for the copper oxide superconductors. Our preliminary physical studies demonstrate that the electrical properties change systematically with variations in x and δ, and, furthermore, these data provide evidence for superconductivity in $Sr_{0.9}CuO_2$. We believe that continued efforts using PLD to prepare crystalline $MCuO_2$ materials containing different (i) metals, (ii) metal stoichiometries, and (iii) oxygen stoichiometries will lead to new superconducting phases and to an improved understanding of superconductivity in the copper oxide materials.

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Quantitative Expression of Dynamic Kinetic Resolution of Chirally Labile Enantiomers: Stereoselective Hydrogenation of 2-Substituted 3-Oxo Carboxylic Esters Catalyzed by BINAP-Ruthenium(II) Complexes

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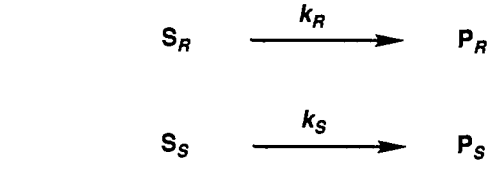
Abstract: Hydrogenation of chirally unstable 2-substituted 3-oxo carboxylic esters gives a mixture of four stereoisomeric hydroxy esters. Use of BINAP-Ru(II) complex catalysts allows selective production of one stereoisomer among four possible isomers. The stereoselectivity obtained by the dynamic kinetic resolution depends on facile in situ racemization of the substrates, efficient chirality recognition ability of the catalysts, and the structures of the ketonic substrate. The factors controlling the efficiency of the stereoselective hydrogenation are experimentally determined by reaction of racemic oxo esters using enantiomerically pure and racemic BINAP complexes. Quantitative expression of the dynamic kinetic resolution has been made by defining the product partition coefficients (w, x, y, and z), the relative reactivities of the enantiomeric substrates (k_{fast}/k_{slow}), and the relative ease with which stereoinversion and hydrogenation take place (k_{inv}/k_{fast}). The validity of the equations has been demonstrated by the graphical exhibition of the enantioselectivity and diastereoselectivity as a function of conversion of the substrates.

Under certain chiral circumstances, substrate enantiomers S_R and S_S react at different rates, k_R and k_S, yielding enantiomeric products P_R and P_S as illustrated in Scheme I. This principle allows chemical or biological kinetic resolution of racemic compounds. As studied extensively by Kagan, Sharpless, Sih, and others,[1] the k_R/k_S ratio of eq 1 is correlated to the extent of

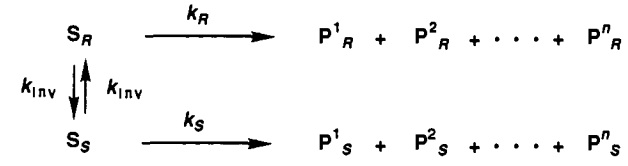
$$\frac{k_R}{k_S} = \frac{\ln (1 - \text{convn})(1 - \text{ee}_S)}{\ln (1 - \text{convn})(1 + \text{ee}_S)} = \frac{\ln [1 - \text{convn}(1 + \text{ee}_P)]}{\ln [1 - \text{convn}(1 - \text{ee}_P)]} \quad (1)$$

substrate conversion and the enantiomeric excess of the recovered substrate and product, ee_S and ee_P, respectively. This value has been utilized for assessing the efficiency of the resolution.[2] Such ordinary kinetic resolution, though very useful, suffers from the inherent disadvantage that the maximum yield of one enantiomer is 50% and, furthermore, that ee's of the product and recovered substrate are profoundly influenced by the extent of conversion. On the other hand, racemic compounds possessing a chirally labile stereogenic center allowing its in situ racemization during reaction can, in principle, be converted in 100% yield to enantiomerically pure products regardless of the extent of substrate conversion. This paper further elaborates on the dynamic kinetic resolution of enantiomers outlined in Scheme II. This reaction system is characterized not only by the presence of the substrate stereoinversion, $S_R \rightleftarrows S_S$, but also by formation of diastereomeric products, where both enantioselection and diastereoselection are exhibited.[3] Thus, under appropriate conditions, this kinetic resolution method can convert a racemic compound to one stereoisomer among many. In Scheme II the competitive reactions are closely interrelated, in contrast to the conventional kinetic resolution of Scheme I where the two pathways are independent of one another. Although the

Scheme I



Scheme II



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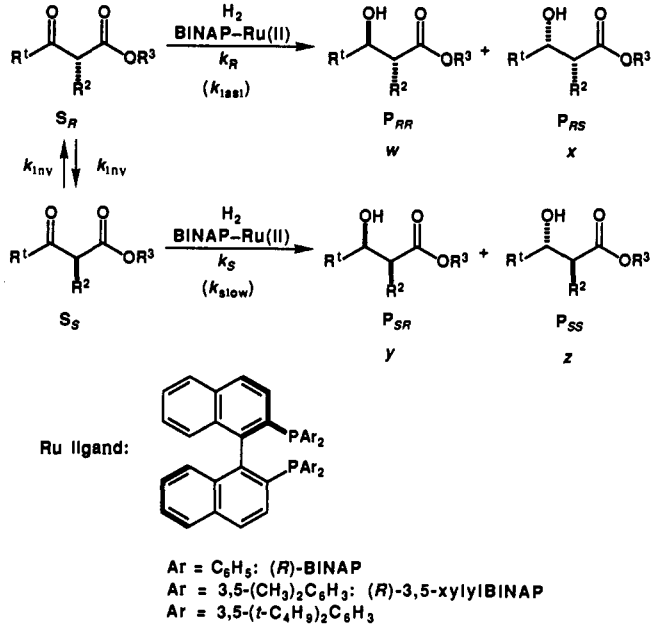
Scheme III



quantitative analysis of such a dynamic kinetic resolution is desirable, no mathematical treatment has been made.[1a] We here present for the first time a quantitative expression for a kinetic resolution of this type.

Mathematical Treatment

Stereoselective hydrogenation of racemic 2-substituted 3-oxo carboxylic esters catalyzed by BINAP–Ru(II) complexes,[4] outlined in Scheme III, provides a typical example of dynamic kinetic resolution.[5] Hydrogenation of the 2*R* oxo ester S_R occurs at rate k_R to give diastereomeric 2*R*,3*R* and 2*R*,3*S* hydroxy esters, P_{RR} and P_{RS}, and the reaction of the 2*S* enantiomer S_S at rate k_S gives the 2*S*,3*R* and 2*S*,3*S* diastereomers, P_{SR} and P_{SS}. P_{RR} and P_{SS} or P_{RS} and P_{SR} are enantiomers having 2,3-anti and 2,3-syn relative configuration, respectively. Here *w*, *x*, *y*, and *z* are partition coefficients of these isomers ($w + x + y + z = 1$), where *S_R and S_S are assumed to be present in equal amounts.*

