21
Diastereoselective Hydrogenation

Takamichi Yamagishi

21.1
Introduction

The stereochemical control of a reaction is a continuing challenge in the synthesis of complex organic compounds, especially those with stereogenic center(s) or molecular chirality. Homogeneous catalytic hydrogenation is a simple and widely applicable method for the construction of stereogenic centers and enantioselective hydrogenation using chiral transition metal complexes. It has undergone striking development during the past two decades [1]. In enantioselective hydrogenation, prochiral substrates with unsaturated linkages are converted to chiral compounds by using chirally modified transition metal complexes based on rhodium, iridium, ruthenium, cobalt, and lanthanide metals, etc. In enantioselective hydrogenation, stereochemical control is performed through the selection of one diastereomeric intermediate composed of a prochiral (achiral) substrate and a chiral metal complex. For this purpose, many chiral ligands (representatives of which include chiral diphosphine ligands) have been developed to realize the production of almost homochiral products with stereogenic center(s). In the hydrogenation of compounds with a stereogenic center, an achiral metal complex can induce a new stereogenic center selectively, by utilizing the steric factor of the stereogenic center in the substrate to afford compounds with two or more stereogenic centers. These diastereoselective hydrogenations also go through the selection of diastereomeric intermediates by differentiating the reaction face of unsaturated bonds. This is termed "intramolecular asymmetric induction".

21.2
Hydrogenation of Alkenes, Ketones, and Imines

In the hydrogenation of alkenes, rhodium–, ruthenium– and iridium–phosphine catalysts are typically used [2–4]. Rhodium–phosphine complexes, such as Wilkinson's catalyst, are effective for obtaining alkanes under atmospheric pres-

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Table 21.1 Diastereoselective hydrogenation of olefinic bonds.

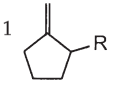
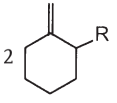
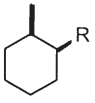
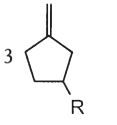
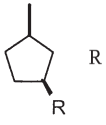
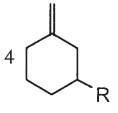
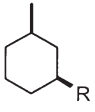
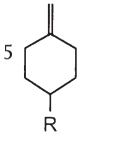
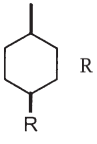
	Substrate	Major diastereomer		Catalyst	mol%	P_{H_2}	Solvent	Temp. [°C]	Diastereomeric ratio	TOF	Reference
1			R = *i*-Bu	Sm	10	1 atm	c-C_5H_{10}	r.t.	100:0	1.7	6
2			R = Me	Sm	3	1 atm	c-C_5H_{10}	–20	93:7	5.1	6
			R = *t*-Bu	Sm	5	1 atm	c-C_5H_{10}	r.t.	100:0	6.3	6
			R = Ph	Sm	5	1 atm	c-C_5H_{10}	50	100:0	6.4	6
			R = $(CH_2)_3NMe_2$	Sm	3	1 atm	c-C_5H_{10}	50	91:9	6.4	6
3			R = *n*-Bu	Sm	3	1 atm	c-C_5H_{10}	0	60:40	5.6	6
4			R = Me	Yb	3	1 atm	c-C_5H_{10}	–20	61:39	4.9	6
			R = Et	Yb	3	1 atm	c-C_5H_{10}	–20	73:27	5.3	6
5			R = *t*-Bu	Yb	3	1 atm	c-C_5H_{10}	–20	77:23	4.9	6
				Cat: $Cp^*_2LnCH(SiMe_3)_2$ (Ln = Sm, Yb)							

Table 21.1 (continued)

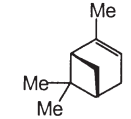
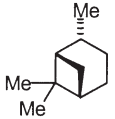
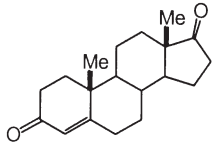
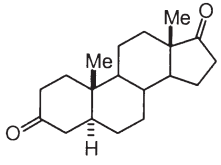
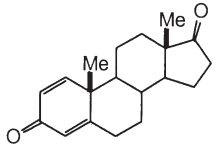
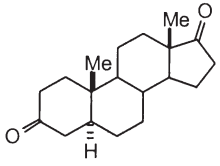
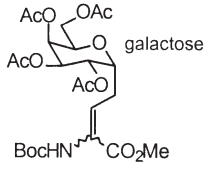
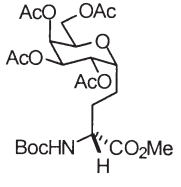
	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Temp. [°C]	Diastereomeric ratio	TOF	Reference
6	 (1*S*,5*S*)-α-pinene	 (1*S*,2*R*,5*S*)-*cis*-pinane	$Ru_2(CO)_4(OAc)_2(PPh_3)_2$	0.9	50 bar	THF	90	98.3:1.7	2.7	7
7			$[Ir(PCy_3)(py)(nbd)]^+$	20	1 atm	CH_2Cl_2	r.t.	100:0	0.87	8
8			$[Ir(PCy_3)(py)(nbd)]^+$	15	1 atm	CH_2Cl_2	r.t.	100:0	0.27	8
9			$[Rh(diphos\text{-}4)]^+$ $[Rh((R,R)\text{-Me-Duphos})]^+$ $[Rh((R,R)\text{-Et-Duphos})]^+$ $[Rh((R,R)\text{-Pr-Duphos})]^+$		90 psi 90 psi 90 psi 90 psi	MeOH MeOH MeOH MeOH		50:50 79:21 91:9 88.5:11.5		9

Table 21.1 (continued)

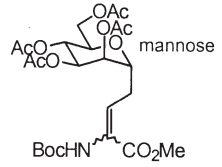
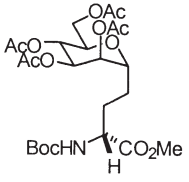
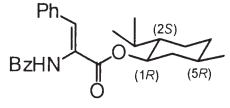
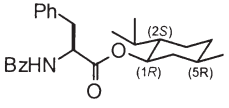
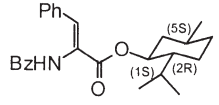
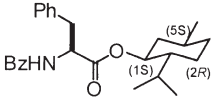
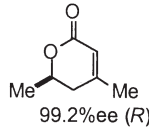
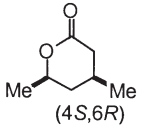
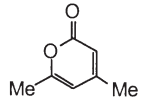
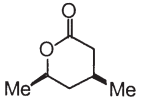
	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Temp. [°C]	Diastereomeric ratio	TOF	Reference
10			[Rh(diphos-4)]$^+$		90 psi	MeOH		50:50		9
			[Rh((*R*,*R*)-Me-Duphos)]$^+$		90 psi	MeOH		87:13		
			[Rh((*R*,*R*)-Et-Duphos)]$^+$		90 psi	MeOH		>97.5:2.5		
			[Rh((*R*,*R*)-Pr-Duphos)]$^+$		90 psi	MeOH		>97.5:2.5		
11			[Rh(Ph-β-glup-OH)]$^+$	1	0.1 MPa	MeOH		96.3:3.7		10
			[Rh(Ph-β-glup-OH)]$^+$	1	0.1 MPa	benzene		91:9		
			[Rh(Me-α-glu)]$^+$	1	0.1 MPa	acetone		86:14		
			[Rh(Me-α-glu)]$^+$	1	0.1 MPa	benzene		75:25		
12			[Rh(Ph-β-glup-OH)]$^+$	1	0.1 MPa	MeOH		97.4:2.6		10
			[Rh(Ph-β-glup-OH)]$^+$	1	0.1 MPa	benzene		79:21		
			[Rh(Me-α-glu)]$^+$	1	0.1 MPa	MeOH		66:34		
			[Rh(Me-α-glu)]$^+$	1	0.1 MPa	benzene		14:86		
13	 99.2%ee (*R*)	 (4*S*,6*R*)	$Ru(OAc)_2$((*S*)-3,5-xylyl-biphep)	0.2	60 bar	*i*-PrOH		80:20		11
14			$Ru(OAc)_2$((*S*)-3,5-xylyl-biphep)	0.2	60 bar	*i*-PrOH		92:8	25	11

Table 21.2 Diastereoselective hydrogenation of ketones and imines.

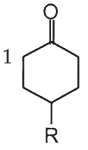
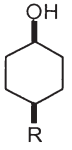
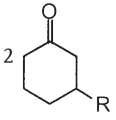
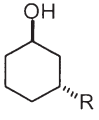
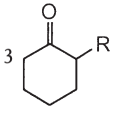
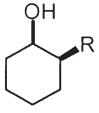
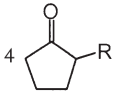
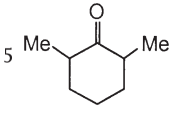
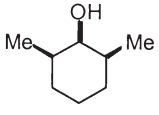
	Substrate	Major diastereomer		Catalyst	mol%	P_{H_2}	Solvent	Temp. [°C]	Diastereo-selectivity	TOF	Reference
1			R = Me	Ru	0.2	4 atm	*i*-PrOH	28	92:8	485	12
			R = Ph	Ru	0.2	4 atm	*i*-PrOH	28	96:4	500	12
			R = *t*-Bu	Ru	0.2	4 atm	*i*-PrOH	28	98.4:1.6	500	12
2			R = Me	Ru	0.2	4 atm	*i*-PrOH	28	96:4	500	12
3			R = Me	Ru	0.2	4 atm	*i*-PrOH	28	98:2	475	12
			R = *t*-Bu	Ru	0.2	4 atm	*i*-PrOH	28	>99.8:0.2	500	12
4			R = Me	Ru	0.2	4 atm	*i*-PrOH	28	99:1	500	12
5				Ru	0.2	4 atm	*i*-PrOH	28	98.7: 1.1:0.2		12

Table 21.2 (continued)

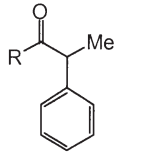
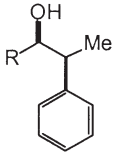
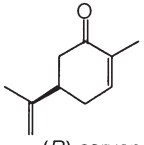
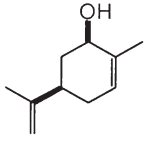
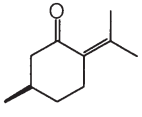
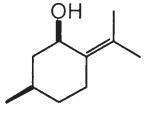
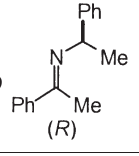
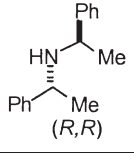
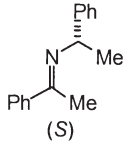
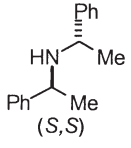
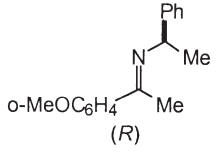
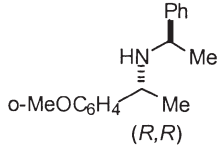
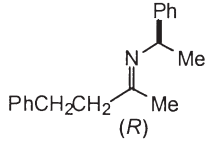
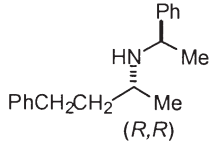
Substrate	Major diastereomer		Catalyst	mol%	P_{H_2}	Solvent	Temp. [°C]	Diastereo-selectivity	TOF	Reference
6 	 *syn*	R=Me	Ru-a	0.2	4 atm	*i*-PrOH	28	96:4		12
		R=Me	Ru-b	0.2	4 atm	*i*-PrOH	28	95:5		12
		R=Me	Ru	0.2	4 atm	*i*-PrOH	28	86:14	480	12
		R=*n*-Bu	Ru	0.2	4 atm	*i*-PrOH	28	93:7	480	12
		R=Ph	Ru	0.2	4 atm	*i*-PrOH	28	98:2	480	12
7  (*R*)-carvone		Ru		0.2	4 atm	*i*-PrOH	28	81:19	66.4	13
		$RuCl_2$((*S*)-binap)(dmf)m-(*R*,*R*)-DPEN-KOH/*i*-PrOH								
				0.2	4 atm	*i*-PrOH	28	100:0	143	13
		$RuCl_2$((*R*)-binap)(dmf)m-(*S*,*S*)-DPEN-KOH/*i*-PrOH								
				0.2	8 atm	*i*-PrOH	28	34:66	29.4	13
8  (*R*)-pulegone		$RuCl_2$((*S*)-binap)(dmf)m-(*S*,*S*)-DPEN-KOH/*i*-PrOH								
				0.4	8 atm	*i*-PrOH	28	98:2	15.1	13
		$RuCl_2$((*R*)-binap)(dmf)m-(*R*,*R*)-DPEN-KOH/*i*-PrOH								
				0.4	8 atm	*i*-PrOH	28	95:5	14	13
9  (*R*)	 (*R*,*R*)	[RhCl(diphos-3)]Cl		2	1000 psi	MeOH	r.t.	91:9		14
		[RhCl((*S*,*S*)-bdpp)]Cl		2	1000 psi	MeOH	r.t.	99.7:0.3		
		[RhCl((–)-diop]Cl		2	1000 psi	MeOH	r.t.	93:7		

Table 21.2 (continued)

	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Temp. [°C]	Diastereo-selectivity	TOF	Reference
10	 (*S*)	 (*S,S*)	[RhCl((*S,S*)-bdpp)]Cl	2	1000 psi	MeOH	r.t.	93.8:6.2		14
11	 (*R*)	 (*R,R*)	[RhCl((*S,S*)-bdpp)]Cl	2	1000 psi	MeOH	r.t.	98.1:1.9		14
12	 (*R*)	 (*R,R*)	[RhCl(diphos-3)]Cl [RhCl((*S,S*)-bdpp)]Cl	2 2	1000 psi 1000 psi	MeOH MeOH	r.t. r.t.	67:33 84:16		 14

Ru = $RuCl_2(PPh_3)_3$-EN-KOH; Ru-a = $RuCl_2(P(C_6H_4\text{-}p\text{-}OMe)_3)_3$-EN-KOH; Ru-b = $RuCl_2(P(C_6H_4\text{-}p\text{-}Me)_3)_3$-EN-KOH

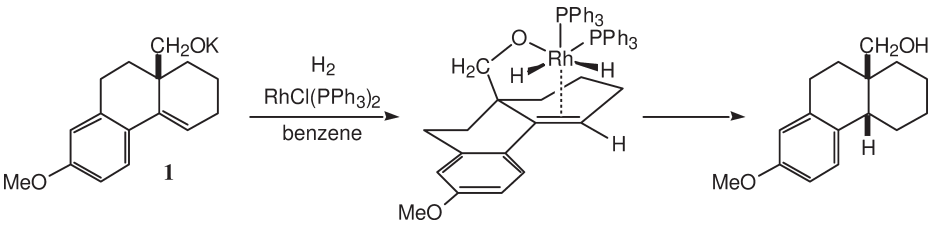
sure. The reactivity of rhodium complexes in homogeneous hydrogenation is sensitive to the degree of substitution on the olefinic bond, and trisubstituted or tetrasubstituted alkenes are intact in the hydrogenation, whereas iridium catalysts can hydrogenate the multi-substituted olefins under atmospheric hydrogen pressure. The unreactivity of trisubstituted alkenes towards rhodium complexes is overcome by increasing the hydrogen pressure, and the selectivity is comparable to (or a little better than) that obtained with iridium catalysts under atmospheric pressure [5]. The results of the hydrogenation of alkenes with lanthanide, ruthenium and iridium catalysts are listed in Table 21.1 [6–8]. In these reductions, the catalyst approaches the face of the double bond from the less-hindered side, and selection of the diastereoface of the substrate is straightforward when the stereogenic center is disposed adjacent to the double bond [6]. In the hydrogenation of double bonds in steroidal compounds, diastereoselectivity induced by iridium catalysts is very high [8]. In the reduction of dehydroamino acid derivatives with a chiral unit, an achiral rhodium catalyst resulted in stereorandom products (Table 21.1, entries 9 and 10) [9]. In the reaction of pyrone, the hydrogenation does not stop at the dihydropyrone stage, and *cis*-lactone is obtained in high diastereoselectivity, whereas hydrogenation of (*R*)-dihydropyrone afforded *cis*-lactone in lower diastereoselectivity, suggesting the complex character of the second hydrogenation step (Table 21.1, entries 13 and 14) [11]. Ruthenium–phosphine complexes combined with a diamine ligand effectively reduced ketones with a stereogenic center, and high diastereoselectivities are obtained (Table 21.2, entries 1–6) [12, 13]. The apparent effect of an adjacent stereogenic center was also observed in the reduction of imines [14]. For high stereoinduction, the proximity of the aromatic ring to the C=N bond seems to be essential.

21.3
Substrate-Directive Diastereoselective Hydrogenation

21.3.1
Hydrogenation of Cyclic Alcohols with Endo- or Exo-Cyclic Olefinic Bond

In the diastereoselective hydrogenation of olefinic, keto or imino double bonds, enhanced diastereoface differentiation will be possible by utilizing the interaction of functional groups in the substrates with the metal or with the ligand of the complex. Heteroatom(s) in the functional group would ligate to the metal and serve to fix the coordination mode of the substrate onto the catalyst. The key factor in the enantioselective hydrogenation of dehydroamino acids and esters is the formation of the rhodium–enamide chelate complex in which olefinic and amidocarbonyl units ligate to the metal [15]. Also in the diastereoselective hydrogenation, chelation of the substrate would serve to control the course of the hydrogenation. This potentiality of functional group-directed hydrogenation was first disclosed by Thompson and McPherson in 1974. In the hydrogenation

of a cyclic homoallyl alcohol derivative by $RhCl(PPh_3)_3$, the reaction did not even proceed under forced conditions (100 psi at 50 °C), but the substrate was hydrogenated by converting the alcohol to the potassium alkoxide **1** to afford the *cis*-product predominantly [Eq. (1)] [16].



(1)

It was proposed that the chloride ion is displaced by the alkoxide ion from the coordination sphere of the dihydride complex, while delivery of the hydride to the unsaturated bond is controlled to afford the *cis*-product. In the case of the alcohol form, the chloride ion is not displaced, and the substrate is strongly resistant to hydrogenation by $RhCl(PPh_3)_3$. The heteroatom-directive hydrogenation would generally require vacant sites on the metal complex for the binding of H_2, the olefin unit and the directing heteroatom to the metal under hydrogenation conditions; thus, an active catalyst would be of 12-electron structure. Cationic [Rh(diphosphine)(cod)]$^+$ complex and cationic iridium complex (e.g., [Ir(PCy_3)(py)(nbd)]$^+$: Crabtree's catalyst [18]) and ruthenium complexes (e.g., Ru(binap)$(OAc)_2$) could hydrogenate the olefinic substrate with a directing heteroatom moiety to cause diastereoselective hydrogenation. Using [Rh(diphosphine)(cod)]$^+$ or [Ir(PCy_3)(py)(nbd)]$^+$ complexes, coordinating dienes are easily reduced by treatment with H_2, and 12-electron species are easily formed in a non-coordinating solvent such as dichloromethane (DCM). Brown reported the selective hydrogenation of acyclic allylic alcohols to produce chiral acyclic alcohols diastereoselectively using [Rh(diphos-4)]$^+$ catalyst in 1982 [19, 20]. Crabtree and Stork reported the highly diastereoselective hydrogenation of diverse types of cyclic alcohols in 1983 (allyl and homoallyl alcohols), using the cationic iridium complex ([Ir(PCy_3)(py)(nbd)]PF_6: Ir$^+$) [21, 22]. The data provided in Tables 21.3, 21.4 and 21.5 indicate the hydrogenation of diverse types of cyclic allylic and homoallylic alcohols.

In these reactions, the major diastereomer is formed by the addition of hydrogen *syn* to the hydroxyl group in the substrate. The cationic iridium catalyst [Ir(PCy_3)(py)(nbd)]$^+$ is very effective in hydroxy-directive hydrogenation of cyclic alcohols to afford high diastereoselectivity, even in the case of bishomoallyl alcohols (Table 21.4, entries 10–13) [5, 34, 35]. An intermediary dihydride species is not observed in the case of rhodium complexes, but iridium dihydride species are observed and the interaction of the hydroxyl unit of an unsaturated alcohol with iridium is detected spectrometrically through the presence of diastereotopic hydrides using NMR spectroscopy [21].

Table 21.3 Diastereoselective hydrogenation of cyclic allyl alcohols.

