O-silylation of the chiral ligand in the mixed cuprate at −78 °C.

The chiral ligand **3**, $[\alpha]^{23}_D$ +105.1° (*c* 2.5, chloroform), and its enantiomer are available starting with (*R*)-(−)- or (*S*)-(+)-mandelic acid, respectively.[16] Conversion of **3** to the chiral mixed methyl cuprate using methyllithium reagent in ether and toluene as the other solvent afforded a homogeneous reagent which upon reaction at −78 °C with 2-cyclohexenone afforded in 60% yield (*R*)-(+)-3-methylcyclohexanone of 90% ee. Although less work has been done with **3** because its synthesis requires four steps, it is obviously an effective ligand for enantioselective conjugate addition.

The results reported herein represent a major advance from earlier findings with chirally complexed cuprates[9] and provide a strong indication that excellent progress is possible in this area. The study of other ligands should yield valuable information.[17]

(16) The synthetic sequence used for the synthesis of **3** was as follows: (1) conversion of mandelic acid to the acetate (acetyl chloride, 98% yield); (2) formation of acid chloride (thionyl chloride, 99% yield); (3) reaction with trimethylethylenediamine (96% yield); (4) reduction with lithium aluminum hydride (90% yield) to form **3**, $[\alpha]^{23}_D$ −106.0° (*c* 1.5, $CHCl_3$).

(17) This research was assisted financially by grants from the National Science Foundation and the National Institutes of Health.

**Table I.** Enantiodivergent Synthesis of Steroidal Side Chains[a]

| entry | steroidal acetal | organometal | isomer ratio[b] | isolated yield, % | chirality of a major isomer[c]: template | Cram rule |
|---|---|---|---|---|---|---|
| | | | **6:7** | | | |
| 1 | **1** (*S-R,R*) | **4a** | >99:<1 | 93 | + | + |
| 2 | | **4b** | >99:<1 | 90 | + | + |
| 3 | | **4c** | 96:4 | 85 | + | + |
| 4 | **2** (*S-S,S*) | **4a** | 90:10 | 93 | − | + |
| 5 | | **4b** | 88:12 | 88 | − | + |
| 6 | | **4c** | 30:70 | 84 | + | − |
| 7 | | **4d** | 76:24 | 80 | − | + |
| | | | **8:9** | | | |
| 8 | **1** (*S-R,R*) | **5a** | 95:5 | 80 | + | + |
| 9 | | **5b** | 95:5 | 82 | + | + |
| 10 | | **5c** | 98:2 | 72 | + | + |
| 11 | **2** (*S-S,S*) | **5a** | 10:90 | 78 | + | − |
| 12 | | **5b** | 8:92 | 78 | + | − |
| 13 | | **5c** | 92:8 | 82 | − | + |

[a] All reactions were carried out on 1-mmol scale according to the literature procedure.[1b-d] The isomer ratio of the final products were essentially identical with those of the initial adducts (steroidal ethers). [b] By 400-MHz $^1H$ NMR spectroscopy (supplementary material). [c] (+) The chirality of a major isomer is consistent with the chirality predicted either by the template or by Cram rule. (−) The chirality of a major isomer is opposite from the predicted chirality.

## Importance of the Timing of Bond Breaking and Bond Making in Acetal Templates. Enantiodivergent Synthesis of Steroidal Side Chains†

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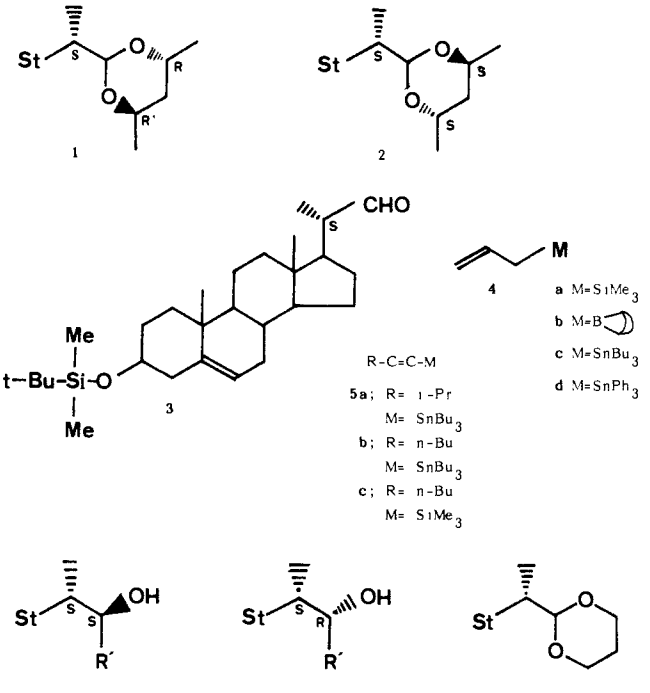
Asymmetric syntheses via chiral acetal templates are becoming increasingly important for modern organic chemistry.[1] A mechanistic rationale which readily accounts for the observed high asymmetric induction is provided by Johnson and Bartlett.[1b,c] However, an important unanswered question remains concerning the timing of bond breaking and bond making in the chiral cyclic acetal templates. The $S_N2$-like transition state is proposed, and thus a fully synchronous process must be needed for the high asymmetric induction. In other words, the enantiomeric excess or even the direction of asymmetric induction should strongly depend upon both the Lewis acidity of $MX_n$ and the nucleophilicity of Nu.[2]

