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Accounts

Stereoselective Organic Synthesis via Dynamic Kinetic Resolution

Ryoji Noyori,* Makoto Tokunaga, and Masato Kitamura

Department of Chemistry, Nagoya University, Chikusa, Nagoya 464-01

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Asymmetric catalysts, either chemical or biological, effect the reactions of enantiomeric substrates at unequal rates, allowing for the kinetic resolution of racemates. The asymmetric reaction of chirally labile compounds capable of undergoing in situ racemization can, in principle, afford a single stereoisomer in 100% ee and in 100% yield. The second-order reaction provides a powerful tool for the stereoselective synthesis of chiral compounds, as exemplified by, among others, the biochemical hydrolysis of hydantoins or oxazolinones and microbial reductions or BINAP–Ru(II) catalyzed hydrogenation of certain α-substituted β-keto esters. Such transformations are characterized by the presence of parallel reactions interrelated by the stereoinversion of the enantiomeric substrates. The efficiency is decisively affected by the kinetic parameters, particularly the relative rates of the stereoinversion and reaction as well as the intrinsic stereochemical parameters of the catalyst and substrate. Such stereoselective reactions via dynamic kinetic resolution are expressed mathematically and the stereochemical profiles are displayed graphically. The validity of this basic approach has been verified by the correlation to the experimental results.

Enantiomers react at different rates under asymmetric circumstances. This principle allows the kinetic resolution of racemic compounds.[1] Figure 1 illustrates a simple case. In the presence of a chiral catalyst (reagent) or enzyme, an R substrate (S_R) and an S enantiomer (S_S) react with unequal rate constants, k_R and k_S, respectively, to give products P_R and P_S. In practice, such a reaction is mainly utilized for the recovery of a slow-reacting substrate of high enantiomeric purity, where the synthetic efficiency is directly correlated to the k_R/k_S ratio. For example, if S_R reacts 25-times faster than S_S, almost enantiomerically pure S_S can be recovered at 60% conversion. In Fig. 1, P_R and P_S are often chiral, though they could be an identical achiral compound. The enantiomeric purity of P_R and P_S is limited by the degrees of the enantiomer discrimination and stereoselectivity of the reaction; however,

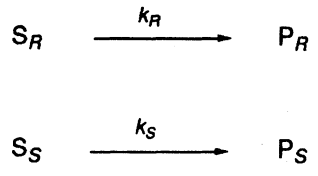


Fig. 1. Kinetic resolution of a racemate.

when these are excellent, kinetic resolution can also be useful for access to P_R or P_S.

The first example of kinetic resolution dates back to 1858 when Pasteur discovered that the fermentation of an aqueous solution of racemic ammonium tartrate by a *Penicillium glaucum* mold resulted in a faster metabolism of the dextrorotatory enantiomer than the levorotatory one.[2] This finding stimulated a study of kinetic resolution by enzymatic or microbial oxidation, esterification, and hydrolysis; some of the thus-developed ones are feasible on the industrial scale.[3] Now, various natural and unnatural α-amino acids are being produced by the biochemical hydrolysis of racemic *N*-acyl α-amino acids[4] and α-amino acid amides.[5] In 1874 Le Bel showed the possibility of the chemical resolution of a racemic compound by the irradiation of circularly polarized light.[6] The first reproducible result by purely chemical means was presented by Marckward and McKenzie in 1899, who reported that partial esterification of racemic mandelic acid by (−)-menthol left slow-reacting (*R*)-mandelic acid in excess.[7] Although the efficiency of the chemical resolution had long remained low relative to the biological means, Sharpless' work in 1981 concerning resolution of allylic alcohols with chiral titanium catalyst provided a true breakthrough in this area.[8] Since

then, various efficient chemical methods have been reported, which include transition metal-catalyzed hydrogenation,[9] electrophilic allylation,[10] hydroacylation,[11] and olefin isomerization[12] among others.[13]

The kinetic resolution shown in Fig. 1 is thus becoming an attractive tool in organic synthesis. Such ordinary kinetic resolution, however, suffers from an inherent drawback in that the maximum yield of one enantiomer is 50%. In addition, the enantiomeric purity of the recovered substrate and product are profoundly affected by the extent of conversion. This situation dramatically changes when racemic substrates have a chirally labile stereogenic center, and, hence, are capable of undergoing in situ racemization during reaction.[14] Figure 2 illustrates the simplest framework for such a case. Now, the asymmetric process is unsuitable for the recovery of an optically active substrate. Instead, this dynamic kinetic resolution concentrates on the *stereoselective synthesis of the enantiomeric product*, P_R or P_S. Thus, when the rate of the stereomutation of S is sufficiently high with respect to the rate of the reaction, viz., $k_{inv} > k_R$ or k_S, this second-order asymmetric reaction can, in principle, produce enantiomerically pure P_R or P_S in 100% yield, rather than 50%, starting from racemic S. The utility of the dynamic kinetic resolution is not limited to such a selective synthesis of an enantiomer. When the reaction occurs along with the creation of a new stereogenic center, an enantioselective synthesis of a diastereomer is also possible, as outlined in Fig. 3. Here, S_R is converted with a rate constant of k_R to diastereomers P_{RR} and P_{RS}, while S_S reacts with constant k_S to afford diastereomers P_{SR} and P_{SS}. This asymmetric method can, under appropriate conditions, convert a racemic compound to one stereoisomer among four stereoisomers. The dynamic kinetic resolution is characterized by a pair of competitive reactions which are closely interrelated by the stereoinversion of the chiral substrates. The efficiency of such an asymmetric synthesis is markedly influenced by the kinetic parameters of the parallel reactions and racemization in addition to the ordinary structural parameters of the catalyst (enzyme) and substrate.

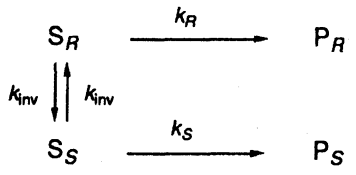


Fig. 2. Stereoselective synthesis of an enantiomer via dynamic kinetic resolution.

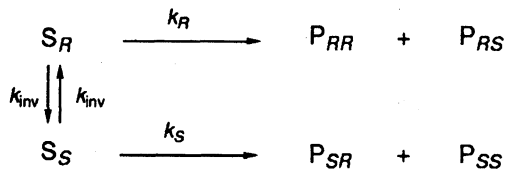


Fig. 3. Enantioselective synthesis of a diastereomer via dynamic kinetic resolution.

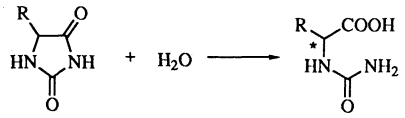
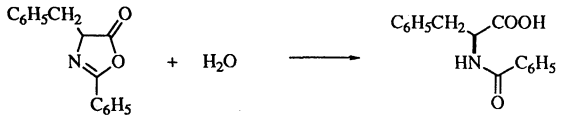
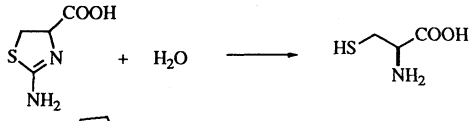
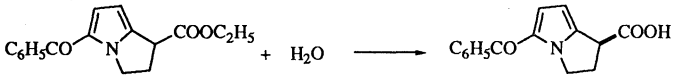
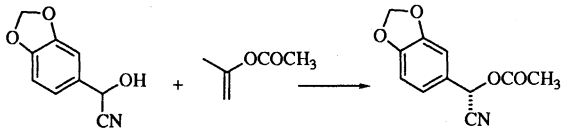
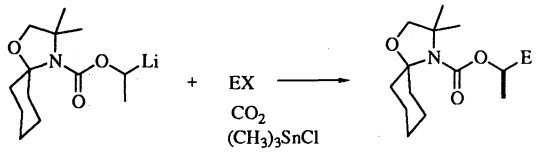
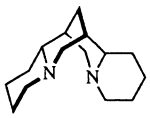
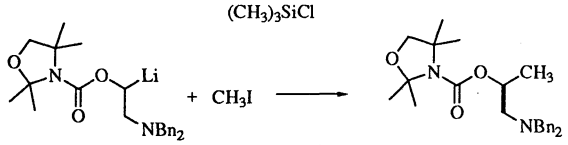
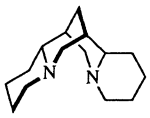
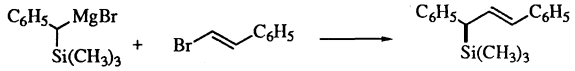
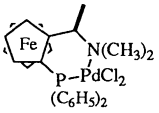
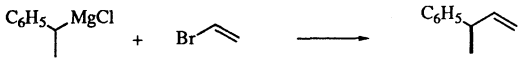
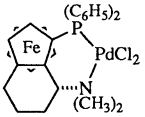
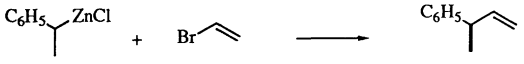
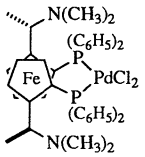
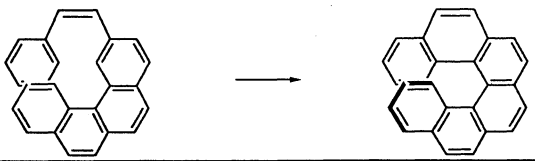
Certain second-order asymmetric syntheses via dynamic kinetic resolution provide a truly useful tool for preparing important chiral compounds. This paper gives an overview of the utility of the biological and chemical methods and describes the mathematical analysis of the selectivity profile. The quantitative method coupled with the vast accumulated knowledge in synthetic chemistry will permit useful predictions in designing efficient asymmetric catalysis.

Stereoselective Synthesis

Stereoselective Synthesis of Enantiomers. Stereoselective syntheses by the method given in Fig. 2 are exemplified in Table 1. This type of reaction can be classified into several categories. The first is kinetic differentiation of substrate enantiomers, where the stereogenic center is unaffected throughout the reaction. This simple type of reaction is often used for the asymmetric synthesis of amino acids.[15—18,30] Hydantoins (imidazolidinediones) or oxazolinones formed from racemic amino acids are efficiently resolved in the presence of suitable enzymes to give single enantiomeric amino acid derivatives in high yields and with high ee's (Entries 1 and 2).[15,16] This method is used for the industrial synthesis of unnatural D-amino acids.[31] Ketorolac acid, a strong anti-inflammatory agent, was obtained by the hydrolysis of its ester with a protease obtained from *Streptomyces griseus* (Entry 4).[19] The efficiency of these instances is ascribed to a rapid racemization of the substrate achieved by adjusting the hydrogen-ion concentration in addition to the high chiral recognition ability of the enzymes. A lipase promotes enantiomer-selective esterification of a cyanohydrin with isopropenyl acetate with high selectivity (Entry 5).[20] The presence of an anion-exchange resin facilitating the substrate racemization is important for this stereoselective reaction. The reduction of racemic 2-formylpropanoate with bakers' yeast[21,23] or *Candida humicola*[22] gives the corresponding alcohol in a moderate to high ee (Entry 6).

