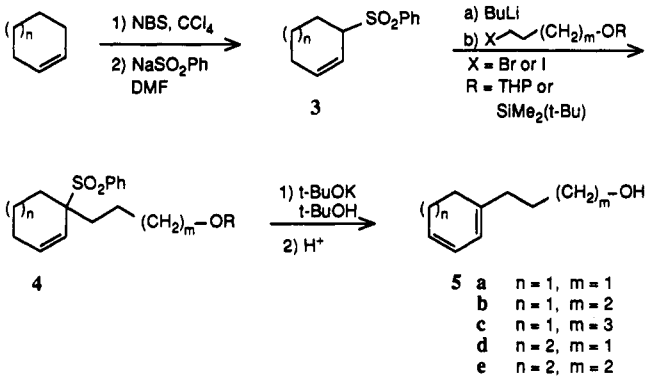
Scheme II



one of the nucleophiles in accordance with previous results.[1,2b,4] In this reaction it was found that chloride ions had an accelerating effect on the aromatization of the starting material. To prevent this, LiCl was dissolved in acetic acid and added parallel with the diene.

Extending the hydroxyalkyl chain with one carbon led to six-membered oxaspirocycles. Thus, in the same manner as described above **5b** was transformed to **8** and **9** in 82 and 70% yield, respectively (entries 3 and 4, Table I). Applying the same reaction conditions to the diene analogue **5c**, with five carbons in the alkyl chain, did not give the expected seven-membered oxaspirocycle.

Spirocyclization of cycloheptadiene derivatives **5d** and **5e** was slower than for their six-membered analogues. However, in these systems no side products were detected and slow addition of the reagents was no longer needed. Interestingly, for diene **5d** it was now possible to obtain the dual stereocontrol generally associated with palladium-catalyzed 1,4-oxidations.[1,2b,4] In the absence of added salts, **5d** afforded mainly the trans addition product **10b**. Addition of Li_2CO_3 (3 equiv), which is a source for LiOAc and thus favors the external attack, reversed the stereoselectivity and then the cis addition product predominated, **10a**:**10b** being 80:20. The corresponding spiro-oxychlorination of the seven-membered ring derivatives was very slow at 20 °C, after 36 h the conversion of **5d** to **11** was only about 15%. Instead, these reactions (entries 7 and 9) were performed at a slightly elevated temperature (35 °C),[9] and it was then possible to isolate **11** and **13** in 40 and 60% yield, respectively. Spirocyclization of **5e** with a 4-carbon chain afforded **12** in 82% yield.

With the present procedure stereodefined spiro ethers are readily accessible from simple starting materials.[10] They can be further functionalized in a stereospecific manner[1,4] and should provide useful entries to oxaspirocyclic natural products.

General Experimental Procedure: Preparation of 8c-Chloro-2*r*-oxaspiro[4.5]dec-6-ene (7). $Pd(OAc)_2$ (8.1 mg, 0.036 mmol), benzoquinone (160 mg, 2.17 mmol), and Li_2CO_3 (160 mg, 2.17 mmol) were dissolved in acetone/HOAc (2 mL, 4:1). To this solution were then added the dienol **5a** (110 mg, 0.796 mmol, dissolved in 1 mL of acetone) and LiCl (62 mg, 1.45 mmol, dissolved in 1 mL of HOAc) during 16 h with a syringe pump. One hour after the addition was completed, ether (7 mL) was added and the resulting solution was washed with aqueous NaOH (2 × 4 mL, 2 M) and brine (3 mL). The organic phase was then dried ($MgSO_4$), concentrated in vacuo, and distilled in a Kugelrohr apparatus at an oven temperature of 100 °C under reduced pressure (0.01 mmHg) to give **7**[11] (100 mg, 0.579 mmol, 73%).

Acknowledgment. We are grateful to the Swedish Natural Science Research Council for financial support and to Johnson Matthey for a loan of palladium chloride.

(9) Attempts to increase the temperature further resulted in a relative increase of Diels-Alder side products.

(10) For other syntheses of spiro ethers see: (a) Simkins, N. S.; Middleton, D. S. *Tetrahedron* **1990**, *46*, 545. (b) Baxter, J. S.; Green, M.; Lee, T. V. *J. Chem. Soc., Chem. Commun.* **1989**, 1595. (c) Cannone, P.; Belanger, D.; Lemay, G.; Foscolos, G. B. *J. Org. Chem.* **1981**, *46*, 3091. (d) Stanton, S. A.; Felman, S. W.; Parkhurst, C. S.; Godleski, S. A. *J. Am. Chem. Soc.* **1983**, *105*, 1964.