Suppose that (1) S_R is the fast-reacting enantiomer giving P_{RR} as the most abundant stereoisomer, (2) rates of hydrogenation, k_R (k_{fast}) and k_S (k_{slow}), and stereoinversion of the substrate, k_{inv}, are the pseudo-first order in substrate concentration,[6] (3) S_R and S_S racemize at the same rate, and (4) the reaction is irreversible and the products are stable under reaction conditions. Since S_R is consumed at k_R and k_{inv} and supplied from S_S at k_{inv}, the rate equations of eqs 2 and 3 are derived:

$$-d[S_R]/dt = (k_R + k_{inv})[S_R] - k_{inv}[S_S] \quad (2)$$

$$-d[S_S]/dt = (k_S + k_{inv})[S_S] - k_{inv}[S_R] \quad (3)$$

Their transformation affords eqs 4 and 5 which state the substrate concentrations as a function of time elapsed:

$$S_R(t) = C_1 e^{\lambda_1 t} + C_2 e^{\lambda_2 t} \quad (4)$$

$$S_S(t) = C_3 e^{\lambda_1 t} + C_4 e^{\lambda_2 t} \quad (5)$$

Integration of these equations gives two sets of product concentrations given by eqs 6 and 7, where C_1, C_2, C_3, C_4, λ_1, and λ_2 are coefficients correlating with k_R, k_S, and k_{inv} (eqs 8–13, for details see Appendix):

$$P_{RR}(t) + P_{RS}(t) = \int k_R S_R(t)\, dt = k_R\left[\frac{C_1}{\lambda_1}(e^{\lambda_1 t} - 1) + \frac{C_2}{\lambda_2}(e^{\lambda_2 t} - 1)\right] \quad (6)$$

$$P_{SR}(t) + P_{SS}(t) = \int k_S S_S(t)\, dt = k_S\left[\frac{C_3}{\lambda_1}(e^{\lambda_1 t} - 1) + \frac{C_4}{\lambda_2}(e^{\lambda_2 t} - 1)\right] \quad (7)$$

$$\lambda_1 = \frac{1}{2}\left[-(k_R + k_S) - 2k_{inv} + \sqrt{(k_R - k_S)^2 + 4k_{inv}^2}\right] \quad (8)$$

$$\lambda_2 = \frac{1}{2}\left[-(k_R + k_S) - 2k_{inv} - \sqrt{(k_R - k_S)^2 + 4k_{inv}^2}\right] \quad (9)$$

$$C_1 = \frac{-(k_R - k_S) + 2k_{inv} + \sqrt{(k_R - k_S)^2 + 4k_{inv}^2}}{2\sqrt{(k_R - k_S)^2 + 4k_{inv}^2}} \quad (10)$$

$$C_2 = \frac{(k_R - k_S) - 2k_{inv} + \sqrt{(k_R - k_S)^2 + 4k_{inv}^2}}{2\sqrt{(k_R - k_S)^2 + 4k_{inv}^2}} \quad (11)$$

$$C_3 = \frac{(k_R - k_S) + 2k_{inv} + \sqrt{(k_R - k_S)^2 + 4k_{inv}^2}}{2\sqrt{(k_R - k_S)^2 + 4k_{inv}^2}} \quad (12)$$

$$C_4 = \frac{-(k_R - k_S) - 2k_{inv} + \sqrt{(k_R - k_S)^2 + 4k_{inv}^2}}{2\sqrt{(k_R - k_S)^2 + 4k_{inv}^2}} \quad (13)$$

Although kinetic behavior of chiral substrates leading to two sets of product enantiomers is well described by eqs 4–7, the dynamic kinetic resolution giving four stereoisomers must be treated by introduction of product distribution factors, *w*, *x*, *y*, and *z*. Thus the amounts of these four isomeric products at time *t* are written by:

$$P_{RR}(t) = \frac{w}{w + x}k_R\left[\frac{C_1}{\lambda_1}(e^{\lambda_1 t} - 1) + \frac{C_2}{\lambda_2}(e^{\lambda_2 t} - 1)\right] \quad (14)$$

$$P_{RS}(t) = \frac{x}{w + x}k_R\left[\frac{C_1}{\lambda_1}(e^{\lambda_1 t} - 1) + \frac{C_2}{\lambda_2}(e^{\lambda_2 t} - 1)\right] \quad (15)$$

$$P_{SR}(t) = \frac{y}{y + z}k_S\left[\frac{C_3}{\lambda_1}(e^{\lambda_1 t} - 1) + \frac{C_4}{\lambda_2}(e^{\lambda_2 t} - 1)\right] \quad (16)$$

$$P_{SS}(t) = \frac{z}{y + z}k_S\left[\frac{C_3}{\lambda_1}(e^{\lambda_1 t} - 1) + \frac{C_4}{\lambda_2}(e^{\lambda_2 t} - 1)\right] \quad (17)$$

The quantities of the chiral compounds, $S_R(t)$, $S_S(t)$, $P_{RR}(t)$, $P_{RS}(t)$, $P_{SR}(t)$, and $P_{SS}(t)$, relate to the ee of the unreacted slow-reacting substrate [$ee_S(t)$],[7] ee's of the major and first minor

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products P_{RR} and P_{SR} [$ee_{RR}(t)$ and $ee_{SR}(t)$, respectively], diastereoselectivity [$D(t)$], ratio of the 2*R* and 2*S* products [$P_{R/S}(t)$], composition of the most abundant isomer P_{RR} in the whole product [$SEL(t)$], and conversion [$convn(t)$] as shown in eqs 18–24.

$$ee_S(t) = \frac{S_S(t) - S_R(t)}{S_R(t) + S_S(t)} \tag{18}$$

$$ee_{RR}(t) = \frac{P_{RR}(t) - P_{SS}(t)}{P_{RR}(t) + P_{SS}(t)} \tag{19}$$

$$ee_{SR}(t) = \frac{P_{SR}(t) - P_{RS}(t)}{P_{SR}(t) + P_{RS}(t)} \tag{20}$$

$$D(t) = \frac{P_{RR}(t) + P_{SS}(t)}{P_{RR}(t) + P_{RS}(t) + P_{SR}(t) + P_{SS}(t)} \tag{21}$$

$$P_{R/S}(t) = \frac{P_{RR}(t) + P_{RS}(t)}{P_{SR}(t) + P_{SS}(t)} \tag{22}$$

$$SEL(t) = \frac{P_{RR}(t)}{P_{RR}(t) + P_{RS}(t) + P_{SR}(t) + P_{SS}(t)} \tag{23}$$

$$convn(t) = \frac{P_{RR}(t) + P_{RS}(t) + P_{SR}(t) + P_{SS}(t)}{S_R(0) + S_S(0)} \tag{24}$$

The features of the dynamic aspects of Scheme III are described by the parameters, k_R, k_S, k_{inv}, *w*, *x*, *y*, and *z*. Thus the selectivity profiles at time *t* are computed as a function of the k_{fast}/k_{slow} and k_{inv}/k_{fast} ratios, namely k_R/k_S and k_{inv}/k_R, respectively, as well as the product distribution parameters. Consequently the time-dependent values can be visually traced by graphic representation.

The next task is the correlation of these mathematical equations and experimental results. The distribution coefficients, *w*, *x*, *y*, and *z*, are defined as values obtained by the reaction employing equal amounts of S_R and S_S (Scheme III). These parameters can be determined experimentally using an enantiomerically pure catalyst and then a racemic catalyst. The former allows determination of w/x and y/z simply by knowing the P_{RR}/P_{RS} and P_{SR}/P_{SS} ratios, respectively. Unfortunately this reaction is unable to determine w/y or w/z, because, as the reaction proceeds, the S_R/S_S ratio deviates from unity. However, the reaction using the racemic catalyst occurs via mutual kinetic resolution where the concentration of the enantiomeric substrates remains equal throughout the reaction.[8] Therefore, the observed diastereoselectivity, $(P_{RR} + P_{SS})/(P_{SR} + P_{RS})$, is expressed by $(w + z)/(y + x)$. To achieve the desired mutual kinetic resolution, it is presumed that the catalyst enantiomers do not interact and function independently.[9] This is indeed the case in the reaction of Scheme III (see below). Alternatively, *w*, *x*, *y*, and *z* values may be estimated from the product distribution of the reaction with a very low conversion, if one has a method to suitably analyze the products. As such combination of the three experimentally derived ratios, w/x, y/z, and $(w + z)/(y + x)$, leads to the *w*, *x*, *y*, and *z* values. Because the k_R/k_S ratio is equal to the product ratio under mutual kinetic resolution conditions, the relative velocity is also obtained by eq 25.[8,10] This expression can be applied to any type of kinetic resolution regardless of the rate order of the substrate concentration.

$$\frac{k_R}{k_S} = \frac{w + x}{y + z} \tag{25}$$

Selectivity is highly affected by the relative ease of the reaction and stereoinversion. In the limiting case with $k_{inv}/k_R = \infty$, the efficiency remains constant (k_R/k_S) throughout the reaction.[11] The $P_{R/S}$ value in actual (*not* ideal) dynamic kinetic resolution of enantiomers is often conversion-dependent as in ordinary resolution without stereoinversion. If k_{inv} is not large enough with respect to k_{fast} (k_R) the value tends to significantly decrease from the initial value, $P_{R/S}{}^0$.