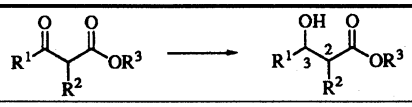
The second type reactions given in Fig. 2 utilize racemic substrates possessing a chemically reactive stereogenic center. Now, a chirally labile center normally creates a new stereogenic center with a different atomic composition. Their examples are seen in the reaction of a chiral organometallic reagent and an electrophile in the presence of a chiral compound. When certain secondary alkoxyalkyllithium compounds are reacted with carbon dioxide in the presence of (−)-sparteine, highly optically pure carboxylic acids are obtained (Entry 7).[24] Trimethyltin chloride, trimethylsilyl chloride, or methyl iodide also gives enantiomeric product selectively (Entries 7 and 8).[25] Under the in-

Table 1. Enantioselective Synthesis via Dynamic Kinetic Resolution

Entry	Reaction[a]		Method[b]	Yield/%	ee/%	Ref.
1		$R = C_6H_5$	Hydantoinase from *Alkalophilic bacillus* sp 121–3	91	—[c]	15)
		$R = p\text{-}HOC_6H_4$	Hydantoinase from *Pseudomonas striata* IFO 12996	82	—[c]	15)
		$R = NH_2CONHCH_2$	Hydantoinase from *Agrobacterium radiobacter*	69	>98	16)
2			Porcine pancreatic lipase	100[d]	>99	17)
3			*Pseudomonas thiazolinophilum* AJ 3854	100	100	18)
4			Protease from *Streptomyces griseus*	92	85	19)
5			Lipase from *Pseudomonas* sp M-12-33 + amberlite IRA-904	81	91	20)
6		$R = C_2H_5$	Bakers' yeast	70–80	65	21)
		$R = C_2H_5$	*Candida humicola*	>50	98	22)
		$R = (CH_3)_3CCH_2$	Bakers' yeast	78	90	23)
7				75 76 67	>95 >95 —[e]	24)
8				72	>95	25)
9				93	95	26)
10				95	79	27)
11				100[d]	93	28)
12			Right circularly polarized light + I_2	85	—[f]	29)

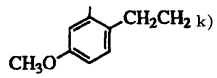
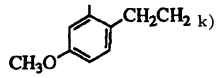
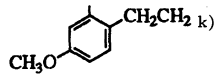
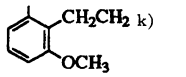
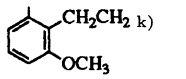
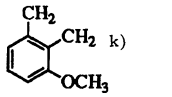
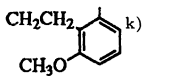
a) The starting material is racemic. b) Chiral method, catalyst, or additive. c) Not detailed. d) Conversion. e) $[\alpha]_D^{22-23}$ −22.5 (*c* 1.4—2.8, CH_2Cl_2). f) $[\alpha]_{436}^{23}$ −7.6 ± 0.4 (*c* 1.29, $CHCl_3$).

Table 2. Enantioselective Synthesis of Diastereomers via Dynamic Kinetic Resolution



Entry	Substrate[a] R^1	R^2	R^3	Method	Product Yield/%	*syn* : *anti*	ee/% (Abs config) *syn*	*anti*	Ref.
1	CH_3	CH_3	CH_3	H_2/Raney Ni + (*R*,*R*)-tartaric acid	ca. 95	78.4 : 21.6	56.7 (2*S*,3*R*)	64.4 (2*R*,3*R*)	36)
2	CH_3	CH_3	C_2H_5	Bakers' yeast	65	75 : 25	100 (2*R*,3*S*)	100 (2*S*,3*S*)	37)
3	CH_3	CH_3	C_2H_5	Bakers' yeast + methyl vinyl ketone	96[b]	96 : 4	—[c]	—[c]	38)
4	CH_3	CH_3	C_2H_5	*Geotrichum candidum*	80	4 : 96	—[c]	97 (2*S*,3*S*)	39)
5	CH_3	CH_3	C_2H_5	Oxidoreductase from *Geotrichum candidum*	93	<0.5 : 99.5	—[c]	92 (2*S*,3*S*)	40)
6	CH_3	CH_3	C_2H_5	H_2/(*R*)-BINAP–Ru(II) in CH_2Cl_2	100[b]	32 : 68	86 (2*S*,3*R*)	94 (2*R*,3*R*)	41)
7	CH_3	CH_3	C_2H_5	H_2/(*R*)-BINAP–Ru(II) in C_2H_5OH	100[b]	51 : 49	97 (2*S*,3*R*)	97 (2*R*,3*R*)	41)
8	CH_3	CH_3	n-C_8H_{17}	Bakers' yeast	82	95 : 5	>98 (2*R*,3*S*)	—[c]	42)
9	CH_3	Allyl	C_2H_5	Enzyme fraction from bakers' yeast	70	>99.9 : 1	>99.9 (2*R*,3*S*)	—[c]	43)
10	CH_3	CH_2NHBz	CH_3	H_2/(*R*)-BINAP–Ru(II) in CH_2Cl_2	100[b]	94 : 6	99 (2*S*,3*R*)	97 (2*R*,3*R*)	44,45)
11	CH_3	CH_2NHBz	CH_3	H_2/(*R*)-BINAP–Ru(II)[d] in CH_2Cl_2	100[b]	96 : 4	99 (2*S*,3*R*)	98 (2*R*,3*R*)	45,46)
12	CH_3	CH_2NHBz	CH_3	H_2/(*R*)-BINAP–Ru(II)[e] in CH_2Cl_2–CH_3OH	55[b]	99 : 1	99 (2*S*,3*R*)	—[c]	45,46)
13	CH_3	CH_2NHBz	CH_3	H_2/(*R*)-BINAP–Ru(II) in CH_3OH	100[b]	50 : 50	93 (2*S*,3*R*)	97 (2*R*,3*R*)	45)
14	CH_3	CH_2NHBz	C_2H_5	*Rhodotorula glutinis*	90[b]	92 : 8	100 (2*R*,3*S*)	100 (2*S*,3*S*)	47)
15	CH_3	NHAc	CH_3	H_2/(*R*)-BINAP–Ru(II) in CH_2Cl_2	100[b]	99 : 1	98 (2*S*,3*R*)	>90 (2*R*,3*R*)	44)
16	CH_3	NHAc	CH_3	H_2/(*R*)-BINAP–Ru(II) in CH_3OH	100[b]	71 : 29	90 (2*S*,3*R*)	96 (2*R*,3*R*)	44)
17	CH_3	NHAc	CH_3	H_2/(*S*,*S*)-CHIRAPHOS–Ru(II)[f] in CH_2Cl_2	40[b]	97 : 3	85 (2*R*,3*S*)	99 (2*R*,3*R*)	48)
18	CH_3	NHAc	CH_3	H_2/(*R*,*R*)-DIPAMP–Rh(I)[g] in THF	50[b]	94 : 6	39 (2*R*,3*S*)	28 (2*R*,3*R*)	48)
19	CH_3	NHBz	—[c]	H_2/(*R*)-BINAP–Ru(II) in CH_2Cl_2	—[c]	98 : 2	90 (2*S*,3*R*)	—[c]	49)
20	CH_3	OH	C_2H_5	Bakers' yeast	68	19 : 81	90 (2*R*,3*S*)	>99 (2*S*,3*S*)	50)
21	CH_3	OBz	C_2H_5	Bakers' yeast	70	6 : 94	>95 (2*R*,3*S*)	>95 (2*S*,3*S*)	51)
22	CH_3	F	CH_3	Bakers' yeast	78	81 : 19	92 (—[c])	44 (—[c])	52)
23	CH_3	Cl	—[c]	H_2/(*R*)-BINAP–Ru(II) in CH_2Cl_2	—[c]	90 : 10	95 (2*S*,3*R*)	—[c]	49)
24	CH_3	SCH_3	CH_3	Bakers' yeast	72	72 : 28	>96 (2*R*,3*S*)	>96 (2*S*,3*S*)	53)
25	n-C_6H_{13}	CH_3	K	Bakers' yeast	68	<1 : 99	—[c]	>98 (2*R*,3*R*)	54)
26	i-C_3H_7	CH_3	CH_3	H_2/(*R*)-BINAP–Ru(II) in CH_3OH	94	88 : 12	58 (2*S*,3*R*)	—[c]	55)
27	Ar[h]	NHAc	CH_3	H_2/(*R*)-BINAP–Ru(II) in CH_2Cl_2	100[b]	99 : 1	94 (2*S*,3*R*)	—[c]	44)
28	Ar[h]	$NHCO_2Bn$	CH_3	H_2/(*R*)-BINAP–Ru(II) in CH_2Cl_2	100[b]	99 : 1	92 (2*S*,3*R*)	—[c]	44)
29	Ar[i]	NHBoc	CH_3	H_2/(*R*)-BINAP–Ru(II) in CH_3OH–CH_2Cl_2	92	95 : 5	90 (2*S*,3*R*)	—[c]	56)

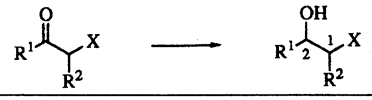
Table 2. (Continued)

Entry	Substrate[a] R[1]	R[2]	R[3]	Method	Product Yield/%	*syn* : *anti*	ee/% (Abs config) *syn*	*anti*	Ref.
30	CH_3	$(CH_2)_2$[j]		H_2/(*R*)-BINAP–Ru(II) in CH_3OH	100[b]	98 : 2	94 (2*S*,3*R*)	60 (2*R*,3*R*)	41)
31	*n*-$C_{15}H_{31}$	$(CH_2)_2$[j]		H_2/(*S*)-BINAP–Ru(II) in CH_2Cl_2	85	99 : 1	96 (2*R*,3*S*)	—[c]	57)
32	$(CH_2)_3$[k]		C_2H_5	Bakers' yeast	52	>99.5 : 0.5	99 (2*R*,3*S*)	—[c]	58,59)
33	$(CH_2)_3$[k]		CH_3	H_2/(*R*)-BINAP–Ru(II) in CH_2Cl_2	100[b]	1 : 99	93 (2*S*,3*R*)	92 (2*R*,3*R*)	41,45)
34	$(CH_2)_3$[k]		CH_3	H_2/(*R*)-BINAP–Ru(II) in CH_3OH	100[b]	14 : 86	99 (2*S*,3*R*)	91 (2*R*,3*R*)	41,45)
35	$(CH_2)_4$[k]		C_2H_5	Bakers' yeast	72—85	>99.5 : 0.5	99 (2*R*,3*S*)	—[c]	58,59)
36	$(CH_2)_4$[k]		C_2H_5	H_2/(*R*)-BINAP–Ru(II) in CH_2Cl_2	100[b]	5 : 95	45 (2*S*,3*R*)	90 (2*R*,3*R*)	41)
37	$(CH_2)_4$[k]		C_2H_5	H_2/(*R*)-BINAP–Ru(II) in C_2H_5OH	100[b]	49 : 51	94 (2*S*,3*R*)	88 (2*R*,3*R*)	41)
38	$(CH_2)_5$[k]		CH_3	H_2/(*R*)-BINAP–Ru(II) in CH_2Cl_2	100[b]	13 : 87—7 : 93	53 (2*S*,3*R*)	93 (2*R*,3*R*)	41,45)
39	$(CH_2)_5$[k]		CH_3	H_2/(*R*)-BINAP–Ru(II) in CH_3OH	100[b]	42 : 58	97 (2*S*,3*R*)	95 (2*R*,3*R*)	45)
40	$CH_2CO(CH_2)_2$[k]		CH_3	H_2/(*S*)-BINAP–Ru(II) in CH_2Cl_2	81	—[c]	—[c]	97 (2*S*,3*S*)	60)
41			C_2H_5	H_2/(*R*)-BINAP–Ru(II) in CH_2Cl_2	95	1.5 : 98.5	68 (2*S*,3*S*)	96 (2*R*,3*S*)	61)
42			C_2H_5	H_2/(*R*,*R*)-DIOP–Ru(II)[1] in CH_3OH	100	3.5 : 96.5	79 (2*S*,3*S*)	25 (2*R*,3*S*)	61)
43			C_2H_5	*Rhizopus arrhizus* ATCC 24563	98	>99 : 1	>99 (2*S*,3*S*)	—[c]	62)
44			C_2H_5	H_2/(*S*)-BINAP–Ru(II) in CH_3OH	100	2 : 98	43 (2*R*,3*R*)	88 (2*S*,3*R*)	61)
45			C_2H_5	*Sporotrichum exile* QM1250	88	>99 : 1	99 (2*S*,3*S*)	—[c]	62)
46			C_2H_5	Bakers' yeast	63—70	>99 : 1	67—73 (2*R*,3*S*)	—[c]	59)
47			CH_3	Bakers' yeast	67	>99 : 1	75 (2*R*,3*S*)	—[c]	59)
48	CH_2CH_2S[k]		CH_3	Bakers' yeast	62	96 : 4	>95 (2*R*,3*S*)	—[c]	63)
49	$CH_2CH_2SCH_2$[k]		CH_3	Bakers' yeast	71	99 : 1	85 (2*R*,3*S*)	—[c]	64)
50	CH_2CH_2NBoc[k]		CH_3	*Dipodascus sp.*	80	—[c]	>99 (2*R*,3*S*)	—[c]	65)

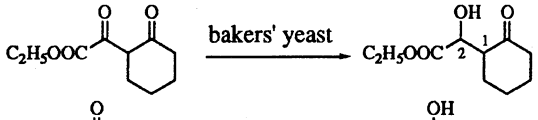
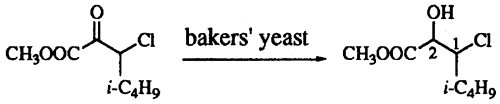
fluence of a chiral phosphine–Pd catalyst, a *s*-alkyl Grignard reagent reacts with (*E*)-*β*-bromostyrene to afford the coupling product in 93% yield and in 95% ee (Entry 9).[26] Since most asymmetric reactions catalyzed by transition-metal complexes proceed via a multistep mechanism, care must be taken in identifying the stereodetermining step. Sometimes enantiomers of a racemic compound are consumed at nearly the same rates ($k_R \cong k_S$); nevertheless, the reaction forms a chiral product of high enantiomeric purity. Notable examples include the reaction of a racemic allyl acetate and a stabilized carbanion[32] and reduction of a racemic allyl acetate with formic acid,[33] both catalyzed by a chiral phosphine–Pd(0) complex. In these instances, the kinetic bias is given in the diastereomeric π-allyl–Pd(II) intermediates reacting with a carbanion or a hydride source at different rates.

