is 320 M^{-1}, indicating that only a slightly tighter complex is formed within the cavity. The sigmoidal curve in Figure 4 is consistent with initial binding at the exo phosphoryl presumably due to steric interactions since the derived chemical shift of the 1:1 complex (7.82 ppm) is close to that of the free host, but significantly different from that of the 1:2 complex (7.59 ppm). The $^{exo}K_{assoc}$ is 866 M^{-1}, and the $^{endo}K_{assoc}$ is 223 M^{-1}. The larger $^{exo}K_{assoc}$ of **5** relative to **3** is under investigation. Scheme I displays the proposed mechanism for 1:2 complex formation of **5** with PNP.

In conclusion, we have shown that phosphine oxide bifunctional macrocycles (**2**–**5**) form 1:2 complexes with PNP. While exo–exo hosts (**2** and **4**) form only extracavity complexes, the endo–exo hosts (**2** and **5**) also exhibit intracavity complexation. The diyne (**3**) initially complexes at the endo site, while the saturated bridge host (**5**) initially complexes at the exo phosphoryl due to the reduction of intracavity space present in **5**. The specificity of complexation is under current investigation.

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Supplementary Material Available: X-ray data for **2** and **5** including space-filling representations, SHELXTL PLUS drawings, crystal data, solution and refinement data, atomic coordinates and equivalent isotropic displacement parameters, bond lengths and angles, anisotropic displacement parameters, and hydrogen atom coordinates and isotropic displacement parameters (27 pages). Ordering information is given on any current masthead page.

Stereoselective Hydrogenation via Dynamic Kinetic Resolution

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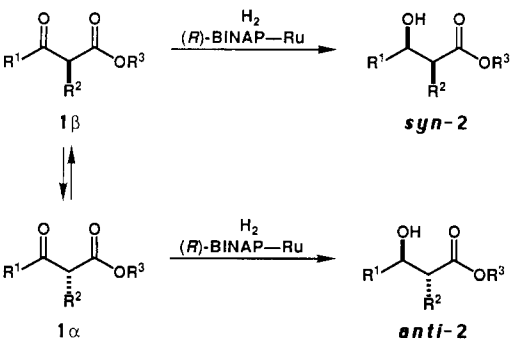
Although kinetic resolution of racemic compounds is increasing in synthetic significance,[1] most reactions suffer from the disadvantage that the yield of the desired chiral product does not exceed 50%. The chiral lability of 2-substituted 3-oxo carboxylic esters, coupled with the high chiral recognition ability of the BINAP–Ru(II) complexes,[2-5] has prompted us to investigate the possibility of stereoselective hydrogenation utilizing dynamic stereomutation as outlined in Scheme I. If the racemization of the enantiomers **1**α and **1**β could be rapid enough with respect to the hydrogenation giving **2**, then when rates of the reaction of **1**α and **1**β are substantially different, the hydrogenation would form one isomer selectively among the four possible stereoisomeric hydroxy esters. This second-order stereoselective transformation, if feasible, constitutes an ideal asymmetric catalysis which, in theory, is

Scheme I



a: $R^1 = R^2 = CH_3$; $R^3 = C_2H_5$
b: $R^1 = R^3 = CH_3$; R^2 = NHCOCH$_3$
c: R^1 = 3,4-methylenedioxyphenyl; R^2 = NHCOCH$_3$; $R^3 = CH_3$
d: R^1 = 3,4-methylenedioxyphenyl; R^2 = NHCOOCH$_2$C$_6$H$_5$; $R^3 = CH_3$
e: $R^1 = R^3 = CH_3$; $R_2 = CH_2NHCOC_6H_5$

capable of converting a racemic starting material in 100% yield to a single chiral product possessing stereodefined vicinal asymmetric centers. We here disclose examples of both syn- and anti-selective hydrogenation based on this principle.