(11) ^1H NMR for **7**: δ 5.81 (dd, J = 3.6, 9.7 Hz, 1 H), 5.70 (d, J = 9.7 Hz, 1 H), 4.52 (m, 1 H), 3.88 (app t, J = 6.6 Hz, 2 H), 2.17-1.92 (m, 5 H), 1.86-1.69 (m, 2 H), 1.62 (m, 1 H).

Enantioselective Chiral Borane-Mediated Aldol Reactions of Silyl Ketene Acetals with Aldehydes. Novel Effect of the Trialkylsilyl Group of the Silyl Ketene Acetal on the Reaction Course

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Summary: Highly enantioselective aldol reactions of silyl ketene acetals with a variety of aldehydes were achieved by using chiral boranes prepared from the sulfonamides of α-amino acids.

Chiral Lewis acid mediated reactions have been recognized as useful tools for the stereoselective formation of carbon-carbon bonds.[1] However, few examples of the aldol reaction of silyl ketene acetals with aldehydes have been reported.[2] Yamamoto[3a] and Helmchen[3b] independently reported the synthesis of new chiral Lewis acids from borane and the sulfonamides of α-amino acids and applied them to promote asymmetric Diels-Alder reactions. In the course of studies of stereoselective Lewis acid mediated aldol reactions,[4] we examined the ability of such chiral

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(2) Reetz, M. T.; Kyung, S.-H.; Bolm, C.; Zierke, T. *Chem. Ind.* **1985**, 824. Kobayashi, S.; Sano, T.; Mukaiyama, T. *Chem. Lett.* **1989**, 1319 and references cited therein.

(3) (a) Takasu, M.; Yamamoto, H. *Synlett* **1990**, 194. (b) Sartor, D.; Saffrich, J.; Helmchen, G. *Ibid.* **1990**, 197.

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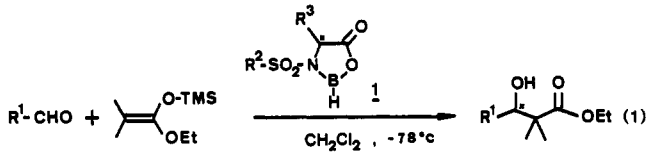
Table I. Enantioselectivity of the Lewis Acid Mediated Aldol Reaction of 1-(Trimethylsiloxy)-1-ethoxy-2-methyl-2-propene with Aldehydes[a]

entry	R^1CHO, R^1	chiral borane 1a–d R^2	chiral borane 1a–d R^3	% yield[b] of β-hydroxy ester	% ee[c]
1	C_6H_5	p-$CH_3C_6H_4$	i-C_3H_7[d] (1a)	86	83
2	C_6H_5	p-$CH_3C_6H_4$	t-C_4H_9[e] (1b)	77	92[f]
3	C_6H_5	α-naphthyl	i-C_3H_7[d] (1c)	79	90
4	C_6H_5	β-naphthyl	i-C_3H_7[d] (1d)	85	93
5	(E)-C_6H_5CH=CH	p-$CH_3C_6H_4$	i-C_3H_7[d] (1a)	80	85
6	$C_6H_5CH_2CH_2$	p-$CH_3C_6H_4$	i-C_3H_7[d] (1a)	87	93

[a] Reaction conditions were as described in the text and ref 5. [b] Isolated yields after flash column chromatography. [c] Determined by HPLC analysis with a chiral Daicel OD column. [d] Derived from (S)-valine. [e] Derived from (R)-tert-leucine. [f] The opposite enantiomer was obtained.

boranes to promote the reaction of silyl ketene acetals with aldehydes. We found that the nature of the trialkylsilyl group of the ketene acetals had a novel effect on the reaction course. The reaction yielded different products, but still with high enantioselectivity.

