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.

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(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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Table I. Asymmetric Hydrogenation Catalyzed by BINAP-Ru Complexes[a]

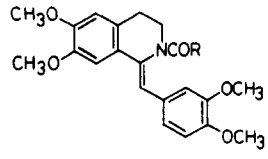
substrate	catalyst	reaction time, h	product % yield[b]	product % ee[c]	product confign
(*Z*)-**2a**	Δ-(*R*)-**1**	48	100	>99.5[d]	*R*
(*Z*)-**2a**	Λ-(*S*)-**1**	48	100	>99.5[d]	*S*
(*Z*)-**2a**	Λ-(*S*)-**1**	46[e]	100	>99.5[d]	*S*
(*Z*)-**2a**	Λ-(*S*)-**1**	46[f]	100	>99.5[d]	*S*
(*Z*)-**2a**	*g*	40	98	99	*R*
(*E*)-**2a**	Λ-(*S*)-**1**	48	0		
(*Z*)-**2b**	Λ-(*S*)-**1**	167	10		
(*Z*)-**2c**	Λ-(*S*)-**1**	48	100	50[h]	*S*
(*Z*)-**2d**	Λ-(*S*)-**1**	158	100	96	*S*
(*E*)-**2d**	Λ-(*S*)-**1**	48	0		
(*Z*)-**2f**	Δ-(*R*)-**1**	48	100	>99.5[d]	*R*
(*Z*)-**2f**	Λ-(*S*)-**1**	48	100	>99.5[d]	*S*
9	Δ-(*R*)-**1**	72	93	97	*R*
9	Λ-(*S*)-**1**	96	100	96	*S*
10	Δ-(*R*)-**1**	48	92	95	*R*
10	Λ-(*S*)-**1**	49	97	96	*S*
11	Λ-(*S*)-**1**	48	100	96	*S*

[a] Reaction was carried out in C_2H_5OH–CH_2Cl_2 (5:1) at 23 °C under an initial hydrogen pressure of 4 atm unless otherwise specified. [b] Isolated yield. [c] Determined by HPLC analysis of the GITC derivatives. [d] The enantiomer could not be detected by HPLC analysis. [e] A 5:1 CH_3OH–CH_2Cl_2 mixture was used as solvent. [f] Initial hydrogen pressure was 1 atm. [g] $[Ru((R)\text{-}(+)\text{-binap})Cl_2]_2(C_2H_5)_3N$ was used as catalyst [Ikariya, T.; Ishii, Y.; Kawano, H.; Arai, T.; Saburi, M.; Yoshikawa, S.; Akutagawa, S. *J. Chem. Soc., Chem. Commun.* **1985**, 922]. [h] Calculated from the optical rotation of the pivaloyl derivative of (*S*)-**5** prepared by optical resolution.

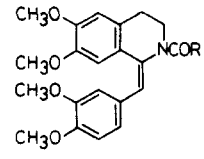
quinolines to give the 1*R* or 1*S* products in 95–100% ee.

Catalytic hydrogenation of the *Z* enamides [(*Z*)-**2**] was conducted in the presence of 0.5–1 mol % of the chiral Ru complex **1** in a 5:1 mixture of ethanol and dichloromethane under 1–4 atm of hydrogen at 23 °C. Concentration of the reaction mixture followed by short-path chromatography on silica gel gave the hydrogenation products. The enantiomeric excess of the 1*R* product **3** derived from (*Z*)-**2a**, for instance, was determined after conversion of the crude product to (*R*)-tetrahydropapaverine (**5**) by deacetylation (KOH, hydrazine/ethylene glycol, 170 °C, 70% yield). Reversed-phase HPLC (Nomura Chemical Co., Develosil ODS-5, 2:3 acetonitrile–water) of the adduct of synthetic **5** and 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (GITC)[6] revealed a single peak, indicating >99.5% ee of **5**. This assay was consistent with the result of HPLC analysis using a chiral stationary phase (Daicel Chemical Industry, CHIRALCEL OC, ethanol) of the *N*-ethyl derivative **6** formed by lithium aluminum hydride reduction of crude **3**, exhibiting again a single peak. The generality of the asymmetric hydrogenation is illustrated in Table I. The Ru-catalyzed reduction of (*Z*)-**2** having an appropriate *N*-acyl group proceeded smoothly to give the tetrahydropapaverine derivatives in high yield and with excellent enantioselectivity. The reaction using Δ-(*R*)-**1** as catalyst gave generally the 1*R* products predominantly, whereas the 1*S* enantiomers were available by catalysis with Λ-(*S*)-**1**. The strongly electron-withdrawing trifluoroacetyl group at the nitrogen decreased the reactivity. Rhodium complexes such as $[Rh(binap)(cod)]ClO_4$ or $[Rh(binap)(CH_3OH)_2]ClO_4$[4] in place of **1** did not give satisfactory result (only ~70% enantioselectivity with (*Z*)-**2a** as substrate). Notably, the *E* enamide substrates [(*E*)-**2**] were inert to the present Ru-catalyzed hydrogenation conditions.