However, to the best of our knowledge, the results reported until now do not show such a sign.[3] We herein report for the first time evidence that the bond making and bond breaking are in fact concerted for the high asymmetric induction via acetal templates and an enantiodivergent synthesis of a steroidal side chain by use of this concept.

Treatment of the chiral steroidal acetal **1** (S-R,R isomer), prepared from the steroidal aldehyde **3**[4] and (2*R*,4*R*)-(−)-pentanediol,[5] with allylsilane **4a** in the presence of $TiCl_4$ followed by the usual workup[1b] gave **6** exclusively. On the other hand, the




† Dedicated to Professor G. Zweifel on the occasion of his 60th birthday.

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(2) For a review on the importance of combination between Lewis acids and nucleophiles (organometallic compounds) and for their compatibility, see: Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.*, in press.

(3) Organomagnesium, -lithium, -copper, -silicon, and -aluminum compounds exhibit the same tendency in chiral induction; the *R,R* acetal induces *S* chirality and the *S,S* acetal induces *R* chirality; ref 1 and references cited therein.

(4) The chiral aldehyde was prepared from pregnenolone by the literature procedure: Midland, M. M.; Kwon, Y. C. *Tetrahedron Lett.* **1984**, 5981.

(5) Purchased from Waco Chemical Ind., Japan.

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reaction of the *S*-*S*,*S* isomer **2**, prepared from **3**[4] and (2*S*,4*S*)-(+)-pentanediol,[5] with **4a** produced a mixture of **6** (*S*,*S* isomer) and **7** (*S*,*R* isomer) in a ratio of 90:10, respectively. This result was quite unexpected, since the *SS* acetal normally induces *R* chirality at the carbon bearing both oxygen atoms.[1] Accordingly we investigated the reaction of **1** and **2** with representative organometallic compounds, and the results are summarized in the Table I.

The reaction of **1** with **4a–c** produced **6** either exclusively or very predominantly (entries 1–3). This is quite reasonable, since chirality dictated by the acetal template is in the same direction as the chirality by Cram rule. The reaction of **2** with **4a** or **4b** again produced **6** predominantly (entries 4 and 5), indicating that the direction of asymmetric induction was dictated primarily by Cram rule and an influence of the template was negligible. However, **7** was produced predominantly with allyltributylstannane (**4c**), pointing out that violation of Cram's rule took place and the chiral induction was dictated essentially by the template. Quite interestingly, **6** was obtained preferentially with allyltriphenylstannane (**4d**) (entry 7).

Since tributylstannyl derivatives seemed to be highly promising for enantiodivergent synthesis, we examined the reactions of stannylacetylenes. Here again, the reaction of **1** with **5a** or **5b** produced **8** very predominantly (entries 8 and 9). As expected, the reaction of **2** with **5a** or **5b** gave **9** with high stereoselectivity (entries 11 and 12). On the other hand, the reaction of silylacetylene (**5c**) with **1** or with **2** exhibited the similar trend as observed in the allylsilane (entries 10 and 13); **8** was obtained predominantly, regardless of the starting acetals. Further, we examined the reaction of **10** with **4c** or **5b** for comparison purposes. The Cram isomer was produced predominantly, as expected.

Consequently, the present development provides a useful method for an enantiodivergent synthesis of chiral substances.[6] Especially on the steroidal side chain, **8** can be easily converted into brassinolide and related brassinosteroids,[7] and the anti-Cram isomers such as **7** and **9** can be transformed into ecdysone derivatives.[8]

Mechanistically, the present results clearly indicate an importance of the timing of bond breaking and bond making. The organometallic reagents with low nucleophilicity, such as silicon and boron compounds (**4a** and **4b**), presumably react after the bond-breaking process and thus the chiral induction is dictated primarily by the Cram rule. On the other hand, the tributylstannyl derivatives **4c**, **5a**, and **5b** possess higher nucleophilicity than **4a** and **4b** and therfore react simultaneously as the bond breaking takes place. The nucleophilicity of triphenylstannyl derivative **4d** is in between that of **4a,b** and **4c** owing to the phenyl substituent.