The chiral borane reagents **1a–d** were prepared by treating the sulfonamides[5] obtained from the corresponding α-amino acids and sulfonyl chlorides with an equimolar amount of borane·THF complex in CH_2Cl_2 at ambient temperature for 0.5 h. The reaction of 1-(trimethylsiloxy)-1-ethoxy-2-methyl-1-propene with aldehydes at −78 °C for 3 h in the presence of a stoichiometric amount of one of the chiral promoters 1 gave β-hydroxy esters 2 (eq 1). Table I summarizes the results. High



2

enantioselectivity was observed even without optimizing the reaction conditions.[6] As shown in entry 2 of Table I, the use of chiral borane **1b**, which possesses a bulky *tert*-butyl group, enhanced the enantioselectivity of the reaction and provided the opposite enantiomer of the β-hydroxy ester almost exclusively. Also, the enantioselectivity of the reaction increased as the bulkiness of the sulfonyl group increased (entries 3 and 4, Table I).

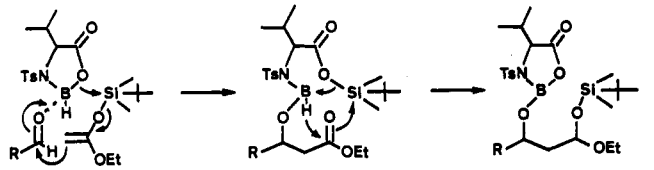
Changing the trialkylsilyl group of the silyl ketene acetal from trimethylsilyl (TMS) to *tert*-butyldimethylsilyl (TBDMS) had a dramatic effect on the reaction course. Condensation of the TBDMS ketene acetal 3 with aldehyde in the presence of the chiral borane **1a** gave, surprisingly, good yield of the diastereomeric β-hydroxy acetal 4 (eq 2).[7] Acetal 4 arose, apparently, from the reduction

Table II. Enantioselective Aldol Reactions of *tert*-Butyldimethylsilyl Ketene Acetals 3 with Aldehydes under the Influence of Chiral Lewis Acid 1a[a]

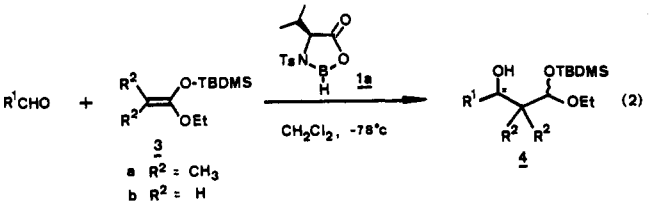
entry	R^1CHO, R^1	silyl ketene acetal 3 R^2	% yield[b] of acetal 4	% ee[c]
1	C_6H_5	H	77	45[d]
2	C_6H_5	CH_3	83	98
3	(E)-C_6H_5CH=CH	H	76	54
4	(E)-C_6H_5CH=CH	CH_3	79	92
5	$C_6H_5CH_2CH_2$	H	82	62
6	$C_6H_5CH_2CH_2$	CH_3	85	96

[a] Reaction conditions were as described in the text and ref 7. [b] Isolated yields after flash column chromatography. [c] Determined by HPLC analysis of the diols 6 with a chiral Daicel OD column. [d] The % ee was determined by HPLC analysis of 3-ethoxy-1-phenyl-1-propanol derived from the acetal 4 (R^1 = C_6H_5, R^2 = H) (ref 8).

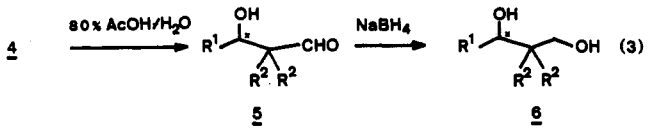
Scheme I



7 8 9



of an intermediate ester by hydride transfer from the promoter **1a**. The diastereomeric TBDMS acetals 4 were converted to the β-hydroxy aldehydes 5 by treatment with 80% AcOH–H_2O in yields ranging from 70 to 80% when R^2 = CH_3 and from 40 to 50% when R^2 = H.[8] $NaBH_4$ reduction of compounds 5 afforded the diols 6. Table II summarizes the results of the reactions of TBDMS ketene acetals 3 with various aldehydes (eqs 2 and 3). The en-



5 6

antioselectivity of the reactions of **3a**, as determined by HPLC analysis of the diols 6 with a chiral Daicel OD column, appeared to be higher than that of the reactions of the corresponding TMS ketene acetal. Furthermore, very high enantioselectivity was observed in the reactions of **3a**, whereas in the reactions of **3b**, the enantioselectivity was only moderate (entries 1, 3, and 5, Table II). Optically active β-hydroxy aldehydes such as 5, which could be easily

(4) Kiyooka, S.-I.; Nakano, M.; Shiota, F.; Fujiyama, R. *J. Org. Chem.* **1989**, *54*, 5409.