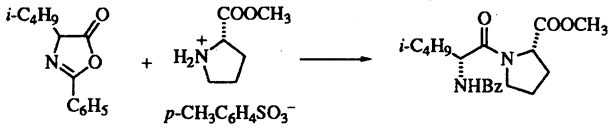
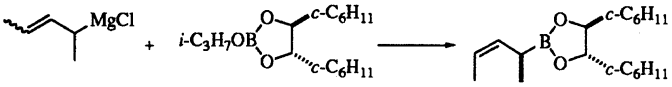
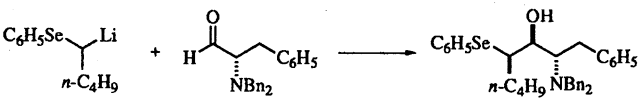
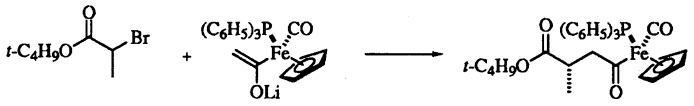
Enantiomerization of substrates normally requires a configurational inversion at the stereogenic center. The third class of asymmetric reactions, however, involves differentiation of equilibrating enantiomeric conformers of achiral substances. Although many enantio-

Table 2. (Continued)



Entry	Substrate[a] R^1	R^2	X	Method	Product Yield/%	*syn* : *anti*	ee/% (Abs config) *syn*	*anti*	Ref.
51	CH_3	CH_3	$CSSCH_3$	Bakers' yeast	65	94 : 6	>96 (1*R*,2*S*)	>96 (1*S*,2*S*)	66)
52	CH_3	CH_3	$COSCH_3$	Bakers' yeast	77	81 : 19	>96 (1*R*,2*S*)	—[c]	66)
53	CH_3	Br	$PO(OCH_3)_2$	H_2/(*S*)-BINAP–Ru(II) in CH_3OH	91	90 : 10	98 (1*R*,2*S*)	94 (1*S*,2*S*)	67)
54	CH_3	Allyl	$SO_2C_6H_5$	Bakers' yeast	65	29 : 71	86 (1*R*,2*S*)	100 (1*S*,2*S*)	68)

Entry	Reaction	Product Yield/%	*syn* : *anti*	ee/% (Abs config) *syn*	*anti*	Ref.
55		57	10 : 90	99 (1*R*,2*R*)	99 (1*S*,2*R*)	69)
56		56	90 : 10	>99 (1*R*,2*S*)	>99 (1*S*,2*S*)	70)

Entry	Reaction	Product Yield/%	Diastereomer ratio	Ref.
57		—[c]	90 : 10	71)
58		89	97 : 3	72)
59		93	56 : 44	73)
60		29	40 : 1[m]	74)

a) Racemate. b) Conversion. c) Not detailed. d) (*R*)-2,2′-Bis[bis(3,5-dimethylphenyl)phosphino]-1,1′-binaphthyl (3,5-xylylBINAP) is used as ligand of the Ru catalyst. e) 2,2′-Bis[bis(3,5-di-*t*-butylphenyl)phosphino]-1,1′-binaphthyl is used as ligand of the Ru catalyst. f) CHIRAPHOS = 2,3-bis(diphenylphosphino)butane. g) 1,2-Bis[(*o*-methoxyphenyl)phenylphosphino]ethane. h) Ar = 3,4-methylenedioxyphenyl. i) Ar = 4,4′-dibenzyloxy-3′-(1,3-dioxan-2-yl)-3-biphenylyl. j) R^2 and R^3 are linked to make a cyclic substrate. k) R^1 and R^2 are connected to make a cyclic structure. l) DIOP = 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane. m) In a solution saturated with LiBr, a better dynamic kinetic resolution is observed (personal communication from Dr. S. G. Davies of Oxford University).

face- and enantiotopos-differentiating reactions of flexible molecules are actually accomplished by this mechanism, particularly noteworthy is the asymmetric cyclization of 1,2-diarylethylenes to helicenes by the irradiation of circularly polarized light (Entry 12).[29] The enzymatic hydrolysis of epoxycyclohexane also presents a historically important example.[34] The asymmetric bromination of cyclohexene catalyzed by *Cinchona* alkaloids might involve kinetic resolution of conformational isomers of the olefinic substrate or bromonium ion intermediates.[35]

Enantioselective Synthesis of Diastereomers. Appropriate use of dynamic kinetic resolution provides an opportunity for the enantioselective synthesis of a diastereomer, according to Fig. 3. The reduction of α-substituted β-keto esters is among the most typical reaction. The chiral substrates that undergo ready racemization via the enol form are converted to a series of important β-hydroxy esters. Although four stereoisomeric products are possible in this reaction, the selection of suitable conditions may result in a single product with high stereoselectivity. Table 2 lists examples accomplished by biological or chemical means. Although various microorganisms and enzymes effect this trans-

formation, the bakers' yeast reduction is probably the most convenient biological method. The treatment of 2-substituted 3-oxobutanoates with a mixture of bakers' yeast and sucrose in water produces the (3*S*)-hydroxybutanoates, as observed in enantioselective reduction of parent ethyl 3-oxobutanoate.[75] The sense of diastereoselection is highly affected by the nature of the C(2) substituents. Methyl, allyl, halogeno, and methylthio substituents tend to afford 2,3-*syn* products predominantly, while the *anti* isomers are favored with the oxygen functionalities (Entries 20 and 21). The chiral efficiency can be improved by structural modifications of the substrates. For example, the extent of the 2,3-*syn* selectivity is increased from 75 : 25 to 95 : 5 by changing the methyl ester to octyl ester (Entries 2 and 8). *O*-Benzoylation of the 2-hydroxy compound also enhances the *anti* selectivity (Entries 20 and 21). The reaction of the potassium salt of 2-methyl-3-oxononanoic acid shows an excellent *anti* diastereoselection (Entry 25). This reaction can be extended to related thio esters (Entries 51 and 52). Since micro-organisms normally contain various enzymes having different reactivities and stereoselectivities, the selectivity of the reduction is sensitive to the reaction conditions, including the addition of selective enzyme inhibitors. The addition of methyl vinyl ketone, for instance, gives a *syn* selectivity as high as 96 : 4 (Entry 3). The use of pure enzymes sometimes increases the selectivity (Entries 4, 5, and 9).

Catalytic hydrogenation provides an operational simplicity in this transformation. Unfortunately, heterogeneous hydrogenation with Raney nickel modified by (*R*,*R*)-tartaric acid showed only moderate enantio- and diastereoselectivity in the reaction of methyl 2-methyl-3-oxobutanoate (Entry 1).

Homogeneous hydrogenation of prochial β-keto esters catalyzed by BINAP–Ru(II) complexes **1** (BINAP = 2,2′-bis(diarylphosphino)-1,1′-binaphthyl) proceeds with a high degree of enantioselection, as shown in Fig. 4.[76,77] The hydrogenation finds a very wide generality and high chiral flexibility; a reaction using the (*R*)-BINAP catalyst, (*R*)-**1**, produces the *R* hydroxy ester in >98% ee, while the use of the *S* catalyst, (*S*)-**1**, affords the *S* hydroxy ester.[77a] The asymmetric hydrogenation can be performed in organic media, normally alcohols, with up to 50% substrate concentration under 4—100 atm[78] of hydrogen at room temperature with a substrate/catalyst mole ratio of up to 10000 on any scale using <100 mg to >100 kg of the substrate.[79] The products are easily isolated from the reaction mixtures. The reaction is applicable to the synthesis of biologically significant compounds, such as carnitine,[77c] γ-amino-β-hydroxybutyric acid (GABOB),[77c] statine series,[80] compactin,[77b,l] FK-506,[77e,g] and theonellamido F.[81]

The reaction probably proceeds via Ru monohydride species formed from **1** and hydrogen.[82] The ester function in the substrate accelerates the hydrogenation and at the same time directs the stereochemical outcome through an interaction with the Ru center. The high chiral efficiency obviously relies on the unique chiral en-

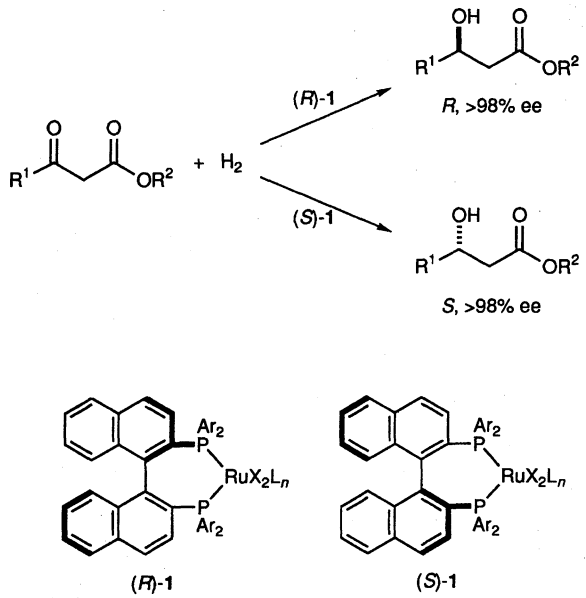


Fig. 4. Enantioselective hydrogenation of β-keto esters catalyzed by BINAP–Ru(II) complexes. X = anionic ligand; L = neutral ligand. In most cases, Ar = phenyl.

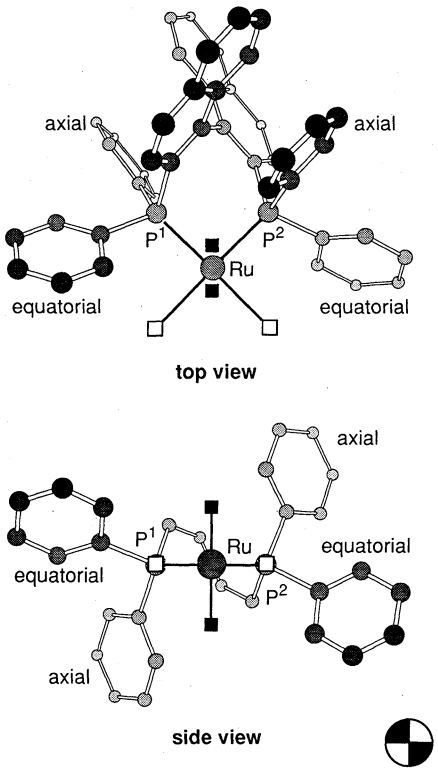


Fig. 5. Chiral environment of an (*R*)-BINAP–Ru(II) complex. The naphthalene rings are omitted in the side view.

vironment of the BINAP–Ru(II) complex.[83] Figure 5 illustrates the C_2 chiral template created by the (*R*)-BINAP and Ru(II) element.[76,84] The chirality originally generated by the binaphthyl skeleton is transmitted spatially through the *P*-phenyl rings to the in-plane and out-of-plane coordination sites, indicated by □ and ■. The stereo-determining step would be the reaction of the Ru–H element and the coordinated β-keto ester that takes place in such a way as to minimize the nonbonded repulsion between the *P*-phenyls and substrate substituents. Particularly, the "equatorial" *P*-phenyl rings exert a profound steric influence on the ligand in the P^1–Ru–P^2 in-plane sites, □. Figure 6 explains the origin of the high degree of *R* selection by comparing the diastereomeric transition structures leading to the enantiomeric hydroxy products.[85] It is clear that the *S*-generating structure, $\mathbf{2}_S$, is highly unlikely because, in the fourth quadrant, the R^1 substituent suffers a serious nonbonded interaction with the equatorial *P*-phenyl ring in the (*R*)-BINAP ligand; such an unfavorable interaction is absent in the *R*-generating transition state, $\mathbf{2}_R$. The OR^2 moiety present approximately in the P^1–Ru–P^2 plane is far from the *P*-phenyl substituents, and, hence, unimportant for producing a stereochemical bias.