A number of reactions of silicon reagents with chiral acetal templates, which have the chiral center only at the acetal portion, have been examined.[1] Moreover, several reactions of chiral acetals having multichiral centers have also been reported.[9] In these previous reactions the asymmetric induction is dictated completely by the acetal template even by using silicon reagents. Consequently, a delicate shade of the timing is, for the first time, brought to light by the present 1,2-system. We are now exploring an extention of this concept to the 1,3-system and will report it shortly.[10]

**Supplementary Material Available:** $^1$H NMR spectra for compounds **6–9** (2 pages). Ordering information is given on any current masthead page.

(6) Only two methods are known for the stereoselective synthesis of anti-Cram isomer from ordinary chiral aldehydes having no ability to be chelated. Via aluminum reagents: Maruoka, K.; Itoh, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 4573. Via cuprate-crown reagents: Yamamoto, Y.; Maruyama, K. *Ibid.* **1985**, *107*, 6411.

(7) Yamamoto, Y.; Nishi, S.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1986**, *102*, and references cited therein.

(8) Huppi, G.; Siddal, J. B. *J. Am. Chem. Soc.* **1967**, *89*, 6790. Kerb, U.; Wiechert, R.; Furlenmeir, A.; Fürst, A. *Tetrahedron Lett.* **1968**, 4277. Bannai, K.; Morisaki, M.; Ikekawa, N. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2116. Morisaki, M.; Sato, S.; Ikekawa, N. *Chem. Pharm. Bull.* **1977**, *25*, 2576. Kyler, K. S.; Watt, D. S. *J. Org. Chem.* **1981**, *46*, 5182. Sayo, N.; Azuma, K.; Mikami, K.; Nakai, T. *Tetrahedron Lett.* **1984**, 565. Tsai, D. J. S.; Midland, M. M. *J. Org. Chem.* **1984**, *49*, 1842.

(9) Although our substances (**1** and **2**) possess the 1,2-chiral induction system which means that there is a chiral center at the next position to the newly formed chiral center, the papers on the 1,3-system and 1,5-system have appeared; ref 1d,g.

(10) The Lewis acidity effect should be explored. A $TiCl_4$–$Ti(OiPr)_4$ combination provides a better result for silicon reagents than $TiCl_4$ itself. This may be due to lower Lewis acidity of $TiCl_n(O\text{-}i\text{-}Pr)_{4-n}$ which delays the bond-breaking process.

## Asymmetric Synthesis of Isoquinoline Alkaloids by Homogeneous Catalysis

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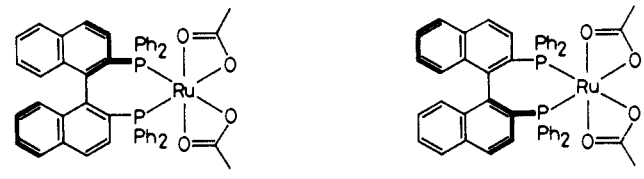
Since 1-benzylated tetrahydroisoquinolines possess important physiological properties and also serve as key intermediates for the synthesis of a variety of isoquinoline alkaloids,[1] development of an efficient asymmetric synthesis of such compounds is highly desirable. The most elegant example was recently given by Meyers;[2] diastereoselective alkylation of 1-lithiated tetrahydroisoquinolines containing an amino acid derived *N*-imino function followed by removal of the chiral auxiliary provides the tetrahydroisoquinolines having the 1*S* configuration. Among various other possibilities,[3] enantioselective *catalytic hydrogenation* of the dehydro precursors, if feasible, offers obviously the simplest solution to this problem. We describe here that the newly devised hexacoordinate ruthenium complexes bearing a chiral BINAP ligand, Δ-(*R*)-**1** and Λ-(*S*)-**1**,[4,5] catalyze efficient, homogeneous




Δ-(*R*)-**1** Λ-(*S*)-**1**

asymmetric hydrogenation of *N*-acyl-1-alkylidenetetrahydroiso-

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(5) The complex, Δ-(*R*)- or Λ-(*S*)-**1**, was prepared by treatment of $[Ru(cod)Cl_2]_n$ with BINAP and triethylamine and then sodium acetate. The procedure is given in the supplementary material. The Δ and Λ structures with respect to the carboxylate ligation were established by single-crystal X-ray analysis of the related dipivalate complex.

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