(5) The sulfonamides used were prepared by the Schotten–Baumann procedure. See: McChesney, E. W.; Swann, W. K. *J. Am. Chem. Soc.* **1937**, *59*, 1116. The spectroscopic data are presented in the supplementary material. All new compounds were characterized by elemental analysis. **General Procedures.** An equimolar amount of a 1.0 M solution borane·THF complex was added drop-by-drop to a solution of 1.0 equiv of the sulfonamide in CH_2Cl_2 (0.1 M) at ambient temperature over 0.5 h. To the resulting solution was added a solution of 1.0 equiv of the aldehyde in CH_2Cl_2 at −78 °C. Then 1.1 equiv of the silyl ketene acetal was added. After 3 h at −78 °C, the reaction was quenched at −78 °C by the introduction of buffer solution (pH 6.8). The mixture was extracted with Et_2O. After the usual workup, the pure products and the sulfonamide were isolated by flash column chromatography. After desilylation of the silyl ether by treatment with 1.0 M solution of n-Bu_4NF in THF, the yield and % ee were determined.

(6) Reaction in which chiral reagents prepared from *N*-tosyl-(*S*)-valine and other Lewis acids, e.g. BBr_3, Et_2AlCl, and i-Bu_3Al were used, were less enantioselective (<15% ee).

(7) All the reactions listed in Table II, performed according to the general procedure,[5] gave the β-hydroxy acetals 4. Compounds 4 were converted to the β-hydroxy aldehydes by treatment with 80% AcOH/H_2O at ambient temperature for 10 min. $NaBH_4$ reduction of the β-hydroxy aldehydes in EtOH gave the diols 6. The % ee of the reaction was determined by HPLC analysis of the diols after they had been purified by flash chromatography.

(8) Hydrolysis of the acetal 4 (R^1 = C_6H_5, R^2 = H) gave cinnamaldehyde. The acetal 4 was converted to 3-ethoxy-1-phenyl-1-propanol in 94% yield by LAH/$AlCl_3$ reduction.

obtained from the products 4, would have considerable utility in synthesis.

A mechanism which accounts for the formation of compounds 4 is shown in Scheme I. It features a cyclic transition state (7).[9] In the transition state, coordination of the boron atom of the borane with the oxygen atom of the carbonyl group would lower the energy of activation for nucleophilic attack and concurrently facilitate desilylation. The difference in the reaction course, as a function of the trialkylsilyl group of silyl ketene acetal, may be due to that group's effect on the stability of the transient intermediate 8.[10] The stability of 8 would be enhanced if the trialkylsilyl group were TBDMS rather than TMS. Reduction of the ester group of the transient complex 8 by intramolecular hydride transfer from the borane and retransfer of the TBDMS group would form the acetal complex 9.

Supplementary Material Available: Spectroscopic data for the sulfonamides and compounds 2, 4, 5, and 6 (10 pages). Ordering information is given on any current masthead page.

(9) A similar eight-membered cyclic transition state was proposed by Trost to explain the high selectivity of the Lewis acid mediated aldol reaction. See: Trost, B. M.; Urabe, H. *J. Org. Chem.* **1990**, *55*, 3982.

(10) Additional support for this argument was provided by the experimental finding that mono-TBDM-silylated binaphthol was recovered from the aldol reaction in which a promoter prepared from chiral binaphthol and borane·THF was used. The % ee of the reaction was, however, low.

Control of Ring-Junction Stereochemistry via Radical Cyclization. A New Construction of *trans*-Hydrindans

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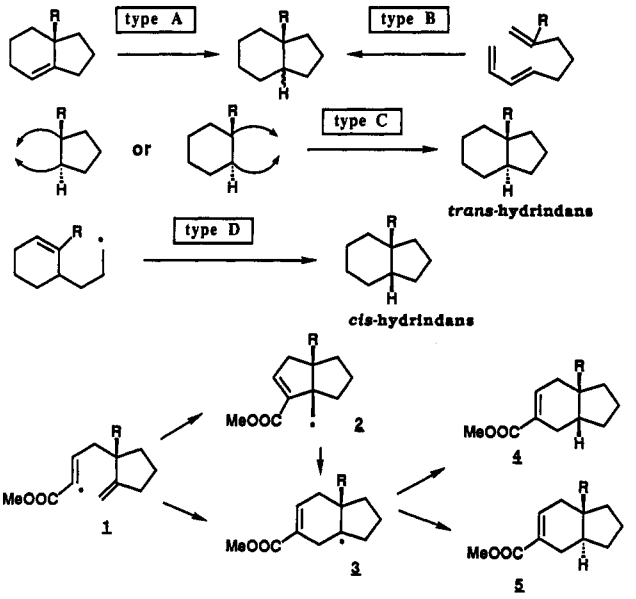
Received January 2, 1991

