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Asymmetric Hydrogenation of α,β-Unsaturated Carboxylic Acids Catalyzed by Ruthenium(II) Complexes of Spirobifluorene Diphosphine (SFDP) Ligands

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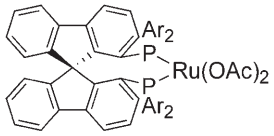
Abstract: The ruthenium diacetate complexes ligated by chiral spirobifluorene diphosphines (SFDP) were very effective catalysts for the asymmetric hydrogenation of tiglic acid derivatives and α-methylcinnamic acid derivatives with high activities and excellent enantioselectivities (up to 98% *ee*). The α-aryloxybutenoic acids can also be hydrogenated by these catalysts to provide the corresponding saturated α-aryloxybutanoic acids in high yields (89–93%) and enantioselectivities (up to 95% *ee*). In this reaction, the SFDP ligand with *para*-methyl groups on the *P*-phenyl rings gave the best results.

Keywords: asymmetric hydrogenation; diphosphanes; P ligands; ruthenium; spirobifluorenes; α,β-unsaturated carboxylic acids

Introduction

Optically active carboxylic acids are a fundamental class of chiral compounds, which are widely used as chiral drugs or important intermediates in the synthesis of pharmaceutically interesting compounds.[1] Enantioselective hydrogenation of α,β-unsaturated carboxylic acids by transition metal complexes is a straightforward method for the synthesis of chiral carboxylic acids.[2] In the past decades, considerable efforts have been expended in this field and the Ru diacetate complexes ligated by chiral diphosphines were found to be efficient catalysts for the asymmetric hydrogenation of α,β-unsaturated carboxylic acids. The ligands reported to be highly enantioselective in this transformation included BINAP,[3] H_8-BINAP,[4] MeO-BIPHEP,[5] P-Phos,[6] BITIANP,[7] as well as BITIOP.[8] This asymmetric hydrogenation has also been successfully applied for the synthesis of non-steriodal anti-inflammatory drugs (NSAIDs), such as isobuprofen and naproxen[9] and other chiral materials.[10] However, the catalytic efficiency of the developed Ru catalysts is strongly substrate-dependent in the asymmetric hydrogenation of α,β-unsaturated carboxylic acids. High turn-over number and high enantioselectivity were only achieved in the hydrogenations of a limited number of substrates such as α-arylacrylic acids and tiglic acid.[2] As for the hydrogenations of α-substituted cinnamic acids, α-aryloxy- or alkoxybutenoic acids and other α,β-unsaturated carboxylic acids, effective catalysts are still lacking.[4b,11] Recently, we developed a new class of chiral spiro-diphosphine ligands, SFDP, with a large dihedral angle based on a chiral spirobifluorene backbone and demonstrated that they are highly efficient in the Ru diacetate complexes-catalyzed asymmetric hydrogenation of α-methylcinnamic acid derivatives and tiglic acid derivatives with excellent activities and enantioselectivities (Figure 1).[12] Here we report the results of our detailed studies on this reaction and the new application of these Ru catalysts in the asymmetric hydrogenation of α-aryloxy-α,β-unsaturated carboxylic acids to provide optically active α-aryloxy-carboxylic acids in high enantioselectivities.



(*R*)-**1a** Ar = C_6H_5
(*R*)-**1b** Ar = *p*-Me-C_6H_4
(*R*)-**1c** Ar = *p*-MeO-C_6H_4
(*R*)-**1d** Ar = 3,5-Me_2-C_6H_3
(*R*)-**1e** Ar = 3,4,5-Me_3-C_6H_2

Figure 1. Ru-diacetate complexes of SFDP ligands.

