. The hydrosilylation of 3-methyl-1-phenyl-5-trimethylsilyl-4-pentyn-1-one **17** with Ph_2-MeSiH in the presence of 2 mol % of $B(C_6F_5)_3$ gave the *anti*-product **18** stereoselectively (**18**:**19** = 6.5:1) (eq 3). In contrast, no selectivity was observed in the reaction of the saturated analogue **20** (eq 4). The stereostructure of **18** was unambiguously



determined by converting **18** to **23**[10] via a similar route to that shown in Scheme 2. The *anti*-stereoselectivity in the reaction of **17** can be accounted for by the $\sigma-\pi$ chelation model **24**, which involves hydride attack on the less hindered face of a conformationally locked, internally chelated intermediate.[2a]



Now it is clear that the $\sigma-\pi$ chelation is operative not only in the 1,2- but also in the 1,3-asymmetric induction of certain acetylenic ketones. The *syn*-diastereoisomers obtained either exclusively or predominantly in the reaction of **4** or the *anti*-isomer in the reaction of **17** can be converted, upon reduction of the triple bond, to the *anti*-Felkin−Anh products which are not easily available through the ordinary reducing methods. We are now in a position to apply the $\sigma-\pi$ coordination concept along with the well-known $\sigma-\sigma$ chelation to control stereoselectivities.

Supporting Information Available: Spectroscopic and analytical data for **2**, **3**, **5**, **6**, **9**, **10**, **18**, **19**, **21**, **22**, **23**, **26**, and **28**, and the representative procedure for the synthesis of **5h** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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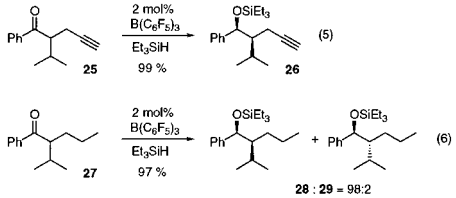
(7) The $B(C_6F_5)_3$-catalyzed hydrosilylation of **25** with Et_3SiH afforded the *syn*-isomer **26** as a sole product in 99% yield (eq 5). Both the $\sigma-\pi$ chelation and Felkin−Anh model leads to the *syn*-isomer, since isopropyl group at the α-position of **25** is sterically larger than propargyl group. On the other hand, the *syn*-selectivity was decreased (*syn*-**28**:*anti*-**29** = 98:2) in the hydrosilylation of **27** bearing a saturated propyl group instead of a propargyl group at the α-position, under the same reaction condition (eq 6). These results clearly imply the $\sigma-\pi$ chelation can be used not only for reversing the Felkin−Anh selectivity but also for increasing it by choosing the substituent at the α-position of carbonyl compounds.



(8) For reviews, see: (a) Lambert, J. B. *Tetrahedron* **1988**, *46*, 2677−2689. (b) Apeloig, Y. In *The Chemistry of Organic Silicon Compounds*; Patai, S., Rappoport, Z., Eds.; Wiley-Interscience: New York, 1989; pp 57−225. (c) Fleming, I. *Chemtracts: Org. Chem.* **1993**, *6*, 113−116.

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