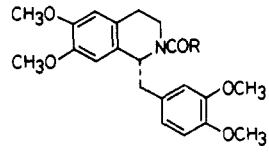
The starting *Z* and *E* enamide substrates **2** were prepared by acylation of 3,4-dihydropapaverine (**8**) by acyl chlorides and triethylamine. The requisite *Z* enamides are usually much less soluble in ethanol than the *E* isomers and hence are readily obtainable by recrystallization. Further, since the geometrical isomers are interconvertible by irradiation of a tungsten lamp, the second-order[7] stereomutation technique utilizing the photolability and lattice-energy effects is even more convenient for selective preparation of the *Z* substrates. The configurations of the enamide substrates were established by the UV and ^1H NMR analyses[8] and single-crystal X-ray study of the (*Z*)-pivaloyl and -*p*-bromobenzoyl derivatives [(*Z*)-**2c** and (*Z*)-**2e**, respectively].[9] The sterically rather constrained *Z* enamides exist, in both solid and solution phase, as a mixture of the two enantiomeric conformers and possess a sickle C=C—N—C=O geometry which is unfavorable for metal chelation.[10] Nevertheless, they undergo smooth, highly enantioselective hydrogenation. Use of a formyl protective group at the nitrogen atom enhances the synthetic utility, because (1) formylation of the imines of type **8** with formic pivalic anhydride and pyridine leads to the desired *Z* enamides with high selectivity (*Z*/*E* ~12:1), (2) deblocking of the formyl group from the hydrogenated products is accomplishable under mild conditions (2 N NaOH in ethanol, 80 °C) without loss of optical purity, and (3) naturally ubiquitous *N*-methylated tetrahydroisoquinolines can be easily obtained by the reduction.



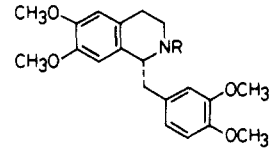
(*Z*)-**2**
a: R = CH_3
b: R = CF_3
c: R = $C(CH_3)_3$



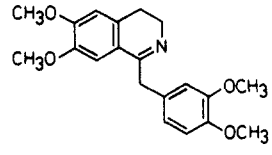
(*E*)-**2**
d: R = C_6H_5
e: R = *p*-BrC_6H_4
f: R = H



3, R = CH_3
4, R = H



5, R = H
6, R = C_2H_5
7, R = CH_3



8

This homogeneous catalysis finds a wide applicability in the synthesis of various naturally occurring or other physiologically significant products. The hydrogenation of (*Z*)-**2f** catalyzed by Δ-(*R*)-**1** and subsequent lithium aluminum hydride reduction produced (*R*)-laudanosine (**7**) in >99.5% ee. The Δ-(*R*)-**1**-aided hydrogenation of the *Z* enamide **9** followed by deacetylation affording (*R*)-**12** (97% ee), and debenzylation (Pd/C, H_2, HCl, ethanol) gave after recrystallization homochiral (*R*)-tretoquinol [(*R*)-**13**].[11] The enantiomer, (*S*)-**13**, was also obtained by using Λ-(*S*)-**1** as the chiral hydrogenation catalyst. In a similar manner, enamide **10** was converted in two steps to (*R*)-norreticuline (**14**) in 95% ee. Transformation of **14** to natural morphine is known.[12]

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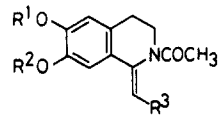
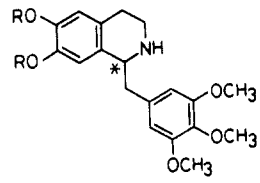
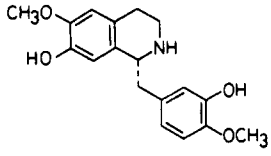




9, $R^1 = R^2 = C_6H_5CH_2$; $R^3 = 3,4,5\text{-}(CH_3O)_3C_6H_2$
10, $R^1 = CH_3$; $R^2 = CH_3CO$; $R^3 = 3\text{-}CH_3COO\text{-}4\text{-}(CH_3O)C_6H_3$
11, $R^1 = R^2 = CH_3$; $R^3 = H$

12, R = $C_6H_5CH_2$
13, R = H



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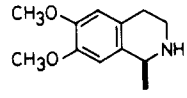

15

The catalyzed reduction of the simple methylene derivative **11** afforded after deacetylation (*S*)-salsolidine (**15**) in 96% ee. Thus the present catalytic method is chirally flexible and allows synthesis of both antipodal products in high enantiomeric excesses with equal ease by choosing the handedness of the BINAP-Ru catalysts. Most of the tetrahydroisoquinoline products are crystalline and the homochiral materials are readily accessible by single recrystallization.