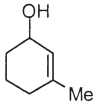
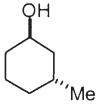
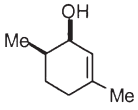
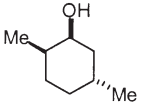
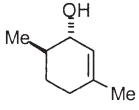
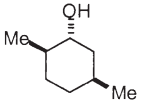
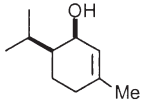
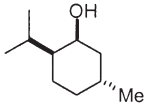
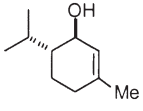
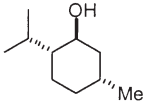
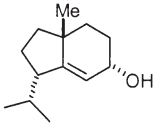
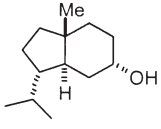
	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Temp. [°C]	Diastereomeric ratio	TOF	Reference(s)
1			Rh^+	3.5	375 psi			290:1	28	23
			Ir^+	20	15 psi	CH_2Cl_2	r.t.	98.5:1.5	>2.5	22
				20	15 psi	CH_2Cl_2	r.t.	98:2	>2.5	24
				2.5	15 psi	CH_2Cl_2	r.t.	140 ~ 150:1	20, 80	24, 25
2			Ir^+	2.5	1 atm	CH_2Cl_2	r.t.	99:1	80	25
3			Ir^+	2.5	1 atm	CH_2Cl_2	r.t.	940:1	80	25
4			Ir^+	2.5	1 atm	CH_2Cl_2	r.t.	98.5:1.5	80	25
5			Ir^+	2.5	1 atm	CH_2Cl_2	r.t.	96:4	80	25
6			Rh^+	5	800 psi	THF		98.6:1.4		5
			Ir^+	30	1 atm	CH_2Cl_2		highly selective		26

Table 21.3 (continued)

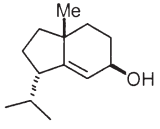
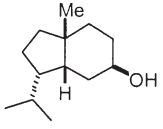
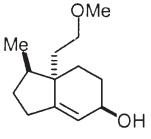
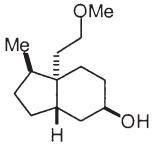
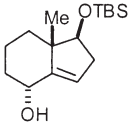
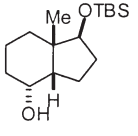
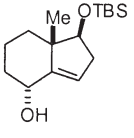
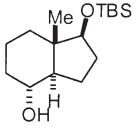
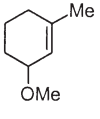
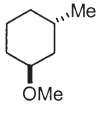
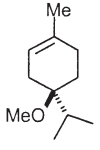
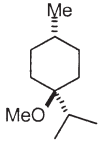
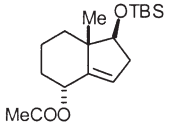
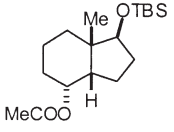
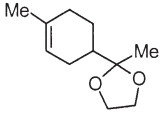
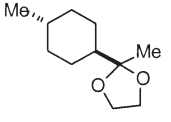
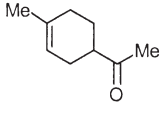
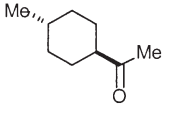
	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Temp. [°C]	Diastereomeric ratio	TOF	Reference(s)
7			Ir^+	20	1 atm	CH_2Cl_2		100:0		26
8			Rh^+	5	55 atm	THF		95:5	8	27
9			Ir^+	20	40 psi	CH_2Cl_2		highly selective	0.16	28
10			Rh	25	40 psi	benzene		75:25	0.15	28
11			Ir^+	2.5	1 atm	CH_2Cl_2		>99.9:0.1	80	25

Table 21.3 (continued)

	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Temp. [°C]	Diastereomeric ratio	TOF	Reference(s)
12			Ir^+	2.5	1 atm	CH_2Cl_2		>99.9:0.1	80	25
13			Ir^+	20	40 psi	CH_2Cl_2		100:0	0.13	28
14			Ir^+	2.5	15 psi	CH_2Cl_2		62:38	36	25
15			Ir^+	2.5	15 psi	CH_2Cl_2		99:1	80	25

$Rh = RhCl(PPh_3)_3$; $Rh^+ = [Rh(diphos\text{-}4)(cod)]^+$; $Ir^+ = [Ir(PCy_3)(py)(nbd)]^+$

Table 21.4 Diastereoselective hydrogenation of cyclic homoallyl and bishomoallyl alcohols.

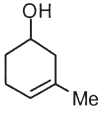
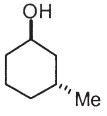
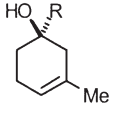
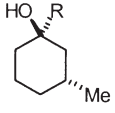
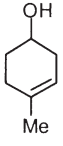
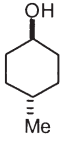
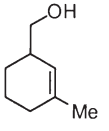
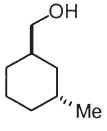
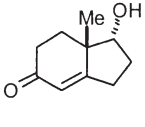
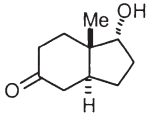
	Substrate	Major diastereomer		Catalyst	mol%	P_{H_2}	Solvent	Temp. [°C]	Diastereomeric ratio	TOF	Reference
1				Ir^+	20	15 psi	CH_2Cl_2	r.t.	96.5:3.5	>2.5	22
2			R = Me	Ir^+	20	15 psi	CH_2Cl_2	r.t.	>100:1	>2.5	22
			R = ^{i}Pr	Ir^+	2.3	1 atm	CH_2Cl_2	0	1000:1	28.7	21
3				Rh^+	10	640 psi	CH_2Cl_2	r.t.	98.5:1.5	10	5
				Ir^+	20	15 psi	CH_2Cl_2	r.t.	97:3	>2.5	24
					2.5	15 psi	CH_2Cl_2	r.t.	98.1:1.9	20	24
4				Ir^+	20	15 psi	CH_2Cl_2	r.t.	86:14	>2.5	22
5				Ir^+	20	15 psi	CH_2Cl_2		96:4	<0.21	22

Table 21.4 (continued)

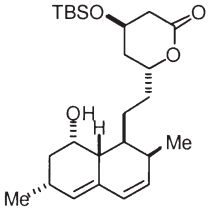
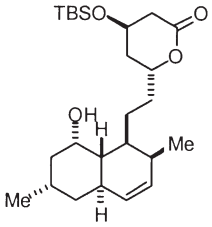
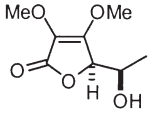
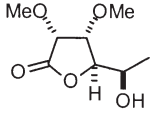
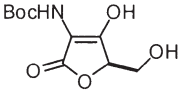
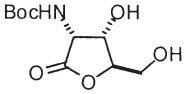
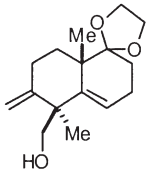
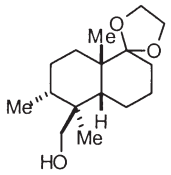
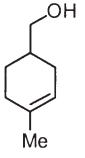
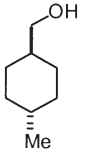
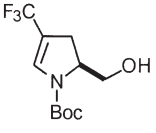
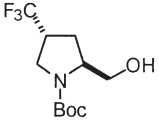
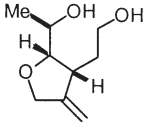
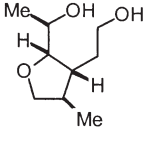
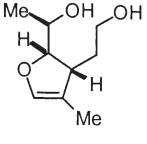
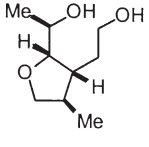
	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Temp. [°C]	Diastereomeric ratio	TOF	Reference
6			Ir^+	2.5	1 atm	CH_2Cl_2/ ^iPrOH		highly selective	1.9	30
7			Rh^+	20	1850 psi	CH_2Cl_2		100:0		31
8			Rh^+	20	130 atm	CH_2Cl_2	r.t.	91:9	0.25	32
9			Ir^+	0.11	1000 psi	CH_2Cl_2		100:0	6.3	33

Table 21.4 (continued)

	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Temp. [°C]	Diastereomeric ratio	TOF	Reference
10			Rh^+	10	1000 psi	CH_2Cl_2	r.t.	95:5	10	5
			Ir^+	20	15 psi	CH_2Cl_2	r.t.	96.2:3.8	>2.5	5
11			Ir^+	15	15 psi	CH_2Cl_2	r.t.	95:5		34
				2	15 psi	CH_2Cl_2	r.t.	99.4:0.6	12.5	34
12			Ir^+	1	15 psi	CH_2Cl_2		>99:1		35
			Rh^+	6		CH_2Cl_2		90:10		
			Rh	100		toluene		6:94		
13			Ir^+	0.5	15 psi	CH_2Cl_2		>99:1		35

$Rh = RhCl(PPh_3)_3$; $Rh^+ = [Rh(diphos\text{-}4)(cod)]^+$; $Ir^+ = [Ir(PCy_3)(py)(nbd)]^+$

Table 21.5 Diastereoselective hydrogenation of alcohols with exocyclic double bond.

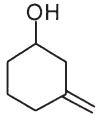
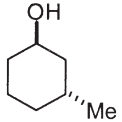
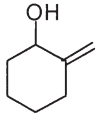
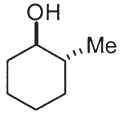
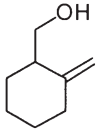
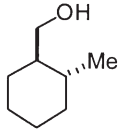
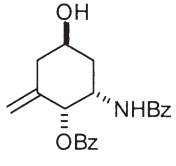
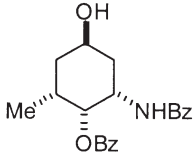
	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Temp. [°C]	Diastereomeric ratio	TOF	Reference
1			Rh^+	2	15 psi			>98:2		36
2			Rh^+ Rh^+	3.5 2	500 psi 15 psi			75:25 45:55		23 36
3			Rh^+	2	15 psi			47:53		36
4			Rh^+ Ir^+	35 17.5	15 psi 15 psi	CH_2Cl_2 CH_2Cl_2	r.t. r.t.	100:0 72:28	0.12	37 37

Table 21.5 (continued)

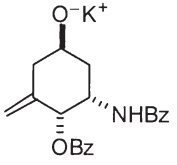
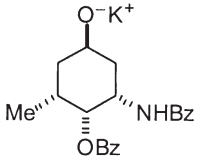
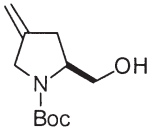
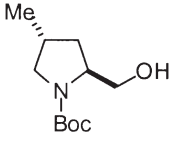
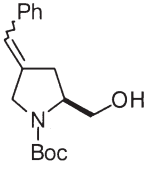
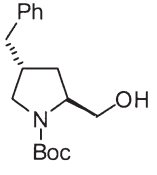
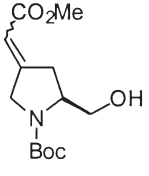
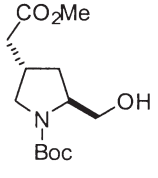
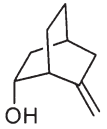
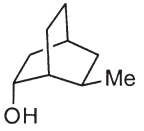
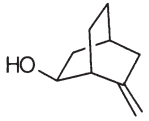
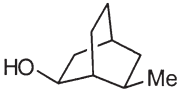
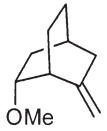
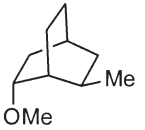
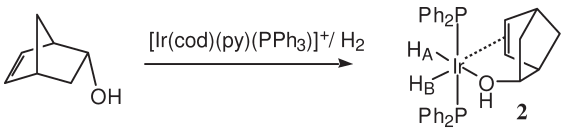
	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Temp. [°C]	Diastereomeric ratio	TOF	Reference
5			Rh	100 3.6	15 psi 15 psi	CH_2Cl_2 CH_2Cl_2	r.t. r.t.	95:5 no reaction		37 37
6			Ir^+	3	15 psi	CH_2Cl_2	r.t.	>97.5:2.5	1.67	38
7			Ir^+	3	15 psi	CH_2Cl_2	r.t.	>97.5:2.5	1.7	38
8			Ir^+	3	15 psi	CH_2Cl_2	r.t.	94:6	1.85	38

Table 21.5 (continued)

	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Temp. [°C]	Diastereomeric ratio	TOF	Reference
9			Rh^+	2	15 psi	CH_2Cl_2		95:5	10	29
			Ir^+	2	15 psi	CH_2Cl_2		99.7:0.3	1500	39
						CH_2Cl_2		99.7:0.3	6000	29
10			Ir^+	2	15 psi	CH_2Cl_2		55:45	16.7	29
11			Rh^+	2	15 psi	CH_2Cl_2		86.5:14.5	600	29
			Ir^+	2	15 psi	CH_2Cl_2		97.4:2.6	1000	29

Rh = $RhCl(PPh_3)_3$; Rh^+ = $[Rh(diphos\text{-}4)(cod)]^+$; Ir^+ = $[Ir(PCy_3)(py)(nbd)]^+$



(2)

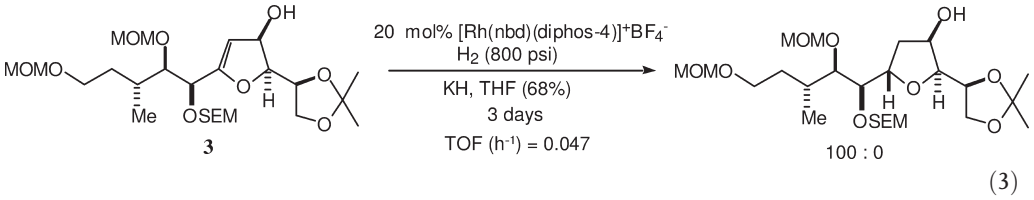
$\delta(H_A) = -29.4$, $\delta(H_B) = -9.6$ ppm

Thus, coordination of the OH-group controls the selection of the face to be reduced, and in some cases may also induce higher reactivity compared with the simple olefins not bearing OH-groups. Even in the presence of exceptional levels of steric congestion which are disposed to override the directivity of hydroxyl group, the addition of hydrogen occurs predominantly on the diastereoface bearing the hydroxyl group (Table 21.3, entry 6) [5, 26]. The concentration of the iridium catalyst strongly affects the stereoselectivity: a low concentration of the iridium complex is necessary to effect high diastereoselectivity; the decreases in stereoselectivity at a higher iridium concentration is ascribed to the formation of more than one complex, including trinuclear cluster complexes [24] in solution (Table 21.3, entry 1 and Table 21.4, entries 2 and 3). Cationic rhodium complexes such as $[Rh(nbd)(diphos\text{-}4)]^+$ are also effective for directive-hydrogenation of cyclic unsaturated alcohols, although in terms of selectivity they are somewhat inferior to the iridium catalysts. In entry 9 of Table 21.3, an attempt to obtain the *trans*-hydroindane product using a cationic iridium catalyst (Crabtree's catalyst) unexpectedly produced *cis*-hydroindanol highly selectively [28]. This suggests direction by the ether linkage of the TBSO unit. In contrast, hydrogenation by 25 mol.% of Wilkinson's catalyst in benzene (entry 10) afforded the *trans*-hydroindanol as a 3 : 1 mixture by the approach of rhodium catalyst from the less-hindered face of the double bond [28]. Even an exocyclic hydroxyl group can direct high diastereoselectivity with a rhodium or iridium catalyst in entries 7 and 9 of Table 21.4 [31, 33], though in entry 8 the directivity of the hydroxyl group is depressed by competition with the carbamate unit [32]. The hydroxyl group in bishomoallyl type alcohols also serves to direct the hydrogenation course to afford high diastereoselectivity. In entries 10–13 of Table 21.4, a cationic iridium complex can induce high diastereoselectivity by adding hydrogen from the face bearing the hydroxyl group [5, 34, 35]. With the Wilkinson catalyst, however, the reversed diastereoselectivity was again observed by the approach of the complex from the less-hindered side of the double bond without interaction with a hydroxyl unit (Table 21.4, entry 12).

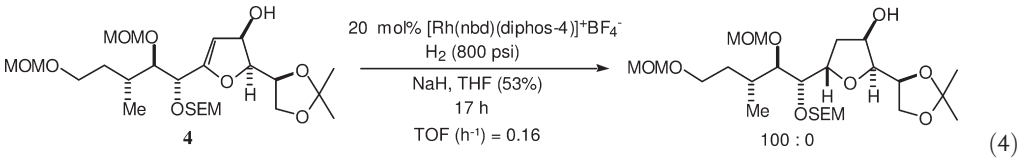
Cationic iridium and rhodium catalysts are also effective for the hydrogenation of exocyclic olefinic alcohols (see Table 21.5), except for 2-exomethylenecyclohexanol and 2-methylenecyclohexanemethanol (entries 2 and 3). In entry 4, a cationic rhodium catalyst gave a single product whilst a cationic iridium catalyst induced only modest selectivity (72 : 28).

This lowering of the selectivity may be attributed to competitive binding between the hydroxyl and amide groups to iridium [37]. In entries 6, 7 and 8, the directivity of the hydroxyl group at the bishomoallylic position effectively overrides the effect of the carbamate unit [38]. In the hydrogenation of methylenebi-

cyclo[2.2.2]octan-2-ol, the exo hydroxyl group does not serve as a directive group, and stereorandom hydrogenation proceeds contrary to the hydrogenation of methylenebicyclo[2.2.2]octan-2-ol with an endo hydroxyl group (entries 9 and 10) [29]. In entry 11 of Table 21.5, the methylenebicyclo[2.2.2]octane compound is hydrogenated in lower selectivity but at a higher rate than the parent alcohol with rhodium catalyst [29].



(3)



(4)

As exemplified by Thompson for the case of tricyclic alcohol **1** [Eq. (1)], alkoxide has a strong coordinative ability to the metal, and high diastereoselectivity is realized in spite of the presence of a proximal bulky substituent in dihydrofuran derivatives [Eqs. (3) and (4)] [17].

Other functional groups which have a heteroatom rather than a hydroxyl group capable of directing the hydrogenation include alkoxyl, alkoxycarbonyl, carboxylate, amide, carbamate, and sulfoxide. The alkoxy unit efficiently coordinates to cationic iridium or rhodium complexes, and high diastereoselectivity is induced in the reactions of cyclic substrates (Table 21.3, entries 11–13) [25, 28]. An acetal affords much lower selectivity than the corresponding unsaturated ketone (Table 21.3, entries 14 and 15) [25].

Table 21.6 indicates the hydrogenation results of substrates with ester and carboxyl functionalities. An ester functionality also serves well as a directive unit, and high selectivity is reported for β,γ-unsaturated esters with both rhodium and iridium catalysts (Table 21.6, entries 1 and 2) [40, 41]. Directivity of the alkoxycarbonyl unit of an γ,δ-unsaturated ester is slightly diminished (entry 3) [25, 40, 41], and an acyloxy unit in the homoallylic position does not direct apparent stereoselectivity (entry 4) [41]. In the Wilkinson catalyst, hydroxyl, ether, esters or amide units cannot displace chloride ion from the metal, but carboxylate – being a better nucleophile – may be able to replace the chloride ion. In the hydrogenation of β,γ-carboxylic acids (Table 21.6, entries 8 and 9), the carboxylates are generated *in situ* by the addition of triethylamine, and the hydrogenation proceeds cleanly under 60 psi. As a consequence, one diastereoisomer is formed predominantly with a high selectivity of more than 99% diastereomeric

Table 21.6 Diastereoselective hydrogenation of double bond in cyclic esters and carboxylic acids.

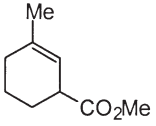
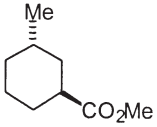
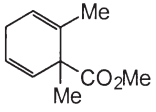
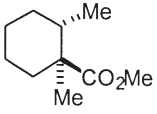
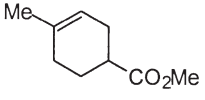
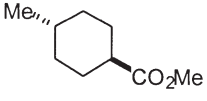
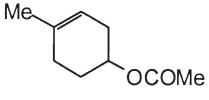
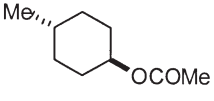
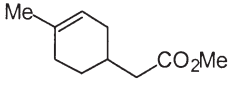
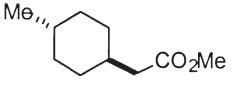
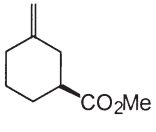
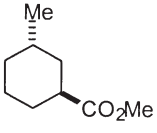
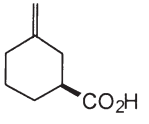
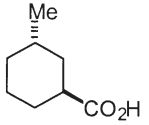
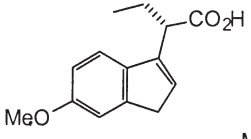
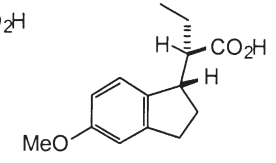
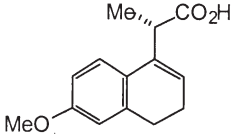
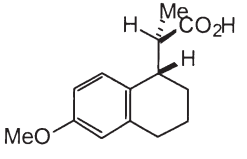
	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Temp. [°C]	Diastereomeric ratio	TOF	Reference
1			Rh^+	2	1 atm	CH_2Cl_2	r.t.	97:3	>1.8	40
			Ir^+	2	1 atm	CH_2Cl_2	r.t.	99.9:0.1	300	40
2			Ir^+	5	1 atm	CH_2Cl_2	r.t.	99:1	4.5 ~ 9	41
3			Rh^+	2	1 atm	CH_2Cl_2	r.t.	88:12	<0.23	40
			Ir^+	2	1 atm	CH_2Cl_2	r.t.	89:11	200	40
			Ir^+	2.5	1 atm	CH_2Cl_2	r.t.	95:5	77	25
			Ir^+	5	1 atm	CH_2Cl_2	r.t.	97.6:2.4	4.5–9	41
4			Ir^+	5	1 atm	CH_2Cl_2	r.t.	50:50		41
5			Ir^+	5	1 atm	CH_2Cl_2	r.t.	54.5:45.5		41
6			Rh^+	2	1 atm	CH_2Cl_2	r.t.	90:10	0.88	40
			Ir^+	2	1 atm	CH_2Cl_2	r.t.	81:19	300	40

Table 21.6 (continued)

	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Temp. [°C]	Diastereomeric ratio	TOF	Reference
7			Rh^+	2	1 atm	CH_2Cl_2	r.t.	50:50	<0.33	40
			Ir^+	2	1 atm	CH_2Cl_2	r.t.	88:12	8.3	40
8			Rh	5	60 psi	THF/EtOH(1/9) (1.5 eq TEA)		>99.5:0.5	1.7	42
			Rh	5	60 psi	THF/EtOH(1/9) (0 eq TEA)		94:6	1.0	42
9			Rh	5	60 psi	THF/EtOH(1/9) (1.5 eq TEA)		>99.5:0.5		42

$Rh = RhCl(PPh_3)_3$; $Rh^+ = [Rh(diphos\text{-}4)(cod)]^+$; $Ir^+ = [Ir(PCy_3)(py)(nbd)]^+$

excess (d.e.). The carboxylate anion binds to the rhodium complex, and discrimination of the diastereoface is caused by minimizing interaction of the stereogenic center with the peri-aromatic proton [42]. Even in the absence of amine, hydrogenation using the Wilkinson catalyst induces moderate reactivity and selectivity (88% d.e.) (entry 8), because part of the carboxylic acid undergoes dissociation to afford carboxylate in polar tetrahydrofuran (THF)/EtOH solution. In entry 7, the hydrogenation proceeds incompletely in DCM under the standard conditions. This implies the formation of inactive carboxylate complex in dichloromethane.