The limiting $P_{R/S}$ ratio at 100% conversion is expressed as

$$P_{R/S}{}^{100} = \lim_{t \to \infty} \frac{P_{RR}(t) + P_{RS}(t)}{P_{SR}(t) + P_{SS}(t)} = \lim_{t \to \infty} \frac{k_R\left[\frac{C_1}{\lambda_1}(e^{\lambda_1 t} - 1) + \frac{C_2}{\lambda_2}(e^{\lambda_2 t} - 1)\right]}{k_S\left[\frac{C_3}{\lambda_1}(e^{\lambda_1 t} - 1) + \frac{C_4}{\lambda_2}(e^{\lambda_2 t} - 1)\right]} \tag{26}$$

Substitution of eqs 8–13 into eq 26 followed by rearrangement of the equation yields

$$\frac{k_{inv}}{k_R} = \frac{1 - P_{R/S}{}^{100}}{2\left(P_{R/S}{}^{100} - \frac{k_R}{k_S}\right)} \tag{27}$$

Putting the observed values into eq 27 gives the k_{inv}/k_R ratio.

In the asymmetric reaction of a chiral substrate with a chiral catalyst (or reagent), the stereoselectivity is highly affected by the chirality of both counterparts. The selectivity based on such a double stereodifferentiation is often presumed to be the combined effects of catalyst control (C_{cat}, ability of the catalyst differentiating hypothetical enantiofaces of the substrate) and substrate control (C_{sub}, diastereoselectivity of reaction between the chiral substrate and a hypothetical achiral catalyst).[12] Proper matching of the substrate/catalyst chirality considerably enhances the stereoselectivity giving the diastereomeric products in a $C_{cat}C_{sub}$:1 ratio, while mismatching results in a decrease in stereoselectivity as low as C_{cat}:C_{sub} or C_{sub}:C_{cat}. These effects are conventionally interrelated with *w*, *x*, *y*, and *z* as follows.[13]

$$C_{sub} = \sqrt{wz/xy} \tag{28}$$

$$C_{cat} = \sqrt{wy/xz} \tag{29}$$

In this instance where S_R is assumed to be the fast-reacting enantiomer giving P_{RR} as the major product, *w*, *y*, and *z* are generally greater than *x*. With C_{cat} overwhelming C_{sub}, *y* is greater than *z* and, with the opposite inequality, *y* is smaller than *z*. In some cases, however, the generality, $w, y, z \geq x$, may be lost, affording y or $z < x$. In such cases, more careful scrutiny is required to analyze the origin of the stereoselectivity.

In any event, experiments using an enantiomerically pure catalyst and racemic catalyst can determine *w*, *x*, *y*, and *z* values and then k_{fast}/k_{slow} (eq 25) and k_{inv}/k_{fast} ratios (eq 27). These data then make it possible to infer the overall profile of the stereoselectivity as a function of conversion. Computer-generated graphics sheds more light on the time-dependent dynamic behavior. Figure 1 illustrates several curves generated from eqs 18–21 and eq 23 with some imaginary parameters. Figure 2 visualizes the relationship of k_{inv}/k_{fast}, k_{fast}/k_{slow}, and SEL^{100} (SEL at 100% convn) by a 3D graphic. The top corner denotes the ideal situation.

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Table I. BINAP-Ru(II)-Catalyzed Asymmetric Hydrogenation of 2-Substituted 3-Oxo Carboxylic Esters[a]

substrate	catalyst	solvent	product ratio[b] anti[c] 2*R*,3*R*	anti 2*S*,3*S*	syn[c] 2*S*,3*R*	syn 2*R*,3*S*
(±)-**1a**[d]	$Ru(OCOCH_3)_2$[(*R*)-binap] + 2HCl[e,f]	CH_3OH[g]	82.13	3.87	13.96	0.04
(±)-**1a**[d]	$Ru(OCOCH_3)_2$[(±)-binap] + 2HCl[e,h]	CH_3OH[g]	93.8		6.2	
(±)-**1b**[d]	$Ru(OCOCH_3)_2$[(*R*)-binap] + 2HCl[e,f]	CH_3OH[g]	56.92	1.58	40.84	0.66
(±)-**1b**[d]	$Ru(OCOCH_3)_2$[(±)-binap] + 2HCl[e,h]	CH_3OH[g]	85.0		15.0	
(±)-**1b**[d]	$Ru(OCOCH_3)_2$[(*R*)-binap] + 2HCl[e,f]	CH_2Cl_2[i]	81.63	5.77	10.46	2.14
(±)-**1b**[d]	$Ru(OCOCH_3)_2$[(±)-binap] + 2HCl[e,h]	CH_2Cl_2[i]	91.7		8.3	
(±)-**3**[j]	$Ru(OCOCH_3)_2$[(*R*)-binap] + 2HCl[k]	CH_3OH	49.20	0.80	48.28	1.72
(±)-**3**[j]	$Ru(OCOCH_3)_2$[(±)-binap] + 2HCl[h,k]	CH_3OH	50.8		49.2	
(±)-**3**[l]	$RuCl_2$[(*R*)-binap](dmf)$_x$[k]	CH_2Cl_2[i]	6.00	0.10	93.38	0.52
(±)-**3**[l]	$RuCl_2$[(±)-binap](dmf)$_x$[h,k]	CH_2Cl_2[i]	5.7		94.3	
(±)-**3**[l]	$RuCl_2$[(*R*)-3,5-xylylbinap](dmf)$_x$[k]	CH_2Cl_2[i]	3.57	0.03	95.73	0.67
(±)-**3**[l]	$RuCl_2$[(±)-3,5-xylylbinap](dmf)$_x$[h,k]	CH_2Cl_2[i]	3.2		96.8	

[a] Reactions were carried out under 100 atm of hydrogen at 25 °C unless otherwise specified. [b] Analysis by combination of GC, HPLC, and ^1H NMR of the hydrogenation product and the (*R*)-MTPA esters. For details, see the Experimental Section. [c] Hydroxy ester numbering. [d] 2.7–3.4 M solution of **1** (19–24 mmol). [e] 0.08–0.10 mol % of the catalyst. [f] The reaction was carried out with (*S*)-BINAP-Ru catalyst. For convenience the product ratios were converted to those with (*R*)-BINAP-Ru catalyst. [g] Methanol contains 6.8–9.2 mol % of 1-octanol for the substrate as an internal standard. [h] Racemic catalyst was prepared by mixing the *R* complex and *S* complex in a 1:1 ratio. [i] Reaction at 50 °C. [j] 0.8 M solution of **3** (4.0 mmol). [k] 0.45–0.63 mol % of the catalyst. [l] 0.2 M solution of **3** (0.60 mmol).