Acknowledgment. We are grateful to Tanabe Pharmaceutical Co. for a generous gift of the commercial (*S*)-tretoquinol sample. We thank Dr. K. Mashima, Institute for Molecular Science, for valuable contribution in the X-ray crystallographic analyses.

Supplementary Material Available: Descriptions of the determination of crystal structures including complete listings of atomic parameters, anisotropic temperature factors, bond distances, and bond angles for (*Z*)-**2c** and (*Z*)-**2e**, preparation of Δ-(*R*)-**1** and Λ-(*S*)-**1**, and physical properties of the new compounds (37 pages). Ordering information is given on any current masthead page.

Phosphine Oxides as NMR Probes for Adsorption Sites on Surfaces

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Studies of small basic probe molecules by NMR to identify surface acidic sites on oxides of aluminum and silicon have yielded information on the types of surface acid sites, on the numbers of these sites, and about the molecular dynamics of the adsorbed probe molecules. Initial work in this area employed amines as probes via ^{13}C and ^{15}N magic-angle spinning (MAS) NMR.[1-7]

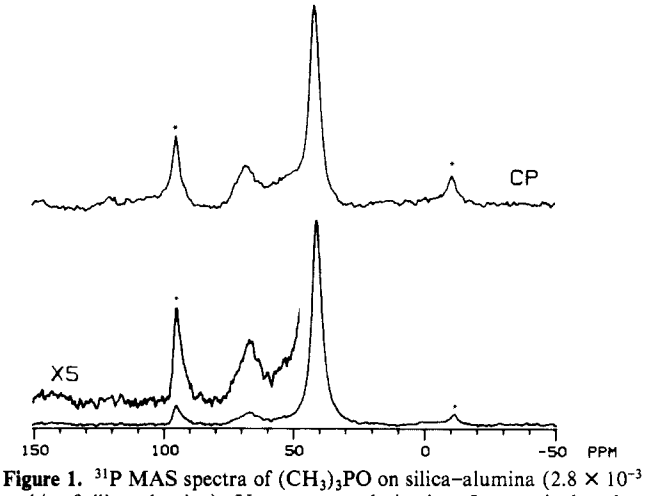

Figure 1. ^{31}P MAS spectra of $(CH_3)_3PO$ on silica–alumina (2.8×10^{-3} mol/g of silica–alumina). Upper, cross polarization. Lower, single pulse. Asterisks designate spinning sidebands.

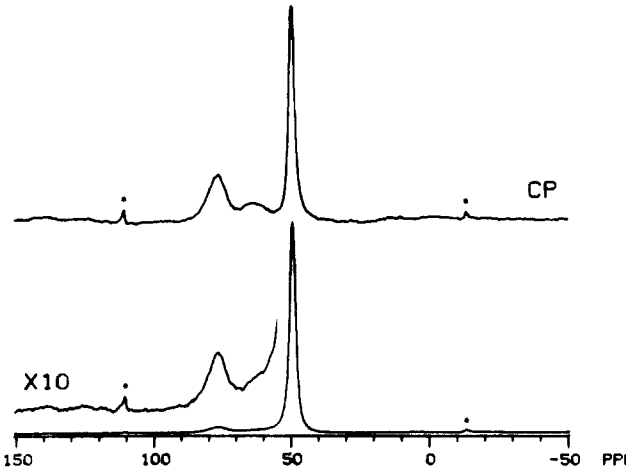

Figure 2. ^{31}P MAS spectra of $(C_2H_5)_3PO$ on silica–alumina (3.0×10^{-3} mol/g of silica–alumina). Upper, cross polarization. Lower, single pulse. Asterisks designate spinning sidebands.

More recent work has focused on the study of phosphines via ^{31}P NMR.[8-10] ^{31}P has the advantage over ^{15}N of greater NMR sensitivity due to a higher magnetogyric ratio and 100% natural abundance of the spin-$^1/_2$ isotope, therefore permitting extensive sets of experiments over a wide range of surface coverage of phosphines. Although studies of silica–alumina with trialkylphosphines have been successful in the quantitative analysis of surface Brønsted sites,[10] the quantitative analysis of surface Lewis sites has been hampered not only by small chemical shift differences between Lewis-bound and physisorbed phosphines but also by the similarity of surface binding equilibrium constants for these two types of sites; these factors result in the absence of a break point in the "titration" curves for Lewis-bound phosphines from which the concentration of Lewis sites could otherwise be calculated.

In an effort to find a probe molecule that would give a good distinction between the Lewis-bound and physisorbed molecules on surfaces, we have investigated the use of trialkylphosphine oxides as probe molecules for surface acid sites of amorphous materials. In the present paper we report promising ^{31}P NMR results obtained on $(CH_3)_3PO$ and $(C_2H_5)_3PO$ on silica–alumina.

Figure 1 shows ^{31}P MAS NMR spectra of high-surface-loading $(CH_3)_3PO$ on amorphous silica–alumina (75%/25% by weight)

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