The amide group shows a prominent directivity in the hydrogenation of cyclic unsaturated amides by a cationic iridium catalyst, and much higher diastereoselectivity is realized than in the corresponding ester substrates (Table 21.7). In the case of β,γ-unsaturated bicyclic amide (entry 3), the stereoselectivity surpasses 1000 : 1 [41]. An increase of the distance between the amide carbonyl and olefinic bond causes little decrease in the selectivity (δ,ε-unsaturated amide, entry 6) compared with the case of the less-basic ester functionality (Table 21.6, entry 5).

In the case of cyclopentenyl carbamate in which a directive group is present at the homoallyl position, the cationic rhodium $[Rh(diphos\text{-}4)]^+$ or iridium $[Ir(PCy_3)(py)(nbd)]^+$ catalyst cannot interact with the carbamate carbonyl, and thus approaches the double bond from the less-hindered side. This affords a *cis*-product preferentially, whereas with the chiral rhodium–duphos catalyst, directivity of the carbamate unit is observed (Table 21.7, entry 7). The presence of a hydroxyl group at the allyl position induced hydroxy-directive hydrogenation, and higher diastereoselectivity was obtained (entry 8) [44].

21.3.2
Hydrogenation of Acyclic Allyl and Homoallyl Alcohols

The hydrogenation of acyclic allyl alcohols with a 1,1-disubstituted olefinic bond are listed as entries 1 to 5 of Table 21.8. The reduction of (α-hydroxyalkyl)acrylates proceeds stereoselectively with the cationic rhodium catalyst $[Rh(diphos\text{-}4)(nbd)]^+$, and 1,2-*anti*-compounds are obtained as the major product by the direction of the hydroxyl group. Under these reaction conditions, isomerization of the olefinic unit occurs to afford about 20% of the corresponding methyl ketone. If the isomerization occurs prior to the hydrogenation, diminished stereoselectivity would be observed, even if the individual reduction mode were to occur discriminately [5]. With a cationic iridium catalyst, the degree of isomerization is greater than with the rhodium catalyst, and the hydrogenation occurs with lower diastereoselectivity (Table 21.8, entries 5–7). This is in contrast to the high stereoinduction ability of iridium catalysts for cyclic unsaturated compounds, but the isomerization can be suppressed by increasing the hydrogen pressure. The concentration of iridium catalyst strongly affects the stereoselectivity, and at higher concentration stereorandom hydrogenation almost occurs

Table 21.7 Amido-directive diastereoselective hydrogenation.

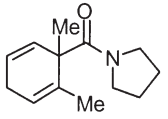
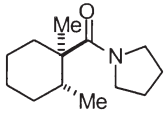
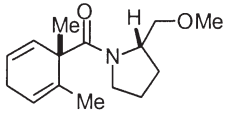
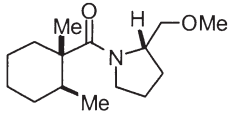
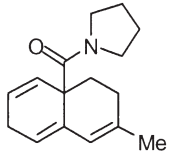
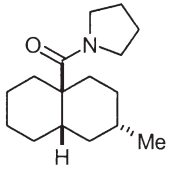
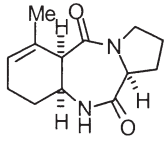
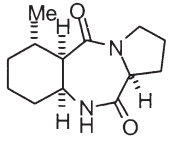
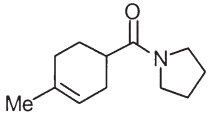
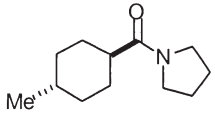
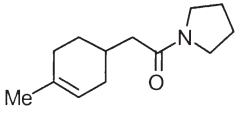
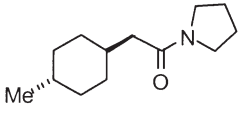
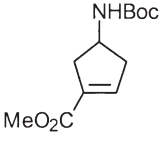
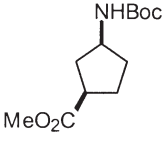
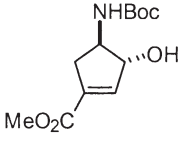
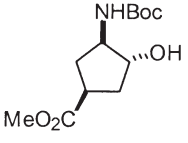
	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Diastereomeric ratio	TOF	Reference
1			Ir^+	5	1 atm	CH_2Cl_2	170:1	4 ~ 8	41
2			Ir^+	5	1 atm	CH_2Cl_2	530:1	4.5 ~ 9	41
3			Ir^+	5	1 atm	CH_2Cl_2	>1000:1	4.5 ~ 9	41
4			Ir^+ Ir^+	5 5	1 atm 1 atm	CH_2Cl_2 CH_2Cl_2	>99:1 >99:1	4.5 ~ 9 3.3	41 43
5			Ir^+	5	1 atm	CH_2Cl_2	130:1	4.5 ~ 9	41

Table 21.7 (continued)

	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Diastereomeric ratio	TOF	Reference
6			Ir^+	5	1 atm	CH_2Cl_2	>100:1	4.5 ~ 9	41
7			Ir^+	1	5 atm	CH_2Cl_2	92.5:7.5	7.1	44
			Rh^+	1	5 atm	MeOH	78.5:21.5	7.1	44
			[Rh((*R*,*R*)-Me-Duphos)]$^+$	1	5 atm	MeOH	20:80	7.1	44
			[Rh((*S*,*S*)-Me-Duphos)]$^+$	1	5 atm	MeOH	9:91	7.1	44
8			Ir^+	1	5 atm	CH_2Cl_2	97:3	7.1	44
			Rh^+	1	5 atm	MeOH	80:20	7.1	44
			[Rh((*R*,*R*)-Me-Duphos)]$^+$	1	5 atm	MeOH	4:96	7.1	44
			[Rh((*S*,*S*)-Me-Duphos)]$^+$	1	5 atm	MeOH	33.5:66.5	7.1	44

Rh^+ = [Rh(diphos-4)(cod)]$^+$; Ir^+ = [Ir(PCy_3)(py)(nbd)]$^+$

Table 21.8 Hydroxy-directed hydrogenation of acyclic allyl aclohols.

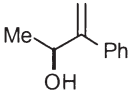
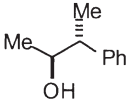
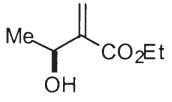
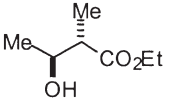
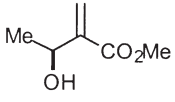
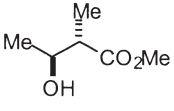
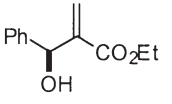
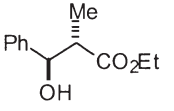
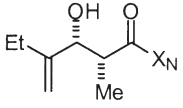
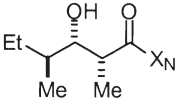
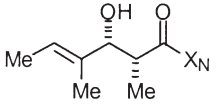
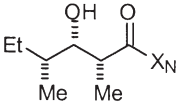
	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Temp. [°C]	Diastereomeric ratio	TOF	Reference
1			Rh^+	2	15 psi	CH_2Cl_2	0	97:3		19
2			Rh^+	1	15 psi	CH_2Cl_2		100:1	50	45
						MeOH		100:1	50	45
3			$Rh(OAc)_2$((*S*)-binap)		4 atm	MeOH	25	>23:1		46
			$Rh(OAc)_2$((*R*)-binap)		4 atm	MeOH	25	>23:1		46
4			Rh^+	1	15 psi	CH_2Cl_2	20	100:1	50	45
						MeOH	20	97.5:2.5		
5			Rh^+	17.5	640 psi	CH_2Cl_2	25	93:7	>2.8	5
			Ir^+	20	15 psi	CH_2Cl_2	25	57:43	>2.5	24
			Ir^+	2.5	15 psi	CH_2Cl_2	25	85:15	>20	24
6			Rh^+	17.5	640 psi	CH_2Cl_2	25	91:9	>2.8	5
			Ir^+	20	15 psi	CH_2Cl_2	25	43:57	>2.5	24
			Ir^+	2.5	15 psi	CH_2Cl_2	25	73:27	>20	24

Table 21.8 (continued)

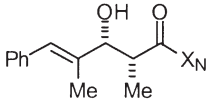
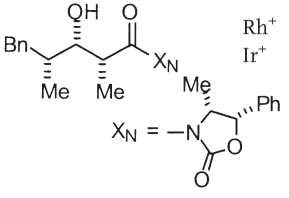
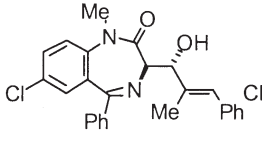
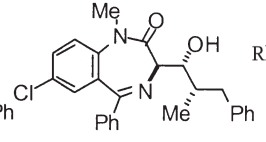
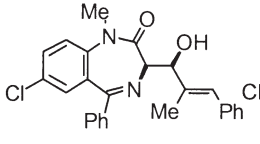
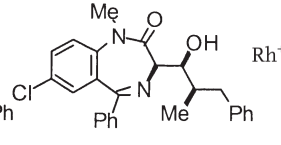
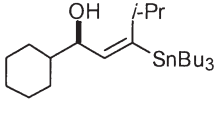
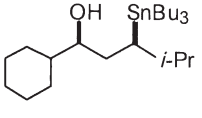
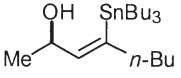
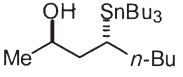
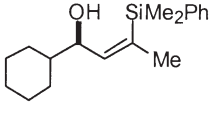
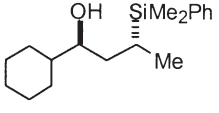
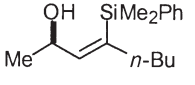
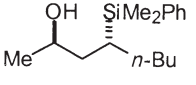
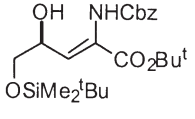
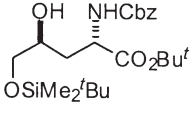
	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Temp. [°C]	Diastereomeric ratio	TOF	Reference
7			Rh^+ Ir^+	17.5 2.5	640 psi 15 psi	CH_2Cl_2 CH_2Cl_2	25 25	94:6 48:52	>2.8 <0.4	24 24
8			Rh^+	10	45 bar	CH_2Cl_2		75:25	1.1	47
9			Rh^+	10	45 bar	CH_2Cl_2		80:20	1.3	47
10			Rh^+	5	1500 psi	CH_2Cl_2	r.t.	300:1	0.47	48

Table 21.8 (continued)

	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Temp. [°C]	Diastereomeric ratio	TOF	Reference
11			Rh^+	5	1500 psi	CH_2Cl_2	r.t.	>100:1	0.2	48
12			Rh^+	5	1500 psi	CH_2Cl_2	r.t.	>500:1	0.4	48
13			Rh^+	5	1500 psi	CH_2Cl_2	r.t.	>500:1	0.4	48
14			[Rh((*R*,*R*)-dipamp)]$^+$	0.7	3 bar	MeOH		highly selective	11.8	49

Rh^+ = [Rh(diphos-4)(cod)]$^+$; Ir^+ = [Ir(PCy_3)(py)(nbd)]$^+$

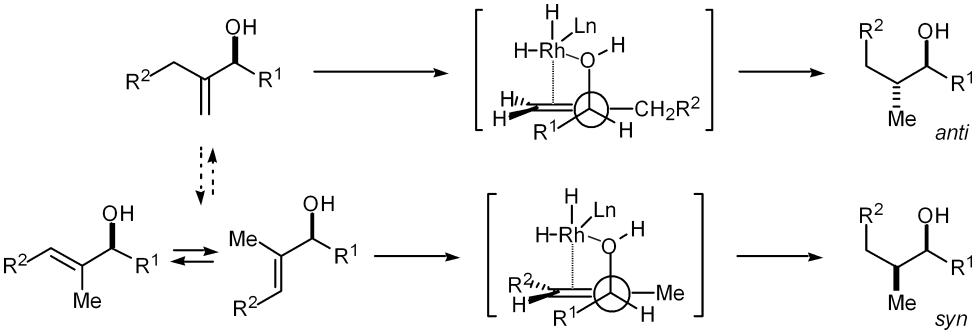
(Table 21.8, entries 5 and 6) [5, 24], similarly to the reduction of cyclic compounds.

The configuration of the product in diastereoselective hydrogenation – whether 1,2-*syn* or 1,2-*anti* – is related to the substitution pattern of the starting alkene. The allyl alcohol with a 1,1-disubstituted olefin unit affords the *anti*-product, while the *syn*-product is formed from the allyl alcohol with a trisubstituted olefinic bond (Table 21.8, entries 6–9). The complementarity in diastereoselective hydrogenation of di- and tri-substituted olefins may be rationalized based on the conformation analysis of the intermediary complex (Scheme 21.1) [23].

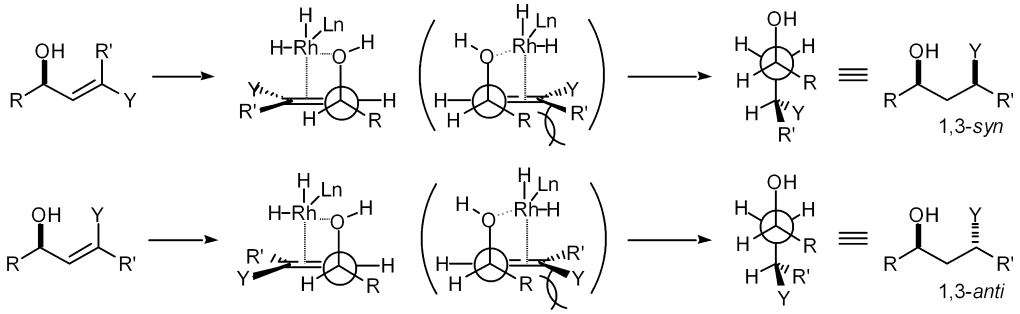
In entries 10–13 (Table 21.8) of trisubstituted alkenes, very high diastereoselectivity is realized by the use of a cationic rhodium catalyst under high hydrogen pressure, and the 1,3-*syn*- or 1,3-*anti*-configuration naturally corresponds to the (*E*)- or (*Z*)-geometry of the trisubstituted olefin unit [48, 49]. The facial selectivity is rationalized to be controlled by the A(1,3)-allylic strain at the intermediary complex stage (Scheme 21.2) [48].

Entries 8–13 in Table 21.9 illustrate the effect of S–O coordination on the hydrogenation of allyl alcohols. The hydrogenation of (*α*-hydroxyalkyl)vinyl sulfones follows the same stereochemical course as the corresponding acrylate via HO coordination (entries 8 and 9). However, the hydrogenation of (*α*-hydroxyalkyl)vinyl sulfoxides is directed by S–O coordination, which overrides the HO-participation in the stereochemical course (entries 10–13) [56]. The directing power of S–O may be limited to vinylic examples, as compounds having the S–O and double bond in an allylic relationship failed to reduce under the standard conditions.

The hydrogenation of acyclic homoallylic alcohols with a 1,1-disubstituted olefinic bond by cationic $[Rh(diphos\text{-}4)]^+$ catalyst proceeds in modest to moderate stereoselectivity, generally forming 1,3-*anti* compounds (Table 21.10, entries 1, 4 and 5), and the effect of the stereogenic center at the allylic position overrides the directivity of hydroxyl group. The 1,3-*syn* product is then observed though in poor selectivity (entry 3) [19, 57, 58]. Inspection of the hydrogenation prod-



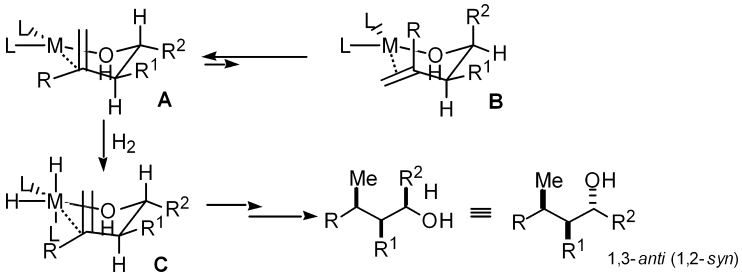
Scheme 21.1



Scheme 21.2

ucts indicates that the substituent at the allylic position dictates the stereochemistry to afford the 1,2-*syn* product preferentially. The observed stereochemistry in 1,1-disubstituted homoallylic alcohols can be explained by considering the conformational analysis of the alkene complexes (Scheme 21.3). In conformation A, unfavorable A(1,2) interactions between R and R^1 are minimized and through A and C the 1,3-*anti* product will be formed. In the case of homoallylic alcohols without an allylic substituent, the group at the homoallylic carbon will adapt the pseudoequatorial orientation to afford the 1,3-*anti* product. In homoallylic alcohols with a stereogenic center at the allyl position, the group in the allylic position will also prefer the pseudoequatorial orientation so that the A(1,2) strain will be minimized [23, 57].

In the case of tri-substituted alkenes, the 1,3-*syn* products are formed in moderate to high diastereoselectivities (Table 21.10, entries 6~12). The stereochemistry of hydrogenation of homoallylic alcohols with a trisubstituted olefin unit is governed by the stereochemistry of the homoallylic hydroxy group, the stereogenic center at the allyl position, and the geometry of the double bond (Scheme 21.4). In entries 8 to 10 of Table 21.10, the product of 1,3-*syn* structure is formed in more than 90% d.e. with a cationic rhodium catalyst. The stereochemistry of the products in entries 10 to 12 shows that it is the stereogenic center at the allylic position which dictates the sense of asymmetric induction



Scheme 21.3 Conformation of 1,1-disubstituted alkenes in the hydrogenation.

Table 21.9 Functinoal group-directed hydrogenation.

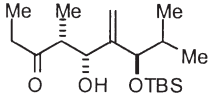
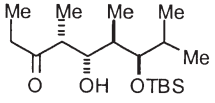
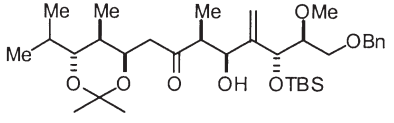
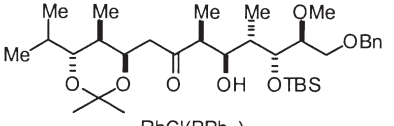
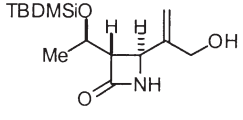
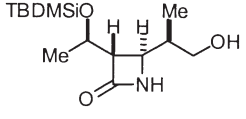
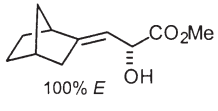
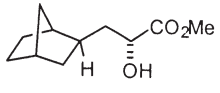
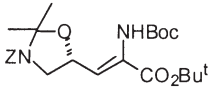
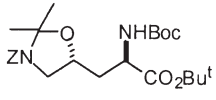
	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Diastereomeric ratio	TOF	Reference
1			$[RhCl(PPh_3)_3]$		50 bar	benzene	99:1		50
2			$RhCl(PPh_3)_3$		15 bar	benzene	>99:1		51
3			$Ru(OAc)_2((R)$-tol-binap)	0.2	1 atm	MeOH	99.9:0.1	10.4	52
			$Ru(OAc)_2((S)$-tol-binap)	0.2	1 atm	MeOH	22:78	10.4	52
			$RuBr_2((R)$-MeO-biphep)		15 bar		>99:1		53
4			$[RuCl((R)$-binap)$]_2NEt_3$	2	70 atm	MeOH	99:1	1.07	54
5			$[Rh((S,S)$-dipamp$))]^+$	0.23	3 bar	MeOH	80:20	28.6	49
			$[Rh((R,R)$-dipamp$)]^+$	0.23	3 bar	MeOH	20:80		49

Table 21.9 (continued)

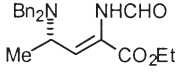
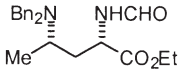
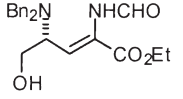
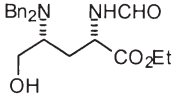
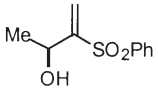
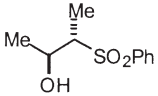
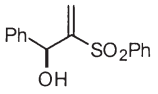
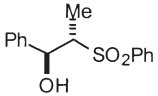
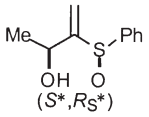
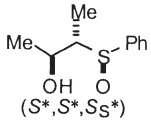
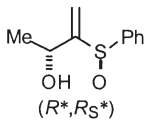
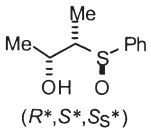
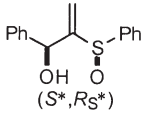
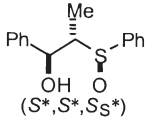
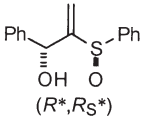
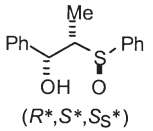
	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Diastereomeric ratio	TOF	Reference
6			$[Rh(diphos\text{-}2)]^+$	10	25 atm	MeOH	88:12	0.25	55
7			$[Rh(diphos\text{-}2)]^+$	10	85 atm rt	MeOH	90:10	0.24	55
8			Rh^+	1	15 psi	CH_2Cl_2 MeOH	99.85:0.15 99.5:0.5		56
9			Rh^+	1	15 psi	CH_2Cl_2 MeOH	99.85:0.15 400:1		56
10			Rh^+	1	15 psi	$Cl(CH_2)_2Cl$ MeOH	99.5:0.5 97.5:2.5		56
11			Rh^+	1	15 psi	$Cl(CH_2)_2Cl$ MeOH	99:1 80:20		56

Table 21.9 (continued)

	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Diastereomeric ratio	TOF	Reference
12	 (*S**,*R*S*)	 (*S**,*S**,*S*S*)	Rh^+	1	15 psi	CH_2Cl_2 MeOH	99.5:0.5 92.5:7.5		56
13	 (*R**,*R*S*)	 (*R**,*S**,*S*S*)	Rh^+	1	15 psi	CH_2Cl_2 MeOH	98.5:1.5 90.5:9.5		56

$Rh^+ = [Rh(diphos.4)(cod)]^+$; $Ir^+ = [Ir(PCy_3)(py)(nbd)]^+$

Table 21.10 Hydroxy-directed hydrogenation of acyclic homoallyl alcohols.