Results and Discussion

Asymmetric Hydrogenation of Tiglic Acid and its Derivatives

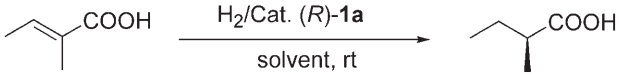
The catalysts **1a–e** were prepared as red powers from SFDP ligands and $[RuCl_2(C_6H_6)]_2$ in DMF, followed

by the addition of NaOAc.[12] These red powers showed a single resonance signal in their ^{31}P NMR spectra at around 65 ppm and were used directly in the catalytic reactions. In the study of the activity of these catalysts in the asymmetric hydrogenation of α,β-unsaturated carboxylic acids, we first chose the commercially available tiglic acid as standard substrate to test the effect of the dihedral angle of the chiral diphosphine ligands on the enantioselectivity of the reaction. The ligands BINAP, SDP and SFDP, which have different dihedral angles [the P–Pd–P bite angles of $PdCl_2$(BINAP),[13] $PdCl_2$(SDP),[14] and $PdCl_2$(SFDP)[12] complexes are 92.7°, 96.0° and 96.7°, respectively] were employed. The reactions were performed in MeOH at room temperature under 6 atm hydrogen pressure in the presence of 0.5 mol% of catlyst, and the product **3a** was obtained in 91% *ee* [$Ru(OAc)_2$((*S*)-BINAP)], 95% *ee* [$Ru(OAc)_2$((*R*)-SDP)], and 96% *ee* [(*R*)-**1a**], respectively. These results clearly showed that the ligands SFDP, which have a larger dihedral angle, are superior to BINAP and SDP in terms of enantioselectivity. To optimize the reaction conditions, we systematically investigated the effects of solvents, hydrogen pressure and the reaction temperature using (*R*)-**1a** as catalyst. The results are summarized in Table 1.

The solvent experiments showed that the alcoholic solvents, such as MeOH, *i*-PrOH and *t*-BuOH were suitable for this reaction. Complete conversions were realized after 13–24 h reaction and the *ee* values of hydrogenated product **3a** were around 95%. The best result was achieved in MeOH (Table 1, entries 1–3). When toluene was used as a solvent, the enantioselectivity was lower (89% *ee*, entry 4). While in other solvents, such as CH_2Cl_2, EtOAc, or THF, no reaction occurred (entries 5–7). Further studies indicated that the enantioselectivity of the reaction strongly depended on the hydrogen pressure. Lower hydrogen pressure was beneficial to the enantioselectivity of the reaction, but reduced the reaction rate (entries 8–10 and 1). When the hydrogenation temperature was elevated to 50 °C the reaction time could be shorted to 4 h without causing an obvious decrease of enantioselectivity (entry 11 *vs.* 1).

Under the optimized reaction conditions, the catalysts **1a–e** were compared and the catalysts **1d** and **1e**, which have 3,5-dimethyl and 3,4,5-trimethyl groups on the *P*-phenyls of the ligand, were found to be the most effective, giving the product **3a** in 97% *ee* (entries 14 and 15). The catalyst loading is a very important parameter to evaluate a new catalyst from the viewpoint of practical application. We were delighted to find that the *ee* values increased from 97% to 98%

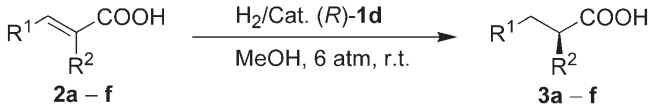
Table 1. Asymmetric hydrogenation of tiglic acid.[a]



2a **3a**

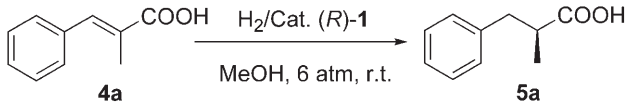
Entry	Cat.	Solvent	PH_2 [atm]	Time [h]	Conv. [%]	*ee* [%][b]
1	**1a**	MeOH	6	13	100	96
2	**1a**	*i*-PrOH	6	24	100	93
3	**1a**	*t*-BuOH	6	24	100	95
4	**1a**	Toluene	6	24	97	89
5	**1a**	CH_2Cl_2	6	24	0	
6	**1a**	EtOAc	6	24	0	
7	**1a**	THF	6	24	0	
8	**1a**	MeOH	3	20	100	96
9	**1a**	MeOH	10	11	100	94
10	**1a**	MeOH	50	6	100	75
11[c]	**1a**	MeOH	6	4	100	95
12	**1b**	MeOH	6	13	100	96
13	**1c**	MeOH	6	13	99	94
14	**1d**	MeOH	6	13	100	97
15	**1e**	MeOH	6	13	100	97
16[d]	**1d**	MeOH	6	30	100	98
17[e]	**1d**	MeOH	6	100	100	98