This asymmetric hydrogenation can now be utilized for chirally labile α-substituted β-keto esters, leading to the *syn* and *anti* diastereomers (Fig. 7). Table 2 gives some examples. The general sense of the catalyst-to-product chirality relationship, *R* to *R* and *S* to *S*,[77] is not violated. Thus, the absolute configuration of the hydroxyl-bearing β position is determined by the chirality of the BINAP ligand, and the stereoselectivity is generally high. On the other hand, the configuration of the α stereogenic center is highly affected by the structures of the keto substrates as well as the reaction conditions. Some synthetically notable features are described below.

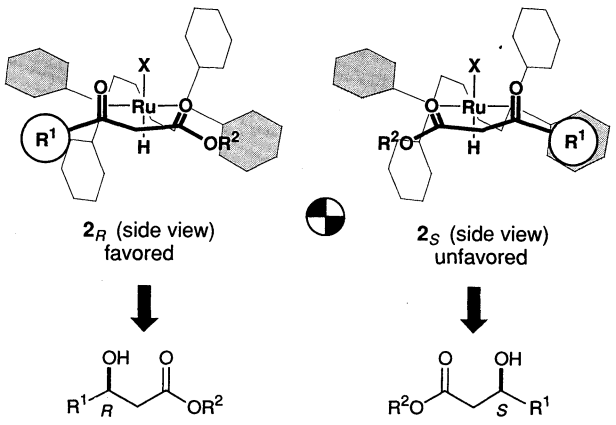


Fig. 6. Stereo-determining step in the (*R*)-BINAP–Ru(II) catalyzed hydrogenation of β-keto esters. Hydrogen on Ru moves to the carbonyl carbon. The sterically demanding "equatorial" *P*-phenyl rings are shaded. X = halogen, H_2, solvent, etc.

As shown in Fig. 8, the hydrogenation of racemic 2-acetyl-4-butanolide (**3**) with (*R*)-BINAP–Ru catalyst proceeds with a 98 : 2 *syn* selection to give the (*R*)-1-hy-

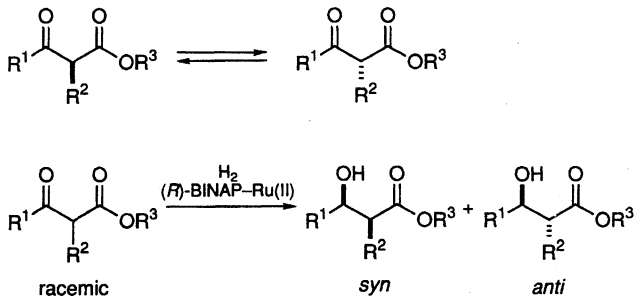
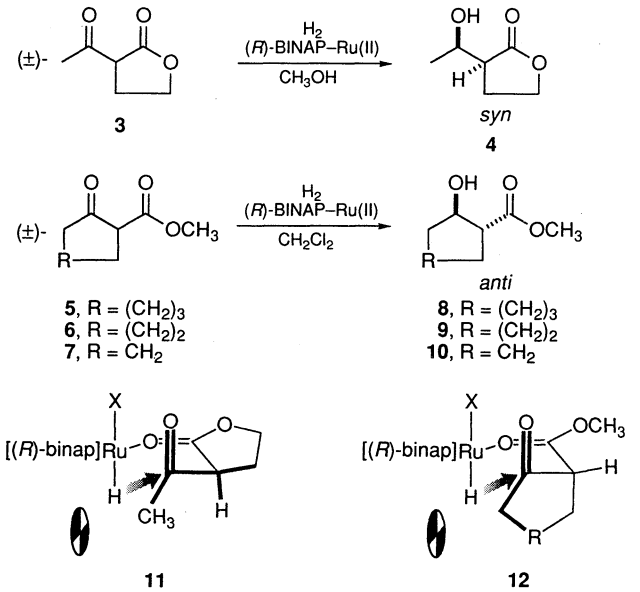


Fig. 7. Stereoselective hydrogenation of α-substituted β-keto esters.



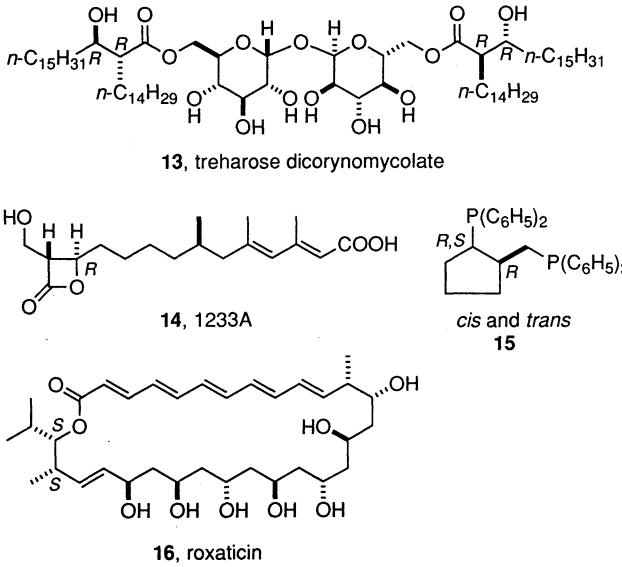


Fig. 8. Stereoselective hydrogenation of racemic keto esteres catalyzed by BINAP–Ru(II) complexes.

droxyethyl compound **4** in 94% ee (Entry 30).[41] In contrast, 2-(alkoxycarbonyl)cycloalkanones, **5**—**7**, are hydrogenated to give the corresponding *trans* or *anti* products, **8**—**10**, with high diastereo- and enantioselectivity (Entries 33, 36, 38, 41, and 44).[41,45,61] The nature of the solvent strongly affects the extent of the diastereoselectivity. A high *anti* selectivity is obtained in dichloromethane instead of ordinary alcoholic solvents. As the ring size increases from five to seven, the diastereoselectivity is lowered to some extent. An aromatic ring can also be incorporated in the cyclic substrates (Entries 41, 42, and 44). The *anti* selection is contrasted to the *syn* selectivity observed in the bakers' yeast reduction of cyclic keto esters (Entries 32, 35, and 46—49). These stereoselectivities accomplished with the (*R*)-BINAP–Ru catalyst are easily understood by considering the stereo-determining transition structures, **11** and **12**,[85] where the stereochemical argument of the BINAP complex in Fig. 6 and characteristics of the cyclic substrates are taken into account. As expected, the hydrogenation of a simple 2-methylated 3-oxobutanoate occurs with high enantioselectivity, particularly in ethanol, but with low *syn*/*anti* diastereoselectivity (Entry 7). These reactions have been utilized for the synthesis of treharose dicorynomycolate (**13**),[57,86] HMG-CoA synthase inhibitor 1233 A (**14**),[60,86] chiral diphosphine **15**[86,87] and roxaticin (**16**).[55,86]

A relevant dynamic kinetic resolution has been seen with chirally labile diastereomeric substrates (Fig. 9). When the racemic bicyclic ketone **17**, possessing one chirally labile and two stable stereogenic centers, is hydrogenated with an (*R*)-BINAP–Ru complex in dichloromethane, the alcoholic product **18**, a synthetic intermediate of carbacyclins **22**,[86] is formed in 86% ee and in 32% yield.[41] The hydrogenation takes place selectively from the convex face of the bicyclo[3.3.0]-octane skeleton via a transition state like **12** among eight possible stereoisomers. In a similar manner, an (*S*)-BINAP–Ru catalyzed reaction of racemic cyclopetanone **19** with an all-*trans* geometry affords **20** with 84% ee and **21** in 90% ee in nearly equal amounts, respectively.[88] In this instance, both (3*R*,4*S*)- and (3*S*, 4*R*)-diarylcyclopentanones are consumed by asymmetric hydrogenation. This reaction is useful for synthesis of the chiral diphosphine **23**.[86]

Open-chain β-keto esters with an α-amido or -(alkoxycarbonyl)amino substituent are hydrogenated with excellent *syn* selectivity, as exemplified by the reaction **24**→**25** in Fig. 10 (Entries 15—19 and 27—29).[44,48,56] Both natural and unnatural threonine **26** as well as related compounds can be produced in high ee's by selecting the chirality of BINAP. This hydrogenation is applicable to the synthesis of anti-Perkinsonian L-*threo*-3-(3,4-dihydroxyphenyl)serine (L-DOPS) (**27**)[44] as well as a key intermediate for the synthesis of biphenomycin A (**28**).[56,86] The *syn* diastereoselectivity is interpreted primarily in terms of the Felkin–Anh transition

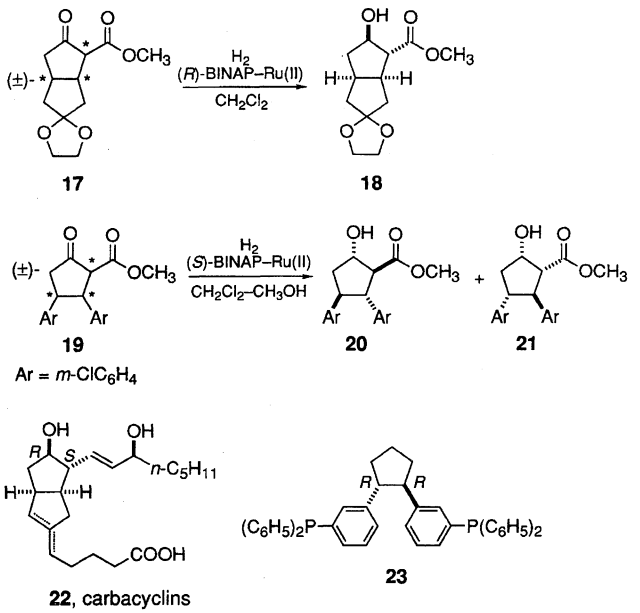


Fig. 9. Stereoselective hydrogenation of diastereomeric keto esters catalyzed by BINAP–Ru(II) complexes.

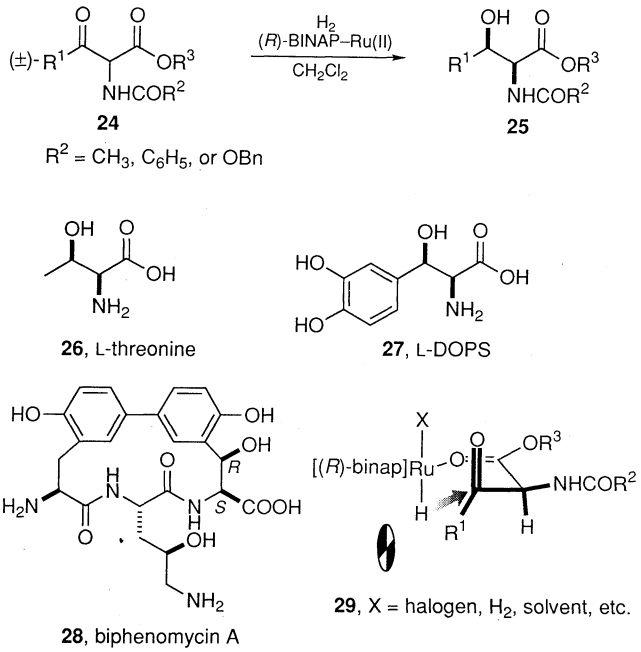


Fig. 10. Stereoselective synthesis of threonine-type compounds by BINAP–Ru catalyzed hydrogenation.

state **29**,[85,89] where the electronegative α substituent is *anti* to the incoming hydrogen. The *syn* transition state may be further stabilized by possible NH/OR^3 hydrogen-bond formation. This view is consistent with the difference in the *syn*: *anti* diastereoselectivity, 99 : 1 vs. 71 : 29, seen with dichloromethane and methanol as solvent.[44] Even more important is the hydrogenation of the racemic benzamidomethyl substrate **30** of Fig. 11 (Entries 10—12).[44—46] The controlled reaction in dichloromethane containing the (*R*)-BINAP–Ru(II) cata-

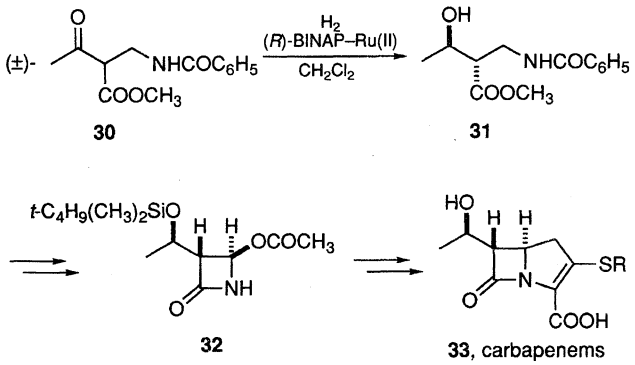


Fig. 11. Stereoselective synthesis of carbapenem antibiotics.

lyst gives the hydrogenation product **31** in 99% ee and with 94 : 6 to 99 : 1 *erythro*/*threo*[90] diastereoselectivity. This reaction after extensive technical refinements is now used for the industrial preparation of the azetidinone **32** (120 ton/year),[91] a common intermediate for the synthesis of carbapenem antibiotics **33**.