Table II. Parameters of Stereoselective Hydrogenation of 2-Substituted 3-Oxo Carboxylic Esters Catalyzed by BINAP-Ru Complexes

entry	substrate	catalyst ligand	conditions: solvent	temp, °C	parameters[a]: SEL^0	SEL^{100}	k_{fast}/k_{slow}	k_{inv}/k_{fast}	C_{cat}[b]	C_{sub}[c]
1	(±)-**1a**	(*R*)-BINAP	CH_3OH	25	0.921[d]	0.821[d]	12[e]	0.25[f]	86	24
2	(±)-**1b**	(*R*)-BINAP	CH_3OH	25	0.845[d]	0.569[d]	5.9[e]	0.040[f]	47	1.8
3	(±)-**1b**	(*R*)-BINAP	CH_2Cl_2	50	0.884[d]	0.816[d]	9.8[e]	0.45[f]	8.3	4.6
4	(±)-**3**	(*R*)-BINAP	CH_3OH	25	0.475[g]	0.483[g]	0.93[h]		42	1.5
5	(±)-**3**	(*R*)-BINAP	CH_2Cl_2	50	0.938[g]	0.934[g]	15[h]	6.1[i]	104	9.0
6	(±)-**3**[g]	(*R*)-3,5-xylylBINAP	CH_2Cl_2	50	0.962[g]	0.957[g]	26[h]	3.6[i]	130	24

[a] All parameters were calculated by using the experimental data of Table I. [b] Catalyst control. [c] Substrate control. [d] $SEL = P_{RR}/(P_{RR} + P_{RS} + P_{SR} + P_{SS})$. [e] k_R/k_S((*R*)-**1** is the fast-reacting substrate). [f] k_{inv}/k_R. [g] $SEL = P_{SR}/P_{RR} + P_{RS} + P_{SR} + P_{SS})$. [h] k_S/k_R((*S*)-**3** is the fast-reacting substrate). [i] k_{inv}/k_S.

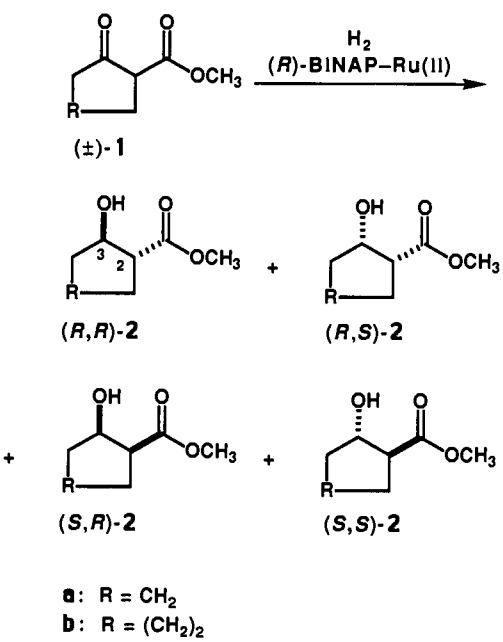
It is obvious that high k_{fast}/k_{slow}, k_{inv}/k_{fast}, and SEL^0 (SEL at $t = 0$) values are desirable to accomplish a highly stereoselective reaction via dynamic kinetic resolution. SEL^0 is the maximal composition of the major isomer among the four products, while SEL^{100} which is ultimately obtained is the minimal value. As the rate ratio k_{inv}/k_{fast} decreases, SEL decreases extensively from the initial SEL^0.

The above treatment generally applies to the cases with $k_{inv}/k_R > 0$. It should be noted, however, that, in the limiting case, $k_{inv} = 0$, the chiral efficiency is to be expressed by eq 1.

Case Studies

BINAP-Ru(II) complexes are known to be extremely effective catalysts for asymmetric hydrogenation of functionalized ketones.[4,14] With certain 2-substituted 3-oxo carboxylic esters as substrates (Scheme III), the chiral catalyst can select one of the four possible diastereomeric transition states. The efficiency of this dynamic kinetic resolution is profoundly affected by the nature of the substrates, particularly, the skeleton and functionality, and also by reaction conditions. In general, chirality of the BINAP ligand in the catalyst determines the absolute configuration at C-3 of the hydroxy ester products, while the anti/syn relative configuration is controlled by the structures of the ketonic substrates. In addition, reaction media remarkably affect the extent of the stereoselectivity. However, to actually find the ideal situations for synthetically meaningful selectivity requires a trial-and-error approach. In this context, the above generalized formulation is of great help in finding the optimized conditions for stereoselective hydrogenation.

Scheme IV



Several reactions that verify the mathematical expressions are exemplified below. The reaction was carried out in dichloromethane and/or methanol at 25 and 50 °C under 100 atm of hydrogen. Hydrogenation was normally faster in methanol than in dichloromethane. The reaction employed as catalyst 0.08–0.6 mol % of an enantiomerically pure BINAP-Ru(II) complex or a 1:1 mixture of the (*R*)- and (*S*)-BINAP-Ru(II) complexes. These were in situ prepared either by mixing $Ru(OCOCH_3)_2$(binap) with 2 equiv of hydrochloric acid[14a] or by heating a mixture of $[RuCl_2(benzene)]_2$ and BINAP.[15] The experimental results

(14) (a) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856. (b) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629. (c) Kitamura, M.; Ohkuma, T.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1988**, *29*, 1555. (d) Nishi, T.; Kitamura, M.; Ohkuma, T.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *29*, 6327.

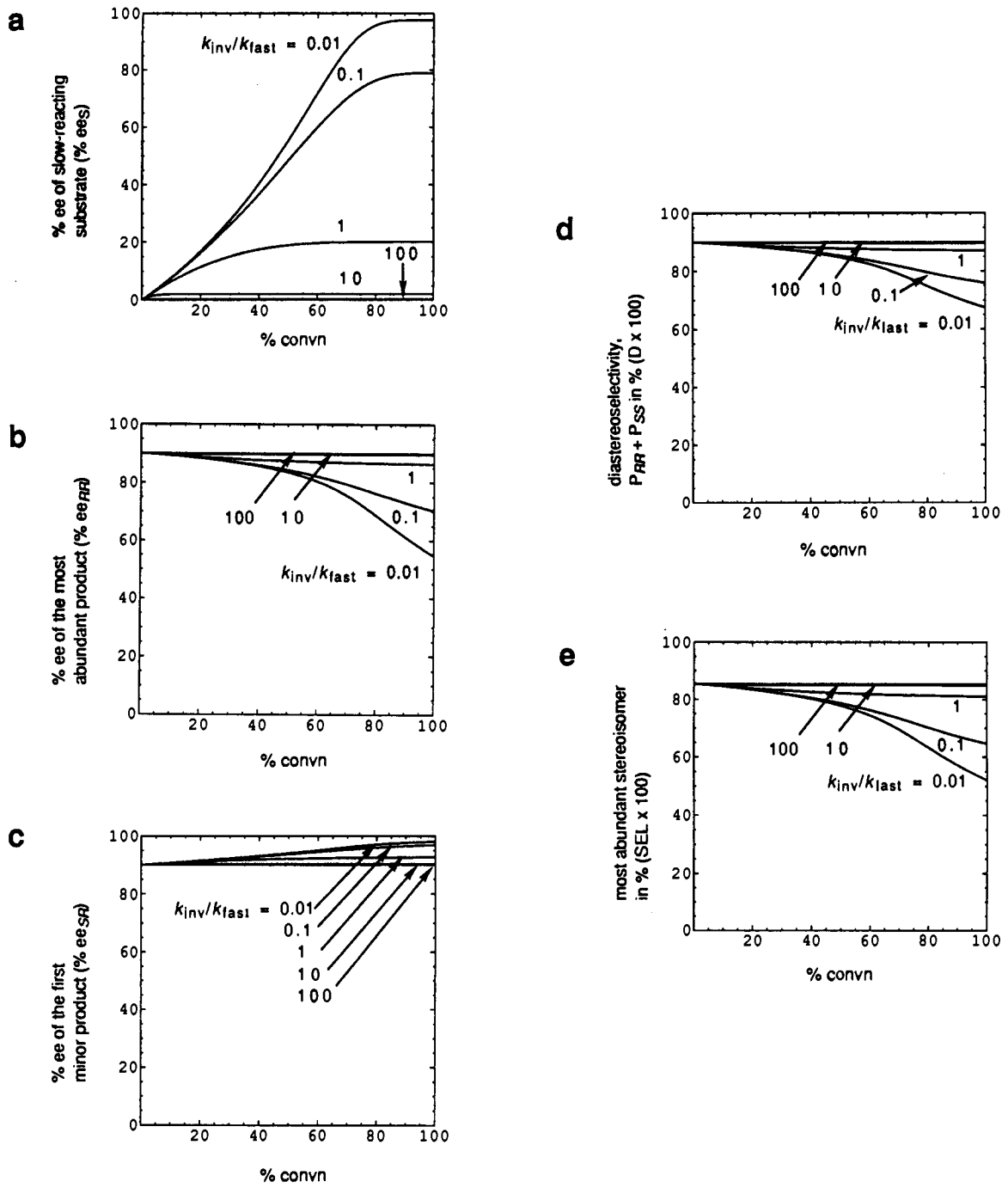


Figure 1. Simulation of the selectivity profiles as a function of conversion of a racemic keto ester with imaginary w, x, y, z (0.855, 0.005, 0.095, and 0.045), k_{fast}/k_{slow} (6.14), and k_{inv}/k_{fast} parameters (100, 10, 1, 0.1, 0.01): (a) ee of the slow-reacting substrate (ee_S); (b) ee of the major product (ee_{RR}); (c) ee of the first minor product (ee_{SR}); (d) composition of the major diastereomer [D, $(P_{RR} + P_{SS})/(P_{RR} + P_{RS} + P_{SR} + P_{SS})$]; (e) composition of the major product [SEL, $P_{RR}/(P_{RR} + P_{RS} + P_{SR} + P_{SS})$].