[a] Reaction conditions: [substrate] = 0.25 mol/mL in solvent, S/C = 200, T = 25–28 °C, unless otherwise stated.
[b] The *ee* value was determined by HPLC analysis of the respective anilide with chiral column AD-H. The absolute configuration was *S*.
[c] At 50 °C.
[d] [substrate] = 0.625 mol/L, S/C = 1000.
[e] [substrate] = 6.25 mol/L, S/C = 10,000, at 50 °C.



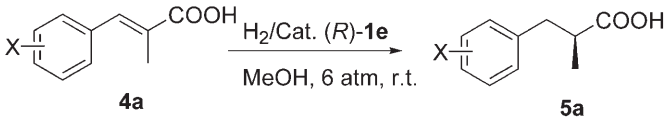
a R^1 = Me, R^2 = Me: 92%, 97% ee (16 h)
b R^1 = Et, R^2 = Me: 94%, 96% ee (24 h)
c R^1 = *n*-Pr, R^2 = Me: 91%, 96% ee (30 h)
d R^1 = *n*-Pr, R^2 = Et: 82%, 94% ee (40 h)
e R^1 = *n*-Bu, R^2 = Me: 92%, 96% ee (35 h)
f R^1 = *i*-Bu, R^2 = Me: 88%, 97% ee (40 h)

Scheme 1. Asymmetric hydrogenation of tiglic acid derivatives catalyzed by (*R*)-**1d**.



(*R*)-**1a** 93%, 60% ee (48 h)
(*R*)-**1b** 91%, 70% ee (30 h)
(*R*)-**1c** 89%, 45% ee (48 h)
(*R*)-**1d** 93%, 87% ee (24 h)
(*R*)-**1e** 91%, 94% ee (18 h)

Scheme 2. Asymmetric hydrogenation of α-methylcinnamic acid catalyzed by (*R*)-**1**.



a X = H	94% ee (91%)	**i** X = *m*-Cl	92% ee (94%)
b X = *p*-Me	90% ee (93%)	**j** X = *o*-Cl	93% ee (90%)
c X = *m*-Me	97% ee (93%)	**k** X = *m*-Br	95% ee (90%)
d X = *o*-Me	95% ee (91%)	**l** X = *o*-Br	95% ee (93%)
e X = *p*-OMe	94% ee (91%)	**m** X = *p*-CF_3	92% ee (90%)
f X = *m*-OMe	94% ee (92%)	**n** X = *o*-CF_3	92% ee (94%)
g X = *o*-OMe	94% ee (90%)	**o** X = *o*-NO_2	92% ee (93%)
h X = *p*-Cl	94% ee (90%)	**p** X = -$(CH)_4$-	93% ee (95%)

Scheme 3. Asymmetric hydrogenation of α-methylcinnamic acid derivatives catalyzed by (*R*)-**1e**.

when the substrate-to-catalyst ratio was raised from 200 to 1000 and 10,000 (entries 16 and 17). This phenomenon might imply that this catalytic hydrogenation prefers to be carried out in higher concentration, which is very important for a catalyst used on a production scale.

A variety of tiglic acid derivatives were hydrogenated with catalyst (*R*)-**1d**. The results are outlined in Scheme 1. High enantioselectivities (>94% *ee*) and good yields (around 90%) were obtained for all tested substrates **2** regardless of the bulkiness of the R^1 and R^2 groups. However, the reaction rate was obviously retarded when a larger group was introduced into either the α-position or β-position in the acid. For example, the complete conversion of tiglic acid (**2a**) required 16 h, while the substrate **2d**, which has an *n*-propyl group on the β-position (R^1=*n*-Pr) and an ethyl group on the α-position (R^2=Et) needed 40 h to achieve 100% conversion.[12]