The BINAP–Ru catalyzed hydrogenation utilizing dynamic kinetic resolution has been extended to the stereoselective synthesis of certain α-substituted β-hydroxy phosphonates.[67] Thus, as illustrated in Fig. 12, in the presence of the (*S*)-BINAP–Ru catalyst, racemic dimethyl 1-bromo-2-oxopropylphosphonate (**34**) is hydrogenated with a 90 : 10 *syn*/*anti* selectivity to give dimethyl (1*R*,2*S*)-1-bromo-2-hydroxypropylphosphonate (**35**) in 98% ee (Entry 53). The Felkin–Anh transition structure **37** in the hydrogen transfer step rationalizes the preferred formation of **35** among the four possibilities. This asymmetric reaction opens a practical way to fosfomycin (**36**), a clinically used antibiotic.[92]

As listed in Entries 55 and 56 in Table 2, certain α-keto esters with a labile stereogenic center at the β position can be reduced by bakers' yeast in an enantio- and diastereoselective fashion.

The reaction of racemic leucine oxazolinone and proline methyl ester gives the *R* amide in a 90 : 10 diastereoselectivity (Entry 57). In a similar manner, enantiomers of chirally labile organometallics react with

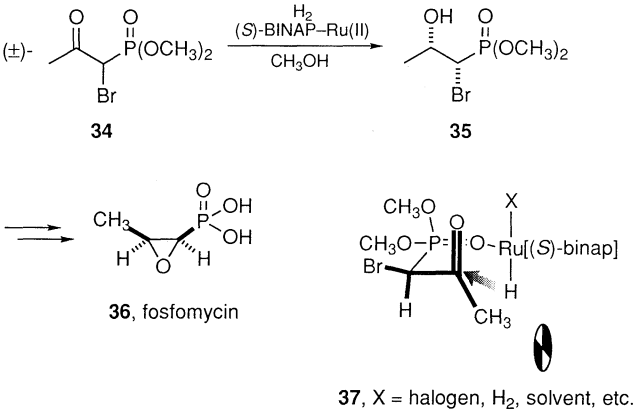


Fig. 12. Stereoselective synthesis of fosfomycin.

enantiomerically pure electrophiles at different rates to give diastereomeric adducts in unequal amounts. The donor–acceptor relationship of the chiral substances may be reversed. At the end of the table (Entries 57—60), some examples are given.

Quantitative Expression

Mathematical Treatment. The mathematical expression of chemical reactions is not only a fundamental subject which discerns the details of a given molecular change, but also provides suitable indications for improving the synthetic efficiency on demand. The reaction via kinetic resolution is characterized by the time dependence of the selectivity. The theoretical treatment of the conventional resolution of Fig. 1 began with the Bredig–Fajans' numerical formulation in 1908,[93] which was followed by a graphical expression by Kuhn[94] and Mislow,[95] and reached the Kagan's diagnostic system.[96] Later, Sharpless and Sih extended this system to more general equations:[8,97] $k_R/k_S = \ln[(1 - \mathrm{convn})(1 - \mathrm{ee_S})]/\ln[(1 - \mathrm{convn})(1 + \mathrm{ee_S})]$ and $k_R/k_S = \ln[1 - \mathrm{convn}(1 + \mathrm{ee_P})]/\ln[1 - \mathrm{convn}(1 - \mathrm{ee_P})]$. Here, the $\mathrm{ee_S}$ and $\mathrm{ee_P}$ are the ee values of the recovered substrate and product, respectively. These are now used to calculate the k_R/k_S value, an index of the efficiency of the resolution, facilitating the use of kinetic resolution as a tool in organic synthesis. Although the concept of dynamic kinetic resolution of Figs. 2 and 3 had already been recognized as early as the 1960's in connection with the Curtin–Hammett principle, the synthetic utility remained unviable. Furthermore, the close interrelation of competitive reactions, which is contrasted to the independence of the two pathways in Fig. 1, did not allow its easy mathematical expression. The progress in modern computer techniques, including both hardware and software, however, has changed this situation. Here, we disclose a general mathematical system for assessing the details of dynamic kinetic resolution.[45,98] This formulation would provide a rational framework for a deeper understanding of the complex stereoselective reaction.

Dynamic Kinetic Resolution of Fig. 2. Figure 2 is the simplest framework of dynamic kinetic resolution, where S_R and S_S are stereospecifically converted to P_R and P_S, respectively. For the analysis, four assumptions are set: (1) reactions of S_R and S_S with rate constants, k_R and k_S, and stereoinversion of the substrate with k_{inv} proceed in first or pseudo-first order in substrate concentrations;[99] (2) S_R reacts faster than S_S, and, hence, P_R is the prevailing enantiomeric product; (3) S_R and S_S racemize at the same rate; (4) the reaction is irreversible, and P_R and P_S are stable under the reaction conditions. Since S_R is consumed with rate constants k_R and k_{inv} and supplied from S_S with constant k_{inv}, the velocities of the consumption of the substrates are expressed as

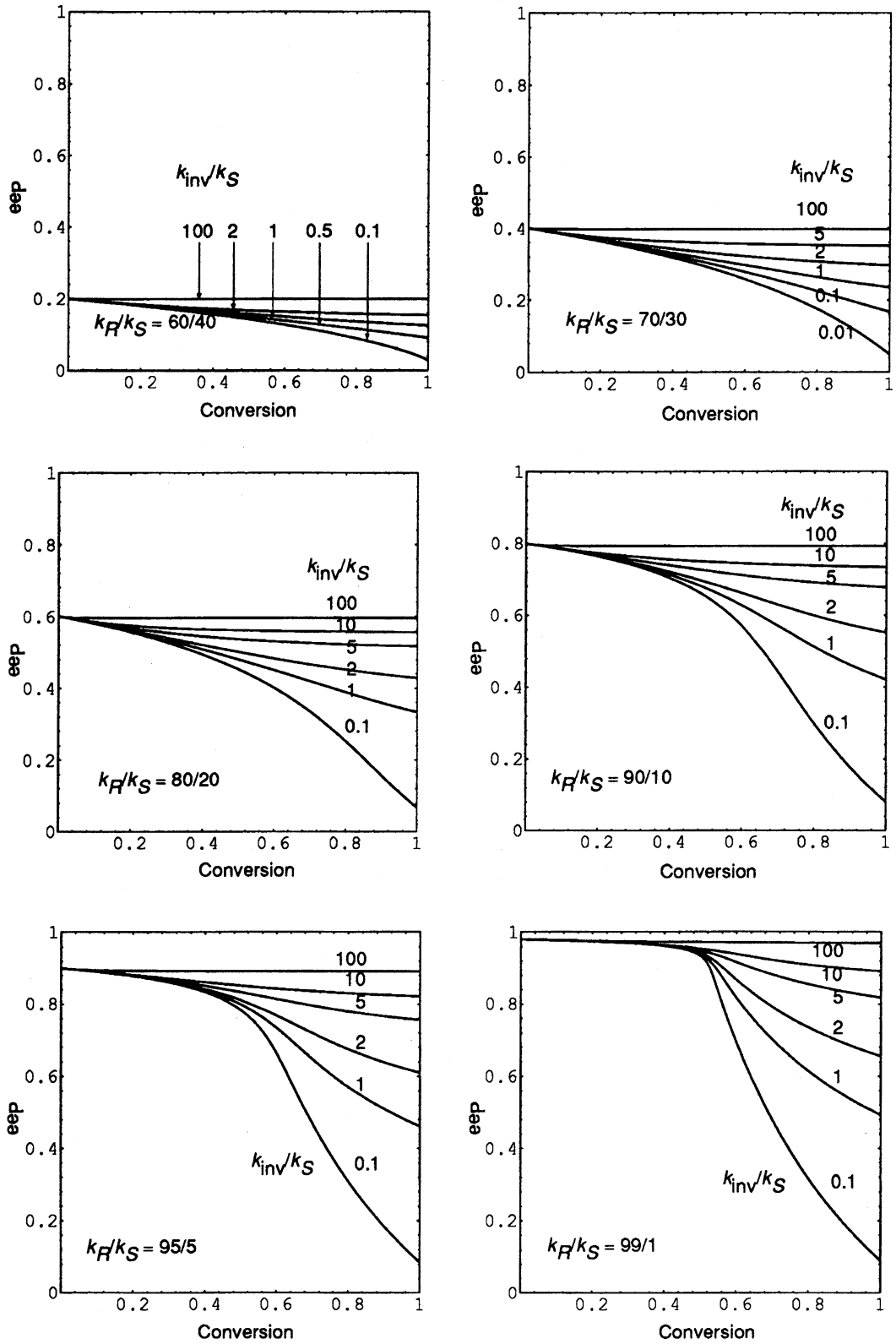


Fig. 13. Simulation of variations of enantiomeric purities of the product as a function of conversion with imaginary k_R/k_S and k_{inv}/k_S parameters.

$$-\frac{d[S_R]}{dt} = (k_R + k_{inv})[S_R] - k_{inv}[S_S] \quad (1)$$

and

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

Since these are two-dimensional linear differential equations with respect to $[S_R]$ and $[S_S]$, their integration through the known mathematical treatment gives Eqs. 3 and 4, which state the substrate quantities as a function

of time elapsed:

$$S_R(t) = C_1 e^{\lambda_1 t} + C_2 e^{\lambda_2 t} \quad (3)$$

and

$$S_S(t) = C_3 e^{\lambda_1 t} + C_4 e^{\lambda_2 t} \quad (4)$$

Further integration of these equations affords Eqs. 5 and 6, which describe the quantities of P_R and P_S at time t:

$$P_R(t) = \int k_R S_R(t) dt = k_R \left[\frac{C_1}{\lambda_1}(e^{\lambda_1 t} - 1) + \frac{C_2}{\lambda_2}(e^{\lambda_2 t} - 1) \right] \quad (5)$$

and

$$P_S(t) = \int k_S S_S(t) dt = k_S \left[\frac{C_3}{\lambda_1}(e^{\lambda_1 t} - 1) + \frac{C_4}{\lambda_2}(e^{\lambda_2 t} - 1) \right] \quad (6)$$

Since λ_1, λ_2, C_1, C_2, C_3, and C_4 in Eqs. 3, 4, 5, and 6 are parameters correlating with the four coefficients of Eqs. 1 and 2, $(k_R + k_{inv})$, $-k_{inv}$, $(k_S + k_{inv})$, and $-k_{inv}$, the amounts of the four components in Fig. 2 ($S_S(t)$, $S_R(t)$, $P_R(t)$, and $P_S(t)$) are now represented by the parameters, k_R, k_S, and k_{inv}. Therefore, the selectivity profiles, $ee_S(t)$ (ee of slow-reacting S_S), $ee_P(t)$ (ee of major product P_R), and convn(t) (conversion), given by Eqs. 7, 8, and 9, are also expressed by these three parameters:

$$ee_S(t) = \frac{S_S(t) - S_R(t)}{S_R(t) + S_S(t)}, \quad (7)$$

$$ee_P(t) = \frac{P_R(t) - P_S(t)}{P_R(t) + P_S(t)}, \quad (8)$$

and

$$\text{convn}(t) = \frac{P_R(t) + P_S(t)}{S_R(0) + S_S(0)} \quad (9)$$

Accordingly, an experimental determination of the k_R/k_S and k_{inv}/k_S ratios allows for a time-parametrical graphic representation of the selectivity profile, such as convn(t)/$ee_S(t)$ and convn(t)/$ee_P(t)$.