are summarized in Table I. Table II lists parameters related to the efficiency of the stereoselective hydrogenation based on dynamic kinetic resolution. Neither racemization nor decomposition of the products occurs during hydrogenation.

Hydrogenation of 2-(Methoxycarbonyl)cyclopentanone (1a). First, the five-membered ketone **1a** was chosen as a model substrate to collect quantitative data of the stereoselective hydrogenation. Although higher efficiency is obtained in dichloromethane giving (*R*,*R*)-**2a** in 94.5% yield together with the other three isomers in a total yield of 5.5% (SEL^{100} = 0.945),[5b] the reaction in methanol was examined to minimize the experimental errors in determining the product distribution factors (Scheme IV). The rate of hydrogenation of **1a** has proved to be first order in substrate concentration. In addition, reactions using the enantiomerically pure BINAP complex and the racemic catalyst showed identical reactivity at the early stages revealing the absence of significant interaction of enantiomeric catalysts under such reaction conditions.

The hydrogenation catalyzed by the (*R*)-BINAP–Ru complex gave predominantly the anti 2*R*,3*R* product, (*R*,*R*)-**2a** (hydroxy ester numbering), among the four stereoisomers. Figure 3 illustrates the changes of ee's of the major alcohol (*R*,*R*)-**2a** and the first minor alcohol (*S*,*R*)-**2a**, diastereoselectivity [anti/(anti + syn)], and composition of the major alcohol (*R*,*R*)-**2a** (SEL) as a function of the conversion of **1a**. The computer-generated curves (lines) based on the parameters in Table II predict the

(15) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Tetrahedron Lett.* **1991**, *32*, 4163. Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Org. Chem.* **1992**, *57*, 4053.

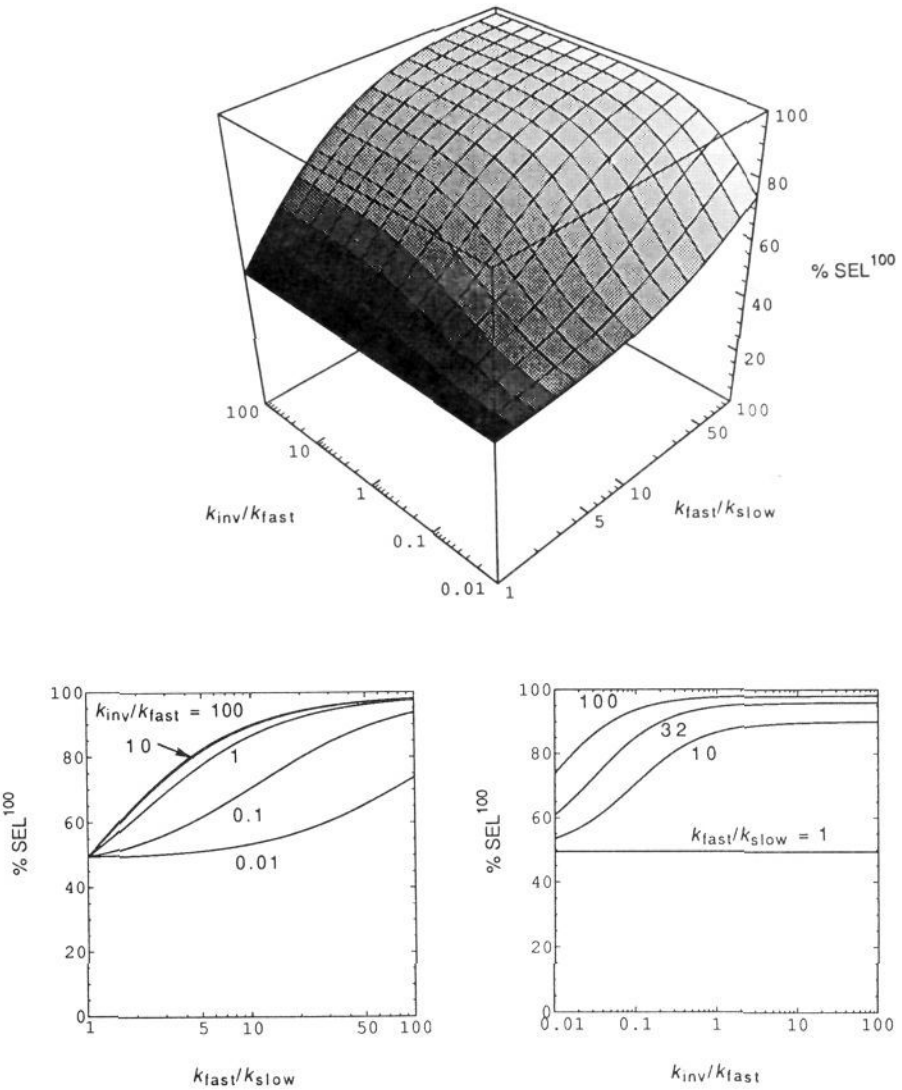
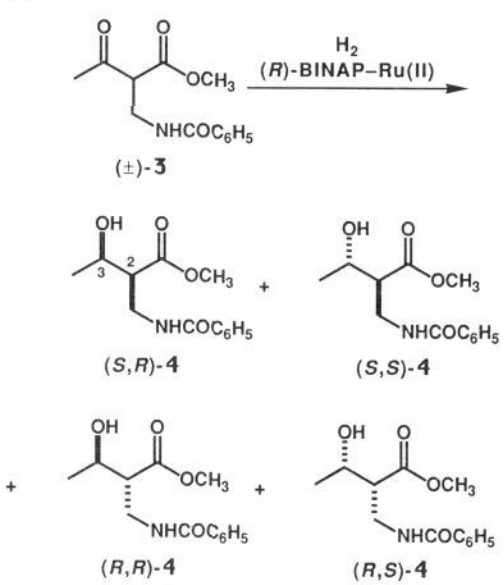


Figure 2. 3D-graphic demonstration of relationship of k_{inv}/k_{fast}, k_{fast}/k_{slow}, and SEL^{100} with $C_{cat} = 10$ and $C_{sub} = 10$.

decrease of ee of the major product and enhancement of ee of the first minor alcohol, which are in good agreement with the experimental observations (dots). The change of SEL value also fits well. The high stereoselectivity giving SEL^0 values of up to 0.921 is interpreted in terms of cooperation of the effective *R*-directing catalyst control, $C_{cat} = 86$, and high substrate control, $C_{sub} = 24$, causing anti diastereoselection. In methanol, (*R*)-**1a** is hydrogenated 12-times faster than the *S* enantiomer, while the stereoinversion of the substrate is slower than the hydrogenation of the fast-reacting (*R*)-**1a** by a factor of 4.

