Highly Efficient Enantioselective Synthesis of Optically Active Carboxylic Acids by $Ru(OCOCH_3)_2$[(*S*)-H_8-BINAP]

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In the presence of a catalytic amount of $Ru(OCOCH_3)_2$[(*S*)-H_8-BINAP] [H_8-BINAP = 2,2′-bis-(diphenylphosphino)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl], the asymmetric hydrogenation of α,β- and β,γ-unsaturated carboxylic acids afforded the corresponding saturated carboxylic acids in higher enantiomeric excesses and at faster reaction rates than those using the $Ru(OCOCH_3)_2$[(*R*)-BINAP] catalyst [BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl]. The hydrogenation of (*E*)-2-alkyl-2-alkenoic acids by the H_8-BINAP catalyst system produced saturated acids in 95−97% ee. 2-Methylcinnamic acid was treated with H_8-BINAP−Ru(II) complex as a catalyst to yield a hydrogenated product in much higher ee than that produced by BINAP−Ru(II) (89 and 30% ee, respectively). This homogeneous catalysis using H_8-BINAP−Ru(II) established a promising synthetic route to (*S*)-ibuprofen in up to 97% ee. Asymmetric hydrogenation of β-disubstituted acrylic acids also proceeded smoothly with good enantioselectivities (70−93% ee). In addition, the hydrogenation of trisubstituted acrylic acids (up to 88% ee) was investigated. Hydrogen pressure effect on the sense and level of enantioselection was shown to be substrate dependent. The difference between the H_8-BINAP− and BINAP−Ru(II) complexes was also discussed.

Introduction

Asymmetric hydrogenation by chiral transition-metal complexes has been one of the most powerful methods for the synthesis of optically active organic compounds.[1] We have already reported that BINAP−Ru(II) complexes are effective catalysts for asymmetric hydrogenation of a wide range of prochiral substrates.[2] Dicarboxylate complex **1**,[3] for example, catalyzes the enantioselective hydrogenation of various mono- and disubstituted α,β-unsaturated carboxylic acids to produce optically active carboxylic acids with very high ee's.[3−6] These products are very important building blocks for the synthesis of new materials, such as non-steroidal anti-inflammatory (NSAI) agents[7] and ferroelectric liquid crystals (FLCs).[8] However, the need remains for improvement with respect to catalytic activities and the application range of the substrates. We previously prepared a new atropisomeric bis(triarylphosphine), H_8-BINAP,[9] which possesses a unique structural feature compared to conventional BINAPs. We have already reported its outstanding asymmetric induction ability in the H_8-BINAP−Ir(I) complex-catalyzed asymmetric hydrogenation of certain β-thiacycloalkanones and benzocycloalkanones.[10] We here report that chiral $Ru(OCOCH_3)_2$(H_8-BINAP) (**2**),[9b] the analogous complex of **1**, and [RuI(H_8-BINAP)(*p*-cymene)]I (**3**)[9b] are more effective catalysts than **1** and the related complexes for the asymmetric hydrogenation of α,β-unsaturated carboxylic acids.[11]

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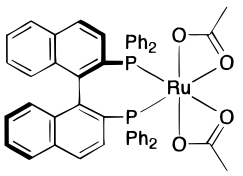
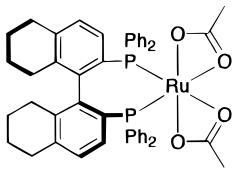
Table 1. Asymmetric Hydrogenation of 4a−f Catalyzed by H_8-BINAP− and BINAP−Ru(II) Complexes[a]

			conditions				product	
run	substrate	catalyst	S/C[b]	H_2, atm	time, h	conv,[c] %	yield,[d] %	ee,[e] %
1	**4a**	(*S*)-**2**	200	1.5	20	100	85	97 (*S*)
2	**4a**	(*S*)-**2**	200	4.0	15	100	83	96 (*S*)
3	**4a**	(*R*)-**3**	200	4.0	15	94	73	96 (*R*)
4	**4b**	(*S*)-**2**	213	1.5	24	100	89	96[f] (*S*)
5	**4b**	(*R*)-**1**	220	1.5	24	75	69	84[f] (*R*)
6	**4c**	(*S*)-**2**	201	1.5	20	100	98	94 (*S*)
7[g]	**4c**	(*S*)-**2**	204	1.5	22	100	90	96 (*S*)
8[g,h]	**4c**	(*S*)-**2**	209	4.0	3	100	83	94 (*S*)
9[g,h]	**4c**	(*S*)-**2**	1074	4.0	4	59	56	93 (*S*)
10[g,h]	**4c**	(*R*)-**1**	1016	4.0	4	27	26	79 (*R*)
11	**4d**	(*S*)-**2**	197	1.5	20	100	80	95[f] (*S*)
12	**4d**	(*R*)-**1**	203	1.5	37	100	95	88[f] (*R*)
13[i]	**4e**	(*S*)-**2**	200	1.8	26	100	93	86 (*S*)
14[i]	**4e**	(*S*)-**2**	200	25	15	100	82	82 (*S*)
15[i]	**4e**	(*S*)-**2**	200	97	8	100	91	75 (*S*)
16	**4e**	(*S*)-**2**	200	1.5	48	95	87	89 (*S*)
17	**4e**	(*R*)-**1**	200	1.5	48	30	29	30 (*R*)
18[j]	**4f**	(*S*)-**2**	200	1.8	182	55		75 (*R*)
19[j]	**4f**	(*S*)-**2**	200	25	90	94		68 (*R*)
20[j]	**4f**	(*S*)-**2**	200	100	74	100	95	61 (*R*)
21[i]	**4f**	(*S*)-**2**	200	1.8	117	77		73 (*R*)
22[i]	**4f**	(*S*)-**2**	200	27	61	100	90	74 (*R*)
23[i]	**4f**	(*S*)-**2**	200	105	16	100	90	71 (*R*)
24[k]	**4f**	(*S*)-**2**	200	5.5	56	89		73 (*R*)
25[k]	**4f**	(*S*)-**2**	200	29	24	100	88	70 (*R*)
26[k]	**4f**	(*S*)-**2**	200	109	6	100	91	72 (*R*)

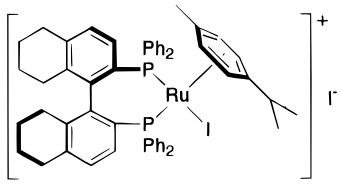
[a] Hydrogenation was carried out in an autoclave at 10−25 °C in methanol (solvent/substrate = 5−50 mL/g) unless otherwise stated, and the chemical selectivity of **5a**−**f** was 100%, as given by ^{1}H NMR analysis. [b] Substrate/catalyst ratio (mol/mol). [c] As given by ^{1}H NMR analysis. [d] Isolation yield obtained on Kugelrohr distillation. [e] Enantiomeric excess was determined by HPLC analysis of the anilide of the saturated carboxylic acid with a Daicel Chiralcel OB or OD column, unless otherwise indicated. Absolute configuration was determined by the sign of optical rotation value. [f] Measured by GLC analysis of the saturated carboxylic acid with a Chrompack CP-cyclodextrin-β-236M-19 capillary column. [g] Solvent system was MeOH/H_2O (10:1). [h] At 50 °C. [i] At 60 °C. [j] At 30 °C. [k] At 90 °C.