Asymmetric Hydrogenation of α-Methylcinnamic Acid Derivatives

In contrast to the excellent results obtained in the asymmetric hydrogenation of tiglic acid derivatives, α-arylacrylic acids and other α,β-unsaturated carboxylic acids, the asymmetric hydrogenation of cinnamic acid derivatives is far from successful. In the hydrogenation of α-methylcinnamic acid (**4a**), the Ru diacetate complexe of BINAP gave product **5a** in a very low enantioselectivity (<40% *ee*). By using Takaya's H_8-BINAP ligand the enantioselectivity of this reaction was improved to 89% *ee*.[4,11] This is, to our knowledge, the highest enantioselectivity reported in the hydrogenation of α-alkylcinnamic acid derivatives. To explore efficient catalysts for the hydrogenation of α-alkylcinnamic acid derivatives, we performed the hydrogenation of α-methylcinnamic acid (**4a**) by using catalysts **1** under our standard conditions (S/C= 400, [substrate]=0.25 mol/L in MeOH, 6 atm of hydrogen pressure at room temperature). It was found that the Ru diacetate complexes of SFDP ligands were efficient catalysts for the asymmetric hydrogenation of α-methylcinnamic acid. Catalyzed by complex **1a** ligated with parent SFDP ligand, the hydrogenation of **4a** was completed in 48 h, providing the saturated acid product **5a** in 93% yield with 60% *ee* (Scheme 2). The enantioselectivity of the reaction was dramatically improved to 94% *ee* (91% yield in 18 h) by using the catalyst **1e** having 3,4,5-trimethyl groups on the *P*-phenyl rings of the ligand. This result showed that the rigid spirobifluorene skeleton and the sterically hindered *P*-phenyl groups are two significant factors for the catalysts **1** to achieve high enantioselectivity.

Using the best catalyst **1e**, various α-methylcinnamic acid derivatives can be hydrogenated in excellent enantioselectivities (90–97% *ee*) and yields (90–95%) (Scheme 3). These results represented the highest level of enantiocontrol to date achieved in the asymmetric hydrogenation of cinnamic acid derivatives. The data illustrated in Scheme 3 showed that the substituents, either electron-withdrawing or electron-donating groups, on the phenyl ring of the substrates **4** had no obvious influence on the enantioselectivity.

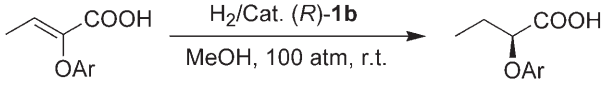
Asymmetric Hydrogenation of α-Aryloxy-α,β-unsaturated Acids

The asymmetric hydrogenation of α-aryloxy- or alkoxy-α,β-unsaturated acids is an important reaction producing optically active α-aryloxy- or alkoxy-carboxylic acids, which exist as a core structure in various biologically active compounds and drugs.[15] However, there are only very limited examples reported for this synthetically useful reaction. Recently, Maligres and Krska reported an enantioselective hydrogenation of α-aryloxy-α,β-unsaturated acids using Ru-BINAP complexes as catalysts and up to 95% *ee* of enantioselectivities were achieved.[16] The blemish of this method is high catalyst loading (up to 20 mol% Ru-diphosphine catalyst) that was employed for obtaining complete conversion and high enantioselectivity for a number of substrates. Houpis and co-workers screened over 250 catalysts including Ru- and Rh-diphosphine complexes in the asymmetric hydrogenation of α-alkoxycinnamic acids and found that Rh complexes ligated by Valphos ligands gave good results. The α-alkoxy-carboxylic acids were produced in up to 92% *ee* and the method was successfully applied to the synthesis of peroxime proliferators activated receptor (PPAR) agonists.[17] We were delighted to find that the chiral spirobifluorene diphosphine ligands (SFDP) are also efficient for the Ru-catalyzed asymmetric hydrogenation of α-aryloxy-α,β-unsaturated acids.