Hydrogenation of 2-(Methoxycarbonyl)cycloheptanone (1b). This seven-membered ketone was hydrogenated in methanol and dichloromethane containing an (*R*)-BINAP–Ru catalyst. As with **1a**, the anti 2*R*,3*R* alcohol (*R*,*R*)-**2b** was the most abundant product. As illustrated in Figure 4, the computer simulation of the selectivity profile again fits well with the experimental monitoring. In methanol, (*R*)-**1b** reacts ca. 6 times faster than the *S* enantiomer and both ee_{RR} and ee_{SR} are kept high throughout the reaction. The ee value of (*R*,*R*)-**2b** at 100% conversion, 94.6%, is excellent, though somewhat lower than the initial ee, 98.4%. Unfortunately, however, the ultimate diastereoselectivity is not satisfactory, anti:syn = 58:42. This is due to the requisite substrate stereoinversion being 25 times slower relative to hydrogenation of (*R*)-**1b**. By changing the solvent from methanol to dichloromethane, this rate ratio is improved by a factor of 11, enhancing the overall efficiency, which leads to an anti:syn ratio of 87:13. This advantage overcomes the somewhat lower ee_{RR} value; the final composition, SEL^{100}, of the *R*,*R* isomer attained in dichloromethane and methanol was 0.816 and 0.569, respectively.

Scheme V



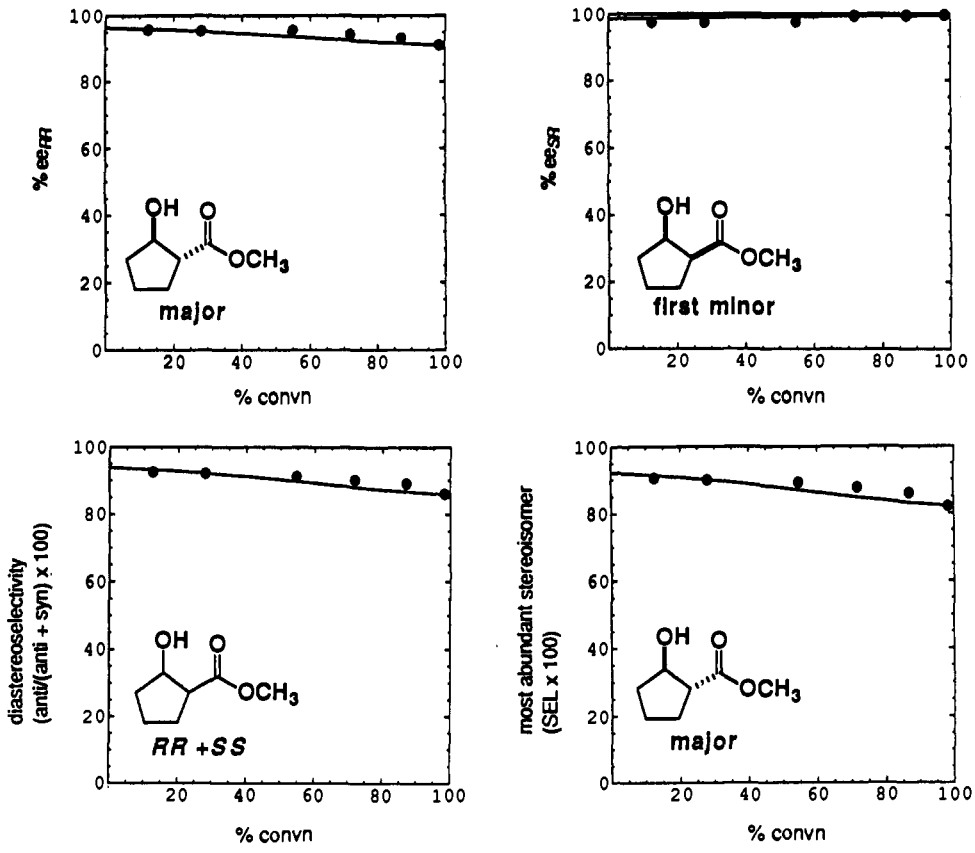


Figure 3. Simulation of hydrogenation of 2-(methoxycarbonyl)cyclopentanone (**1a**) catalyzed by (*R*)-BINAP-Ru(II) (conditions: catalyst, 2.59 mM $Ru(OCOCH_3)_2$(binap) + 2HCl; substrate, 3.33 M; solvent CH_3OH; H_2, 100 atm; temp, 25 °C).

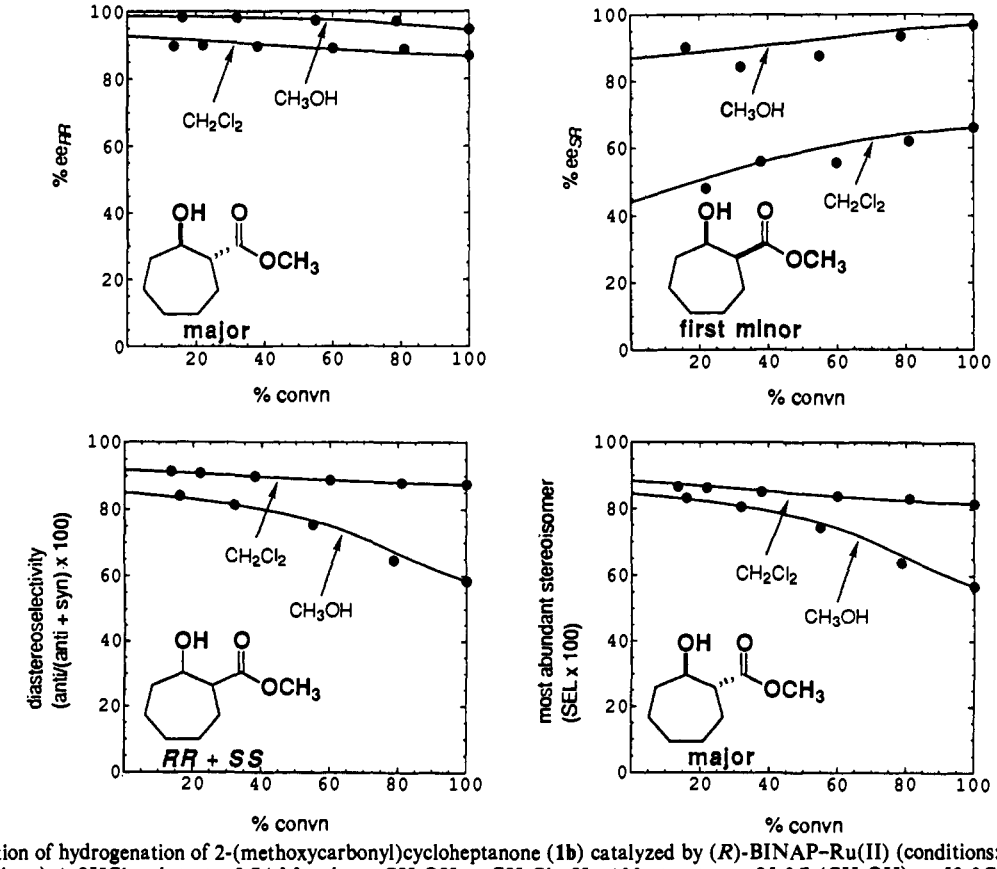


Figure 4. Simulation of hydrogenation of 2-(methoxycarbonyl)cycloheptanone (**1b**) catalyzed by (*R*)-BINAP-Ru(II) (conditions: catalyst, 2.59 mM $Ru(OCOCH_3)_2$(binap) + 2HCl; substrate, 2.74 M; solvent CH_3OH or CH_2Cl_2; H_2, 100 atm; temp, 25 °C (CH_3OH) or 50 °C (CH_2Cl_2)).

Dichloromethane as solvent retards the hydrogenation considerably but the stereoinversion occurs at a reasonable rate. Notably the reaction in methanol proceeds with a z value less than x (0.0054 vs 0.0098), which reflects the enantiomer dependency of stereoselection; the averaged substrate control is indeed moderate, C_{sub} = 1.8.