(*R*)-**1**



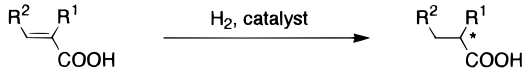
(*S*)-**2**



(*R*)-**3**

Results and Discussion

Asymmetric Hydrogenation of α,β-Disubstituted (*E*)-Acrylic Acids. Table 1 shows the results of the hydrogenation of α-mono-β-monosubstituted (*E*)-acrylic acids **4a**−**f**. Hydrogenation of (*E*)-2-alkyl-2-alkenoic acids (**4a**−**d**) in methanol catalyzed by (*S*)-**2** yielded quantitatively the corresponding saturated acids with exceedingly high enantioselectivities (95−97% ee). In the presence of a catalytic amount of (*S*)-**2** (run 1), for instance, the hydrogenation of tiglic acid (**4a**) under 1.5 atm of hydrogen proceeded smoothly at room temperature, giving exclusively 2-methylbutyric acid (**5a**) in 97% ee. Using the neutral complex (*S*)-**2** (run 2) or the cationic one (*R*)-**3** (run 3) under 4.0 atm of hydrogen, **4a** was hydrogenated in 96% ee. This result is better than those obtained with various chiral BINAP−Ru(II) complexes, including **1** (which gives up to 92% ee,[3a,b] under similar conditions).[4bef,12] The high asymmetric induction ability of (*S*)-**2** was effectively demonstrated in the hydrogenation of other (*E*)-2-alkyl-2-alkenoic acids, i.e., (*E*)-2-methyl-2-pentenoic acid (**4b**, run 4), (*E*)-2-methyl-2-hexenoic acid (**4c**, run 6), and (*E*)-2-ethyl-2-hexenoic acid (**4d**, run 11). Using BINAP as a diphosphine ligand resulted in lower enantioselectivities by 7−14% (runs 5, 10, and 12). As with **4c**, a higher ee was achieved in a 10:1 mixture of methanol and water (run 7) than in methanol (run 6). Furthermore, the elevated reaction temperature (50 °C) resulted in acceleration of the hydrogenation without causing a notable decrease in the enantioselectivity (run 7 vs 8). While the substrate/catalyst ratio had little effect on the enantioselectivity (run 8 vs 9), the catalytic activity is much higher when using H_8-BINAP than when using BINAP (run 9 vs 10).



4 **5**

	R^1	R^2
a:	CH_3	CH_3
b:	CH_3	C_2H_5
c:	CH_3	n-C_3H_7
d:	C_2H_5	n-C_3H_7
e:	CH_3	C_6H_5
f:	C_6H_5	C_6H_5

In the hydrogenation of 2-methylcinnamic acid (**4e**) and 2-phenylcinnamic acid (**4f**), which have a substitution pattern similar to those of **4a**−**d**, using BINAP as a ligand, the catalytic activities were not as high, and enantioselectivities, especially, were insufficient.[3a] We describe the remarkable superiority of H_8-BINAP over BINAP for the hydrogenation of prochiral β-aryl-(*E*)-acrylic acids. At room temperature, the reduction of **4e** catalyzed by (*S*)-**2** yielded (*S*)-2-methyl-3-phenylpropanoic acid (**5e**) with 95% conversion in 48 h and in 89% ee (run 16), significantly surpassing those (merely 30% conversion and 30% ee) catalyzed by (*R*)-**1** (run 17).

As for 2-substituted cinnamic acid (**4e**,**f**), the relationship of ee and hydrogen pressure was the same for (*E*)-2-alkyl-2-alkenoic acids. Enantiomeric excesses of **5e**,**f** improved at lower pressure when the reaction was catalyzed by (*S*)-**2**. The hydrogenation of **4f** was accelerated by elevated temperature (60 and 90 °C), and the enantioselectivities achieved were almost equal to that at 30 °C. However, the effect of H_2 pressure on ee at 90 or 60 °C, was unlike that at 30 °C. At 60 and 90 °C, hydrogen pressure had little influence on enantioselectivity (runs 21−26), while at 30 °C the lower pressure of H_2 brought about higher enantioselectivities. This difference is thought to depend on the isomerization of the substrate in the reaction. However, only the reductant and starting material were observed by the ^{1}H NMR analysis of the reaction mixture over the course of the hydrogenation at 60 °C. Thus, there is no evidence to

(12) Mashima, K.; Kusano, K.; Sato, N.; Matsumura, Y.; Nozaki, K.; Kumobayashi, H.; Sayo, N.; Hori, Y.; Ishizaki, T.; Akutagawa, S.; Takaya, H. *J. Org. Chem.* **1994**, *59*, 3064.

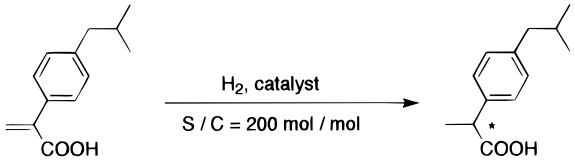
Table 2. Asymmetric Hydrogenation of 2-(4-Isobutylphenyl)propenoic Acid (6) Catalyzed by H_8-BINAP− and BINAP−Ru(II) Complexes[a]

		conditions			product	
run	catalyst	H_2, atm	time, h	conv,[b] %	yield,[c] %	ee,[d] %
1	(*S*)-**2**	4.0	24	100	99	77 (*S*)
2	(*S*)-**2**	25	24	100	99	94 (*S*)
3	(*S*)-**2**	100	8	100	97	97 (*S*)
4	(*R*)-**1**	100	8	100	99	96 (*R*)

[a] Hydrogenation was carried out in an autoclave at 10−25 °C in methanol (solvent/substrate = 25 mL/g, substrate/catalyst = 200), and the chemical selectivity of **7** was 100% as given by ^{1}H NMR analysis. [b] As given by ^{1}H NMR analysis. [c] Isolation yield obtained on column chromatography. [d] Enantiomeric excess was determined by GLC analysis of **7** with a Chrompack CP-cyclodextrin-β-236M-19 capillary column. Absolute configuration was determined by the sign of optical rotation value.

suggest that the isomerization of **4f** occurs. To date, the enantiomeric excess of **5f** obtained under 1.8 atm of H_2 (75% ee, run 18) was the highest ee in the data reported for homogeneous or heterogeneous catalysts.[13,14]

Asymmetric Hydrogenation of α-Substituted Acrylic Acid (Asymmetric Synthesis of Ibuprofen). The hydrogenation of 2-(4-isobutylphenyl)propenoic acid (**6**) using (*S*)-**2** as a catalyst under 100 atm of initial hydrogen pressure was completed in 8 h, producing the important anti-inflammatory agent[7] (*S*)-**7** in 97% ee (Table 2, run 3). The pressure effect on the hydrogenation was similar to that of 2-arylpropenoic acids using (*S*)- or (*R*)-**1**,[3a] in which higher hydrogen pressure results in higher enantioselectivities. In the case of this substrate, (*R*)-**1** matched well (*S*)-**2** in the enantiomeric excess of **7** (run 4).[15]