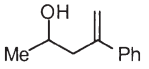
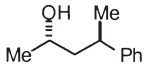
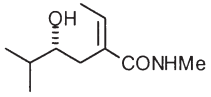
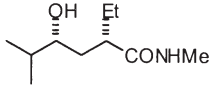
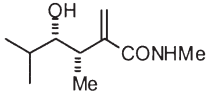
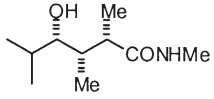
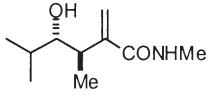
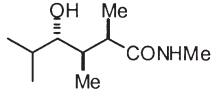
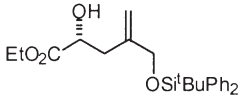
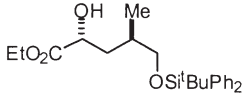
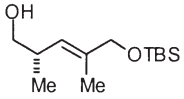
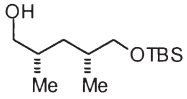
	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Diastereo-selectivity	TOF	Reference
1			Rh^+	2	15 psi	THF	88:12		19
2			Rh^+	5	15 psi	MeOH	89:11	1	57
3			Rh^+	5	15 psi	MeOH	67:33	1	57
4			Rh^+	5	15 psi	MeOH	91:9	1	57
5			Rh^+ $[Rh((S,S)\text{-Et-Duphos})]^+$ $[Rh((R,R)\text{-Et-Duphos})]^+$ $[Rh(R)\text{-phanephos})]^+$ Ir^+		1000 psi 1000 psi 1000 psi 1000 psi 1000 psi	CH_2Cl_2 CH_2Cl_2 CH_2Cl_2 CH_2Cl_2 CH_2Cl_2	60:40 95:5 40:60 25:75 35:65		58 58 58 58 58
6			Rh^+ Ir^+	5 2.5	15 psi 15 psi	CH_2Cl_2 CH_2Cl_2	95:5 73:27		59 59

Table 21.10 (continued)

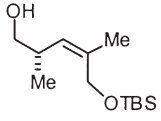
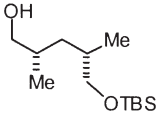
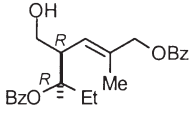
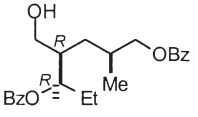
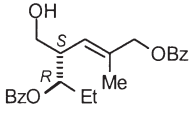
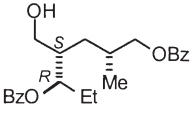
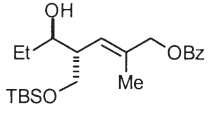
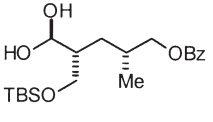
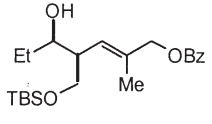
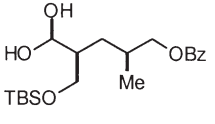
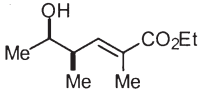
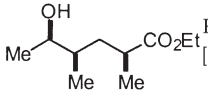
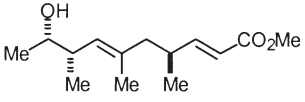
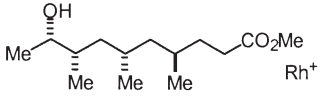
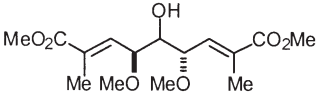
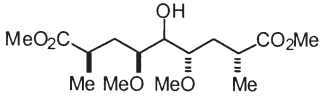
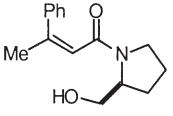
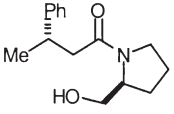
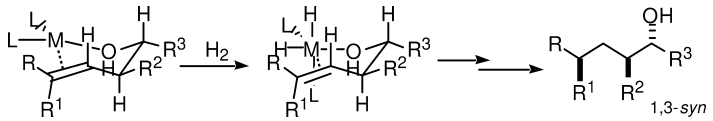
	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Diastereo-selectivity	TOF	Reference
7			Rh^+	5	15 psi	CH_2Cl_2	91:9		59
8			Rh^+ Ir^+	20 2.5	15 psi 15 psi	CH_2Cl_2 CH_2Cl_2	97:3 97:3		59 59
9			Rh^+ Ir^+	20 2.5	15 psi 15 psi	CH_2Cl_2 CH_2Cl_2	99:1 97:3		59 59
10			Rh^+ Ir^+	20 2.5	15 psi	CH_2Cl_2 CH_2Cl_2	97:3 94:6		59 59
11			Rh^+ $[Rh((+)\text{-binap})]^+$ $[Rh((-)\text{-binap})]^+$	20	15 psi 1000 psi 1000 psi	CH_2Cl_2 CH_2Cl_2 CH_2Cl_2	89:11 97:3 92:8		59 59 59

Table 21.10 (continued)

	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Diastereo-selectivity	TOF	Reference
12			Rh^+		1000 psi	CH_2Cl_2	85:15		60
			$[Rh((+)\text{-binap})]^+$		1000 psi	CH_2Cl_2	98:2		59
13									
			Rh^+	5	15 psi	CH_2Cl_2	94:6	1.6	61
14									
			$[Rh(\text{diphos-4})(nbd)]^+$	16	1000 psi	CH_2Cl_2	19:2.2:1	1.56	62
15			$[Rh(\text{diphos-4})(nbd)]^+$	8	640 psi		80:20 1,5-asymmetric induction		23

$Rh^+ = [Rh(\text{diphos-4})]^+$; $Ir^+ = [Ir(PCy_3)(py)(nbd)]^+$



Scheme 21.4 Conformation of trisubstituted alkenes in the hydrogenation.

in combination with the direction by the hydroxyl group [59, 60]. In entries 6 and 7 of Table 21.10, the alkyl group at the allylic stereogenic center is small and the diastereoselectivity is ca. 80∼90% d.e. In the directive hydrogenation of a 5-hydroxy-4,6-dimethoxy-2,7-nonadienedioic acid derivative, which was part of the synthesis of the C_{10}-C_{19} fragment of the immunosuppressive agent FK-506 (entry 14), the diastereoselectivity is controlled by the methoxy units at the allylic positions, and not by the hydroxy group, to afford a product with two 1,3-*syn* disposition in the structure [62].

In some cases of enantioselective hydrogenation of dehydroamino acids with a chiral cationic rhodium catalyst, the less-stable substrate–metal complex (minor species) reacts with hydrogen far more rapidly (∼1000-fold faster) than the more stable complex (major species), and the stereochemistry of the predominant enantiomer is determined by the reaction of the minor species [63]. In these cases, the stereochemical outcome is not related to the initial equilibrium of the substrate–metal complex, and a higher hydrogen pressure and rise in reaction temperature suppress the enantioselectivity. In contrast to the enantioselective hydrogenation of dehydroamino acids, olefinic alcohols are hydrogenated with higher diastereoselectivity at higher hydrogen pressure and at lower reaction temperature [24, 48]. This implies that the major substrate–metal complex determines the stereochemical outcome of the hydrogenation.

In entry 15 of Table 21.10, it is noted that even a remote hydroxyl group directed hydrogenation by the cationic $[Rh(diphos\text{-}4)(nbd)]^+$ catalyst to afford a moderate diastereoselectivity (80 : 20) [23]. This is an interesting example of long-range 1,5-asymmetric induction.

21.3.3
Ester Unit- or Amide-Directive Hydrogenation

The diastereoselective hydrogenation of itaconate derivatives by cationic rhodium catalysts are listed in Table 21.11. The observed high diastereoselectivity indicates a strong directivity by the alkoxycarbonyl unit in the reduction of acyclic systems (entries 1 and 2). Decrease of stereoselectivity in entry 3 indicates the definite effect of the ether functionality on the sense of asymmetric induction, competing with the directivity exerted by the alkoxycarbonyl group [64]. An amide or a carbamate group also serves as an admirable directing group in acrylic acid derivatives (entries 4–6) [65–67], although the hydrogenation of an amine or its corresponding trifluoroacetate salt was quite unselective (entry 7) [65].

Table 21.11 Directive hydrogenation of acrylic acid derivatives.

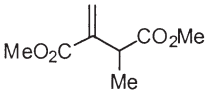
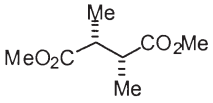
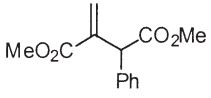
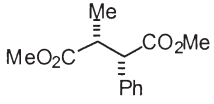
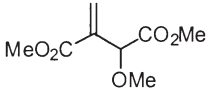
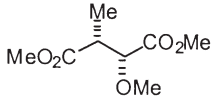
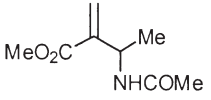
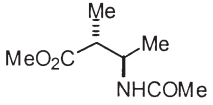
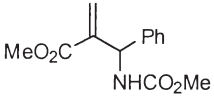
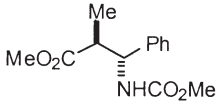
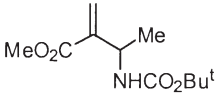
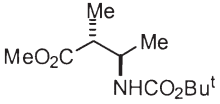
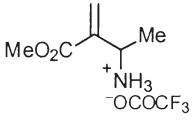
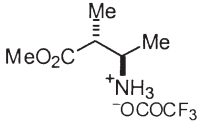
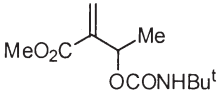
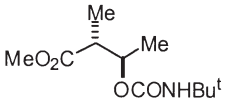
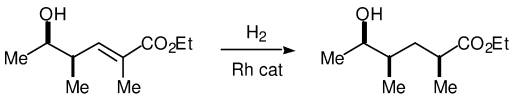
	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Diastereomeric ratio	TOF	Reference
1			Rh^+	2	1 atm	MeOH	99.6:0.4	50	64
2			Rh^+	2	1 atm	MeOH	99.5:0.5		64
3			Rh^+	2	1 atm	MeOH	98:2		64
4			Rh^+ Rh^+	5 5	 1 atm	CH_2Cl_2 MeOH	99:1 100:0		65 65
5			[Rh(diphos-2)]$^+$ [Rh(diphos-2)]$^+$ $Ru(TFA)_2(PPh_3)_2$ $Ru(TFA)_2(PPh_3)_2$ [Rh((*S*)-skewphos)]$^+$ [Rh((*S*)-chiraphos)]$^+$ [Rh((*R*)-binap)]$^+$	1 1 1 1 1 1 1	30 atm 30 atm 30 atm 75 atm 30 atm 30 atm 30 atm	THF MeOH THF MeOH MeOH MeOH MeOH	95:5 98:2 58:42 99:1:0.9 93:7 96:4 71:29	2.1 2.1 0.8 2.5 28.3 5.9 5.7	66 66 66 66 67 67 67

Table 21.11 Directive hydrogenation of acrylic acid derivatives.

	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Diastereomeric ratio	TOF	Reference
6			Rh^+ Rh^+	5 5	 1 atm	CH_2Cl_2 MeOH	99:1 100:0		65 65
7			Rh^+	5		CH_2Cl_2	50:50		65
8			Rh^+	5		CH_2Cl_2	94:6		65

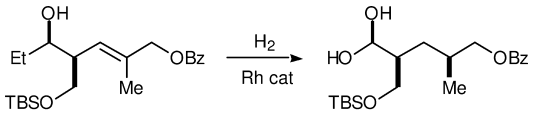
$Rh^+ = [Rh(diphos\text{-}4)(cod)]^+$

As described hitherto, diastereoselectivity is controlled by the stereogenic center present in the starting material (intramolecular chiral induction). If these chiral substrates are hydrogenated with a chiral catalyst, which exerts chiral induction intermolecularly, then the hydrogenation stereoselectivity will be controlled both by the substrate (substrate-controlled) and by the chiral catalyst (catalyst-controlled). On occasion, this will amplify the stereoselectivity, or suppress the selectivity, and is termed "double stereo-differentiation" or "double asymmetric induction" [68]. If the directions of substrate-control and catalyst-control are the same this is a matched pair, but if the directions of the two types of control are opposite then it is a mismatched pair.



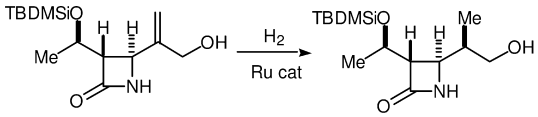
cat	mol%	P_{H2}	solvent	diastereo. ratio
$RhCl(PPh_3)_3$	20	15 psi	CH_2Cl_2	83 : 15
$[Rh((+)\text{-binap})]^+$		1000 psi	CH_2Cl_2	98 : 2
$[Rh((-)\text{-binap})]^+$		1000 psi	CH_2Cl_2	67 : 33

(5) [60]



$[Rh((+)\text{-binap})]^+$	1000 psi	CH_2Cl_2	97 : 3
$[Rh((-)\text{-binap})]^+$	1000 psi	CH_2Cl_2	92 : 8

(6) [59]



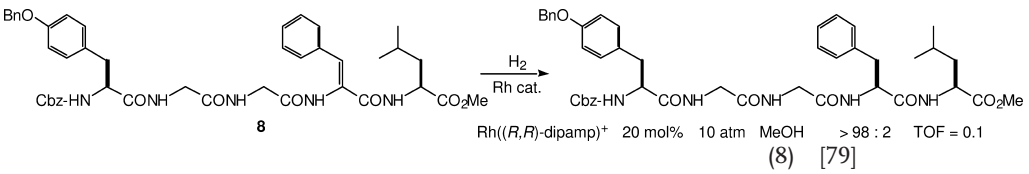
$Ru(OAc)_2((R)\text{-tol-binap})$	0.2	1 atm	MeOH	99.9 : 0.1
$Ru(OAc)_2((S)\text{-tol-binap})$	0.2	1 atm	MeOH	22 : 78

(7) [52]

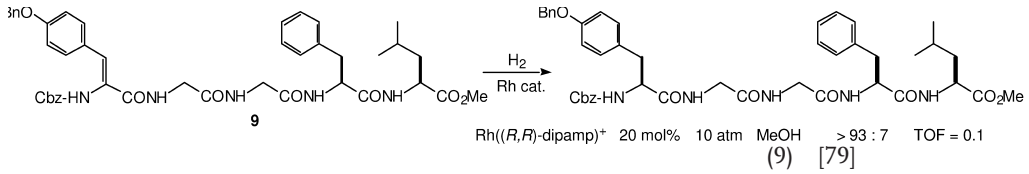
Striking examples of this phenomenon are presented for allyl and homoallyl alcohols in Eqs. (5) to (7). The stereodirection in Eq. (5) is improved by a chiral (+)-binap catalyst and decreased by using the antipodal catalyst [60]. In contrast, in Eq. (6) both antipode catalysts induced almost the same stereodirection, indicating that the effect of catalyst-control is negligible when compared with the directivity exerted by the substrate [59]. In Eq. (7), the sense of asymmetric induction was inversed by using the antipode catalysts, where the directivity by chiral catalyst overrides the directivity of substrate [52]. In the case of chiral dehydroamino acids, where both double bond and amide coordinate to the metal, the effect of the stereogenic center of the substrate is negligibly small and diastereoface discrimination is unsuccessful with an achiral rhodium catalyst (see Table 21.1, entries 9 and 10) [9].

21.4
Hydrogenation of Dehydrooligopeptides

The hydrogenation of dehydrodipeptides and -tripeptides is a versatile method for the synthesis of oligopeptides of various compositions. In the homogeneous hydrogenation of dehydrodipeptide derivatives, coordination of the olefin and the amidocarbonyl oxygen to the metal is also anticipated (similar to the reduction of dehydroamino acid derivatives), and this presents the question of whether the reaction proceeds by substrate-control or by catalyst-control. In general, the chiral center in the dehydrodipeptide was found to have little influence on the stereoselectivity, and this small degree of substrate-control enables the synthesis of dipeptides or tripeptides having a desired configuration at will, with the newly forming chiral center being controlled by the external effect of the chiral catalysts [70, 71, 77, 78]. The structure of dehydrodipeptides also influences stereoselectivity, and dehydrodipeptides of the RCO-ΔAA-AA-OR′ type can be hydrogenated with high stereoselectivities, while those of the RCO-Gly-ΔAA-OR′ type could be converted with only moderate to good stereoselectivities. Ojima conducted the diastereoselective hydrogenation of various dehydrodipeptides and -tripeptides, and succeeded in preparing Leu-enkephalin analogues in high diastereoselectivity by coupling the dipeptide and tripeptide formed via hydrogenation using Rh-(*R,R*)-dipamp and Rh-Ph-CAPP catalysts [70, 73]. In these hydrogenations of dehydrodipeptides, the direction of asymmetric induction generally turned out to be the same as that observed in the asymmetric hydrogenation of (*Z*)-*α*-acylaminocinnamic acid. Kagan reported the diastereoselective synthesis of Leu-enkephalin analogues by the Rh-catalyzed hydrogenation of dehydroenkephalins Cbz-(O)Bn-(*S*)Tyr-(Gly)2-ΔPhe-(*S*)Leu-OMe **8** or Cbz-(O)Bn-ΔTyr-$(Gly)_2$-(*S*)Phe-(*S*)Leu-OMe **9**, with a diastereoselectivity up to 98 : 2 ((*S,S,S*) : (*S,R,S*)) using $[Rh((R,R)\text{-dipamp})]^+$ [79] [Eqs. (8) and (9)]. The substitution of a glycyl residue by (*R*)alanyl in the above dehydropentapeptide had minimal effect on the stereochemical course of the hydrogenation (diastereoselectivity was 89 : 11).



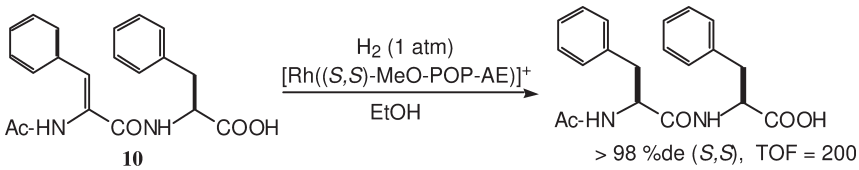
(8) [79]



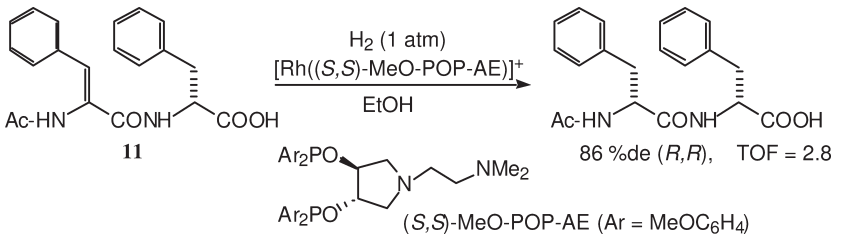
(9) [79]

In the enantioselective hydrogenation of dehydroamino acids, many diphosphine ligands are reported to give high enantioselectivity (often >95% ee). However, in the diastereoselective hydrogenation of dehydrodipeptides, many ligands – with very few exceptions – induce a somewhat lower stereoselectivity, especially in the case of mismatched pairs. Dipamp and Et-Duphos ligands retain their high chiral induction ability in the reduction of dehydrodipeptides [69, 70, 73, 76, 86, 87] (Table 21.12).

In the hydrogenation of dehydrodipeptides possessing a free carboxyl unit, the chiral ligands with an amine moiety would form an ion pair with the substrate which is expected to amplify the stereodifferentiation in the hydrogenation. Yamagishi realized high stereoinduction between 90 and 98% d.e. in the hydrogenation of dehydrodipeptides of the Ac-ΔPhe-AA-OH type in ethanol, using chiral diphosphinite ligands containing a dimethylamino moiety ((*S,S*)-POP-AEs) (Eq. (10)) [80]. In these systems, the chiral induction is governed by the chiral center of the substrate (substrate-control) and (*S,S*)- and (*R,R*)-products are formed highly selectively (Eq. (11)) [81].



(10)



(11)

These diphosphinite ligands are not effective for the hydrogenation of Ac-ΔPhe-AA-OR-type substrates. This striking substrate-controlled behavior is also observed in the hydrogenation of RCO-ΔPhe-AA-OH-type substrates using an *achiral* diphos-3 ligand with a 2-dimethylaminoethyl unit at the 2-position (DPP-AE ligand). The [Rh(I)(DPP-AE)]$^+$ catalyst induced high diastereoselectivity (up to 96% d.e.) in the hydrogenation of Ac-ΔPhe-AA-OH in alcoholic solvents [82]. The kinetic parameters ($\Delta\Delta S^{\ddagger}$ and $\Delta\Delta H^{\ddagger}$) indicate that $\Delta\Delta G^{\ddagger}$ is governed by the $T\Delta\Delta S^{\ddagger}$ term, and not by the $\Delta\Delta H^{\ddagger}$ in the reactions where electrostatic interaction is possible. Moreover, the effect of solvent polarity and of the added amine on stereoselectivity also support the contribution of the attractive electrostatic interaction to the stereodifferentiation. NMR and circular dichroism spec-

Table 21.12 Diastereoselective hydrogenation of dehydrodipeptides.