Table III. Product Distribution Parameters

entry[a]	*w*	*x*	*y*	*z*
1	0.921	0.000449	0.0616	0.0171
2	0.845	0.00979	0.140	0.00542
3	0.884	0.0232	0.0598	0.0330
4	0.475	0.00786	0.500	0.0175
5	0.938	0.00100	0.0560	0.00485
6	0.962	0.000301	0.0317	0.00595

[a] The entry number corresponds to that in Table II.

Hydrogenation of Methyl 2-(Benzamidomethyl)-3-oxobutanoate (3). Behavior of the open-chain keto ester **3** (Scheme V) is vastly different from that of the cyclic substrates **1a** and **1b**. The parameters related to the stereoselectivities are given in Table II. Stereoselective synthesis of the syn product, (*S*,*R*)-**4**, is highly desirable in connection with the industrial production of a carbapenem intermediate.[5a] The (*R*)-BINAP–Ru-catalyzed reaction in methanol proceeds with high 3*R*-enantioselectivity but, unfortunately, with very poor diastereoselectivity to form a 1:1 mixture of (*S*,*R*)-**4** (93% ee) and (*R*,*R*)-**4** (97% ee) at 100% conversion (Table I). SEL^{100} for (*S*,*R*)-**4** thus remained 0.48. Lack of the syn/anti selectivity is seen even at an early stage. Enantiomeric (*S*)- and (*R*)-**3** indeed react at comparable rates under such conditions. In dichloromethane, however, the hydrogenation displayed a high syn-selection to give a 94:6 mixture of (*S*,*R*)-**4** and (*R*,*R*)-**4** in 99% and 97% ee, respectively. The stereoselectivity leading to (*S*,*R*)-**4** is now consistently high from the beginning ($SEL^0 = 0.938$) to the end of the reaction ($SEL^{100} = 0.934$). For some unknown reason, the reaction in dichloromethane, unlike that in methanol, proceeds with high enantiomer discrimination, $k_S/k_R = 15$, and in situ racemization of the substrate is also facile relative to hydrogenation, $k_{inv}/k_S > 6$. The latter rate ratio is more than 10 times larger than those observed with cyclic ketones **1a** and **1b**. The higher reactivity of the 2*S* enantiomer in the (*R*)-BINAP–Ru-catalyzed reaction is contrasted with the prevailing reactivity of 2*R*-configurated **1a** or **1b**.

Under reaction conditions where the kinetic parameters are already sufficient, structural modification of the metal ligand is an obvious way to further increase the level of stereoselectivity. Thus use of the 3,5-xylylBINAP ligand for Ru(II) causes this hydrogenation in dichloromethane at 50 °C with a 26:1 enantiomer discrimination and k_{inv}/k_S ratio of 3.6. This reaction showed 96.4:3.6 syn:anti diastereoselectivity by keeping an excellent ee of (*S*,*R*)-**4**, 99%. The SEL^0 and SEL^{100} values approach as high as 0.96 as a consequence of excellent double stereodifferentiation, $C_{cat} = 130$ and $C_{sub} = 24$ in favor of the syn stereochemistry. The reaction using a Ru complex with a sterically more congested BINAP containing *tert*-butyl groups, 2,2′-bis[bis(3,5-di-*tert*-butylphenyl)phosphino]-1,1′-binaphthyl, achieved the highest SEL, 0.974. However, the hydrogenation in dichloromethane was slow, giving only 70% conversion after a 60-h reaction at 50 °C and 100 atm of hydrogen.[16]

Conclusion

Kinetic resolution utilizing in situ substrate racemization is a powerful tool for stereoselective synthesis of one stereoisomer, among many possible stereoisomers, of high enantiomeric purity. Equations for the quantitative treatment of such dynamic kinetic resolution have been developed. The expressions have been verified by comparison of computer-simulated graphs and the experimental data. This mathematical method coupled with vast knowledge in synthetic chemistry will allow useful predictions in designing efficient asymmetric catalyses.

Experimental Section

Proton nuclear magnetic resonance (^{1}H NMR) spectra were measured on a JEOL JNM-GX270 (270 MHz) spectrometer using tetramethylsilane as an internal standard. Liquid chromatographic (HPLC) analyses were conducted on a Shimadzu LC-6A instrument. A Shimadzu GC-14A or -15A model was used for gas chromatographic (GC) analyses.

Materials. BINAP is available commercially or by the literature procedure.[17] (*R*)-2,2′-Bis[bis(3,5-dimethylphenyl)phosphino]-1,1′-binaphthyl (3,5-xylylBINAP) and 2,2′-bis[bis(3,5-di-*tert*-butylphenyl)phosphino]-1,1′-binaphthyl were provided by Takasago Research Institute.[16] $Ru(OCOCH_3)_2$(binap) and $RuCl_2L_2(dmf)_x$ (L = BINAP, 3,5-xylylBINAP and its analogues; dmf = *N*,*N*-dimethylformamide) were prepared from $[RuCl_2(benzene)]_2$ by the reported methods.[15] 3-Oxo carboxylic esters, (±)-**1a** and (±)-**1b**, were purchased, and (±)-**3** was synthesized by the known method.[18]

Analysis of the Hydrogenation. Hydrogenation was carried out in a 50-mL stainless steel reaction vessel according to the reported procedure under the conditions described in Table I.[14,15] In all cases, (*R*)-BINAP–Ru-catalyzed hydrogenation gave the 3*R* products (hydroxy ester numbering) as major stereoisomers, and (*S*)-BINAP–Ru afforded 3*S* enantiomers. At appropriate time intervals, an aliquot was taken and analyzed, directly or after converting the (*R*)-α-methoxy-β,β,β-trifluoro-α-phenylpropionates [(*R*)-MTPA esters], to determine the conversion (convn), the diastereomer ratio (anti/syn), and the enantiomeric excess (ee) of the product. No noticeable kinetic resolution was seen in the MTPA ester formation. Physical properties of all the compounds were identical with the reported values.[5a,b]

Convn of **1** in methanol and dichloromethane was determined by GC (column, PEG 20M on chromosorb WAW; injection temp, 220 °C; column temp, 190 °C; N_2 pressure, 1.5 kg/cm^2; t_R of 1-octanol (factor 1.000), 8.7 min; t_R of (2*R*,3*S*)- and (2*S*,3*R*)-**2a** (factor 0.706), 18.6 min; t_R of (2*R*,3*R*)- and (2*S*,3*S*)-**2a** (factor of 0.706), 29.2 min; t_R of (2*R*,3*S*)- and (2*S*,3*R*)-**2b** (factor 0.911), 40.1 min; t_R of (2*R*,3*R*)- and (2*S*,3*S*)-**2b** (factor 0.911), 55.9 min) and by comparison of the areas of the signals at δ 3.55 (dd, *J* = 4.1 and 12.2 Hz, C*H*COOCH$_3$ of **1b**), 12.65 (s, OH of **1b**), 3.98 (dt, *J* = 4.0 and 9.2 Hz, C*H*OH of (2*R*,3*R*)- and (2*S*,3*S*)-**2b**), and 4.21 (m, C*H*OH of (2*R*,3*S*)- and (2*S*,3*R*)-**2b**) in ^{1}H NMR in $CDCl_3$, respectively. Convn of (±)-**3** was determined by ^{1}H-NMR analysis of the crude product. Anti/syn ratios of **2** and **4** were determined by GC (for conditions, see convn analysis of **1** in methanol) and by HPLC (column, Develosil 100-3; eluent, 1:20 ethanol–hexane; detection, 254-nm light; t_R of *syn*-**4**, 25.5 min; t_R of *anti*-**4**, 32.2 min), respectively. Ee was analyzed by HPLC of the (*R*)-MTPA ester. Conditions for (*R*)-MTPA esters of **2**: column, YMC 003-3 SIL and 002-3 SIL; eluent, 1:10 ether–hexane; detection, 254-nm light; t_R of (2*R*,3*R*)-**2a** (hydroxy ester numbering), 23.4 min; t_R of (2*S*,3*S*)-**2a**, 24.9 min; t_R of (2*S*,3*R*)-**2a**, 40.2 min; t_R of (2*R*,3*S*)-**2a**, 44.6 min; t_R of (2*R*,3*R*)-**2b**, 39.7 min; t_R of (2*S*,3*S*)-**2b**, 43.1 min; t_R of (2*S*,3*R*)-**2b**, 46.2 min; t_R of (2*R*,3*S*)-**2b**, 55.4 min. Conditions for (*R*)-MTPA esters of **4**: column, YMC 003-3 SIL and 002-3 SIL; eluent, 2:15:200 2-propanol–THF–hexane; detection, 254-nm light; t_R of (2*S*,3*R*)-**4**, 38.5 min; t_R (2*R*,3*S*)-**4**, 40.8 min; t_R of (2*R*,3*R*)-**4**, 47.2 min; t_R of (2*S*,3*S*)-**4**, 55.6 min. The product distribution parameters (*w*, *x*, *y*, *z*), calculated on the assumption that (*R*)-BINAP–Ru catalyst was used and the products derived from the fast-reacting substrate were partitioned in a *w*:*x* ratio (*w* > *x*), are listed in Table III.