6 **7**

Asymmetric Hydrogenation of β-Disubstituted Acrylic Acid. Fluorinated unsaturated acid **8a** was found to be converted by (*S*)-**2** to **9a** in 93% ee (Table 3, run 2). Conversely, the use of the analogous complex (*R*)-**1** decreased the ee by 18% (run 3). As for **8a**, the enantioselectivities of the reaction became better at higher pressure (runs 1 and 2). (*E*)-3-Phenyl-2-butenoic acid (**8b**) showed the same pattern as **8a** in the H_2 pressure effect on the sense and degree of enantioselectivity, in that β-enantioface selectivity (*vide infra*, Chart 1, **I**) was dramatically increased by (*S*)-**2** at higher pressure (runs 4 and 5). The superiority of H_8-BINAP over BINAP then became larger in ee by 43% (run 6). On the other hand, the asymmetric hydrogenation of (*Z*)-3-phenyl-2-butenoic acid (**8c**), the *E*−*Z* isomer of **8b**, showed a hydrogen pressure effect the reverse of that of **8b**, and the lower H_2 pressure resulted in a slightly higher β-enantioface selectivity (runs 7 and 8). In the

(13) In this connection, reduction of **4f** by (*S*)-**1** gave **5f** in 41% ee (S/C = 136, an initial H_2 pressure of 4.0 atm, 40 °C, 100 h).[3a]

(14) For heterogeneous catalysts, see: Nitta, Y.; Ueda, Y.; Imanaka, T. *Chem. Lett.* **1994**, 1095.

(15) Previously, Stahly and co-workers obtained (*S*)-**7** in 91% ee by reduction of **6** catalyzed by (*S*)-**1** or *in-situ*-generated Ru(acac)$_2$[(*S*)-binap] (S/C = 800, H_2 68 atm).[4h]

Table 3. Asymmetric Hydrogenation of 8a−c Catalyzed by H_8-BINAP− and BINAP−Ru(II) Complexes[a]

			conditions				product	
run	substrate	catalyst	S/C[b]	H_2, atm	time, h	conv,[c] %	yield,[d] %	ee,[e] %
1	**8a**	(*S*)-**2**	209	1.5	24	100	87	65 (+)
2	**8a**	(*S*)-**2**	200	100	8	100	86	93 (+)
3	**8a**	(*R*)-**1**	200	100	8	100	83	75 (−)
4	**8b**	(*S*)-**2**	200	4.0	25	100	97	5 (*R*)
5	**8b**	(*S*)-**2**	200	100	7	100	90	70 (*S*)
6	**8b**	(*R*)-**1**	200	100	7	89		27 (*R*)
7	**8c**	(*S*)-**2**	200	4.0	25	100	93	92 (*R*)
8	**8c**	(*S*)-**2**	200	100	6	100	89	79 (*R*)
9	**8c**	(*R*)-**1**	200	4.0	25	100	98	92 (*S*)

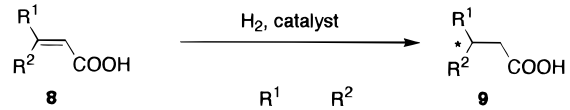
[a] Hydrogenation was carried out in an autoclave at 10−25 °C in methanol (solvent/substrate = 5−33 mL/g), and the chemical selectivity of **9a**,**b** was 100% as given by ^{1}H NMR analysis. [b,c,d,e] See footnotes in Table 1.

Table 4. Asymmetric Hydrogenation of 3-Phenyl-3-butenoic acid (10) Catalyzed by H_8-BINAP− and BINAP−Ru(II) Complexes[a]

		conditions				product	
run	catalyst	S/C[b]	H_2, atm	time, h	conv,[c] %	yield,[d] %	ee,[e] %
1	(*S*)-**2**	200	1.5	2	100	92	83 (*R*)
2	(*S*)-**2**	200	4.0	15	100	92	71 (*R*)
3	(*S*)-**2**	200	100	8	100	96	41 (*R*)
4	(*R*)-**1**	200	1.5	2	39		74 (*S*)

[a] Hydrogenation was carried out in an autoclave at 10−25 °C in methanol (solvent/substrate = 31 mL/g), and the chemical selectivity of **9b** was 100%, as given by ^{1}H NMR analysis. [b,c,d,e] See footnotes in Table 1.

cases of **8a**,**b**, at high pressure (100 atm of H_2), the catalyst seemed to distinguish mainly the olefinic carbon α to carboxylic acid moiety, because the β-enantioface selectivities of **8b**,**8c** were close [70% ee (*S*) for **8b** and 79% ee (*R*) for **8c** by (*S*)-**2**]. In other words, the arrangement of phenyl and methyl substituents on carbon β to carboxylic acid moiety showed a large effect on the enantioselectivity at a low pressure of H_2. For the reduction of **8b**,**c**, only the product and substrate were observed by ^{1}H NMR analysis, while the reduction was not completed; therefore, *E*−*Z* isomerization did not significantly occur over the course of the hydrogenation.



8 **9**

	R^1	R^2
a:	CF_3	CH_3
b:	C_6H_5	CH_3
c:	CH_3	C_6H_5

Asymmetric Hydrogenation of β,γ-Unsaturated Carboxylic Acid. To examine the catalytic performance of H_8-BINAP−Ru(II) and the isomerization of the substrate during the course of the hydrogenation, β,γ-unsaturated carboxylic acid **10** was studied (Table 4).[4f,16] 3-Phenyl-3-butenoic acid (**10**) was hydrogenated by (*S*)-**2** under 1.5 atm of hydrogen to yield **9b** in 83% ee, and this reaction was completed within 2 h because the C=C moiety was not so crowded (run 1). Considering this substrate, the hydrogen pressure effect[17] is similar to that of the reduction of **8c**, (*Z*)-isomer, and the absolute

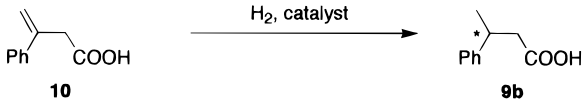
(16) For asymmetric hydrogenation of **10** catalyzed by DIOP−Rh(I) complexes, see: Yamamoto, K.; Ikeda, K.; Yin, L. L. *J. Organomet. Chem.* **1989**, *370*, 319.