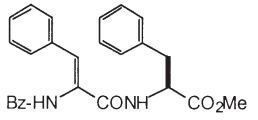
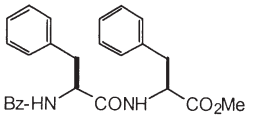
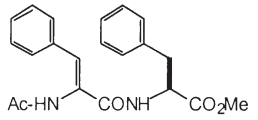
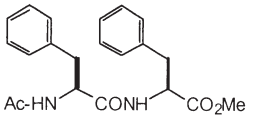
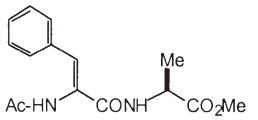
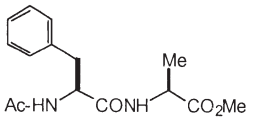
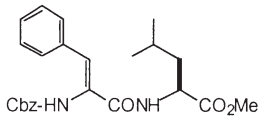
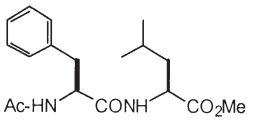
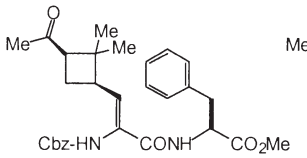
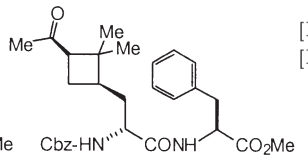
	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Diastereomeric ratio	TOF	Reference
1			[Rh(diphos-4)]$^+$	1	1 atm	EtOH	62.2:37.8	17	69
			[Rh((*R*,*R*)-dipamp)]$^+$	1	10 atm	EtOH	97.8:2.2	6.7	70
			[Rh((+)-diop)]$^+$	1	5 atm	EtOH	83.6:16.4	6.7	70
			[Rh((–)-diop)]$^+$	1	5 atm	EtOH	84.1:15.9	6.7	70
			[Rh(Br-Ph-CAPP)]$^+$	1	1 atm	EtOH	0.8:99.2	33	69
2			[Rh((+)-diop)]$^+$	1	5 atm	EtOH	92.7:7.3	4.2	70
			RhCl((+)-diop)	1	1 atm	MeOH	95:5		71
			RhCl((–)-diop)	1	1 atm	MeOH	10:90		71
			[Rh(Br-Ph-CAPP)]$^+$	1	5 atm	EtOH	2:98	4.2	70
3			[Rh(Br-Ph-CAPP)]$^+$	1	5 atm	EtOH	1:99	5.5	70
			[Rh((+)-diop))$^+$	1	5 atm	EtOH	91.4:8.6	10.6	70
			[RhCl((+)-diop)]	3.5	1 atm	MeOH	85.6:14.4		72
			[RhCl((–)-diop)]	3.5	1 atm	MeOH	10.2:89.8		72
4			[Rh((*R*,*R*)-dipamp)]$^+$	2	20 atm	EtOH	97.8:2.2	2.5	73
5			[Rh((*R*,*R*)-Et-Duphos))$^+$	4	2 atm	MeOH	>99.5:0.5	0.9	74
			[Rh((*S*,*S*)-Et-Duphos)]$^+$	4	2 atm	MeOH	5:95	0.4	74

Table 21.12 (continued)

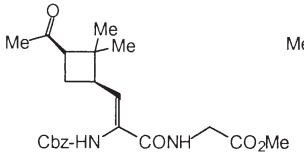
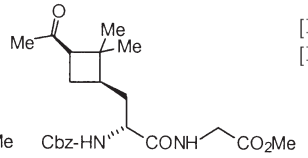
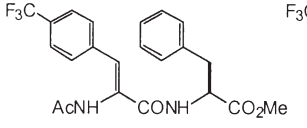
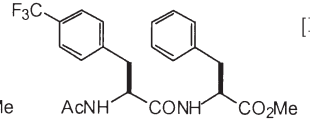
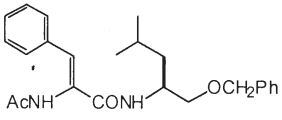
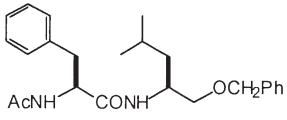
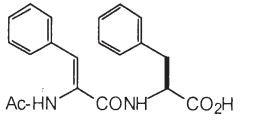
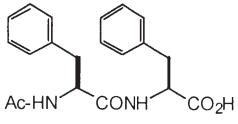
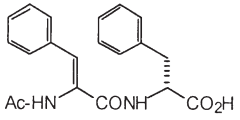
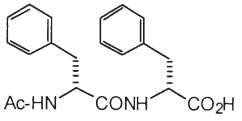
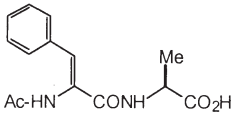
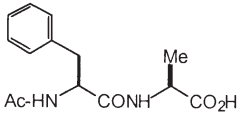
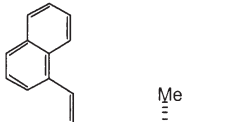
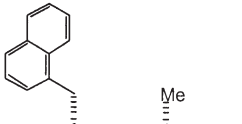
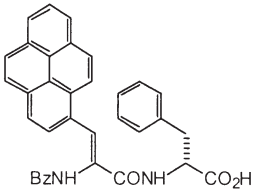
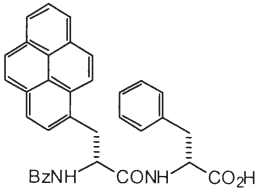
	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Diastereomeric ratio	TOF	Reference
6			[Rh((*R*,*R*)-Et-Duphos)]$^+$	4	2 atm	MeOH	91:9	1	74
			[Rh((*S*,*S*)-Et-Duphos)]$^+$	4	2 atm	MeOH	11:89	0.9	74
7			[Rh((*S*)-Pindophos)]$^+$		0.1 MPa	MeOH	95.5:4.5		75
8			[Rh(diphos-4)]$^+$	0.33	5 atm	EtOH	58.7:41.3	7.6	76
			[Rh((+)-BPPM)]$^+$	1	5 atm		99.1:0.9	2.5	76
			[Rh(Ph-CAPP)]$^+$	1	5 atm		1.3:98.7	2.4	76
9			[Rh(diphos-4)]$^+$	1	10 atm	EtOH	65.9:34.1	5.9	69
			[Rh((*R*,*R*)-dipamp)]$^+$	1	5 atm	EtOH	98.6:1.4	4.5	69
			[Rh((*R*,*R*)-bppm)]$^+$	1	10 atm	EtOH	99.4:0.6	4.9	69
			[Rh(DIOXOP)]$^+$	4	1 atm	EtOH	93:7	1	77
			[Rh((*S*,*S*)-Chiraphos)]$^+$	1	10 atm	EtOH	39.1:60.9	1	69
			[Rh((*S*,*S*)-MeO-POP-AE)]$^+$	2	1 atm	EtOH	>99:1	200	80
			[Rh(DPP-AE)]$^+$	2	1 atm	MeOH	97:3	100	82

Table 21.12 (continued)

	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Diastereomeric ratio	TOF	Reference
10			[Rh((*S*,*S*)-MeO-POP-AE)]$^+$	2	1 atm	EtOH	93:7	2.8	81
			[Rh((*S*,*S*)-POP-AE)]$^+$	2	1 atm	EtOH	93:7	2.8	81
11			[Rh((*S*,*S*)-MeO-POP-AE)]$^+$	2	1 atm	EtOH	98:2	100	80
			[Rh(DIOXOP)]$^+$	4	1 atm	EtOH	86:14	1	77
			[Rh(DPP-AE)]$^+$	2	1 atm	MeOH	94:6	63	82
			[Rh((–)-diop)]$^+$	1	1 atm	EtOH/ C_6H_6	9:91		78
12			[Rh(DPP-AE)]$^+$	2	1 atm	MeOH	94.5:5.5	50	83
			[Rh((–)-bppm)]$^+$	2	1 atm	MeOH	>99:1	50	83
13			[Rh(diphos-3)]$^+$	2	1 atm	MeOH	59:41	>1.7	83
			[Rh(DPP-AE)]$^+$	2	1 atm	MeOH	94.5:5.5	150	83
			[Rh((–)-bppm)]$^+$	2	1 atm	MeOH	94.5:5.5	5	83

troscopy suggest that the change of catalyst conformation occurs by electrostatic interaction between the (*S*)-substrate and the achiral ligand (induced fitting) to form a complex of the λ-conformation preferentially. Without electrostatic interaction, the rhodium complex exists as a 1:1 mixture of δ- and λ-conformations [82]. The effect of attractive electrostatic interactions on chiral induction was also reported by Hayashi, for the enantioselective hydrogenation of acrylic acid derivatives. A ferrocenyldiphosphine ligand having a dimethylaminoalkyl moiety induced a high enantioselectivity of more than 95% by utilizing electrostatic interactions with the substrate [84].

Kagan reported tandem asymmetric syntheses from achiral bisdehydrodipeptides by the sequential hydrogenation of two prochiral units [85]. With the [Rh((*R*,*R*)-dipamp)]$^+$ catalyst, a high diastereoselectivity ratio of 98:2 ((*RR* and *SS*)/(*RS* and *SR*) ratio) was reported (Table 21.13, entries 1–3). In this case, the major diastereomer has a high ee-value (97.6% (*S*,*S*)), and the minor diastereomer has a negligible ee (15% (*S*,*R*)). This result indicates that, in each step of the reaction, the same stereoselectivity is realized. In the symmetrical bis(dehydroamino acid) derivatives, similar high diastereo-differentiation of 95–99% d.e. is realized using dipamp or duphos ligands, and in some cases the enantioselectivity of the major diastereomer reaches 100% (Table 21.13, entries 7 and 8) [86, 87]. Because of the high chiral induction ability of the catalyst, almost all of the minor monohydrogenated enantiomer is converted to the *meso*-product in the second hydrogenation step, and this results in an extremely high enantioselectivity of the major product.

Several attempts towards the asymmetric reduction of *N*-(α-ketoacyl)-α-amino acid derivatives by rhodium catalysts are reported to give chiral depsipeptide building blocks, *N*-(α-hydroxyacyl)-α-amino acid derivatives (Table 21.14). Using rhodium catalysts containing an electron-rich chiral diphosphine (Cydiop) or a chiral diphosphinite (Cy-POP-AE) ligand, the hydrogenation proceeds under atmospheric hydrogen pressure affording moderate to good diastereoselectivity (entries 2, 3 and 6) [89, 90], while the catalysts based on diop or bppm required high hydrogen pressure and only low selectivity is obtained [88].

21.5
Diastereoselective Hydrogenation of Keto-Compounds

For the hydrogenation of keto-compounds, ruthenium–phosphine catalysts are efficient in obtaining compounds with a stereogenic hydroxyl unit, though the reduction usually requires high hydrogen pressure. Ruthenium–diphosphine–diamine catalyst plus strong base, as was first reported by Noyori, functions well at lower pressures in the hydrogenation of keto-compounds [91, 92]. For enantio- and diastereoselective hydrogenation of keto-compounds, atropisomeric diphosphines such as binap [93], bichep [94], biphemp or biphep [95] are used effectively.

Table 21.13 Tandem asymmetric hydrogenation of didehydrodipeptides with two double bonds.

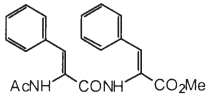
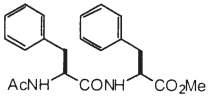
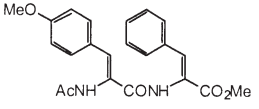
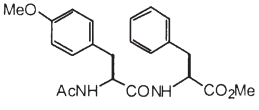
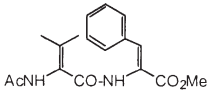
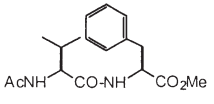
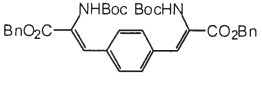
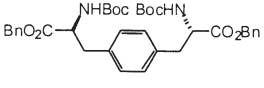
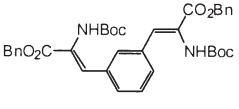
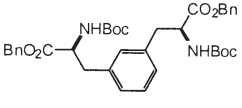
	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Diastereomeric ratio	%ee of major diastereomer	TOF	Reference
1			[Rh((*R*,*R*)-dipamp)]$^+$	3.5	1 atm	MeOH	98:2	99 (*S*,*S*)		85
			[Rh((*S*,*S*)-bppm)]$^+$	3.5	1 atm	MeOH	74.8:25.2	85 (*R*,*R*)		85
			[Rh(+)-(*R*,*R*)-diop)]$^+$	3.5	1 atm	MeOH	55:45	60 (*R*,*R*)		85
2			[Rh((*R*)-dipamp)]$^+$	3.5	1 atm	MeOH	98:2	97.6 (*S*,*S*)		85
3			[Rh((*R*,*R*)-dipamp)]$^+$	3.5	79 atm	MeOH	68:32	90.9 (*S*,*S*)	0.71	85
4			[Rh(cod)((*R*,*R*)-dipamp)]$^+$	2	2.8 atm	MeOH	>99:1	>98 (*S*,*S*)	0.52	86
5			[Rh(cod)(*S*,*S*)-Me-Duphos)]$^+$	1.8	2.7 atm	MeOH	>99:1	>98 (*S*,*S*)	12.3	86

Table 21.13 (continued)

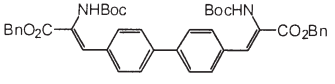
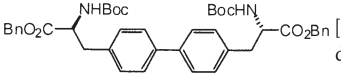
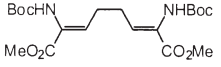
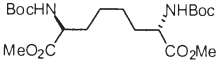
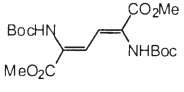
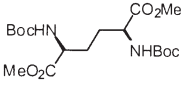
	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Diastereomeric ratio	%ee of major diastereomer	TOF	Reference
6			[Rh(cod)((*R*,*R*)-dipamp)]$^+$	3.6	3.5 atm	MeOH/THF	>99:1	>98 (*S*,*S*)	0.31	86
7			[Rh(cod)((*S*,*S*)-Et-Duphos)]$^+$	0.84	60 psi		99.5:0.5	100 (*S*,*S*)	6.6	87
			[Rh(cod)((*S*,*S*)-Me-Duphos)]$^+$		60 psi		98.5:1.5	100 (*S*,*S*)		87
			[Rh(cod)((*R*,*R*)-dipamp)]$^+$		60 psi		97.5:2.5	100 (*S*,*S*)		87
			$[RuCl_2(binap)]_2$ (TEA)		60 psi		85:15			87
			[Rh(cod)((*R*,*R*)-Chiraphos)]$^+$	0.84	60 psi		69.4:30.6	86 (*R*,*R*)	6.6	87
8			[Rh(cod)((*S*,*S*)-Et-Duphos)]$^+$	0.84	60 psi		98.5:1.5	100 (*S*,*S*)	6.6	87

Table 21.14 Diastereoselective hydrogenation of dehydrodepsipeptide.

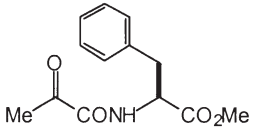
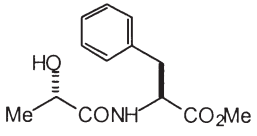
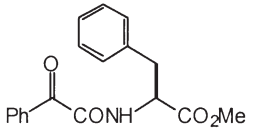
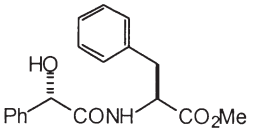
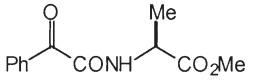
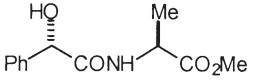
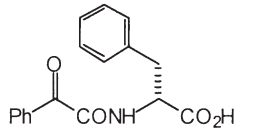
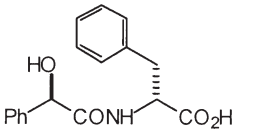
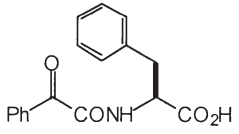
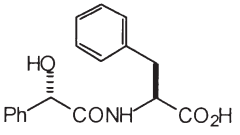
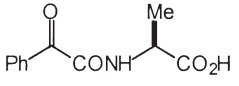
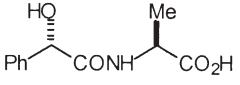
	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Diastereomeric ratio	TOF	Reference
1			$RhCl(PPh_3)_3$	1	50 atm	C_6H_6	60:40	5	88
			RhCl((+)-diop)	1	50 atm	C_6H_6	63:37	5	88
			RhCl((+)-bppm)	1	50 atm	C_6H_6	64:36	5	88
			RhCl((–)-cydiop)	5	1 atm	THF	73:27	0.8	89
			RhCl((+)-Cydiop)	5	1 atm	THF	26:74	0.7	89
2			RhCl((–)-Cydiop)	5	1 atm	THF	86:14	1	89
			RhCl((+)-Cydiop)	5	1 atm	THF	16:84	1	89
3			RhCl((–)-Cydiop)	5	1 atm	THF	83:17	1	89
			RhCl((+)-Cydiop	5	1 atm	THF	18:82	1	89
			RhCl((*S*,*S*)-Cy-POP-AE)	2	1 atm	MeOH	33.5:66.5	2.1	90
4			RhCl((*S*,*S*)-Cy-POP-AE)	2	1 atm	MeOH	75:25	2.1	90
			$[Rh((S,S)\text{-Cy-POP-AE})]^+$	2	1 atm	MeOH	76.5:23.5	2.1	90

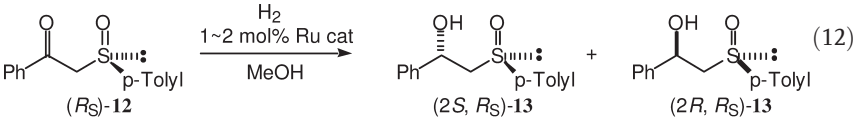
Table 21.14 (continued)

	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Diastereomeric ratio	TOF	Reference
5			[Rh((*S*,*S*)-Cy-POP-AE)]$^+$	2	1 atm	MeOH	73.5:26.5	2.1	90
6			RhCl((*S*,*S*)-Cy-POP-AE)	2	1 atm	MeOH	83.5:16.5	2.1	90

21.5.1
Substrate-Directive Hydrogenation of Keto-Compounds

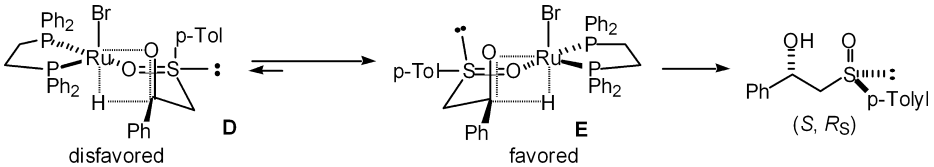
Several examples of substrate-directive reduction (hydroxyl, alkoxyl, carbamate or sulfoxide groups) have been reported in the hydrogenation of keto-compounds with ruthenium catalysts. In the reduction of β-keto ester derivatives, the γ- or δ-stereogenic center in the substrates significantly affects the degree of diastereoselection (Table 21.15). The hydrogenation of a β-keto ester with a carbamate unit at the γ-position ((*S*)-substrate) in the presence of Ru–(*R*)-binap (matched pair) exclusively afforded the *threo* product with the (3*S*,4*S*) configuration, whereas in the presence of Ru–(*S*)-binap (mismatched pair) the (3*R*,4*S*)-product was formed preferentially (Table 21.15, entry 1) [96]. The β-keto esters with a pyrrolidine unit showed similar behavior (entry 4) [97]. A silyloxy group at the δ-position could dictate the sense of asymmetric induction, and high diastereoselectivity is induced by using an achiral ruthenium catalyst, whereas the chiral ruthenium (*R*)-binap catalyst and the (*S*)-binap catalyst (matched and mismatched pairs, respectively) afford the same diastereomer, albeit in different selectivity (entry 7). On the other hand, the directivity of a hydroxy group was overwhelmed by the chirality of the catalyst, and a different diastereomer was formed preferentially by the antipode ruthenium catalysts (entry 8) [99].

In the hydrogenation of chiral sulfoxide **12**, the sulfoxide unit exerts strong stereodirectivity and, with axially stereogenic diphosphine ligands, high diastereoselectivity is realized whilst the antipode ligand affords lower diastereoselectivity (Scheme 21.5) [100]. The sense of asymmetric induction is rationalized by the favored conformation **E**, where the *p*-tolyl unit is disposed at a quasiequatorial position with a sulfoxide oxygen ligating to ruthenium [100].



(12)

Catalyst	H_2(bar)	temp(ºC)	time(h)	yield	(2*S*, R_S) : (2*R*, R_S)	TOF
$RuBr_2$(diphos-4)	50	50	24	12	78 : 22	0.25
$RuBr_2(PPh_3)_3$	50	20	64	99	80 : 20	1.6
$RuBr_2$((*S*)-MeO-biphep)	50	20	63	70	> 99 : 1	0.55
$RuBr_2$((*R*)-MeO-biphep)	50	20	63	95	10 : 90	0.75



Scheme 21.5

Table 21.15 Hydroxy-directed hydrogenation of β-keto esters.