Summary: Treatment of **7b** with Bu_3SnH in toluene containing Et_3B at −30 °C afforded *trans*-hydrindan **8b** exclusively (97% yield, trans:cis = 100:0). Furthermore, exposure of **13a** to Bu_3SnH in the presence of Et_3B at −30 °C gave the trans angularly methylated hydrindan **14a** in a highly stereocontrolled manner (87% yield, trans:cis = 95:5).

trans-Hydrindans are found in many biologically significant compounds such as steroids and vitamin D derivatives, and therefore, quite a number of synthetic routes to them have been developed. These known synthetic routes may be divided into three types (A,[1] B,[2] and C[3]) as shown in Scheme I.[4] It is noteworthy that in type B control of the ring-junction sterochemistry is achieved at the stage of *trans*-hydrindan ring formation. In the case of angularly methylated hydrindan systems, however, high stereochemical control is rather difficult in general. *exo-trig*-Radical cyclization has been also utilized for the construction of hydrindans (type D), giving *cis*-hydrindans stereoselectively.[5] In this paper, we report a conceptually new synthetic route to *trans*-hydrindans **5** via radical cyclization (Scheme I).

Scheme I



In general, it is known that 1,5-hexadienyl radicals afford kinetically controlled 5-*exo* cyclized products.[5] On the other hand, Beckwith[6] and Stork[7] have reported that these

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(3) (a) Stork, G.; Shiner, C. S.; Winkler, J. D. *J. Am. Chem. Soc.* **1982**, *104*, 310. (b) Stork, G.; Winkler, J. D.; Shiner, C. S. *J. Am. Chem. Soc.* **1982**, *104*, 3767. (c) Stork, G.; Saccomano, N. A. *Tetrahedron Lett.* **1987**, *28*, 2087. (d) Takahashi, T.; Shimizu, K.; Doi, T.; Tsuji, J.; Fukazawa, Y. *J. Am. Chem. Soc.* **1988**, *110*, 2674. (e) Takahashi, T.; Shimizu, K.; Doi, T.; Tsuji, J.; Yamamoto, K. *Tetrahedron Lett.* **1989**, *30*, 4999. (f) Doi, T.; Shimizu, K.; Takahashi, T.; Tsuji, J.; Yamamoto, K. *Tetrahedron Lett.* **1990**, *31*, 3313. (g) Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1989**, *111*, 6257. (h) Mikami, K.; Takahashi, K.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 4035. (i) Kim, D.; Kim, S.; Lee, J. J.; Kim, H. S. *Tetrahedron Lett.* **1990**, *31*, 4027. For the synthesis utilizing radical cyclization, see: (j) Dombroski, M. A.; Kates, S. A.; Snider, B. B. *J. Am. Chem. Soc.* **1990**, *112*, 2759. (k) Clive, D. L. J.; Manning, H. W.; Boivin, T. L. B. *J. Chem. Soc., Chem. Commun.* **1990**, 972.

(4) For the synthesis of *trans*-hydrindans using a hydroboration–carbonylation process, see: Brown, H. C.; Negishi, E. *J. Chem. Soc., Chem. Commun.* **1968**, 594.

(5) For reviews, see: (a) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 553. (b) Neumann, W. P. *Synthesis* **1987**, 665. (c) Curran, D. P. *Synthesis* **1988**, 417, 489. For another type of cis-selective radical cyclization, see: (d) Beckwith, A. L. J.; Phillipou, G.; Serelis, A. K. *Tetrahedron Lett.* **1981**, *22*, 2811. (e) Boger, D. L.; Mathvink, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 4003. For the *trans*-hydrindan synthesis using radical cyclization of fixed polycyclic ring systems, see: (f) Hart, D. J.; Huang, H.-C.; Krishnamurthy, R.; Schwartz, T. *J. Am. Chem. Soc.* **1989**, *111*, 7507.

(6) Beckwith, A. L. J.; O'Shea, D. M. *Tetrahedron Lett.* **1986**, *27*, 4525.

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