Table 5. Asymmetric Hydrogenation of 11a,b Catalyzed by H_8-BINAP− and BINAP−Ru(II) Complexes[a]

				conditions				product	
run	sub-strate	catalyst	solvent	S/C[b]	H_2, atm	time, h	conv,[c] %	yield,[d] %	ee,[e] %
1	**11a**	(*S*)-**2**	THF	600	4.0	93	100	89	59 (*S*)
2	**11a**	(*S*)-**2**	THF	600	100	3	100	95	88 (*S*)
3	**11a**	(*R*)-**1**	THF	600	100	44	100		82 (*R*)
4	**11a**	(*S*)-**2**	MeOH	600	100	3	100	90	68 (*S*)
5	**11a**	(*S*)-**2**	*i*-PrOH	600	100	5	100	77	72 (*S*)
6	**11a**	(*S*)-**2**	CH_2Cl_2	600	100	23	100	86	76 (*S*)
7	**11b**	(*S*)-**2**	MeOH	200	4.0	24	100[f]		50 (2*S*,3*S*)
8	**11b**	(*S*)-**2**	MeOH	200	100	5	100[f]	95	55 (2*S*,3*S*)
9	**11b**	(*S*)-**2**	THF	200	100	18	100[f]		58 (2*S*,3*S*)
10	**11b**	(*R*)-**1**	THF	200	100	19	50[f]		53 (2*R*,3*R*)

[a] Hydrogenation was carried out in an autoclave at 10−25 °C in methanol (solvent/substrate = 10 mL/g), and the chemical selectivity of **12a** was 100%, as given by ^{1}H NMR analysis. [b,c,d,e] See footnotes in Table 1. [f] The chemical selectivity of **12b** was 92% (run 7), 100% (run 8), and 98% (run 9 and 10). The rest was *erythro* isomer.

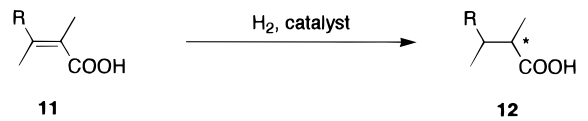
configurations of the products are also the same (runs 1−3). In addition, for this β,γ-unsaturated carboxylic acid, H_8-BINAP was superior to BINAP in both ee and reaction rate (run 1 vs 4). We carried out the ^{1}H NMR analysis of the incomplete reaction mixture and found only **10** and **9b**. There seems to be no isomerization between **8b**,**c**, and **10** under the hydrogenation conditions using **1** or **2** as a catalyst.



10 **9b**

Asymmetric Hydrogenation of Trisubstituted Acrylic Acids. Finally, we carried out the reduction of trisubstituted acrylic acids (tetrasubstituted olefins, Table 5). Although the optically active reductants of those acids have wide applicability, there are few reports where high enantiomeric excesses were obtained.[18]

The hydrogenation of trimethyl-substituted acrylic acid **11a** smoothly proceeded under high H_2 pressure to yield **12a** in 88% ee, while the phenyl-substituted acrylic acid **11b** was converted to **12b** with moderate enantioselectivity. A series of reductions of tiglic acid (**4a**) showed that alcoholic solvents, especially methanol, were the best choice.[3a] However, for the hydrogenation of 2,3-dimethyl-2-butenoic acid (**11a**), tetrahydrofuran was a better solvent choice than alcoholic solvents, methylene chloride (runs 2 vs 4−6), or their variable mixtures. This result indicates that it is not only the polarity of the solvent that influences the enantiomeric excess of the reductant. In this case, the higher pressure of H_2 caused higher ee (runs 1 and 2). The complex (*S*)-**2** as a catalyst was more effective than (*R*)-**1** in ee and, above all, in the reaction rate (run 2 vs 3).



11 **12**

a: R = Me
b: R = Ph

(17) For the reduction of **10**, lower H_2 pressure caused ee of **9b** to increase, but this trend is not applied to the all cases of the reduction of other β,γ-unsaturated carboxylic acids.[3a]

(18) Previously, high ee was obtained for the hydrogenation of 2-aryl-3-disubstituted acrylic acids catalyzed by a chiral (aminoalkyl)-ferrocenylphosphine−Rh(I) complex, see: Hayashi, T.; Kawamura, N.; Ito, Y. *J. Am. Chem. Soc.* **1987**, *109*, 7876.

Chart 1

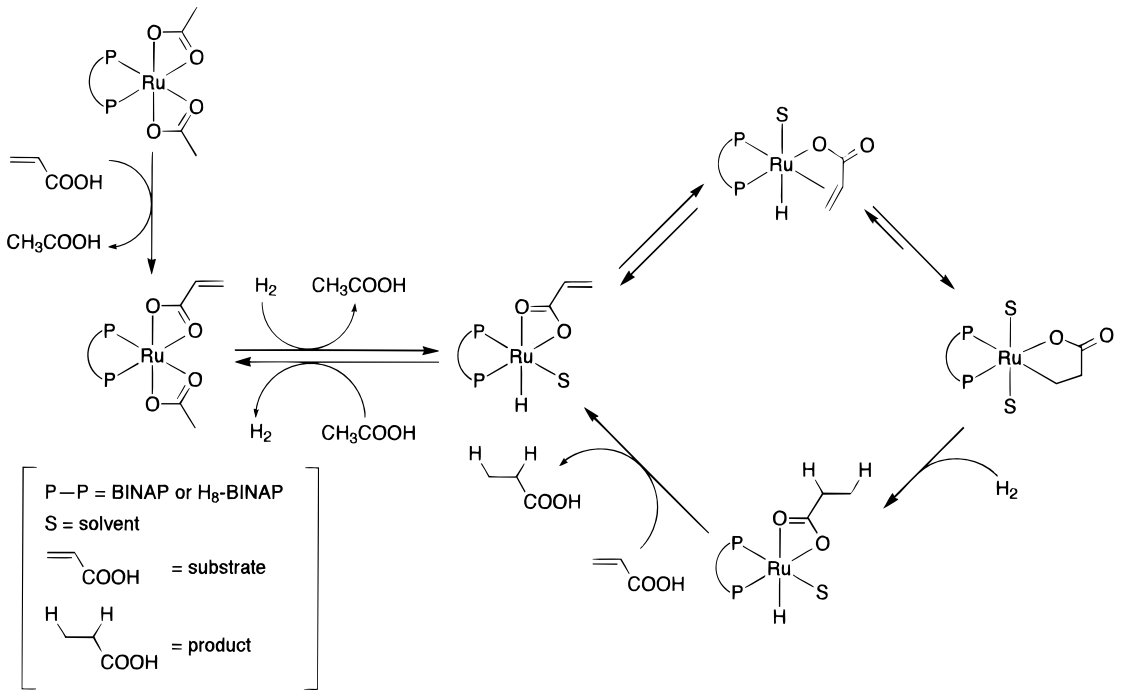
I **II**

H_2 Pressure Effects on Enantioface Selectivities and Enantiomeric Excesses in the Hydrogenation of Substituted Acrylic Acids. The H_2 pressure effect on enantioface selectivities and ee's were summarized with three classes of substrates. First, a better β-enantioface selectivity (Chart 1, **I**) of the hydrogenation by (*S*)-**2** was observed for α,β-disubstituted substrates (**4**) at lower hydrogen pressure. Second, the hydrogenation of **6**, α-substituted acrylic acid, by (*S*)-**2** proceeded in the manner of higher α-enantioface selection (Chart 1, **II**) at higher H_2 pressure. Third, in the case of β-disubstituted acrylic acids, **8b**,**c**, the trend of the H_2 pressure effect on ee's is not clear. In other words, a higher hydrogen pressure caused a higher ratio of β-enantioface selectivity for **8b**, while a slightly higher ee and the same enantioface selectivity were observed under lower hydrogen pressure for **8c**. Namely, if substrates have an α-substituent, then the ratio of β-enantioface selectivity becomes higher under a lower pressure of H_2. On the other hand, the H_2 pressure effect for substrates without an α-substituent depends on the type of β-substituents.