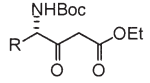
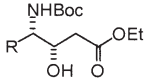
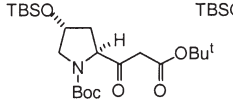
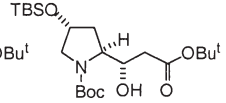
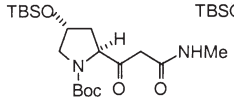
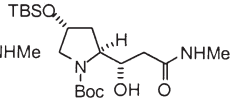
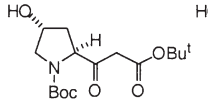
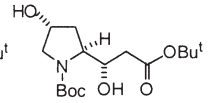
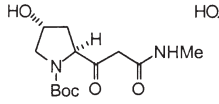
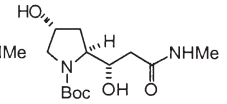
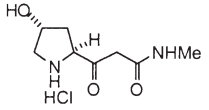
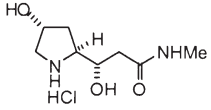
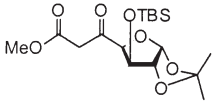
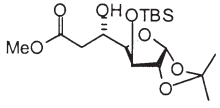
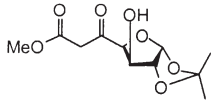
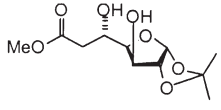
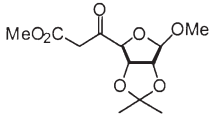
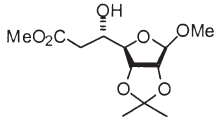
	Substrate	Major diastereomer	R	Catalyst	mol%	P_{H_2}	Solvent	Diastereomeric ratio	%ee (*syn*)	TOF	Reference
1			$PhCH_2$	$RuBr_2$((*R*)-binap)	0.2	100 atm	EtOH	>99:1	99	3.6	96
				$RuBr_2$((*S*)-binap)	0.2	100 atm	EtOH	9:91	>99		96
			CH_2CHMe_2	$RuBr_2$((*R*)-binap)	0.2	100 atm	EtOH	>99:1	97		96
			c-$C_6H_{11}CH_2$	$RuBr_2$((*R*)-binap)	0.2	100 atm	EtOH	>99:1	100		96
2				$RuCl_2$((*R*)-binap)1/2NEt_3	0.1	5 atm	THF/MeOH	96:4		19.2	97
				$RuCl_2$((*S*)-binap)1/2NEt_3	0.1	5 atm	THF/MeOH	ca 1:1		<2	97
3				$RuCl_2$((*S*)-binap)1/2NEt_3	0.1	5 atm	THF/MeOH	34.5:65.5		32.9	97
4				$RuCl_2$((*R*)-binap)Et_2NH	0.25	150 psi	MeOH 0.75 mol% HCl	>99:<1			97
				$RuCl_2$((*S*)-binap)Et_2NH	0.25	150 psi	MeOH 0.75 mol% HCl	12:88			97
5				$RuCl_2$((*S*)-binap)1/2NEt_3	0.1	5 atm	THF/MeOH	23.5:76.5		5.5	98

Table 21.15 (continued)

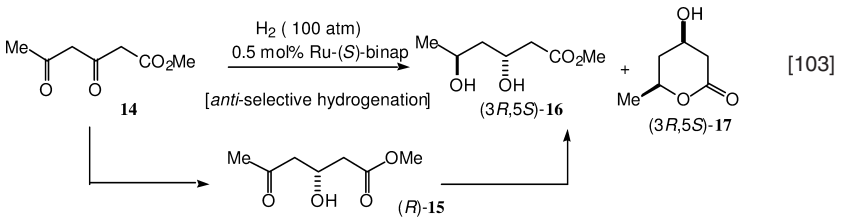
	Substrate	Major diastereomer	R	Catalyst	mol%	P_{H_2}	Solvent	Diastereomeric ratio	%ee (*syn*)	TOF	Reference
6				$RuCl_2$((*S*)-binap)1/2NEt_3	0.1	5 atm	THF/MeOH	1:99		35.4	98
7				$RuBr_2$(diphos-2)	2	1 atm	MeOH	95:5		0.5	99
				$RuBr_2$((*R*)-binap)	2	1 atm	MeOH	>99:1		2.1	99
				$RuBr_2$((*S*)-binap)	2	1 atm	MeOH	82:18		1.5	99
8				$RuBr_2$((*R*)-binap)	2	1 atm	MeOH	85:15		2.1	99
				$RuBr_2$((*S*)-binap)	2	1 atm	MeOH	10:90		1.0	99
9				$RuBr_2$((*R*)-binap)	2	1 atm	MeOH	90:10		2.1	99
				$RuBr_2$((*S*)-binap)	2	1 atm	MeOH	5:95		2.1	99

21.5.2
Hydrogenation of Diketo Esters and Diketones

Reduction of *β,δ*-diketo esters using various atropisomeric diphosphine ligands afforded generally the *anti*-3,5-dihydroxy products in moderate to good diastereoselectivity, and in high enantioselectivity (Table 21.16) [101–104]. This suggests that stereocontrol in the hydrogenation of diketo esters is, in general, very similar to that found in the hydrogenation of diketones with Ru–binap (*vide infra*) [105, 106].

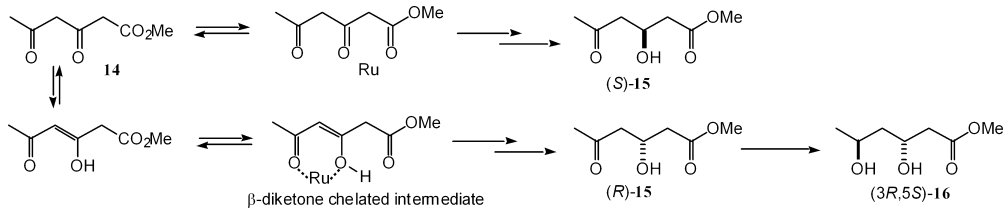
In these cases, using an (*S*)-axially chiral ligand, (3*R*)-3-hydroxy-5-oxoalkanoate is exclusively formed as monohydrogenation product, while the second hydrogenation step is a hydroxy-directed reduction by the Ru–catalyst bearing an (*S*)-axially chiral ligand to afford the (3*R*,5*S*)-dihydroxy product preferentially (Scheme 21.6) [103a]. With Ru–(*R*)-binap, this (3*R*)-3-hydroxy-5-oxoalkanoate is mainly converted to the (3*R*,5*R*)-*syn* dihydroxy compound. Formation of the 3-hydroxy-5-oxoalkanoate intermediate is also supported by the reduction experiment of (5*R*)-5-hydroxy-3-oxoalkanoate by Ru–(*R*)-binap to afford the (3*R*,5*R*)-*syn* diol as the major product [102]. There is a competitive ligation of functionalities to the Ru atom (Scheme 21.7). Because of the intervention of an enolic structure in **14** and the high final *anti*-selectivity, it is plausibly assumed that hydrogenation of the C-3 carbonyl unit of **14** arises mainly from a *β*-diketone chelated intermediate, which gives preferentially the (3*R*)-enantiomer using Ru–(*S*)-binap as catalyst. This is in contrast to the results with simple *β*-keto esters, which afford the (3*S*)-hydroxy product upon use of a Ru–(*S*)-axially chiral diphosphine catalyst [106, 107, 109].

In the consecutive hydrogenation of *β,δ*-diketo esters (Table 21.16), selection of the chiral ligand can determine the sense of diastereoselection, and the 3,5-*syn* dihydroxy product was formed predominantly upon use of a Ru–(*S*)-aminophosphinephosphinite-((*S*)-AMPP) catalyst, although the enantioselectivity of the *syn*-product is poor (Table 21.16, entry 7) [103a]. *Syn* 3,5-diol formation



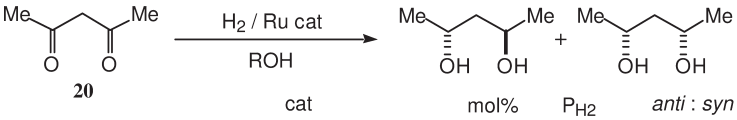
cat	mol%	P_{H2}	solvent	temp (ºC)	**15** selec.	**16 + 17** selec.	*anti* : *syn*	%ee(*anti*)	TOF(h^{-1})
$RuBr_2$((*S*)-tol-binap)	0.5	100 atm	CH_2Cl_2	60	27	73	87 : 13	93 (3*R*,5*S*)	1.1
$RuBr_2$((*S*)-MeO-biphep)	0.5	100 atm	CH_2Cl_2	60	7	86	89 : 11	95 (3*R*,5*S*)	1.8
$RuBr_2$((*S*)-tol-binap)	0.5	100 atm	CH_2Cl_2	40	96	4	nd		5
$RuBr_2$((*S*)-MeO-biphep)	0.5	100 atm	CH_2Cl_2	40	96	4	nd		4.2

Scheme 21.6

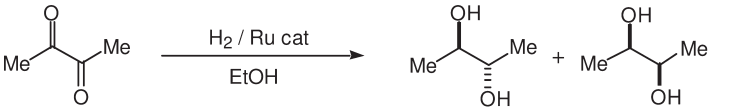


Scheme 21.7 Competitive chelation mode onto a Ru-(*S*)-binap type catalyst.

would lead to the synthesis of inhibitors of HMG-coenzyme A reductase [102]. In this case, an almost complete reversal of the diastereoselectivity was observed by changing the solvent from DCM to a polar solvent consisting of 1 : 1 DCM-methanol. In pure DCM, the Ru–(*S*)-AMPP catalyst induces the *syn*-rich diol (max. 92% d.e.), while in the DCM-methanol mixture the same catalyst leads to the formation of *anti*-rich product (72–84% d.e.). This reversal of diastereoselectivity was also observed in the reduction of *β*-diketones (Table 21.17, entry 13) [103 b].



cat	mol%	P_{H2}	*anti* : *syn*	ee%(*anti*-)	TOF	
Ru_2Cl_4((*R*)-binap)$_2$(NEt_3)	0.2	50 atm	99 : 1	> 99 (*R*,*R*)	25	[105]
$RuCl_2$((*R*)-binap)	0.05	72 atm	99 : 1	100 (*R*,*R*)	22.5	[106]
$RuBr_2$((*S*)-MeO-biphep)	2	20 atm	> 99.5 : 0.5	> 99 (*S*,*S*)	0.8	[110]



			anti : *syn*	ee%(*anti*-)	TOF	
$RuBr_2$((*S*)-binap)	0.15	80 atm	26 : 74	92 (*S*,*S*)	11.1	[106]

In the hydrogenation of diketones by Ru–binap-type catalysts, the degree of *anti*-selectivity is different between *α*-diketones and *β*-diketones [Eqs (13) and (14)]. A variety of *β*-diketones are reduced by Ru-atropisomeric diphosphine catalysts to indicate admirable *anti*-selectivity, and the enantiopurity of the obtained *anti*-diol is almost 100% (Table 21.17) [105, 106, 110–112]. In this two-step consecutive hydrogenation of diketones, the overall stereochemical outcome is determined by both the efficiency of the chirality transfer by the catalyst (catalyst-control) and the structure of the initially formed hydroxyketones having a stereogenic center (substrate-control). The hydrogenation of monohydrogenated product ((*R*)-hydroxy ketone) with the antipode catalyst ((*S*)-binap catalyst) (mis-

Table 21.16 Diastereoselective hydrogenation of β,δ-diketo esters.

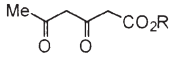
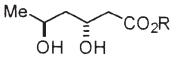
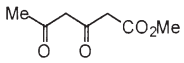
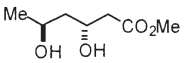
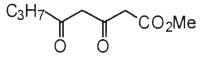
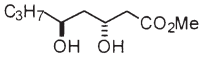
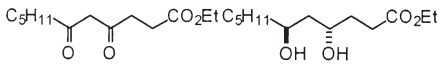
	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Diastereomeric ratio anti:syn	%e.e. of major diastereomer	TOF	Reference
1			$RuCl_2(PPh_3)_3$	0.5	100 atm	CH_2Cl_2	73:27	0	2.6	101
			$[RuCl_2((S)$-binap$)]_2NEt_3$	0.5	100 atm	CH_2Cl_2	83:17	94 (3*R*,5*S*)	8.7	101
			$[RuCl_2((S)$-binap$)]_2NEt_3$	0.5	100 atm	MeOH	76:24	96 (3*R*,5*S*)	8.7	103
			$RuBr_2((S)$-Tolbinap)	0.5	100 atm	CH_2Cl_2	83:17	94 (3*R*,5*S*)	9.5	101
			$RuBr_2((S)$-MeO-biphep)	0.5	100 atm	CH_2Cl_2	84:16	98 (3*R*,5*S*)	5.1	101
			$[RuCl_2((S)$-binap$)]_2NEt_3$	0.1	100 atm	MeOH	81:19	78 (3*R*,5*S*)	10.4	102
			$[RuCl_2((R)$-binap$)]_2$-NEt_3	0.1	100 atm	MeOH	80:20	77 (3*S*,5*R*)	10.4	102
2			RhCl((*S*)-MeO-biphep)	0.5	50 atm	toluene	54:$6	79 (3*R*,5*S*)	0.26	101
			RhCl((*S*,*S*)-bppm)	0.5	50 atm	toluene	54:46	58 (3*R*,5*S*)	0.78	101
			RhCl((*S*)-Cy,Cy-oxoProNOP)	0.5	50 atm	toluene	65:35	80 (3*R*,5*S*)	0.43	101
			RhCl((*R*,*R*)-Me-Duphos)	0.5	50 atm	toluene	46:54		0.07	101
3			$[RuCl_2((S)$-binap$)]_2(NEt_3)$	0.1	100 atm	MeOH	76:24	78 (3*R*,5*S*)	10.4	102
			$[RuCl_2((R)$-binap$)]_2(NEt_3)$	0.1	100 atm	MeOH	78:22	77 (3*S*,5*R*)	10.4	102
4			[RuCl((*S*)-binap)(p-cymene)]Cl		40 atm	MeOH	95:5 ~ 99:1	93 ~ 95 (4*S*,6*S*)		104

Table 21.16 (continued)

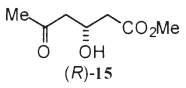
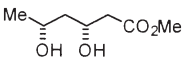
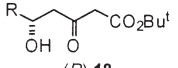
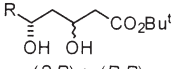
	Substrate	Major diastereomer		Catalyst	mol%	P_{H_2}	Solvent	Diastereomeric ratio	%ee of major diastereomer *anti:syn*	TOF	Reference
5	 (*R*)-**15**		15 ee (%) 66 (*R*) 67 (*R*)	$Ru(TFA)_2$((*R*)-binap)	2	100 atm	CH_2Cl_2	10:90	75 (3*R*,5*R*)	2.4	103
			67 (*R*)	$Ru(TFA)_2$((*R*)-toalbinap)	2	100 atm	CH_2Cl_2	19:81	67 (3*R*,5*R*)	2.4	103
				$Ru(TFA)_2$((*R*)-MeO-biphep)	2	100 atm	CH_2Cl_2	14:86	72 (3*R*,5*R*)	2.2	103
6	 (*R*)-**18**	 (*S*,*R*) or (*R*,*R*)	R = Me	Ru_2Cl_4((*S*)-binap)$_2$(Et_3)	0.2	100 atm	MeOH	95:5			102
			$R = C_3H_7$	Ru_2Cl_4((*R*)-binap)$_2$(Et_3)	0.2	100 atm	MeOH	40:60			102
				Ru_2Cl_4((*S*)-binap)$_2$(Et_3)	0.2	100 atm	MeOH	78:22			102
				Ru_2Cl_4((*R*)-binap)$_2$(Et_3)	0.2	100 atm	MeOH	43:57			102

Table 21.16 (continued)

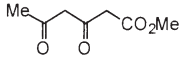
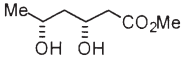
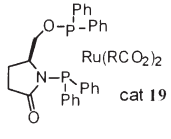
	Substrate	Major diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Diastereomeric ratio	%ee of major diastereomer *anti:syn*	TOF	Reference
7			Ru((*S*)-AMPP)(methallyl)$_2$	0.5	100 atm	CH_2Cl_2	13:87	14 (3*R*,5*R*)	0.85	103
			Ru((*S*)-AMPP)(TFA)$_2$	0.5		CH_2Cl_2	28:72	40 (3*R*,5*R*)	1.4	103
			Ru((*S*)-AMPP)((*R*)-MTPA)$_2$	0.5		CH_2Cl_2	4:96	<5 (3*R*,5*R*)	11.1	103
			Ru((*S*)-AMPP)((*S*)-MTPA)$_2$	0.5		CH_2Cl_2	8:92	5 (3*R*,5*R*)	2.9	103
			Ru((*S*)-AMPP)(TFA)$_2$	0.5		CH_2Cl_2/MeOH (1/1)	86:14	12 (3*S*,5*R*)	1.9	103
			Ru((*S*)-AMPP)((*R*)-MTPA)$_2$	0.5		CH_2Cl_2/MeOH (1/1)	92:8	5 (3*S*,5*R*)	0.85	103
			 cat **19**							

Table 21.17 Consecutive hydrogenation of diketones.

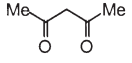
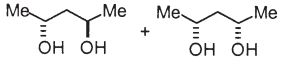
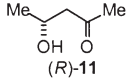
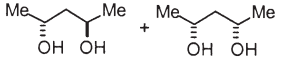
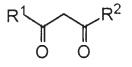
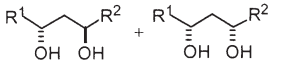
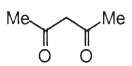
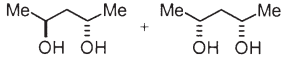
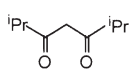
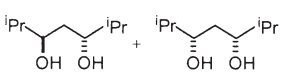
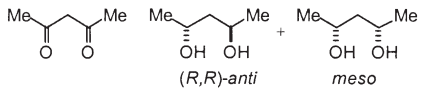
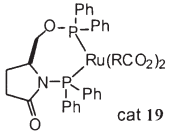
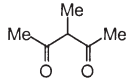
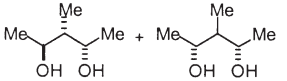
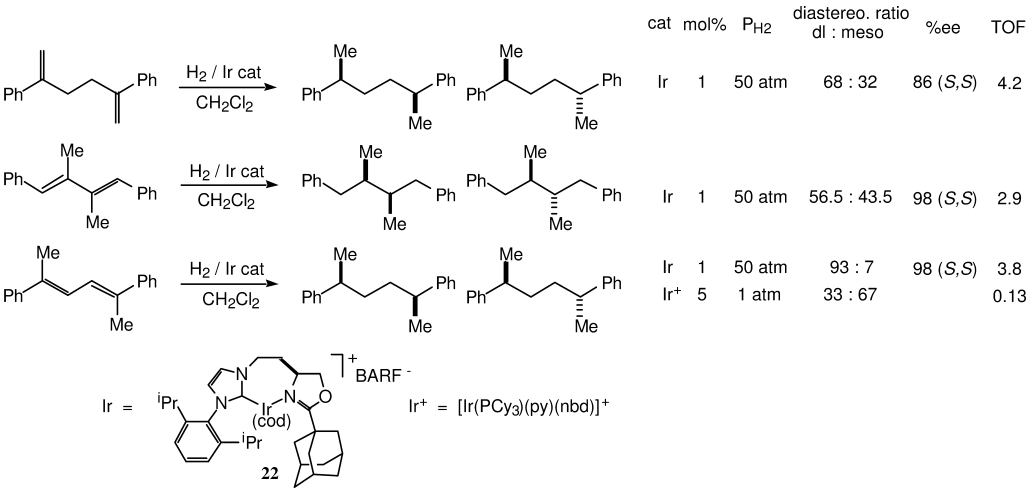
	Substrate	Diastereome	Catalyst	mol%	P_{H_2}	Solvent	Temp. [°C]	Diastereomeric ratio *anti*:*syn*	%ee *anti*	TOF	Reference
1			$RuCl_2$((*R*)-binap)	0.05	72 atm	EtOH		99:1	>99 (*R*,*R*)	22.5	106
2	 (*R*)-**11**		$RuCl_2$((*S*)-binap)	0.05	72 atm	EtOH		15:85			106
											
		R^1 R^2									
3		Me Me	Ru_2Cl_4((*R*)-binap)$_2$(NEt_3)	0.2	50 atm	MeOH		99:1	>99 (*R*,*R*)	25	105
4		Me Et				MeOH		94:6	94 (*R*,*R*)	22	105
5		Me *i*Pr				MeOH		97:3	98 (*S*,*R*)	23	105
6		Me *i*Bu				MeOH		91:9	98 (*S*,*R*)	21	105
7		Et Et				MeOH		98:2	96 (*R*,*R*)	23	105
8		Me Me	$RuBr_2$((*R*,*R*)-Me-duphos)	2	70 atm	MeOH	80	97:3	93 (*R*,*R*)	0.8	110
9		C_6H_{11} C_6H_{11}	$RuBr_2$((*R*)-MeO-biphep)	2	100 atm	MeOH	r.t.	>99.5:0.5	>99 (*S*,*S*)	2.1	110
10		Bn Bn		2	30 atm	MeOH	r.t.	>97.5:2.5	>95 (*R*,*R*)	1.25	110
11			$RuBr_2$((*S*)-MeO-biphep)	2	20	MeOH	r.t.	>99.5:0.5	>99 (*S*,*S*)	0.8	110
			$RuCl_2(PPh_3)$((*S*)-biphep)	0.05	100 atm	MeOH	50	94:6	>99 (*S*,*S*)	133	111
					100 atm	EtOH	50	99.4:0.6	>99 (*S*,*S*)	83.3	112

Table 21.17 (continued)

	Substrate	Diastereome	Catalyst	mol%	P_{H_2}	Solvent	Temp. [°C]	Diastereomeric ratio *anti*:*syn*	%ee *anti*	TOF	Reference
12			$RuBr_2$((*S*)-MeO-biphep)	2	20 atm	MeOH	r.t.	>99.5:0.5	>99 (*R*,*R*)	0.8	110
13	 (*R*,*R*)-*anti* *meso*		**19a** (R = CF_3)	0.5	100 atm	CH_2Cl_2		40:60	93 (*R*,*R*)	8.3	103
				0.5	100 atm	CH_2Cl_2/MeOH (1/1)		88:12	20 (*R*,*R*)	8.3	103
			19b(R = (*R*)-PhC(CF_3)(OMe))	0.5	100 atm	CH_2Cl_2		8:92	86 (*R*,*R*)	2	103
				0.5	100 atm	CH_2Cl_2/MeOH (1/1)		92:8	14 (*R*,*R*)	3.5	103
			 cat **19**								
14			$RuCl_2$((*S*)-(binap)	0.05	94 atm	EtOH		99:1	>99 (*R*,*R*)	35.5	106



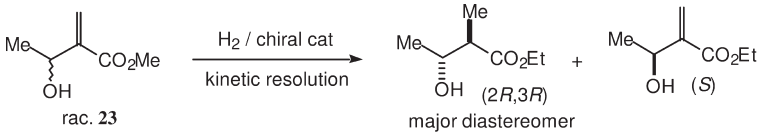
Scheme 21.8 Consecutive hydrogenation of symmetrical dienes [111].

matched pair) affords a *meso*-diol exclusively (Table 21.17, entry 1). This indicates that the catalyst-control in the second step is much more dominant over the substrate-control favoring *anti*-diol formation; thus, the high enantiomeric purity of the *anti*-diol is the result of a double stereodifferentiation [68]. In the reaction of α-diketones, substrate-control in the second hydrogenation step favors *meso*-diol formation, while minor *anti*-diol is obtained with high enantiomeric purities [Eq. (14)] [106]. This *dl*- and *meso*-products formation is also observed in the hydrogenation of symmetrical dienes [113] by an iridium carbene catalyst **22** (Scheme 21.8), or in the symmetrical bis(dehydroamino acids) by rhodium diphosphine catalysts (see Table 21.13, entries 4–8) [86, 87].