The asymmetric hydrogenation of (*Z*)-α-phenoxybutenoic acid (**6a**) was chosen as a model reaction to evaluate the catalysts. The reaction was performed first with the catalyst **1e** (0.5 mol%) under the conditions of 0.25 mol/L in MeOH under 100 atm of hydrogen at room temperature to provided α-phenoxybutanoic acid (**7a**) in 70% *ee* with 100% conversion over 24 h. Comparison of the catalysts led to the finding that **1b** was the most efficient catalyst, which gave complete conversion of substrate in 12 h and afforded the product **7a** in 94% *ee*. This enantioselectivity is comparable to the best result obtained with $RuCl_2$-(BINAP) (94% *ee*).[16] With catalyst **1b** the impact of hydrogen pressure on the hydrogenation reaction was examined. When the hydrogenation was carried out under the 20 atm and 6 atm of hydrogen, the reaction became very slow (20 atm: 24 h, 100% conversion; 6 atm: 24 h, 80% conversion) and the enantioselectivity decreased to 85% *ee* and 78% *ee*, respectively. Reducing the reaction temperature to 0 °C did not improve the enantioselectivity, but further decreased the reaction rate (24 h, 100% conversion in 92% *ee*).

A variety of (*Z*)-α-aryloxybutenoic acids **6**, which were prepared by the literature method,[18] were hydrogenated by using catalyst **1b** under 100 atm of hydrogen in good to excellent enantioselectivities. From the results summarized in Table 2 we found that the steric properties of the substrate have a great influence on the enantioselectivity. When a methyl group exists at the *ortho*-position of phenyl ring in the substrate (**6b**), the enantiomeric excess value of product **7b** decreased to 65% (entry 2). The substrates with a *para*- or *meta*-substituent on the phenyl ring, except for 2-(4-bromophenoxy)but-2-enoic acid (**6g**) gave as high as 95% *ee* in the hydrogenation (entries 5–9). When the aryl group of substrate was a bulky 2-naphthyl (**6m**), the reaction became very slow (40 h), albeit the enantioselectivity was acceptable (80% *ee*) (entry 12).

Table 2. The asymmetric hydrogenation of α-aryloxybutenoic acids.[a]

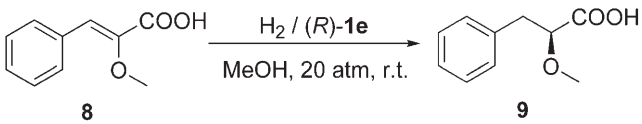


6a – n **7a – n**

Entry	Ar	Time [h]	Yield [%][b]	*ee* [%][c]
1	C_6H_5 (**6a**)	12	93	94 (*S*)
2	*o*-Me-C_6H_4 (**6b**)	16	91	65 (*S*)
3	*o*-MeO-C_6H_4 (**6c**)	16	92	91 (*S*)
4	*o*-Cl-C_6H_4 (**6d**)	16	93	85 (*S*)
5	*p*-Me-C_6H_4 (**6e**)	12	90	95 (*S*)
6	*p*-Cl-C_6H_4 (**6f**)	16	91	95 (*S*)
7	*p*-Br-C_6H_4 (**6g**)	19	93	81 (*S*)
8	*p*-*t*-Bu-C_6H_4 (**6h**)	17	91	95 (*S*)
9	*m*-Me-C_6H_4	12	90	94 (*S*)
10	3,5-$(CF_3)_2$-C_6H_3 (**6j**)	14	91	80 (*S*)
11	3,5-F_2-C_6H_3 (**6k**)	15	92	91 (*S*)
12	2-Naphthyl (**6l**)	40	91	80 (*S*)

[a] Reaction conditions: [substrate] = 0.25 mol/L in MeOH, (*R*)-**1b**, *S/C* = 200, PH_2 = 100 atm, temperature = 25–28 °C.
[b] Conversions were 100% and yields were obtained from distillation.
[c] The *ee* values were determined by HPLC anaylsis of corresponding anilide with a chiral column OD-H. The absolute configuration was determined by comparison of the sign of optical rotation with literature data.