Possible Mechanism. Although the mechanism of this catalysis is not yet clear, Scheme 1 shows a possible pathway. As earlier reported,[5] the monohydride species seem to be important intermediates in the catalytic cycle of the hydrogenation of α,β-unsaturated carboxylic acid by BINAP−Ru(II) diacetate complexes. Important observations of the H_2 pressure effect on enentioselectivities could be affected by the equilibrium between the complex coordinated through the olefin part and the alkyl complex. Namely, the reaction under high pressure produced kinetically favorable products, while thermodynamic equilibrium influences the reaction under low pressure.

The special feature of the H_8-BINAP−metal complexes compared to BINAP−metal complexes is the value of the dihedral angle of the axial biaryl groups. Unfortunately, no X-ray structure of the H_8-BINAP−Ru complex is available; however, the structure of H_8-BINAP− and BINAP−Rh complexes could be used as models. The dihedral angle (80.3°) of the two tetralin rings in [Rh-((*S*)-H_8-BINAP)(cod)]ClO_4[9b] is wider than those of the two naphthalene rings in the BINAP−Rh complexes reported (71.0−75.5°).[19] This difference is a reflection of the larger steric hindrance of the hydrogen atoms attached to sp^3

Scheme 1



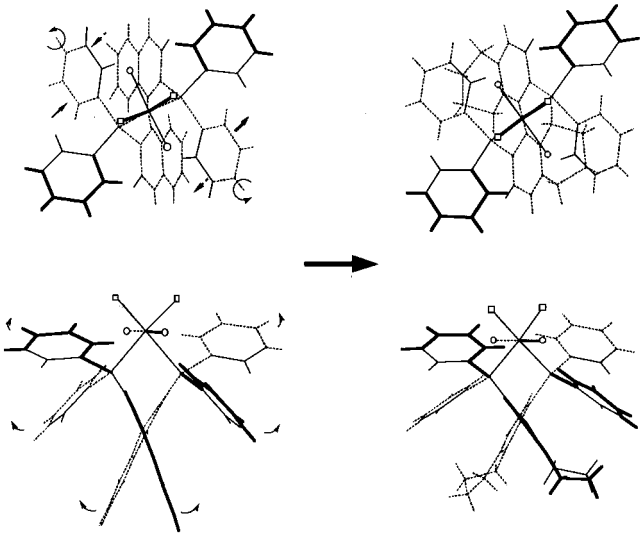


Figure 1. Models of (*S*)-BINAP−Ru (left) and (*S*)-H_8-BINAP−Ru (right) complexes. Circles show apical coordination sites, and squares show equatorial coordination sites.

carbon atoms in tetralin rings than that of hydrogen atoms on sp^2 carbon atoms in naphthalene rings.

In turn, a similar difference in the dihedral angles of the axial biaryl groups between the H_8-BINAP− and BINAP−Ru(II) could be assumed. Simple models of these are shown in Figure 1. From the models, the arrangements of four phenyls on the phosphorous atoms are influenced. These conformational changes made the equatorial coordination sites of the H_8-BINAP−Ru complex more crowded than that of the BINAP−Ru complex and the apical ones wider. Thus, in the case of the H_8-BINAP−Ru complex, the enantioselectivity on the coordination of olefin to ruthenium becomes better than that in the BINAP−Ru complex because of the crowded equatorial site, and the hydrogenolysis of the Ru−C bond by H_2 becomes faster due to a wide apical one.

Although the more electron-donating H_8-BINAP ligand could increase the hydridity of metal hydrides and accelerate the reaction, ruthenium complexes having *p*-Tol-BINAP and *p*-MeO-BINAP, which also seemed more electron-donating than BINAP, showed catalytic activities and selectivities similar to those of the BINAP−Ru catalyst.

Conclusion

In conclusion, the catalytic action of the H_8-BINAP−Ru(II) complex **2** has proven to be superior to that of the ruthenium complexes having BINAPs. We have obtained the highest enantiomeric excesses ever reported in the asymmetric hydrogenation of various mono- and disubstituted α,β-unsaturated carboxylic acids by using the dicarboxylate complex **2** as a catalyst. The substitution pattern, both type and arrangement, affects the pressure effect on the sense and degree of asymmetric induction.

Experimental Section

General. ^{1}H NMR (270 MHz) spectra were recorded on a JEOL JNM-EX270 spectrometer with a TMS internal reference. Optical rotations were measured on a JASCO DIP-360 instrument. Gas chromatographic (GLC) analyses were conducted on a Shimadzu GC-15A equipped with a flame ionization detector on a Chrompack CP-cyclodextrin-β-236M-19 capillary column (0.25 mm id × 25 m df). HPLC analyses were performed with a Toso CO-8000 chromatograph using a Toso UV-8000 detector (column, Daicel Chiralcel OB, OD, or OJ, 25 cm × 0.46 cm id; detection, 254-nm light). All melting points were determined with a Yanako MP-500D melting point apparatus and were not corrected.

Materials. All manipulations involving air- and moisture-sensitive organometallic compounds were carried out with the standard Schlenk technique under argon atmosphere, purified by passing it through a BASF-Catalyst R3-11 column. Ru(OAc)$_2$((*R*)-BINAP) [(*R*)-**1**],[3c] Ru(OAc)$_2$((*S*)-H_8-BINAP) [(*S*)-**2**],[9b]

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and [RuI((*R*)-H_8-BINAP)(*p*-cymene)]I [(*R*)-**3**][9b] were prepared according to previously reported methods. Tiglic acid (**4a**), (*E*)-2-methyl-2-pentenoic acid (**4b**), *N*,*N*′-dicyclohexylcarbodiimide, and 4-(dimethylamino)pyridine were used as purchased. (*E*)-2-Methyl-2-hexenoic acid (**4c**), (*E*)-2-ethyl-2-hexenoic acid (**4d**), 3-(trifluoromethyl)-2-butenoic acid (**8a**), and aniline were distilled under argon before use. 2-Methylcinnamic acid (**4e**) and 2-phenylcinnamic acid (**4f**) were recrystallized from benzene prior to use. 2-(4-Isobutylphenyl)propenoic acid (**6**),[20] 3-phenyl-3-butenoic acid (**10**),[16] ethyl (*E*)- and (*Z*)-3-phenyl-2-butenoate,[21] ethyl 2,3-dimethyl-2-butenoate,[22] and ethyl (*E*)-2-methyl-3-phenyl-2-butenoate[23] were prepared according to the literature methods. For calibration purposes, racemic 2-methylbutyric acid ((±)-**5a**), 2-methylpentanoic acid ((±)-**5b**), 2-methylhexanoic acid ((±)-**5c**), 2-ethylhexanoic acid ((±)-**5d**), and 2-(4-isobutylphenyl)propanoic acid ((±)-**7**) were purchased and used without purification. 2-Methyl-3-phenylpropanoic acid ((±)-**5e**), 2,3-diphenylpropanoic acid ((±)-**5f**), 3-(trifluoromethyl)butyric acid ((±)-**9a**), 3-phenylbutyric acid ((±)-**9b**), 2,3-dimethylbutyric acid ((±)-**12a**), and *threo*-2-methyl-3-phenylbutyric acid ((±)-**12b**) were prepared by the standard hydrogenation technique by 10% Pd/C. All solvents were dried by standard methods and distilled under argon.