The efficiency and sense of the enantio- and diastereoselective synthesis of **2** is highly influenced by substrate structures and reaction conditions. The BINAP–Ru catalyzed hydrogenation of simple 2-alkylated substrate **1a** proceeds with high stereoselectivity with respect to the C-3 position, but no appreciable resolution is seen, resulting in an equimolar mixture of *syn*-**2** and *anti*-**2**.[2a,6,7] However, appropriate skeletal or functional perturbation of substrates leads to clear differentiation of syn and anti transition states, as illustrated in Table I. In dichloromethane containing an (*R*)-BINAP–Ru complex, racemic *cyclic* ketone **3** was hydrogenated with high anti diastereoselectivity, to give a 99:1 mixture of the *trans*-hydroxy ester **4** (92% ee) and its C-2 epimer **5** (93% ee) quantitatively.[8] The reaction in methanol decreased diastereoselectivity (82:18). By contrast, an amide or carbamate group present in certain *acyclic* substrates exhibited remarkable syn directivity, leading to threonine type products in excellent ee's and in high yields. For instance, hydrogenation of 2-acetamido derivative **1b** in dichloromethane gave a protected L-threonine, *syn*-**2b** (98% ee), and allothreonine, *anti*-**2b**, with 99:1 selectivity.[7,9] Use of methanol as solvent lowered the diaster-

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(3) Note: A limited, small quantity of Ru(OCOCH$_3$)$_2$[(*R*)- or (*S*)-BINAP][4] is available. Please contact R. Noyori at Nagoya University, indicating chirality of the complex and type of substrates.
(4) Ohta, T.; Takaya, H.; Noyori, R. *Inorg. Chem.* **1988**, *27*, 566. RuX$_2$(BINAP) (X = Cl or Br, empirical formula) complexes were prepared by mixing Ru(OCOCH$_3$)$_2$(BINAP) and HX in a 1:2 ratio.[2] Use of the freshly prepared complex is recommended for reaction in dichloromethane. Since these polymeric complexes behave similarly to the well-defined monomeric complex [RuCl(C$_6$H$_6$)(BINAP)]Cl, the active catalyst precursor may be represented as RuX$_2$(BINAP)(solvent)$_2$.
(5) Resolution of secondary allylic alcohols: Kitamura, M.; Kasahara, I.; Manabe, K.; Noyori, R.; Takaya, H. *J. Org. Chem.* **1988**, *53*, 708.
(6) Hydrogenation of methyl 2-methyl-3-oxobutanoate catalyzed by Raney nickel modified by (*R*,*R*)-tartaric acid gave methyl (2*S*,3*R*)-3-hydroxy-2-methylbutanoate (56.7% ee) and the 2*R*,3*R* isomer (64.4% ee) in a 3.6:1 ratio. See: Tai, A.; Watanabe, H.; Harada, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1468.
(7) The syn and anti isomers are not interconvertible under the reaction conditions.
(8) For biological methods, see: Buisson, D.; Azerad, R. *Tetrahedron Lett.* **1986**, *27*, 2631. Buisson, D.; Sanner, C.; Larcheveque, M.; Azerad, R. *Ibid.* **1987**, *28*, 3939. Nakamura, K.; Miyai, T.; Nozaki, K.; Ushio, K.; Oka, S.; Ohno, A. *Ibid.* **1986**, *27*, 3155.

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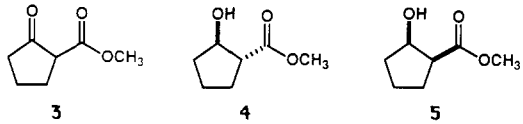
Table I. Stereoselective Hydrogenation of 2-Substituted 3-Oxo Carboxylic Esters[a]

substrate	catalyst[b]	conditions			product	
		S/C[c]	temp, °C	time, h	syn/anti[d]	% ee[d] (config)[d]
(±)-**1b**	$RuBr_2$[(*R*)-BINAP]	270	15	50	99/1	98 (2*S*,3*R*) >90 (2*R*,3*R*)
(±)-**1c**	$RuBr_2$[(*R*)-BINAP]	260	50	120	99/1	94[e] (2*S*,3*R*)
(±)-**1d**	$RuBr_2$[(*R*)-BINAP]	230	50	96	99/1	92[e] (2*S*,3*R*)
(±)-**1e**	Ru_2Cl_4[(*R*)-BINAP]$_2$·$N(C_2H_5)_3$[f]	100	50	20	94/6	98 (2*S*,3*R*) 93 (2*R*,3*R*)
(±)-**3**	[$RuCl(C_6H_6)$((*R*)-BINAP)]Cl[g]	1170	50	70	1/99	93 (1*R*,2*S*) 92 (1*R*,2*R*)