Acknowledgment. We appreciate Takasago Research Institute for providing the generous supply of (*R*)-2,2′-bis[bis(3,5-dimethylphenyl)phosphino]-1,1′-binaphthyl and 2,2′-bis[bis(3,5-di-*tert*-butylphenyl)phosphino]-1,1′-binaphthyl. We thank Professor K. Yoshikawa, Nagoya University, for his valuable suggestions. This work was aided by the Ministry of Education, Science, and Culture, Japan (No. 03403006).

Appendix

Graphical expression of the mathematical equations in Figures 1–4 was aided by the Mathematica program on an Apple Macintosh computer.

Induction of Equations 8–13. λ^1 and λ^2 are unique values in the matrix representation

$$\begin{pmatrix} -(k_R + k_{inv}) & k_{inv} \\ k_{inv} & -(k_S + k_{inv}) \end{pmatrix} = \begin{pmatrix} a & b \\ c & d \end{pmatrix} \qquad (30)$$

and linked to *a*, *b*, *c*, and *d* by

(16) Mashima, K.; Matsumura, Y.; Kusano, K.; Kumobayashi, H.; Sayo, N.; Hori, Y.; Ishizaki, T.; Akutagawa, S.; Takaya, H. *J. Chem. Soc., Chem. Commun.* **1991**, 609.

(17) Takaya, H.; Akutagawa, S.; Noyori, R. *Org. Synth.* **1988**, *67*, 20.

(18) Pfister, K., III; Robinson, C. A.; Shabica, A. C.; Tishler, M. *J. Am. Chem. Soc.* **1949**, *71*, 1101.

$$\lambda_1,\lambda_2 = \tfrac{1}{2}|(a + d) \pm \sqrt{(a + d)^2 - 4(ad - bc)}| \quad (31)$$

The kinetic behavior of $S_R(t)$ and $S_S(t)$ is highly dependent on whether λ is a real or imaginary number and positive or negative. In the dynamic kinetic resolution of Scheme II both λ^1 and λ^2 are proved to be negative real numbers by a simple mathematical treatment of eqs 30 and 31 on the premise k_R, k_S, and $k_{inv} > 0$.

C_1, C_2, C_3, and C_4 can be expressed by

$$C_3 = \alpha C_1 \quad (32)$$

$$C_4 = \beta C_2 \quad (33)$$

where α and β are solutions of the equation

$$bx^2 + (a - d)x - c = 0$$

Initial concentrations of the substrates are formulated by substitution of $t = 0$ into eqs 4 and 5 to be $S_R(0) = C_1 + C_2$ and $S_S(0) = C_3 + C_4$. Combining these equations and eqs 32 and 33 yields, on the assumption that the reaction starts from 2 mol of racemic mixture ($S_R(0) = S_S(0) = 1$ at time $t = 0$),

$$C_1 = \frac{\beta - 1}{\beta - \alpha} \quad (34)$$

$$C_2 = \frac{1 - \alpha}{\beta - \alpha} \quad (35)$$

$$C_3 = \frac{\alpha(\beta - 1)}{\beta - \alpha} \quad (36)$$

$$C_4 = \frac{\beta(1 - \alpha)}{\beta - \alpha} \quad (37)$$

Substitution of a, b, c, and d, which are correlated with k_R, k_S, and k_{inv} by eq 30, into eq 31 and eqs 34-37 affords eqs 8-13.

Mechanistic Aspects of the Rhodium-Catalyzed Enantioselective Transfer Hydrogenation of α,β-Unsaturated Carboxylic Acids Using Formic Acid/Triethylamine (5:2) as the Hydrogen Source[1]

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Abstract: The mechanism of the rhodium-catalyzed enantioselective transfer hydrogenation of methylenebutanedioic acid (itaconic acid) (**1**) and related α,β-unsaturated carboxylic acids using formic acid/triethylamine (5:2) as the hydrogen source is investigated. Kinetic studies using ^1H NMR spectroscopy are presented. Formic acid decomposition is shown to be the rate-limiting step with **1** as the substrate, while hydrogen transfer turns out to be rate determining in the case of (*E*)-(phenylmethylene)butanedioic acid ((*E*)-phenylitaconic acid) (**3**). Furthermore, extensive use is made of deuterium labeling and the analysis of part-deuterated products by ^1H and $^{13}C\{^1H,^2H\}$ NMR spectroscopy. Firstly it is demonstrated that transfer deuteration of (*E*)-phenylitaconic acid (**3**) using DCO_2D as the deuterium source leads to (2*R**,1′*S**)-2-deuterio-2-(1′-deuteriophenylmethyl)butanedioic acid (**9d**) as the only isotopomer. The same isotopomer is obtained using gaseous D_2 under otherwise identical conditions. Use of HCO_2D or DCO_2H leads to a mixture of d_0, d_1, and d_2 isotopomers **9a–d**. Further information is obtained from the transfer hydrogenation of (*RS*)-, (*R*)-, and (*S*)-2-methylene-3-methylbutanedioic acid (β-methylitaconic acid) (**4a**) with the asymmetric in-situ catalyst **8** consisting of $[Rh(norbornadiene)Cl]_2$ and (2*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(diphenylphosphino)-2-((diphenylphosphino)methyl)pyrrolidine (bppm). The pure enantiomers react at rates differing only by a factor of 2, but kinetic resolution of the racemate is efficient with a selectivity factor of 18. Additionally, the reaction of HCO_2NH_4 or HCO_2K with intermediates $[Rh(dppe)L_n]^+$ (dppe = 1,2-bis(diphenylphosphino)ethane; L = MeOH, n = 2, **11**; L = methyl α-acetamidocinnamate, n = 1, **12**) of the catalytic cycle of hydrogenation using gaseous hydrogen is followed by ^{31}P NMR spectroscopy at variable temperature. No indication of a formate coordination to rhodium is observed in these experiments. Taken together, these results indicate that the mechanism of rhodium-catalyzed transfer hydrogenation with formic acid/triethylamine as the hydrogen source most likely involves decarboxylation of a transient formate species to form hydridic complexes of rhodium, in which the Rh–H entity has a long lifetime relative to hydrogen transfer to the substrate.

Introduction

Asymmetric hydrogenation of C=C double bonds is a major application of homogeneous catalysis by chiral transition metal complexes.[2] A wide range of substrates can be reduced with excellent enantioselectivity employing optically pure phosphine complexes of rhodium or ruthenium.[2,3] We reported recently that use of potentially hazardous gaseous hydrogen can be avoided by hydrogen transfer from a mixture of formic acid and an amine in the approximate molar ratio of 5:2 using similar catalysts.[4] The enantioselectivities achieved by this new and simple methodology

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