Asymmetric Hydrogenation of Tiglic Acid (4a). This procedure is illustrative for all asymmetric hydrogenation. To a mixture of $Ru(OAc)_2$[(*S*)-H_8-BINAP] [(*S*)-**2**, 10.7 mg, 12.6 × 10^{-3} mmol] and tiglic acid (**4a**, 252.1 mg, 2.52 mmol; S/C (substrate/catalyst) = 200 mol/mol) was added dry methanol (12.5 mL; S/S (solvent/substrate) = 50 mL/g). After the resulting yellow solution was degassed by three freeze−thaw cycles, it was transferred into a 100-mL autoclave and then stirred under an initial hydrogen pressure of 1.5 atm at room temperature for 20 h. Conversion (100%) of **4a** and chemical selectivity (100%) to 2-methylbutyric acid (**5a**) were determined by ^{1}H NMR analysis of the residue obtained on concentration of the yellow reaction mixture. Kugelrohr distillation of the residue afforded **5a** (214.5 mg, 2.10 mmol, 83% yield) as a colorless liquid: $[\alpha]^{23}_D$ = +20.36 (neat) [lit.[24] $[\alpha]^{25}_D$ = +18.9 (neat) for (*S*)-2-methylbutyric acid]. The product (37.7 mg, 0.37 mmol) was condensed with aniline (51.1 mg, 0.55 mmol) in the presence of 4-(dimethylamino)pyridine (8.0 mg) and *N*,*N*′-dicyclohexylcarbodiimide (91.4 mg, 0.44 mmol) in THF (5 mL) for 21 h at room temperature. The precipitate was filtered off, and the filtrate was evaporated. The residue was chromatographed on silica gel (15 g), eluted with diethyl ether to afford the anilide of 2-methylbutyric acid as colorless crystals in quantitative yield. Enantiomeric excess (97%, *S*) of this anilide was determined by HPLC analysis with a Chiralcel OD column using an authentic sample of the anilide of (±)-2-methylbutyric acid as a reference [hexane/2-propanol 485:15; flow rate, 0.5 mL/min; t_R = 64.37 (*S*) and 68.92 (*R*) min].

Asymmetric Hydrogenation of (*E*)-2-Methyl-2-pentenoic Acid (4b). Typical reaction conditions: $Ru(OAc)_2$[(*S*)-H_8-BINAP] [(*S*)-**2**, 14.3 mg, 16.8 × 10^{-3} mmol], (*E*)-2-methyl-2-pentenoic acid (**4b**, 409.0 mg, 3.58 mmol, S/C = 213 mol/mol), dry methanol (18.0 mL, S/S = 44 mL/g), an initial hydrogen pressure of 1.5 atm, room temperature, 24 h. Conversion (100%) of **4b** and chemical selectivity (100%) to 2-methylpentanoic acid (**5b**) were determined by ^{1}H NMR analysis. **5b**: 370.5 mg, 3.19 mmol, 89% yield, a colorless liquid (Kugelrohr distillation), $[\alpha]^{24}_D$ = +17.56 (neat) [lit.[25] $[\alpha]^{16}_D$ = +18.4 (neat) for (*S*)-2-methylpentanoic acid]. Enantiomeric excess (96%, *S*) of **5b** was directly determined by GLC analysis with a Chrompack CP-cyclodextrin-*β*-236M-19 capillary column [100 °C; He 1.0 kg/cm^2; t_R = 16.80 (*S*) and 19.59 (*R*) min].

Asymmetric Hydrogenation of (*E*)-2-Methyl-2-hexenoic Acid (4c). Typical reaction conditions: $Ru(OAc)_2$[(*S*)-H_8-BINAP] [(*S*)-**2**, 12.6 mg, 14.8 × 10^{-3} mmol], (*E*)-2-methyl-2-hexenoic acid (**4c**, 387.3 mg, 3.02 mmol, S/C = 204 mol/mol), dry methanol/H_2O (10:1, 1.9 mL, S/S = 5 mL/g), an initial hydrogen pressure of 1.5 atm, room temperature, 22 h. Conversion (100%) of **4c** and chemical selectivity (100%) to 2-methylhexanoic acid (**5c**) were determined by ^{1}H NMR and by GLC analysis with a Neutra bond-1 capillary column (programmed from 100 to 140 °C at a rate of 4 °C/min). **5c**: 354.0 mg, 2.72 mmol, 90% yield, a colorless liquid (Kugelrohr distillation), $[\alpha]^{24}_D$ = +19.00 (neat) [lit.[26] $[\alpha]^{25}_D$ = +18.7 (neat) for (*S*)-2-methylhexanoic acid]. Enantiomeric excess (96%, *S*) of the anilide of **5c** was determined by HPLC analysis with a Chiralcel OB column [hexane/2-propanol 92:8; flow rate, 1.0 mL/min; t_R = 10.67 (*S*) and 15.15 (*R*) min].

Asymmetric Hydrogenation of (*E*)-2-Ethyl-2-hexenoic Acid (4d). Typical reaction conditions: $Ru(OAc)_2$[(*S*)-H_8-BINAP] [(*S*)-**2**, 9.7 mg, 11.4 × 10^{-3} mmol], (*E*)-2-ethyl-2-hexenoic acid (**4d**, 320.2 mg, 2.25 mmol, S/C = 197 mol/mol), dry methanol (11.0 mL, S/S = 34 mL/g), an initial hydrogen pressure of 1.5 atm, room temperature, 20 h. Conversion (100%) of **4d** and chemical selectivity (100%) to 2-ethylhexanoic acid (**5d**) were determined by ^{1}H NMR analysis. **5d**: 261.4 mg, 1.81 mmol, 80% yield, a colorless liquid (Kugelrohr distillation), $[\alpha]^{24}_D$ = +8.52 (neat) [lit.[27] $[\alpha]^{25}_D$ = −4.20 (neat) for (*R*)-2-ethylhexanoic acid]. Enantiomeric excess (95%, *S*) of **5d** was directly determined by GLC analysis with a Chrompack CP-cyclodextrin-*β*-236M-19 capillary column [110 °C; He 1.3 kg/cm^2; t_R = 20.28 (*S*) and 21.3 (*R*) min].