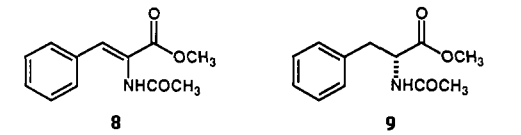
[a] Reaction was carried out in CH_2Cl_2 under 100 atm of H_2. Conversion was 100%. [b] BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl. [c] Substrate/catalyst mole ratio. [d] Details of the analysis are described in the supplementary material. [e] The absolute configuration of the anti isomer was not determined. [f] See ref 12. [g] See ref 13.

eoselectivity (71:29). This method is useful for the stereoselective synthesis of *syn*-**2c** and *syn*-**2d**,[7] which serve as intermediates of L-DOPS, an anti-Parkinsonian agent.[10] Notably, even the 2-amidomethyl substrate **1e** afforded stereoselectively *syn*-**2e** in 98% ee, which was converted to the known β-lactam **6**.[11]

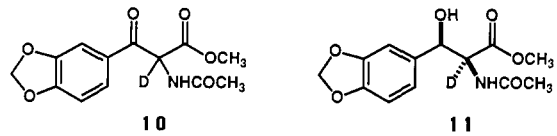


3 **4** **5**

6 **7**



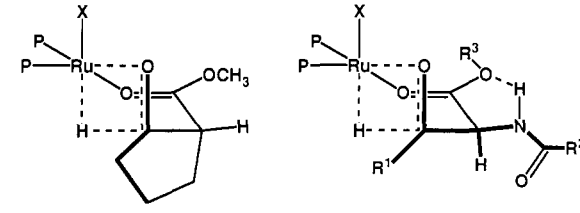
8 **9**



10 **11**

All these hydrogenations of keto esters are proceeding in their keto form in which the ester function is acting as donor trigger, consistent with the trans stereochemistry of **4**, smooth reaction of methyl 2,2-dimethyl-3-oxobutanoate (96% ee in CH_3OH; 88% ee in CH_2Cl_2), and the general sense of asymmetric induction at C-3.[2] The high level of syn selection achieved with the amide or carbamate substrates is held not to be a result of NHCO-directed hydrogenation of prochiral enols of type **7**:[14] Firstly, the C-2 absolute configuration in the products is not consistent with the empirical stereochemical consequences observed with related enamide substrates.[15] For example, hydrogenation of a deoxy analogue **8** with $RuBr_2$[(*R*)-BINAP] at 100 atm gave (*R*)-**9** in 24% (CH_2Cl_2) or 85% (CH_3OH) optical yield. An isotope labeling experiment also supports the ketone mechanism of Scheme I. 2-Deuterio compound **10** easily loses deuterium via enolization. However, hydrogenation of this substrate with $RuBr_2$[(*R*)-BINAP] in dichloromethane gave, at 1.3% conversion, hydroxy ester **11**, which retained 80% of deuterium at C-2 and had no deuterium at C-3 with recovery of **10** containing 70% deuterium at C-2.

Thus we have realized stereoselective hydrogenation utilizing kinetic discrimination of rapidly equilibrating enantiomers.[16] The absolute configuration at C-3 is governed by the handedness of the BINAP ligand while the C-2 configuration is dependent on substrate structures. The remarkably high anti selection observed with **3** is rationalized in terms of the sterically constrained tricyclic transition state **12**. Here the chiral array of BINAP phenyl rings[4] would determine the absolute configuration. As the origin of the unique syn selection directed by an amide or related groups, we envisage a transition state **13** which is stabilized by hydrogen bonding between CONH and the ester OR^3.[14] The solvent effect (CH_2Cl_2 vs CH_3OH) on the diastereoselectivity agrees with this view.



12 **13**

P—P = (*R*)-BINAP
X = halogen, H, H_2, or solvent

Supplementary Material Available: Descriptions of the general procedures of the asymmetric hydrogenation, with a 10-g-scale reaction of methyl 2-acetamido-3-oxobutanoate as example, and determination of the enantiomeric excesses and relative and absolute configurations of the products (6 pages). Ordering information is given on any current masthead page.

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