Because the rate ratio (k_R/k_S) is equivalent to the product ratio when S_R and S_S are present in equal amounts, this is nearly identical with the P_R/P_S ratio at an early stage of the reaction. The indexes, k_R/k_S and ee_P^0 (ee of major product at $t = 0$), are independent of time and the concentrations of the substrate and catalyst or enzyme. These initial values are kept constant throughout the reaction when the stereoinversion, $S_R \rightleftarrows S_S$, is infinitely faster than the reaction ($k_{inv} \gg k_R$ and k_S) and the Curtin–Hammett principle safely applies; however, in reality, the final P_R/P_S ratio at 100% conversion deviates from the initial values. The degree of this deviation is correlated to the k_{inv}/k_S ratio given by Eq. 10, which uses experimentally available values, k_R/k_S and ee_P^{100} or k_R/k_S and $P_{R/S}^{100}$ (ratio of products derived from S_R and S_S).

$$\frac{k_{inv}}{k_S} = \frac{\frac{k_R}{k_S} ee_P^{100}}{\left(\frac{k_R}{k_S} - 1\right) - ee_P^{100}\left(\frac{k_R}{k_S} + ee_P^{100}\right)} = \frac{\frac{k_R}{k_S}\left(1 - P_{R/S}^{100}\right)}{2\left(P_{R/S}^{100} - \frac{k_R}{k_S}\right)} \quad (10)$$

Figure 13 graphically illustrates the relationship between $ee_P(t)$ and convn(t) with some imaginary k_R/k_S and k_{inv}/k_S ratios. This figure provides an overview of the interrelationship between the enantiomeric purity of the product and the various kinetic parameters.

Dynamic Kinetic Resolution of Fig. 3. The above theoretical treatment also holds for the reaction given in Fig. 3, which is typified by the asymmetric reduction of α-substituted β-keto esters. The same definitions and assumptions are set for the reaction of Fig. 14. This reaction of an interchanging mixture of S_R and S_S produces four stereoisomers: P_{RR}, P_{RS}, P_{SR}, and P_{SS}.[100] S_R is again assumed to react faster than S_S, and P_{RR} is chosen to be the most abundant stereoisomer. The quantities of the substrates, $S_R(t)$ and $S_S(t)$, are represented by Eqs. 3 and 4, and the sum of the products derived from S_R and S_S are given by simply replacing $P_R(t)$ and $P_S(t)$ in Eqs. 5 and 6 with $P_{RR}(t) + P_{RS}(t)$ and $P_{SR}(t) + P_{SS}(t)$, respectively. Since each reaction of Fig. 14 affords two diastereomeric products, four stereoisomers are produced in unequal amounts. Thus, the quantities of these stereoisomers are written by Eqs. 11, 12, 13, and 14. Here, w, x, y, and z are partition coefficients of the isomers ($w + x + y + z = 1$), *where S_R and S_S are assumed to be present in equal amounts.*

$$P_{RR}(t) = \frac{w}{w+x} k_R \left[\frac{C_1}{\lambda_1}(e^{\lambda_1 t} - 1) + \frac{C_2}{\lambda_2}(e^{\lambda_2 t} - 1) \right] \quad (11)$$

$$P_{RS}(t) = \frac{x}{w+x} k_R \left[\frac{C_1}{\lambda_1}(e^{\lambda_1 t} - 1) + \frac{C_2}{\lambda_2}(e^{\lambda_2 t} - 1) \right] \quad (12)$$

$$P_{SR}(t) = \frac{y}{y+z} k_S \left[\frac{C_3}{\lambda_1}(e^{\lambda_1 t} - 1) + \frac{C_4}{\lambda_2}(e^{\lambda_2 t} - 1) \right] \quad (13)$$

$$P_{SS}(t) = \frac{z}{y+z} k_S \left[\frac{C_3}{\lambda_1}(e^{\lambda_1 t} - 1) + \frac{C_4}{\lambda_2}(e^{\lambda_2 t} - 1) \right] \quad (14)$$

Now, the amounts of the enantiomeric substrates and four stereoisomeric products at time t are represented by time-dependent functions using w, x, y, z, k_R/k_S, and k_{inv}/k_S as parameters. The ee of the unreacted

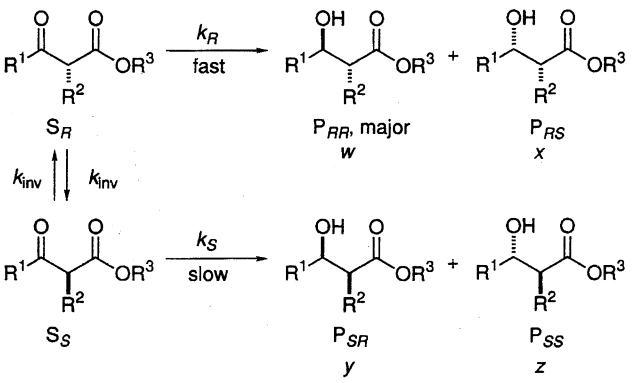


Fig. 14. Hydrogenation of α-substituted β-keto esters.

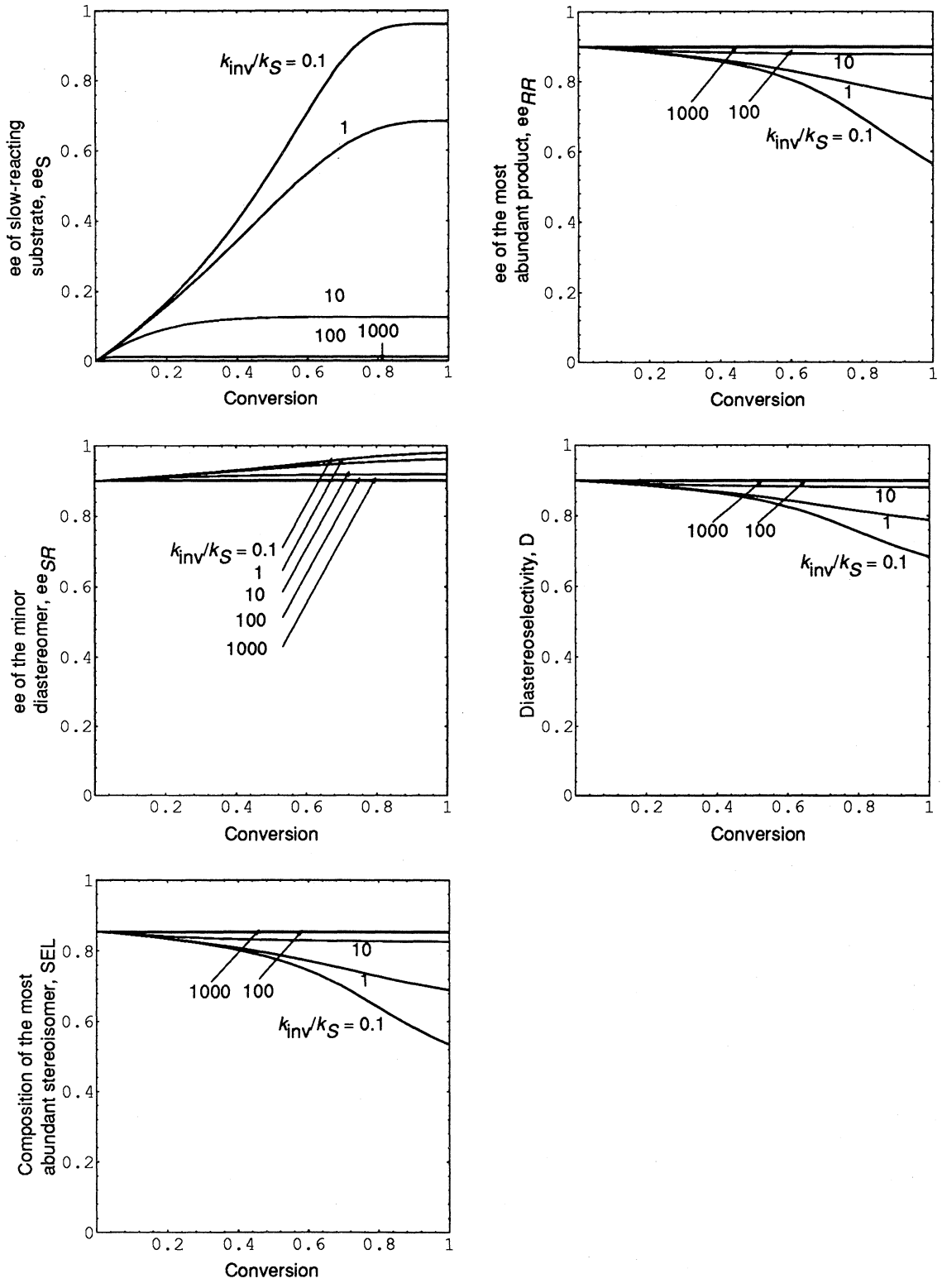


Fig. 15. Simulation of the selectivity profiles as a function of conversion of a racemic keto ester with imaginary w, x, y, z (0.855, 0.005, 0.095, and 0.045, respectively), k_R/k_S (6.14), and k_{inv}/k_S (1000, 100, 10, 1, and 0.1) parameters. $D = (P_{RR} + P_{SS})/(P_{RR} + P_{RS} + P_{SR} + P_{SS})$. $SEL = P_{RR}/(P_{RR} + P_{RS} + P_{SR} + P_{SS})$.

slow-reacting substrate [$ee_S(t)$] is given by Eq. 7, as described earlier. The ee's of the diastereomeric products, P_{RR} and P_{SR} [$ee_{RR}(t)$ and $ee_{SR}(t)$, respectively], diastereoselectivity [$D(t)$], ratio of the $2R$ and $2S$ products [$P_{R/S}(t)$], composition of the most abundant isomer P_{RR} in the whole product [$SEL(t)$], and conversion [$convn(t)$] are given in Eqs. 15, 16, 17, 18, 19, and 20:

$$ee_{RR}(t) = \frac{P_{RR}(t) - P_{SS}(t)}{P_{RR}(t) + P_{SS}(t)}, \quad (15)$$

$$ee_{SR}(t) = \frac{P_{SR}(t) - P_{RS}(t)}{P_{SR}(t) + P_{RS}(t)}, \quad (16)$$

$$D(t) = \frac{P_{RR}(t) + P_{SS}(t)}{P_{RR}(t) + P_{RS}(t) + P_{SR}(t) + P_{SS}(t)}, \quad (17)$$

$$P_{R/S}(t) = \frac{P_{RR}(t) + P_{RS}(t)}{P_{SR}(t) + P_{SS}(t)}, \quad (18)$$

$$SEL(t) = \frac{P_{RR}(t)}{P_{RR}(t) + P_{RS}(t) + P_{SR}(t) + P_{SS}(t)}, \quad (19)$$

and

$$convn(t) = \frac{P_{RR}(t) + P_{RS}(t) + P_{SR}(t) + P_{SS}(t)}{S_R(0) + S_S(0)} \quad (20)$$

Thus, the dynamic aspects of Fig. 14 are clearly described by the experimentally accessible parameters. The expression is general. For the asymmetric reaction, the distribution factors, w to z, can be determined by two experiments. First, the P_{RR}/P_{RS} and P_{SR}/P_{SS} ratios, at any conversion, of a reaction performed with an enantiomerically pure catalyst simply correspond to the w/x and y/z ratios, respectively. Because the S_R/S_S ratio normally deviates from unity as the reaction proceeds, this reaction is unable to determine the w/y or w/z ratio. However, the reaction using the racemic catalyst occurs via mutual kinetic resolution, where the concentration of S_R and S_S remains equal throughout the reaction.[101] Therefore, the observed diastereoselectivity, $(P_{RR} + P_{SS})/(P_{SR} + P_{RS})$, is expressed by $(w + z)/(y + x)$. It should be noted that to achieve the desired mutual kinetic resolution the enantiomeric catalysts must function independently and that they should not interact with one another.[102] When a racemic catalyst is not available, for example, with a biological system, the w, x, y, and z values may be estimated from the product distribution of the reaction with a very low conversion by using a suitably accurate analytical method. Since $w + x + y + z = 1$, these three experimentally obtained values lead to the distribution coefficients. The k_R/k_S ratio is equal to $(w + x)/(y + z)$ and k_{inv}/k_S is defined by Eq. 10.