Asymmetric Hydrogenation of 2-Methylcinnamic Acid (4e). Typical reaction conditions: $Ru(OAc)_2$[(*S*)-H_8-BINAP] [(*S*)-**2**, 12.2 mg, 14.4 × 10^{-3} mmol], 2-methylcinnamic acid (**4e**, 467.4 mg, 2.88 mmol, S/C = 200 mol/mol), dry methanol (14.4 mL, S/S = 31 mL/g), an initial hydrogen pressure of 1.5 atm, room temperature, 48 h. Conversion (95%) of **4e** and chemical selectivity (100%) to 2-methyl-3-phenylpropanoic acid (**5e**) were determined by ^{1}H NMR analysis. **5e**: 410.5 mg, 2.50 mmol, 87% yield, a colorless liquid (Kugelrohr distillation), $[\alpha]^{22}_D$ = +24.88 (neat) [lit.[28] $[\alpha]^{16}_D$ = +18.4 (neat) for (*S*)-2-methyl-3-phenylpropanoic acid]. Enantiomeric excess (89%, *S*) of the anilide of **5e** was determined by HPLC analysis with a Chiralcel OB column [hexane/2-propanol 96:4; flow rate, 1.0 mL/min; t_R = 43.32 (*S*) and 71.88 (*R*) min].

Asymmetric Hydrogenation of 2-Phenylcinnamic Acid (4f). Typical reaction conditions: $Ru(OAc)_2$[(*S*)-H_8-BINAP] [(*S*)-**2**, 4.7 mg, 5.5 × 10^{-3} mmol], 2-phenylcinnamic acid (**4f**, 246.7 mg, 1.10 mmol, S/C = 200 mol/mol), dry methanol (5.0 mL, S/S = 20 mL/g), an initial hydrogen pressure of 27 atm, 60 °C, 61 h. Conversion (100%) of **4f** and chemical selectivity (100%) to 2,3-diphenylpropanoic acid (**5f**) were determined by ^{1}H NMR analysis. **5f**: 226.0 mg, 1.00 mmol, 90% yield, colorless crystals (Kugelrohr distillation), mp 78.0−79.2 °C, $[\alpha]^{24}_D$ = −104.26 (*c* 0.525, acetone) [lit.[28] mp 83−84 °C, $[\alpha]^{20}_D$ = +133.7 (*c* 0.535, acetone) for (*S*)-2,3-diphenylpropanoic acid of 99% ee]. Enantiomeric excess (74%, *R*) of the anilide of **5f** was determined by HPLC analysis with a Chiralcel OD column [hexane/2-propanol 97:3; flow rate, 1.0 mL/min; t_R = 48.86 (*S*) and 56.42 (*R*) min].

Asymmetric Hydrogenation of 2-(4-Isobutylphenyl)-propenoic Acid (6). Typical reaction conditions: $Ru(OAc)_2$-[(*S*)-H_8-BINAP] [(*S*)-**2**, 5.0 mg, 5.9 × 10^{-3} mmol), 2-(4-isobutylphenyl)propenoic acid (**6**, 240.5 mg, 1.18 mmol, S/C = 200 mol/mol), dry methanol (6.0 mL, S/S = 25 mL/g), an initial hydrogen pressure of 100 atm, room temperature, 8 h. Conversion (100%) of **6** and chemical selectivity (100%) to 2-(4-isobutylphenyl)propanoic acid (ibuprofen, **7**) were determined by ^{1}H NMR analysis. Column chromatography of the residue on silica gel (30 g) eluted with diethyl ether afforded **7** (235.1 mg, 1.14 mmol, 97% yield) as yellow crystals: mp 48.2−48.9

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°C, $[\alpha]^{22}_D = +51.63$ (*c* 2.08, ethanol) [lit.[29] mp 50−52 °C, $[\alpha]^{20}_D = +59$ (*c* 2, ethanol) for ibuprofen of 99% ee]. Enantiomeric excess (97%, *S*) of ibuprofen was directly determined by GC analysis with a Chrompack CP-cyclodextrin-β-236M-19 capillary column [170 °C; He 2.0 kg/cm^2; $t_R = 15.64$ (*S*) and 16.64 (*R*) min].

Asymmetric Hydrogenation of (*E*)-3-(Trifluoromethyl)-2-butenoic Acid (8a). Typical reaction conditions: $Ru(OAc)_2$-[(*S*)-H$_8$-BINAP] [(*S*)-**2**, 8.4 mg, 9.9×10^{-3} mmol], (*E*)-3-(trifluoromethyl)-2-butenoic acid (**8a**, 305.8 mg, 1.98 mmol, S/C = 200 mol/mol), dry methanol (10.0 mL, S/S = 33 mL/g), an initial hydrogen pressure of 100 atm, room temperature, 8 h. Conversion (100%) of **8a** and chemical selectivity (100%) to 3-(trifluoromethyl)butyric acid (**9a**) were determined by ^{1}H NMR analysis. **9a**: 267.0 mg, 1.71 mmol, 86% yield, a colorless liquid (Kugelrohr distillation), $[\alpha]^{22}_D = -19.88$ (*c* 1.02, chloroform). Enantiomeric excess (93%, (-)) of the anilide of **9a** was determined by HPLC analysis with a Chiralcel OJ column [hexane/2-propanol 98:2; flow rate, 1.0 mL/min; t_R = 46.49 (−) and 55.74 (+) min].

Synthesis of (*E*)- and (*Z*)-3-Phenyl-2-butenoic Acid (8b,c) from Ethyl (*E*)- and (*Z*)-3-Phenyl-2-butenoate. Spinning-band distillation of an 84:16 mixture of ethyl (*E*)- and (*Z*)-3-phenyl-2-butenoate gave pure (*E*)- and (*Z*)-esters, respectively. Pure (*E*)-acid was obtained by recrystallization from pentane at −20 °C after treatment of pure (*E*)-ester with a mixture of aqueous sodium hydroxide and ethanol at reflux temperature. (*Z*)-Acid was also obtained in a similar manner. ^{1}H NMR spectra of these acids were in accordance with the reported data.[30]

Asymmetric Hydrogenation of (*E*)-3-Phenyl-2-butenoic Acid (8b). Typical reaction conditions: $Ru(OAc)_2$[(*S*)-H$_8$-BINAP] [(*S*)-**2**, 3.5 mg, 4.1×10^{-3} mmol], (*E*)-3-phenyl-2-butenoic acid (**8b**, 133.0 mg, 0.82 mmol, S/C = 200 mol/mol), dry methanol (2.7 mL, S/S = 20 mL/g), an initial hydrogen pressure of 100 atm, room temperature, 7 h. Conversion (100%) of **8b** and chemical selectivity (100%) to 3-phenylbutyric acid (**9b**) were determined by ^{1}H NMR analysis. **9b**: 120.7 mg, 0.74 mmol, 90% yield, colorless liquid (Kugelrohr distillation), $[\alpha]^{24}_D = +38.81$ (*c* 2.72, benzene) [lit.[31] $[\alpha]^{25}_D = -57.6$ (*c* 2.7, benzene) for (*R*)-3-phenylbutyric acid]. Enantiomeric excess (70%, *S*) of the anilide of **9b** was determined by HPLC analysis with a Chiralcel OB column [hexane/2-propanol 95:5; flow rate, 1.0 mL/min; t_R = 34.4 (*S*) and 56.22 (*R*) min].