21.6
Kinetic Resolution to Selectively Afford Diastereomers and Enantiomers

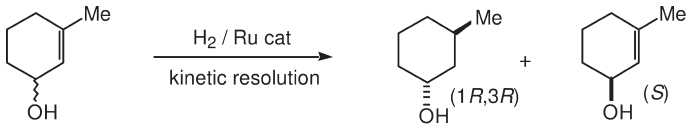
In the hydrogenation of a compound with a stereogenic center by a chiral catalyst, the two possible stereocombinations – the matched pair and the mismatched pair – often afford different degrees of stereoinduction. The reaction rate of the hydrogenation is different for these two combinations (k_R and k_S, $k_R \neq k_S$), and kinetic chemical resolution is possible starting from racemic substrate using chiral catalyst by controlling the chemical conversion [114]. Kinetic resolution is now recognized as a viable tool for obtaining certain optically active compounds. In the homogeneous hydrogenation of unsaturated alcohols with a stereogenic center, various chiral catalysts were applied for their kinetic resolution. Using Rh–(*R*,*R*)-dipamp, racemic methyl (α-hydroxyethyl)acrylate **23** was resolved in THF at 0 °C to afford the (*S*)-substrate in 93% ee and the *anti*-product as the major product with a $k_R : k_S$ ratio of 6.5 : 1 at 75% conversion [Eq.

(15)] [45]. With an increase of conversion, the enantiopurity of unreacted (*S*)-substrate increases and the diastereoselectivity of the product decreases. Using Ru–((*S*)-binap)$(OAc)_2$, unreacted (*S*)-substrate was obtained in more than 99% ee and a 49 : 1 mixture of *anti*-product (37% ee (2*R*,3*R*)) at 76% conversion with a higher $k_R : k_S$ ratio of 16 : 1 [46]. In the case of a racemic cyclic allyl alcohol **24**, high enantiopurity of the unreacted alcohol was obtained using Ru–binap catalyst with a high $k_R : k_S$ ratio of more than 70 : 1 [Eq. (16)] [46]. In these two cases, the transition state structure is considered to be different since the sense of diastereoface selection with the (*S*)- or the (*R*)-catalysts is opposite if a similar OH/C=C bond spatial relationship is assumed.



(15)

cat.	mol%	P_{H2}	solvent	temp (°C)	conv.	diastereo. ratio	recov. **23**	$k_R : k_S$	
[Rh(dipamp)]$^+$		1 atm	THF	0	75%		93 (*S*)	6.5 : 1	[45]
[Ru$(OAc)_2$((*S*))-binap)]	0.06	4 atm	MeOH	25	76%	98 : 2	> 99 (*S*)	16 : 1	[46]
[Ru$(OAc)_2$((*S*))-binap)]	0.1	50 atm	MeOH	20	63%	96.9 : 3.1	97 (*S*)	14 : 1	

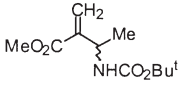
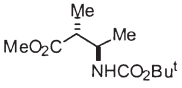
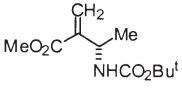
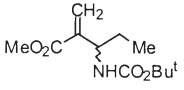
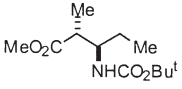
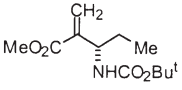
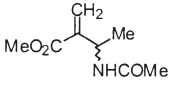
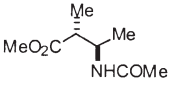
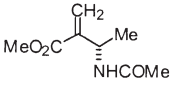
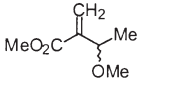
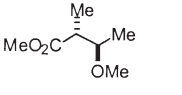
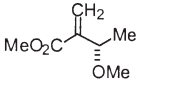
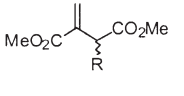
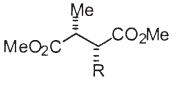
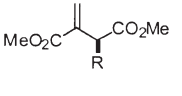


(16)

							recov. **24**		
[Ru$(OAc)_2$((*R*))-binap)]	0.17	4 atm	MeOH	26	54%	300 : 1	> 99 (*S*)	74 : 1	[46]
[Ru$(OAc)_2$((*R*))-binap)]	0.055	100 atm	MeOH	26	51%	98.5 : 1.5	95 (*S*)	76 : 1	

In the case of (*α*-acylaminoethyl)acrylate or (*α*-carbamoylethyl)acrylate, amido or carbamate functional groups work well in the direction of the kinetic resolution (Table 21.18). Reduction proceeded rapidly but then slowed markedly after consumption of 55–60% of the theoretical amount of H_2, indicating the large difference between the values of k_R and k_S (entries 1–3) [115]. The degree of enantiomer differentiation is considerably influenced by the hydrogen pressure, and higher k_f/k_s values were obtained at lower pressure with many substrates. The high selectivity should be noted, since binding of the substrate to rhodium through the olefin and amido units gives a fairly flexible chelate complex. In contrast, the reduction of (*α*-methoxyethyl)acrylate by the rhodium catalyst indicated a poor kinetic resolution (entry 4), in contrast to the effective OMe-directed hydrogenation with the iridium catalyst (see Table 21.3, entries 11 and 12) [25].

Table 21.18 Kinetic resolution of acrylic acid derivatives.

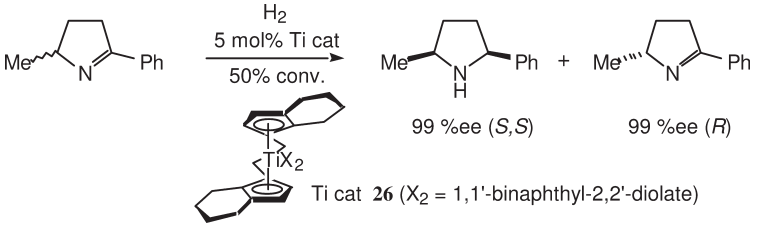
	Substrate	Major product	Recovered substrate	Catalyst	mol%	P_{H_2}	Solvent	Conversion [%]	Diastereomeric ratio	%ee recov.	k_f/k_s	TOF	Reference
1				[Rh(nbd)(*R*,*R*)-dipamp)]$^+$	4	1 atm	MeOH	56	highly sel.	87 (*S*)	15	14	115
2				[Rh(nbd)(*R*,*R*)-dipamp)]$^+$	4	1 atm	MeOH	60	highly sel.	98 (*S*)	22	10	115
3				[Rh(nbd)(*R*,*R*)-dipamp)]$^+$	4	1 atm	MeOH	56	highly sel.	96 (*S*)	21	17.4	115
4				[Rh(nbd)(*R*,*R*)-dipamp)]$^+$	4	1 atm	MeOH	50	80:20	16 (*S*)	1.5	0.3	115
5													
			R = Et	[Rh((nbd)(*R*,*R*)-dipamp)]$^+$	2	1 atm	MeOH	52.7		81 (*S*)	16		64
			R = Ph		2								
			R = OMe	[Rh((nbd)(*R*,*R*)-dipamp)]$^+$	2	1 atm	MeOH	62.3		82 (*S*)	7.2		64
				[Rh((nbd)(*R*,*R*)-dipamp)]$^+$		1 atm	MeOH	62.2		93 (*S*)	11.5		64

In the hydrogenation of 3-substituted itaconate ester derivatives by rhodium–dipamp, the alkoxycarbonyl group at the stereogenic center also exerts a powerful directing effect, comparable to that induced by OH in the kinetic resolution of (*α*-hydroxyethyl)acrylate, leading to a high enantiomer-discriminating ability up to $k_R : k_S = 16 : 1$ (Table 21.18, entry 5) [64].

21.7
Kinetic Resolution of Keto- and Imino-Compounds

Kinetic resolution results of ketone and imine derivatives are indicated in Table 21.19. In the kinetic resolution of cyclic ketones or keto esters, ruthenium atropisomeric diphosphine catalysts **25** induced high enantiomer-discriminating ability, and high enantiopurity is realized at near 50% conversion [116, 117]. In the case of a bicyclic keto ester, the presence of hydrogen chloride in methanol served to raise the enantiomer-discriminating ability of the Ru–binap catalyst (entry 1) [116].

Racemic 2,5-disubstituted 1-pyrrolines were kinetically resolved effectively by hydrogenation with a chiral titanocene catalyst **26** at 50% conversion, which indicates a large difference in the reaction rate of the enantiomers (Table 21.19, entries 4 and 5), while 2,3- or 2,4-disubstituted 1-pyrrolines showed moderate selectivity in the kinetic resolution (entries 6 and 7) [118]. The enantioselectivity of the major product with *cis*-configuration was very high for all disubstituted pyrrolidines. The high selectivity obtained with 2,5-disubstituted pyrrolines can be explained by the interaction of the substituent at C5 with the tetrahydroindenyl moieties of the catalyst [Eq. (17)].



(17)

In the kinetic resolution of acyclic chiral imines derived from *α*-methylbenzylamine and acetophenone derivatives, Rh(I)–(2*S*,4*S*)-bdpp catalyst forming a six-membered chelate ring exerted good kinetic resolution results. Catalysts with 2-carbon bridged diphosphines resulted in low reactivity and low selectivity (Table 21.19, entry 8). The hydrogenation of (*R*)-**27** by Rh(I)–(2*S*,4*S*)-bdpp gives an extremely high diastereomeric ratio of $RR : SR = 333 : 1$ with *threo* stereochemistry, while in the reduction of (*S*)-**27** by Rh(I)–(2*S*,4*S*)-bdpp, the *threo* product is also formed in $SS : RS = 15.2 : 1$ ratio, indicating strong substrate-controlled selectivity [14]. Under kinetic resolution conditions, however, the Rh–bdpp catalyst re-

Table 21.19 Kinetic resolution of ketones and imines.

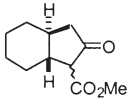
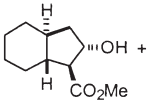
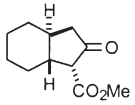
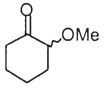
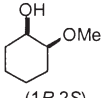
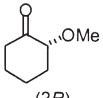
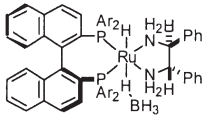
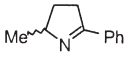
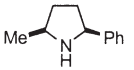
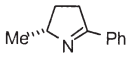
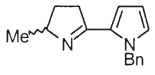
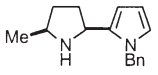
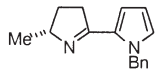
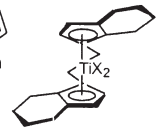
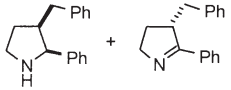
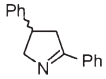
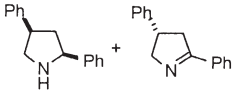
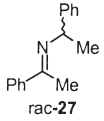
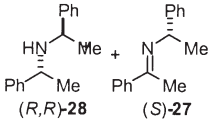
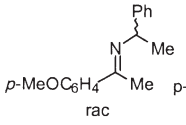
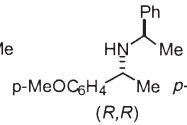
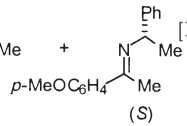
	Substrate	Major diastereomer	Recovered substrate	Catalyst	mol%	HCl (mol%)	P_{H_2}	Solvent	Conversion [%]	Diastereomeric ratio	%ee recov.	k_R/k_S	TOF	Reference
1				$RuCl_2$((*S*)-binap)	1.2	13.0 9.5 8.1	52 psi	MeOH	98.4 43.5 33.0	72:28 98:2 100:0				116
2		 (1*R*,2*R*)	 (2*S*)	(*S*,*SS*)-**25**	0.05		8 atm	*i*-PrOH	53	highly sel. 91 (*S*)		28		117
3		 (1*R*,2*S*)	 (2*R*)	(*S*,*SS*)-**25**  (*S*,*SS*)-**25** Ar = 3,5-$(CH_3)_2C_6H_3$	0.05		8 atm	*i*-PrOH	53	highly sel. 94 (*R*)		38		117
4				Titanocene cat **26**	5		80 psi	THF	50	highly sel. 99 (*R*) 99% ee				118

Table 21.19 (continued)

	Substrate	Major diastereomer	Recovered substrate	Catalyst	mol%	HCl (mol%)	P_{H_2}	Solvent	Conversion [%]	Diastereomeric ratio	%ee recov.	k_R/k_S	TOF	Reference
5				 Titanocene cat **26**	5		80 psi	THF	50	highly sel. 98% ee	96 (*R*)			118
6				Titanocene cat	5		80 psi	THF	50	85:15 >95% ee	75 (*R*)			118
7				Titanocene cat	5		80 psi	THF	50	75:25 99% ee	49 (*R*)			118
8	 rac-**27**	 (*R*,*R*)-**28** (*S*)-**27**		[RhCl((*S*,*S*)-bdpp)]Cl [RhCl((*S*,*S*)-chiraphos)]Cl	2 2		1000 psi 1000 psi	MeOH MeOH	67 82		83 (*S*) 7 (*S*)	5.7		14 14
9	 rac	 (*R*,*R*)	 (*S*)	[RhCl((*S*,*S*)-bdpp)]Cl	2		1000 psi	MeOH	72		98 (*S*)			14

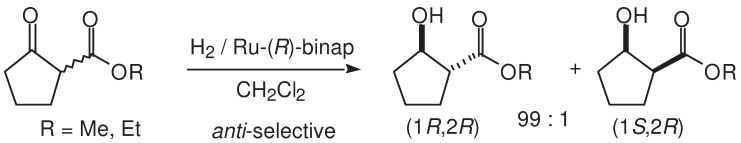
quired relatively high conversion in order to obtain (*S*)-chiral imine of high enantiomeric excess (entries 8 and 9) [14].

21.8
Dynamic Kinetic Resolution

In the kinetic resolution, the yield of desired optically active product cannot exceed 50% based on the racemic substrate, even if the chiral-discriminating ability of the chiral catalyst is extremely high. In order to obtain one diastereomer selectively, the conversion must be suppressed to less than 50%, while in order to obtain one enantiomer of the starting material selectively, a higher than 50% conversion is required. If the stereogenic center is labile in the racemic substrate, one can convert the substrate completely to gain almost 100% yield of the diastereomer formation by utilizing dynamic stereomutation.

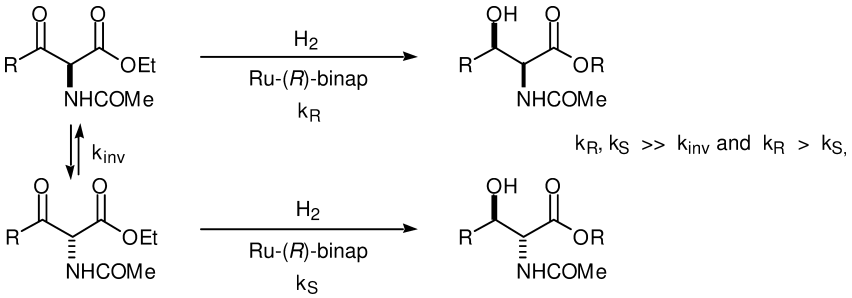
In 1989, Noyori reported the first example of dynamic kinetic resolution in the enantioselective hydrogenation of *α*-substituted *β*-keto esters [119]. If the racemization of enantiomeric keto esters is rapid enough with respect to hydrogenation of the *β*-keto unit and the chiral discriminating ratio ($k_R : k_S$) is high, the hydrogenation will afford only one diastereomer out of four possible stereoisomeric hydroxy esters. The efficiency of the dynamic kinetic resolution and the sense of diastereoselection and enantioselection are strongly dependent on the structure of the substrate and the reaction conditions, including the solvent. The results of the dynamic kinetic resolution of *β*-keto esters are presented in Tables 21.20 to 21.22.

In the hydrogenation of cyclic *β*-keto esters (ketones substituted with an alkoxycarbonyl moiety), Ru(II)–binap reduced a racemic substrate in DCM with high *anti*-diastereoselectivity to give a 99 : 1 mixture of the *trans*-hydroxy ester (92% ee) and the *cis*-hydroxy ester (92% ee), quantitatively [Eq. (18)] [119, 120].

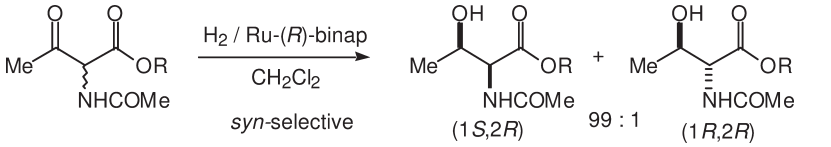


(18)

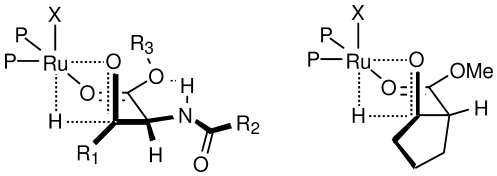
On the other hand, racemic *β*-keto esters with an amide or carbamate group in the *α*-position were reduced with high *syn*-diastereoselectivity (99:1) and with high enantioselectivity, leading to threonine-type products [Eq. (19)]. In polar methanol solution, the diastereoselectivity diminished to 71 : 29 (Table 21.20, entry 1) [123]. Results obtained using isotope-labeling experiments suggest that the hydrogenation proceeds via the ketone, and not via the enol [64]. The origin of the *syn* selectivity directed by an amide or a carbamate group was explained by a transition state stabilized by hydrogen bonding between the CONH and ester OR units [119]. *Anti*-selectivity in the case of cyclic *β*-keto esters is rationalized by the steric constraint of the cyclic ketone moiety (Scheme 21.10).



Scheme 21.9 Dynamic kinetic resolution of β-keto ester.



(19)



Scheme 21.10

Genêt also reported the dynamic kinetic resolution of α-substituted β-keto esters using several atropisomeric diphosphine ligands [121, 122, 124, 125] with high diastereo- and enantioselectivity. The *syn*:*anti* preference is lower using 10 mol.% of catalyst than in the presence of 1 mol.% of catalyst in MeOH [120]. This supported the fact that the hydrogenation needs to be slower than the racemization of the chiral center in order to achieve high stereoselectivities. For effective dynamic kinetic resolution, high hydrogen pressure should generally be avoided. With a rhodium catalyst, β-keto esters were reduced in moderate to good diastereoselectivities, but with low enantioselectivities [121].

The sense of diastereoselectivity in the dynamic kinetic resolution of 2-substituted β-keto esters depends on the structure of the keto ester. The ruthenium catalyst with atropisomeric diphosphine ligands (binap, MeO-biphep, synphos, etc.) induced *syn*-products in high diastereomeric and enantiomeric selectivity in the dynamic kinetic resolution of β-keto esters with an α-amido or carbamate moiety (Table 21.21) [119–121, 123, 125–127]. In contrast to the above examples of α-amido-β-keto esters, the TsOH or HCl salt of β-keto esters with an α-amino unit were hydrogenated with excellent *anti*-selectivity using ruthenium-atropiso-

Table 21.20 Dynamic kinetic resolution of β-keto esters.