In the asymmetric reaction of a chiral substrate with a chiral catalyst (or reagent), the stereoselectivity 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).[103] The reaction of Fig. 14 affords P_{RR} as the most abundant product and P_{SS} as the least abundant isomer. Then $C_{cat} = (wy/xz)^{1/2}$ and $C_{sub} = (wz/xy)^{1/2}$ provide rough indexes of these three-dimensional effects, while $C_{cat} : C_{sub} = y : z$. However, this is not valid when $x > y$ or z.

The profile of the stereoselective synthesis via the dynamic kinetic resolution is fully described by w, x, y, z, k_R/k_S, and k_{inv}/k_S. In order to accomplish a high chiral efficiency, the inherent stereochemical effects should be suitably coupled with the kinetic parameters. The stereoselectivity is obviously time-dependent. Figure 15 gives some computer-generated curves showing the ee_S, ee_{RR}, ee_{SR}, D, and SEL as a function of the conversion with some imaginary parameters. The enantiomeric and diastereomeric purity of the most abundant isomer P_{RR} can not exceed the initial values, $ee_P^0 = (w - z)/(w + z)$ and $D^0 = w + z$, respectively. In a similar manner, SEL^0 is the maximal composition of P_{RR}, while SEL^{100} which is ultimately obtained is the minimal value. Figure 16 illustrates the relationship of k_{inv}/k_S, k_R/k_S, and SEL^{100} by a 3D graph. In this instance, although the stereochemical factors, C_{cat} and C_{sub} of 10, are sufficiently high the picuture indicates that the stereoselective formation of P_{RR} further requires appro-

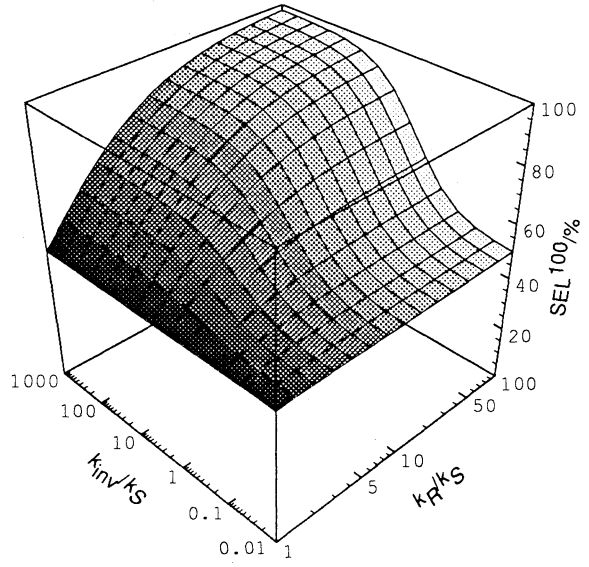


Fig. 16. 3D-graphic demonstration of relationship of k_{inv}/k_S, k_R/k_S, and SEL^{100} with $C_{cat} = 10$ and $C_{sub} = 10$.

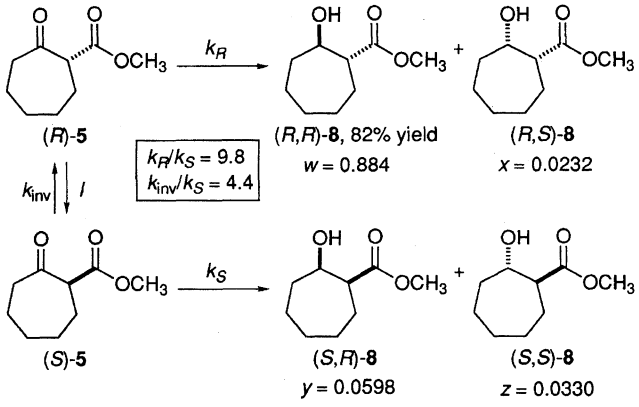


Fig. 17. Hydrogenation of 2-(methoxycarbonyl)cycloheptanone (**5**) (2.7 mol dm^{-3}) catalyzed by (*R*)-BINAP–Ru(II) complex (2.6 mmol dm^{-3}) in dichloromethane at 100 atm at 50 °C for 96 h.

Table 3. Parameters of Stereoselective Hydrogenation of Chirally Labile Ketones Catalyzed by BINAP–Ru Complexes

			Parameters							
Entry	Substrate	Solvent	C_{cat}	C_{sub}	k_{fast}/k_{slow}	k_{inv}/k_{slow}	$ee_P{}^0$	D^0	SEL^0	SEL^{100}
1	(±)-**5**[a)]	CH_2Cl_2	8.3	4.6	9.8	4.4	0.928	0.917	0.884	0.816
2	(±)-**5**[a)]	CH_3OH	47	1.8	5.9	0.24	0.987	0.850	0.845	0.569
3	(±)-**7**[a,b)]	CH_3OH	86	24	12	3.0	0.964	0.938	0.921	0.821
4	(±)-**30**[a)]	CH_2Cl_2	104	9.0	15	92	0.990	0.943	0.938	0.934
5	(±)-**30**[a,c)]	CH_2Cl_2	130	24	26	94	0.988	0.968	0.962	0.957
6	(±)-**30**[a)]	CH_3OH	42	1.5	0.93	—	0.929	0.493	0.475	0.483
7	(±)-**34**[a,d,e)]	CH_3OH	67	4.3	13	11.5	0.991	0.930	0.926	0.894
8	(±)-**34**[e,f)]	CH_3OH	60	4.5	13	2.8	0.989	0.930	0.925	0.818

a) Concentrations of the substrate and catalyst are given in the caption of Figs. 17, 19, and 20. Reaction in methanol and dichloromethane is performed at 25 and 50 °C, respectively, under 100 atm of hydrogen. b) [sub] = 3.3 mol dm^{-3}. [cat] = 2.6 mmol dm^{-3}. c) 3,5-XylylBINAP was used as ligand of the Ru catalyst. d) [sub] = 0.34 mol dm^{-3}. [cat] = 0.18 mmol dm^{-3}. e) At 4 atm. f) [sub] = 0.33 mol dm^{-3}. [cat] = 0.65 mmol dm^{-3}.

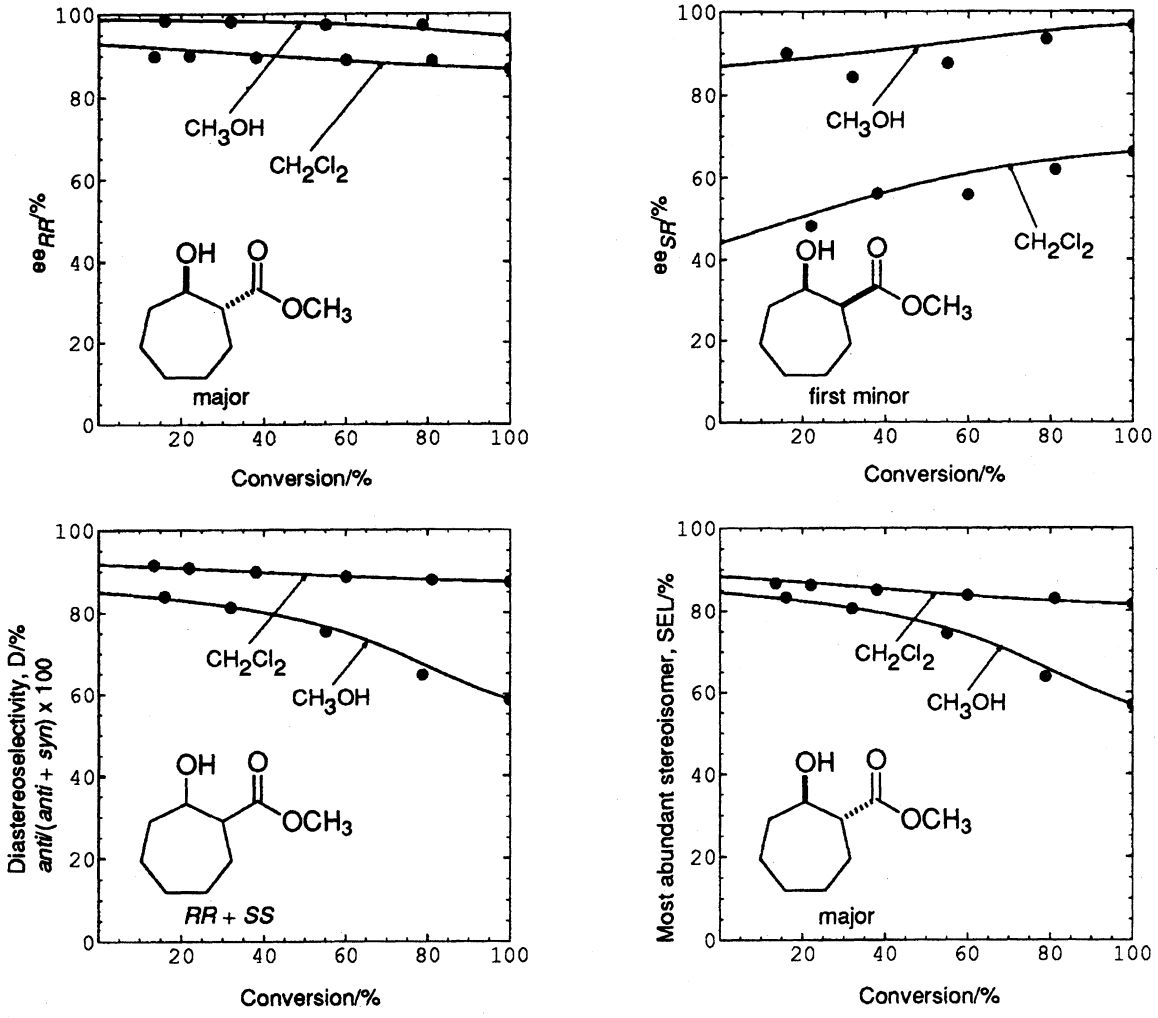


Fig. 18. Computer simulation and experimental results of hydrogenation of 2-(methoxycarbonyl)cycloheptanone (**5**) catalyzed by (*R*)-BINAP–Ru(II) complex. Line: simulation. Dot: observation.

priate kinetic conditions. The top corner denotes the ideal situation (% SEL^{100} = 98.0) obtained with k_R/k_S = 100 and k_{inv}/k_S = 1000, while the front corner is the worst case (% SEL^{100} = 49.5) resulted with k_R/k_S = 1 and k_{inv}/k_S = 0.01.

Correlation between Experiments and Computation. The BINAP–Ru(II) catalyzed hydrogenation of certain α-substituted β-keto esters (Fig. 14)

appears to provide a powerful tool for stereoselective organic synthesis, as described above. In the catalytic cycle, the combination of the chiral Ru–H species and substrate creates four possible diastereomeric transition states in the stereo-determining step, where one of them is selected by the stereochemical characteristics of both counterparts. In all cases so far tested, the absolute configuration of the hydroxyl-bearing stereogenic center is controlled by the chirality of BINAP, while the *anti*/*syn* or *threo*/*erythro*[90] relative configuration is determined by the structures of the substrates. The preference can be reasonably understood by considering the sense of intermolecular asymmetric induction caused by the chiral catalyst and that of intramolecular asymmetric induction based on the skeleton and functionality of the substrate. This is a time-independent stereochemical issue of the chemical system. However, crucially important to secure the inherent stereoselectivity is the acquisition of proper kinetic parameters which rely on the reaction conditions. The general mathematical expressions shed light on the dynamic aspects, thereby suggesting a way to approach the ideal situation. Table 3 lists the quantitative parameters of the stereoselectivities in the BINAP–Ru catalyzed hydrogenation that act as useful diagnostic indicators.