Asymmetric Hydrogenation of (*Z*)-3-Phenyl-2-butenoic Acid (8c). Typical reaction conditions: $Ru(OAc)_2$[(*S*)-H$_8$-BINAP] [(*S*)-**2**, 3.0 mg, 3.5×10^{-3} mmol], (*Z*)-3-phenyl-2-butenoic acid (**8c**, 113.5 mg, 0.70 mmol, S/C = 200 mol/mol), dry methanol (2.3 mL, S/S = 20 mL/g), an initial hydrogen pressure of 4.0 atm, room temperature, 25 h. Conversion (100%) of **8c** and chemical selectivity (100%) to 3-phenylbutyric acid (**9b**) were determined by ^{1}H NMR analysis. **9b**: 107.4 mg, 0.65 mmol, 93% yield, $[\alpha]^{23}_D = -51.73$ (*c* 2.69, benzene), 93% ee (*R*).

Asymmetric Hydrogenation of 3-Phenyl-3-butenoic Acid (10). Typical reaction conditions: $Ru(OAc)_2$[(*S*)-H$_8$-BINAP] [(*S*)-**2**, 8.4 mg, 9.9×10^{-3} mmol], 3-phenyl-3-butenoic acid (**10**, 321.4 mg, 1.98 mmol, S/C = 200 mol/mol), dry methanol (9.9 mL, S/S = 31 mL/g), an initial hydrogen pressure of 1.5 atm, room temperature, 2 h. Conversion (100%) of **10** and chemical selectivity (100%) to 3-phenylbutyric acid (**9b**) were determined by ^{1}H NMR analysis. **9b**: 301.0 mg, 1.83 mmol, 92% yield, $[\alpha]^{25}_D = -48.32$ (*c* 2.69, benzene), 83% ee (*R*).

Synthesis of 2,3-Dimethyl-2-butenoic Acid (11a) from Ethyl 2,3-Dimethyl-2-butenoate. In a 100-mL flask were added ethyl 2,3-dimethyl-2-butenoate (2.87 g, 20.19 mmol), potassium hydroxide (5.15 g, 78.05 mmol), H_2O (20 mL), and ethanol (15 mL). The mixture was stirred at reflux for 4 h. The organic solvent was removed by distillation. The residue was acidified until pH < 2 with 1 N HCl. The organic acid was extracted with diethyl ether (50 mL × 4). The organic layer was washed with water (50 mL), dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by short-column chromatography on silica gel (25 g) with diethyl ether as an eluent to give 2,3-dimethyl-2-butenoic acid (**11a**) as colorless crystals (610.0 mg, 5.34 mmol). ^{1}H NMR spectra were in accordance with the reported data.[16]

Asymmetric Hydrogenation of 2,3-Dimethyl-2-butenoic Acid (11a). Typical reaction conditions: $Ru(OAc)_2$[(*S*)-H$_8$-BINAP] [(*S*)-**2**, 3.8 mg, 4.5×10^{-3} mmol], 2,3-dimethyl-2-butenoic acid (**11a**, 308.2 mg, 2.70 mmol, S/C = 600 mol/mol), dry THF (3.1 mL, S/S = 10 mL/g), an initial hydrogen pressure of 100 atm, room temperature, 3 h. Conversion (100%) of **11a** and chemical selectivity (100%) to 2,3-dimethylbutyric acid (**12a**) were determined by ^{1}H NMR analysis. **12a**: 298.2 mg, 2.57 mmol, 95% yield, a colorless liquid (Kugelrohr distillation), $[\alpha]^{26}_D = +18.72$ (neat) [lit.[32] $[\alpha]^{25}_D = -18.9$ (neat) for (*R*)-2,3-dimethylbutyric acid]. Enantiomeric excess (88%, *S*) of the anilide of **12a** was determined by HPLC analysis with a Chiralcel OD column [hexane/2-propanol 98:2; flow rate, 1.0 mL/min; t_R = 43.01 (*S*) and 49.88 (*R*) min].

Synthesis of (*E*)-2-Methyl-3-phenyl-2-butenoic Acid (11b) from Ethyl (*E*)-2-Methyl-3-phenyl-2-butenoate. In a 100-mL flask were added ethyl (*E*)-2-methyl-3-phenyl-2-butenoate (4.99 g, 24.42 mmol), potassium hydroxide (5.52 g, 98 mmol), H_2O (30 mL), and methanol (10 mL). The mixture was stirred at reflux for 23 h. Two-thirds of the solvent was removed by distillation. The residue was acidified until pH < 2 with 1 N HCl. The organic acid was extracted with diethyl ether (40 mL × 5) and benzene (50 mL × 2). Combined organic layer was washed with water (50 mL), dried over anhydrous $MgSO_4$, and concentrated. The residue was chromatographed on silica gel (170 g) with a 10:1 mixture of hexane and ethyl acetate. The yellow solid obtained was washed with hexane to give (*E*)-2-methyl-3-phenyl-2-butenoic acid (**11b**) as colorless crystals (2.55 g, 14.47 mmol). ^{1}H NMR spectra were in accordance with the reported data.[33]

Asymmetric Hydrogenation of (*E*)-2-Methyl-3-phenyl-2-butenoic Acid (11b). Typical reaction conditions: $Ru(OAc)_2$[(*S*)-H$_8$-BINAP] [(*S*)-**2**, 3.3 mg, 3.9×10^{-3} mmol], (*E*)-2-methyl-3-phenyl-2-butenoic acid (**11b**, 137.5 mg, 0.78 mmol, S/C = 200 mol/mol), dry methanol (1.4 mL, S/S = 10 mL/g), an initial hydrogen pressure of 100 atm, room temperature, 5 h. Conversion (100%) of **11b** and chemical selectivity (100%) to *threo*-2-methyl-3-phenylbutyric acid (**12b**) were determined by ^{1}H NMR analysis. **12b**: 132.1 mg, 0.74 mmol, a colorless liquid (Kugelrohr distillation), $[\alpha]^{24}_D = +53.37$ (*c* 0.540, methanol) [lit.[34] $[\alpha]^{22}_D = +53.1$ (*c* 1.17) for (2*S*, 3*S*)-2-methyl-3-phenylbutyric acid]. Enantiomeric excess (55%, 2*S*,3*S*) of the anilide of **12b** was determined by HPLC analysis with a Chiralcel OD column [hexane/2-propanol 98:2; flow rate, 1.0 mL/min; t_R = 48.01 (2*S*,3*S*) and 61.30 (2*R*,3*R*) min].

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