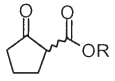
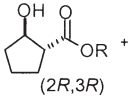
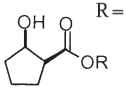
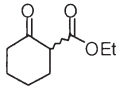
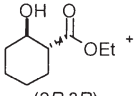
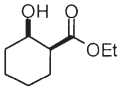
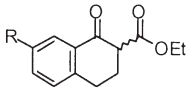
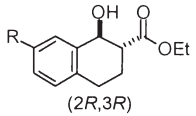
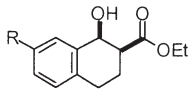
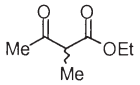
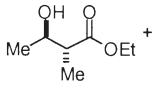
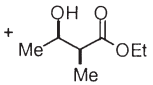
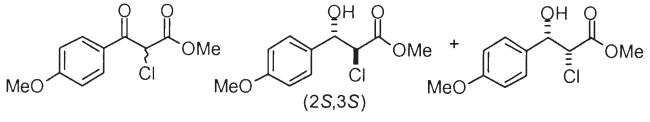
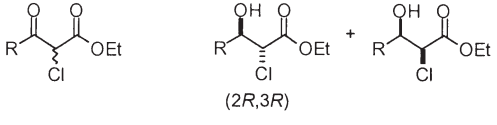
	Substrate	Major diastereomer	Minor diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Temp. [°C]	Diastereomeric ratio [*anti* : *syn*]	%ee (*anti*)	TOF	Reference
1		 (2*R*,3*R*)		R = Et [RuCl(C_6H_6)((*R*)-binap)]Cl	0.085	100 atm	CH_2Cl_2	50	99:1	92 (2*R*,3*R*)	16.7	119
				$RuBr_{2(}$(*R*)-binap)	1	20 atm	MeOH	80	97:3	94 (2*R*,3*R*)	25	122
				$RuBr_2$((*R*)-binap)	1	100 atm	EtOH	80	96:4	85 (2*R*,3*R*)	2.1	133
				R = Me [RuC(((C_6H_6)((*R*)-binap)]Cl	0.085	100 atm	CH_2Cl_2	50	99:1	92 (2*R*,3*R*)	16.7	120
2		 (2*R*,3*R*)		[Rucl(C_6H_6)((*R*)-binap)]Cl	0.085	100 atm	CH_2Cl_2	50	95:5	90 (2*R*,3*R*)	16.7	120
					1	20 atm	CH_2Cl_2	80	76.5:23.5	91 (2*R*,3*R*)	33	122
				$RuBr_2$((*R*)-binap)	1		MeOH		46:54	88 (2*R*,3*R*)	50	122
				$RuBr_2$((*S*)-binap)	1	20 atm	EtOH	80	73.5:26.5	91 (2*S*,3*S*)	33	133
3		 (2*R*,3*R*)										
				R = H $RuBr_2$((*R*)-MeO-biphep)		10 atm	EtOH	80	98.5:1.5	95 (2*R*,3*R*)	1.2	133
				R = OMe $RuBr_2$((*R*)-binap)	3	10 atm	CH_2Cl_2	80	98.5:1.5	96 (2*R*,3*R*)	0.7	122
				$RuBr_2$((*R*)-MeO-biphep)	3	10 atm	MeOH	80	98.5:1.5	95 (2*R*,3*R*)	0.6	122
4				$RuBr_2$((*R*)-binap)	0.083	100 atm	EtOH	25	49:51	97 (2*R*,3*R*)	30	120
				[RuCl(C_6H_6)((*R*)-binap)]Cl	0.085	100 atm	CH_2Cl_2	50	68:32	94 (2*R*,3*R*)	20	107

Table 21.20 (continued)

	Substrate	Major diastereomer	Minor diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Temp. [°C]	Diastereomeric ratio [*anti* : *syn*]	%ee (*anti*)	TOF	Reference
5				Ru(allyl)$_2$((*S*)-binap)	1	80 atm	CH_2Cl_2	80	96:4	94 (2*S*,3*S*)	5.3	124
				Ru(allyl)$_2$((*R*-binap)	0.5	5atm	MeOH	50	8.5:91.5	77 (2*R*,3*R*)	12.5	124
				[Ru((*S*)-MeO-biphep)]	1	60 bar	CH_2Cl_2	80	97.5:2.5	94 (2*S*,3*S*)	2.0	134
6												
			R = Me	Ru(allyl)$_2$((*R*)-binap)	0.5	90 atm	CH_2Cl_2	80	99:1	99 (2*R*,3*R*)	20	124
					1	30 atm	EtOH	27	52:48	93 (2*R*,3*R*)	5	124
				[Ru((*R*)-MeO-biphep)]	1	80 bar	CH_2Cl_2	80	99.5:0.5	98 (2*R*,3*R*)		133
			P = Rh	[Ru((*S*)-binap)]	0.5	86 atm	CH_2Cl_2	80	96:4	83 (2*S*,3*S*)	42.7	124
				$RuBr_2$((*R*)-binap)	1	30 atm	EtOH	27	9.5:90.5	31 (2*R*,3*R*)	5	124

meric diphosphine catalysts to afford *anti*-*β*-hydroxy-*α*-amino acids (Table 21.22, entries 1–4) [128–131]. In this case, a five-membered transition state is envisioned. High *anti*-selectivity was also observed in the reaction of an *α*-phthalimido-*β*-keto ester in methanol (Table 21.22, entry 5) [132], and in the reduction of keto esters having an *α*-chloro group (Table 21.20, entries 5 and 6) [124, 133, 134]. *β*-Keto esters with a cyclic keto unit also afforded *anti*-products selectively, as described [53, 119, 120, 122, 123, 133].

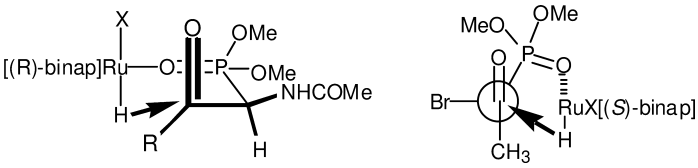
Dynamic kinetic resolution of *β*-keto phosphonic esters containing an *α*-amido group was examined using Ru–(*R*)-binap, and resulted in a phosphonate analogue of *α*-amino acids with (*R,R*)-*syn* configuration and very high selectivity ($k_R/k_S = 39$; $k_{inv}/k_S = 31$) [135]. The overall stereochemical outcome was explained on the basis of the Felkin-Anh model (Scheme 21.11), wherein *β*-keto phosphonic esters with *α*-bromo substituent were hydrogenated with high *syn*-selectivity [136].

In the hydrogenation of simple 2-alkyl-3-oxobutanoates, the interconversion between the enantiomers is relatively slow, and very poor resolution results are observed (see Table 21.20, entry 4) [107, 119, 120, 123]. Efficient dynamic kinetic resolution of 2-alkyl *β*-keto esters was first observed in the asymmetric hydrogenation of *α*-alkyl-*β*-keto esters which are derived from (*S*)-proline bearing a stereogenic center at the *γ*-position. The type of *N*-protecting group played a dramatic role, and the *N*-Boc substrate **29b** afforded naturally occurring (2*R*,3*R*)-dolaproine with *syn*-configuration, while *β*-keto esters *N*-protected as an amine hydrogen chloride salt **29a** afforded an *anti*-adduct in moderate to high diastereoselectivity (Scheme 21.12) [137, 138].

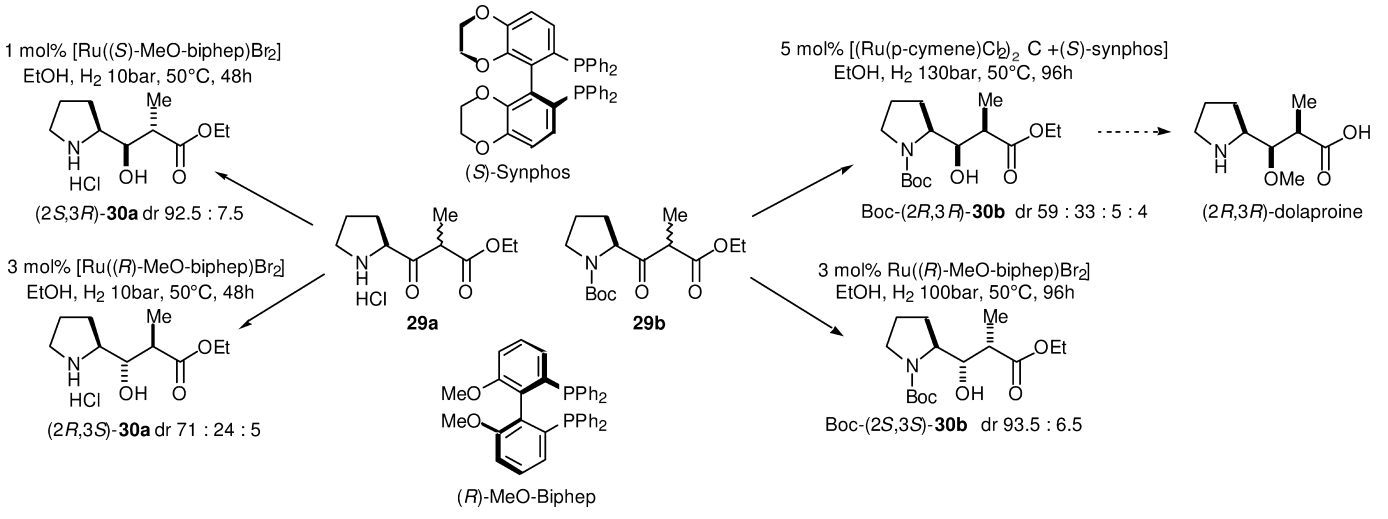
Dynamic kinetic resolution is possible for *α*-alkyl or *α*-alkoxy cyclic ketones in the presence of KOH, which causes mutation of the stereogenic center; *syn*-alcohols were obtained selectively with high enantioselectivity using ruthenium–3,5-xyl-binap. Dynamic kinetic resolution of 2-arylcycloalkanones also proceeded with extremely high *syn*-selectivity and with high enantioselectivity using ruthenium–binap-diamine as catalyst (Table 21.23) [12, 139, 140].

21.9 Conclusions

By linking the steric factor of the stereogenic center of substrates with the chiral-inducing ability of properly designed ligands, homogeneous diastereoselective hydrogenation can attain levels of stereoselectivity that will enable the industrial



Scheme 21.11 Felkin-Anh model for the hydrogenation of keto phosphate.



Scheme 21.12 Effect of *N*-protecting groups on the dynamic kinetic resolution.

Table 21.21 Dynamic kinetic resolution of α-subsituted β-keto esters.

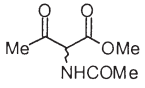
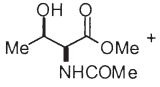
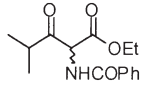
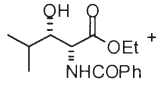
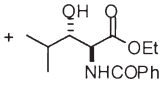
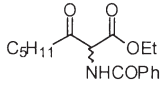
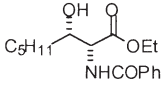
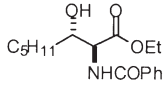
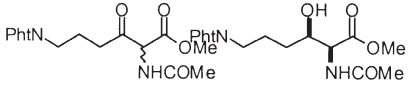
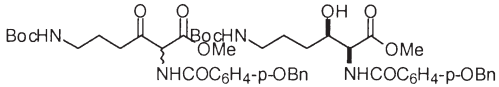
	Substrate	Major diastereomer	Minor diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Diastereomeric ratio [*anti*:*syn*]	%ee (*syn*)	TOF	Reference
1		 (2*S*,3*R*)		$Ru(O_2CCF_3)_2$[(*R*)-binap]	1	90 atm	CH_2Cl_2	95:5	51	0.43	121
				$RuBr_2$[(–)-chiraphos]	1	90 atm	CH_2Cl_2	97:3	85	0.83	121
				[Rh(nbd)((–)-dipamp)]$^+$	1	70 atm	THF	94:6	39	1.0	121
				$RuBr_2$[(*R*)-binap]	0.4	100 atm	CH_2Cl_2	99:1	98	5	119
				$RuBr_2$[(*R*)-binap]	0.4	100 atm	MeOH	71:29	90		123
2		 (2*R*,3*S*)		$RuCl_2$((*S*)-binap)$(dmf)_m$	2	100 atm	CH_2Cl_2	100:0	99	1.0	131
				$RuBr_2$((*S*)-synphos)	2	130 bar	CH_2Cl_2	99.5:0.5	97	0.5	127
3		 (2*R*,3*S*)		$RuBr_2$((*S*)-synphos)	2	130 bar	CH_2Cl_2	99:1	99	0.4	131
4	 (2*S*,3*R*) (major)			$RuBr_2$((*R*)-MeO-biphep)	0.5	100 bar	CH_2Cl_2	>99:1		1.85	125
				$RuBr_2$((*R*)-MeO-biphep)	1	100 bar	MeOH	65:35		1.1	125
5	 (2*S*,3*R*) (major)			$RuBr_2$((*R*)-MeO-biphep)	1	130 bar	CH_2Cl_2	96:5:3.5	94	1.1	126

Table 21.21 (continued)

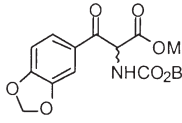
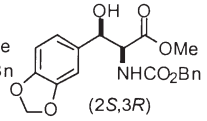
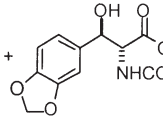
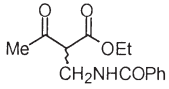
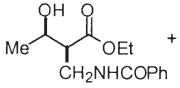
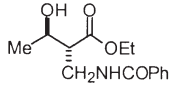
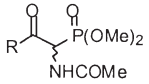
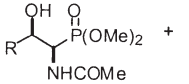
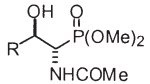
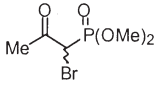
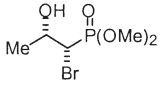
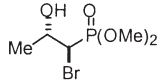
	Substrate	Major diastereomer	Minor diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Diastereomeric ratio [*anti* : *syn*]	%ee (*syn*)	TOF	Reference
6		 (2*S*,3*R*)		$RuBr_2$[(*R*)-binap]	0.4	100 atm	CH_2Cl_2	99:1	92	2.4	119
7		 (2*S*,3*R*)		$[RuCl_2((R)\text{-binap})]_2NEt_3$	1	100 atm	CH_2Cl_2	94:6	98	5	119
				[RuCl((*R*)-3,5-Bu^t_2-binap)(*p*-cymene)]	0.1	50 atm	CH_2Cl_2/MeOH	99:1	99	13.8	123
				[RuBr((*R*)-binap)(benzene)]Br	1	50 atm	CH_2Cl_2/H_2O	89.5:10.5	98	2.3	123
				[RuBr((*R*)-binap)(benzene]Br	1	50 atm	MeOH	54.5:45.5	80	2.4	123
8		 (1*S*,2*R*)									
				R = Ph	[$RuCl_2$(*R*)-binap](dmf)$_n$	1	4 atm	MeOH	98:2	95	0.8	135
				R = Me	[$RuCl_2$(*R*)-binap](dmf)$_n$	0.17	4 atm	MeOH	97:3	>98	9.0	135
								$k_R/k_S = 39$ and $k_{inv}/k_S = 31$			
9		 (1*R*,2*S*)		[$RuCl_2$(*S*)-binap](dmf)$_n$	0.05	4 atm	MeOH	90:10	98	0.8	136
								$k_R/k_S = 13$ and $k_{inv}/k_S = 11.5$			

Table 21.22 Dynamic kinetic resolution of α-substituted β-keto esters.

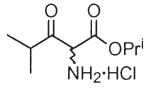
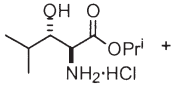
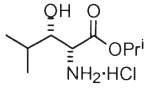
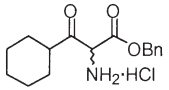
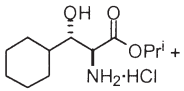
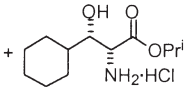
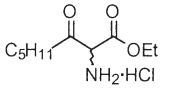
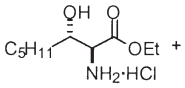
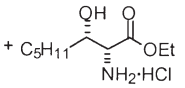
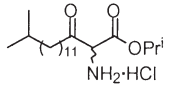
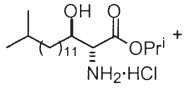
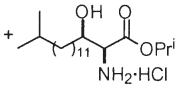
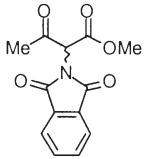
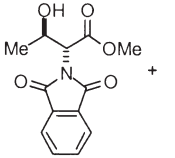
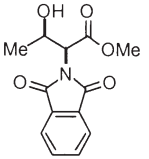
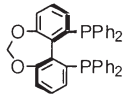
	Substrate	Major diastereomer	Minor diastereomer	Catalyst	mol%	P_{H_2}	Solvent	Diastereomeric ratio [*anti*:*syn*]	%ee (*anti*)	TOF	Reference
1		 (2*S*,3*S*)		$[RuCl_2(S)\text{-binap}](dmf)_n$	4	100 atm	CH_2Cl_2	98:2	92	0.5	128
				$RuBr_2((S)\text{-MeO-biphep})$	1	12 bar	EtOH	99:1	87	4.2	131
				$RuBr_2((S)\text{-synphos})$	2	12 bar	CH_2Cl_2/ 2-PrOH	99.5:0.5	97	1.9	130
2		 (2*S*,3*S*)		$[RuCl(S)\text{-binap}](dmf)_n$	4	100 atm	CH_2Cl_2	>99:1	97	0.44	128
3				$RuBr_2((S)\text{-synphos})$	2	12 bar	CH_2Cl_2 (EtOH)	96.5:3.5	91	1.8	130
4				$RuBr_2((R)\text{-MeO-biphep})$	2	20 bar	MeOH	98:2	41	0.7	129
				$RuBr_2((R)\text{-MeO-biphep})$	2	20 bar	CH_2Cl_2	90:10	88	0.7	129
				$RuBr_2((R)\text{-synphos})$	2	12 bar	CH_2Cl_2/ MeOH	96:4	92	1.7	129
5				 (*R*)-C_3-Tunephos $[Ru(S)\text{-}C_3\text{-Tunephos}]$	2	100 bar	MeOH	>97:3	>99	0.7	132

Table 21.23 Dynamic kinetic resolution of ketones.

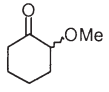
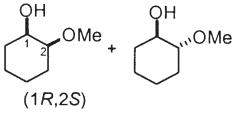
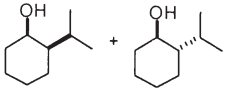
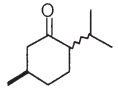
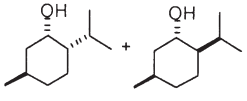
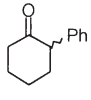
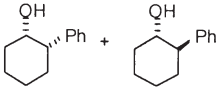
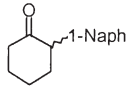
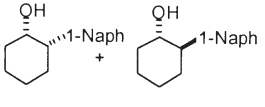
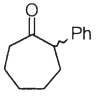
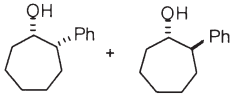
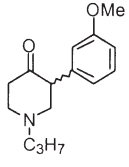
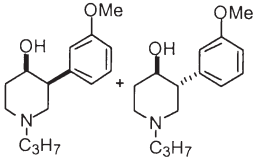
	Substrate	Diastereomers	Catalyst	mol%	P_{H_2}	Solvent	Diastereomeric ratio [*syn*:*anti*]	%ee (*syn*)	TOF	Reference
1		 (1*R*,2*S*)	$[RuCl_2((S)\text{-binap})]_2(NEt_3)$ -(*S*,*S*)-DPEN-KOH	0.1	50 atm	*i*-PrOH	98.5:1.5	92 (*R*,*S*)	1000	139
			$[RuCl_2((S)\text{-3,5-xylyl-binap})]_2(NEt_3)$ -(*S*,*S*)-DPEN-KOH	0.1	50 atm	*i*-PrOH	99.5:0.5	99 (*R*,*R*)	50	139
2			$RuCl_2((S)\text{-binap})(dmf)_m$ -(*R*,*R*)-DPEN-KOH	0.2	4 atm	*i*-PrOH	99.8:0.2	93 (*R*,*R*)	45.5	12
3			$RuCl_2((R)\text{-binap})(dmf)_m$ -(*S*,*S*)-DPEN-KOH	0.2	4 atm	*i*-PrOH	highly selective			12
4			$RuCl_2((R)\text{-tol-binap})(dmf)_m$ -(*S*,*S*)-DPEN-^{t}BuOK	0.05	8 atm	*i*-PrOH	100:0	97 (*S*,*S*)	500	140
5			$RuCl_2((R)\text{-tol-binap})(dmf)_m$ -(*R*,*R*)-DPEN-^{t}BuOK	0.05	8 atm	*i*-PrOH	98:2	93 (*S*,*S*)	125	140

Table 21.23 (continued)

	Substrate	Diastereomers	Catalyst	mol%	P_{H_2}	Solvent	Diastereomeric ratio [*syn*:*anti*]	%ee (*syn*)	TOF	Reference
6			$RuCl_2$((*R*)-tol-binap)(dmf)m -(*S*,*S*)-DPEN-^{t}BuOK	0.05	8 atm	*i*-PrOH	100:0	95 (*S*,*S*)	83	140
7			$RuCl_2$((*S*)-tol-binap)(dmf)m -(*S*,*S*)-DPEN-^{t}BuOK	0.2	8 atm	*i*-PrOH	>99:1	97 (*S*,*R*)	20.8	140

preparation of optically active compounds with several stereogenic centers. Functional group-directed hydrogenation led to good results *via* the interaction of a heteroatom in the substrate with the metal or with the ligand, whilst by selecting the catalyst, diastereoselective hydrogenation can induce excellent stereoselectivity *via* double stereo-differentiation (matched pair). However, in general the activity of hydrogenation catalysts remains poor, especially for those substrates with bulky groups proximal to the reaction site. Consequently, it will be necessary to develop more efficient catalysts to produce higher turnover frequencies.

Abbreviations

d.e.	diastereomeric excess
DCM	dichloromethane
ee	enantiomeric excess
TBSO	tert-butyldimethylsilyloxy
THF	tetrahydrofuran

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