First, the reaction of the seven-membered ketone **5** giving (*R*,*R*)-**8** as the most abundant product is chosen as a model (Fig. 17). The hydrogenation was performed in dichloromethane at 50 °C or in methanol at 25 °C under 100 atm of hydrogen.[45,78] Figure 18 illustrates the changes in the ee's of the major alcohol (*R*,*R*)-**8** and the first minor alcohol (*S*,*R*)-**8**, *anti* diastereoselectivity, and the composition of the major alcohol (*R*,*R*)-**8** in the whole product (SEL) as a function of the conversion of **5**. The computer-generated curves (lines) based on the parameters of Fig. 17 and Entries 1 and 2 in Table 3 predict a decrease in the ee of (*R*,*R*)-**8**, and an enhancement in the ee of (*S*,*R*)-**8**, which are in good agreement with the experimental observations (dots). The change in the SEL value also fits well. In methanol, a standard solvent for the hydrogenation, (*R*)-**5** reacts ca. six-times faster than the *S* enantiomer, and ee_{RR} is kept high throughout the reaction from 98.4 to 94.6%. Unfortunately, however, the ultimate diastereoselectivity, *anti*: *syn*, is 58 : 42, and SEL^{100} is only 57% (Entry 2). This is due to the requisite stereoinversion of (*S*)-**5** being four-times slower relative to its hydrogenation. By changing the solvent from methanol to dichloromethane (Entry 1), this ratio is improved by a factor of 18; now, the inversion is four-times faster than the hydrogenation. As a consequence, the overall efficiency is enhanced to lead to an *anti*: *syn* ratio of 87 : 13 and SEL^{100} of 82%. Although both the stereoinversion and hydrogenation of **5** occurs more facilely in methanol, a higher *relative rate*, k_{inv}/k_{slow}, is secured in dichloromethane.[104]

The kinetic factors are sensitive to any structural variation of the substrate. The lower analogue, 2-(methoxycarbonyl)cyclopentanone (**7**), behaves somewhat differently (Entry 3).[45] Even in methanol, the stereoinversion of the five-membered ketone occurs three-times faster than the hydrogenation of the *S* enantiomer. The enantiomers are differentiated by a factor of 12. Consequently, the reaction gives an *R*,*R* product with 92% initial and 82% final selectivity. The high SEL^0 is a result of the combined effect of the catalyst and substrate control. The SEL^{100} value of the reaction in dichloromethane was 94.5%.

The hydrogenation of Fig. 11 also works better in dichloromethane than in methanol.[45] The desired (*S*,*R*)-**31** is formed selectively by the hydrogenation of racemic **30** with (*R*)-BINAP–Ru catalyst in dichloromethane at 50 °C at 100 atm[78] (Fig. 19). The stereoselectivity is consistently high from the beginning (% SEL^0 = 93.8) to the end of the reaction (% SEL^{100} = 93.4) (Entry 4). The quantitative analysis indicates that (*S*)-**30** is hydrogenated, giving (*S*,*R*)-**31**, 15-times faster than the *R* enantiomer is, and that the slow-reacting (*R*)-**30** also forms the same product because it is inverted to the *S* enantiomer 92-times faster than being hydrogenated. When (*R*)-BINAP in the catalyst is replaced by bulkier (*R*)-3,5-xylylBINAP,[105] the *syn* selectivity as well as the k_{fast}/k_{slow} value are improved to some extent, resulting in SEL^0 and SEL^{100} of up to 96% (Entry 5). When the reaction is conducted in methanol, the diastereoselectivity is drastically reduced to result in a 1 : 1 mixture of (*S*,*R*)-**31** in 93% ee and (*R*,*R*)-**31** in 97% ee (Entry 6). SEL^0 and SEL^{100} are equally low, 48%. This is due to the comparable reactivities of enantiomeric **30** in this solvent, though the reason remains unknown.

The hydrogenation of the racemic ketone **34** to the desired (*R*,*S*)-**35** (Fig. 20) is best effected in methanol at 25 °C and at 4 atm;[67,78] the use of dichloromethane forms the debromination product in a considerable amount. The reactivity and selectivity are little influ-

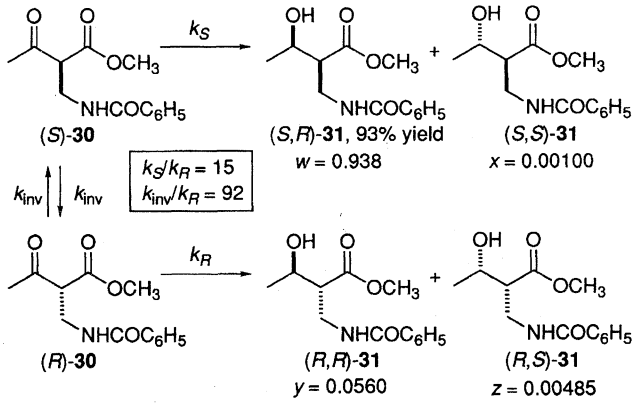


Fig. 19. Hydrogenation of methyl 2-(benzamidomethyl)-3-oxobutanoate (**30**) (0.2 mol dm^{-3}) catalyzed by (*R*)-BINAP–Ru complex (1.3 mmol dm^{-3}) in dichloromethane at 100 atm at 50 °C for 40 h.

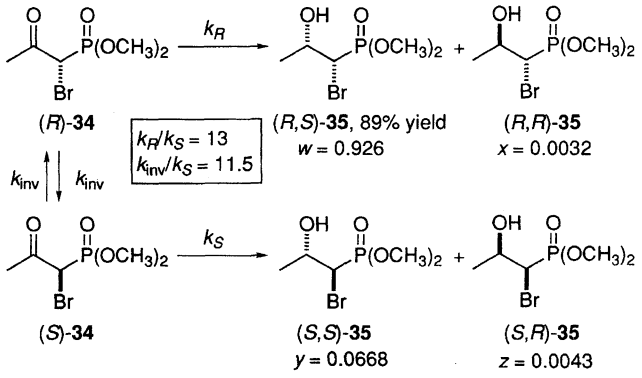


Fig. 20. Hydrogenation of dimethyl 1-bromo-2-oxopropylphosphonate (**34**) (0.34 mol dm^{-3}) catalyzed by (*S*)-BINAP–Ru complex (0.18 mmol dm^{-3}) in methanol at 4 atm at 25 °C for 100 h.

enced by the hydrogen pressure. The (*S*)-BINAP–Ru catalyst kinetically differentiates between (*R*)- and (*S*)-**34** by a factor of 13, where a satisfactory k_{inv}/k_{slow} value, up to 11.5, is obtainable by conducting the reaction with rather low substrate (0.34 mol dm^{-3}) and catalyst (0.18 mmol dm^{-3}) concentrations (Entry 7). The inherent selectivities, $ee_P^0 = 0.991$ and $D^0 = 0.930$, are well kept until the completion of the reaction, giving an SEL^{100} of 89%. When the catalyst concentration is increased four-fold, k_{inv}/k_{slow} is reduced to 2.8 to afford SEL^{100} of 82% (Entry 8).

Thus, high intrinsic stereoselectivities, such as ee_P^0 and D^0, are prerequisites to accomplish a stereoselective synthesis utilizing in situ racemization of substrate enantiomers (Figs. 2 and 3). These indexes are primarily based on the structural features of the chemical or biological reaction system. When the degree of stereoselection is substantially depressed during the late stage of the reaction, one should search for proper kinetic conditions in order to secure the original selectivities. The efficacy is particularly sensitive to the k_{inv}/k_{slow} ratio. The overall selectivities could certainly be improved by choosing a suitable solvent, temperature, concentrations and/or ratios of a substrate, reactant, and catalyst.

Conclusion

The second-order stereoselective synthesis via the dynamic kinetic resolution of chirally unstable racemic substances presents a viable strategy for access to chiral compounds of high enantiomeric purity. The utility is apparent from the examples given in Tables 1 and 2. Suitable three-dimensional elements of a chiral catalyst and substrate are imperative issues to accomplish an efficient asymmetric synthesis. In addition, as repeatedly stated earlier, a satisfactory overall chiral efficiency can be secured by appropriate kinetic factors, particularly the relative ease of the racemization and reaction. So far, the optimum situation giving satisfactory selectivity has been sought by a trial-and-error approach. In this context, the present appraisal system based on mathematical formulation and graphic display is of great help in finding the ideal conditions for stereoselective synthesis. The validity of this approach has been demonstrated by a correlation of the experimental and simulated results, as illustrated graphically.

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102) This is important. For enantiomer recognition of chiral catalysts, see: R. Noyori and M. Kitamura, *Angew. Chem., Int. Ed. Engl.*, **30**, 49 (1991).

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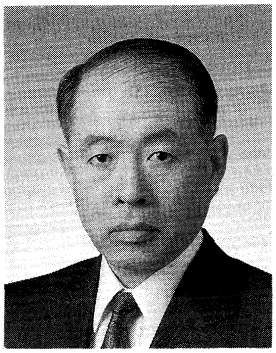
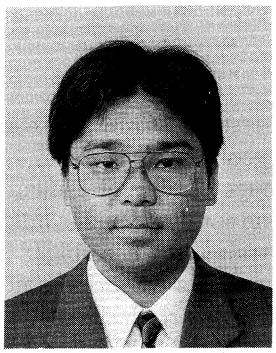
104) As the reaction proceeds, the β-keto ester is consumed and the polar β-hydroxy ester is formed, thereby causing a gradual change in the reaction conditions. Such effects are reflected in the kinetic and stereochemical parameters in this mathematical treatment, displaying a good fit of the computer simulation with the experimental findings. In practice, this factor did not overbalance the solvent effect. For example, an excellent overall stereoselectivity has been accomplished in the hydrogenation of racemic **5**, **7**, **24**, and **30** in dichloromethane (but not methanol), where the high inherent selectivity is well kept throughout the reaction.

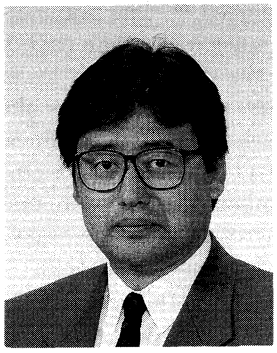
105) 3,5-XylylBINAP = 2,2′-bis[bis(3,5-dimethylphenyl)-phosphino]-1,1′-binaphthyl.



Ryoji Noyori, born in Kobe in 1938, completed his undergraduate study in 1961 and the Master's degree in 1963 at Kyoto University, and immediately became Research Associate in the laboratory of Professor H. Nozaki at the same university. He received his Ph. D. degree in 1967 and in the following year he was appointed Associate Professor in the Department of Chemistry at Nagoya University. Dr. Noyori spent a postdoctoral year with Professor E. J. Corey at Harvard University in 1969—1970, and shortly after returning to Nagoya was promoted to Professor, in 1972. He holds a joint appointment as Professor at Kyushu University and is directing the ERATO Molecular Catalysis Project (1991—1996) of the Research Development Corporation of Japan. His research interests have been mainly in the exploitation of new synthetic methods, particularly organometallic molecular catalysis, and their applications. His work has established truly efficient routes to numerous natural and unnatural compounds of theoretical and practical importance. Noyori's contribution has been recognized with many awards including the Chemical Society of Japan Award (1985), the Centenary Medal from the Royal Society of Chemistry (1989), the Naito Foundation Research Prize (1989), the Toray Science & Technology Prize (1990), the J. G. Kirkwood Award (1991), the Asahi Prize (1993), and the Tetrahedron Prize (1993).



Makoto Tokunaga was born in 1966 in Chiba and graduated from the Department of Chemistry, Nagoya University, in 1990. He continues his graduate research on the BINAP–Ru-catalyzed asymmetric hydrogenation of chirally labile β-keto esters via dynamic kinetic resolution. In 1993, he spent three months in Professor Faller's group at Yale University, where he worked on new chiral poisoning system in hydrogenation using BINAP–Ru complexes. He has been granted a Fellowship of the Japan Society for the Promotion of Science for Japanese Junior Scientists.



Masato Kitamura was born in Nagoya in 1956. He studied agricultural chemistry at Nagoya University where he received his Ph. D. degree on the total synthesis of maytansine, under the supervision of the late Professor T. Goto and Professor M. Isobe. After doing postdoctoral work with Professor G. Stork (Columbia University) on the synthesis of a veratrum alkaloid, he joined the Noyori group at Nagoya University as an Assistant Professor in 1983 and was appointed as an Associate Professor in 1990. He has studied the development of new catalytic asymmetric reactions directed toward efficient synthesis of biologically active compounds. He is a recipient of the Chemical Society of Japan Award for Young Chemists in 1989.