In the hydrogenation of (*Z*)-α-methoxycinnamic acid (**8**), all catalysts **1** provided only moderate enantioselectivities, with **1e** being the best catalyst. Under 20 atm of hydrogen, compound **8** was hydrogenated in 18 h to give 2-methoxy-3-phenylpropionic acid in quantitative yield with 71% *ee* (Scheme 4).



8 **9**

Scheme 4. Asymmetric hydrogenation of (*Z*)-α-methoxycinnamic acid with catalyst (*R*)-**1e**.

Conclusions

The chiral $Ru(OAc)_2$ complexes ligated by spirobifluorene diphosphines (SFDP) were demonstrated to be the highly effective catalysts for the enantioselective hydrogenation of α,β-unsaturated carboxylic acids, such as tiglic acid derivatives, α-methylcinnamic acids, as well as α-aryloxybutenoic acids. A number of optically active α-alkyl-, α-alkoxy- and α-aryloxy carboxylic acids were produced in high enantioselectivities. Further investigations on the application scope of the SFDP ligands in ruthenium and other transtion metal-catalyzed asymmetric reactions are in progress.

Experimental Section

General Remarks

All reactions and manipulations were performed in an argon-filled glovebox (VAC DRI-LAB HE 493) or using standard Schlenk techniques. Hydrogen gas (99.999%) was purchased from Boc Gas Inc., Tianjin. $[Ru(C_6H_6)Cl_2]_2$ and unsaturated carboxylic acids **2** were purchased from Aldrich or Acros chemical companies except for (*E*)-2-methylhept-2-enoic acid (**2e**) and (*E*)-2,5-dimethylhex-2-enoic acid (**2f**), which were prepared using the literature method.[19] α-Methylcinnamic acid derivatives **4a–p** were prepared by the Perkin reaction. (*Z*)-α-Aryloxybutenoic acids **6**,[17] (*Z*)-α-methoxycinnamic acid (**8**)[20] and the catalysts **1a–e**,[12] $[Ru(OAc)_2((S)\text{-BINAP})]$ and $[Ru(OAc)_2((R)\text{-SDP})]$[21] were prepared using the respective literature method. Anhydrous toluene was distilled from sodium benzophenone ketyl. Anhydrous CH_2Cl_2, DMF and *i*-PrOH were freshly distilled from calcium hydride. Anhydrous MeOH and EtOH were distilled from magnesium. HPLC analyses were performed using a Hewlett Packard Model HP 1100 Series or a Waters 600 E.

General Procedure for Asymmetric Hydrogenation of α-Aryloxybutenoic Acids

To a hydrogenation tube was added α-aryloxybutenoic acid (1 mmol), catalyst (*R*)-**1** (0.005 mmol) and 4 mL degassed MeOH at ambient atmosphere. The hydrogenation tube was put into an autoclave. Hydrogen was charged into the autoclave and released. This gas changing operation was repeated for five times. The autoclave was then charged with hydrogen to the reaction pressure, and the reaction mixture was stirred at room temperature for the appropriate time. After releasing hydrogen, the reaction mixture was concentrated on a rotatory evaporator. The conversion of substrate was determined by ^{1}H NMR analysis. The crude product was distilled on a microdistiller under reduced pressure to give pure product as a colorless liquid in the stated yield.

The α-aryloxybutanoic acid (1 mmol) was reacted with aniline (100 μL, 1.1 mmol), DCC (0.22 g, 1.1 mmol), DMAP (8 mg, 0.07 mmol) in 0.8 mL THF for 30 min. The reaction mixture was filtered through celite. The filtrate was diluted with Et_2O, washed with 3 N HCl and dried with Na_2SO_4. After a flash chromatography on silica gel with Et_2O as eluent, the desired anilide was obtained and analyzed on HPLC with a chiral column to determine the *ee* value. The separation conditions of anilides on HPLC are summarized below. All products are known compounds and have been identified by ^{1}H NMR.

Analytical Data of Products 7 and 9

(*S*)-2-Phenoxybutanoic acid (7a): 100% conversion, 93% yield, 94% *ee* [Chiralcel OD-H (25 cm × 0.46 cm ID), hexane/2-propanol = 93:7, 0.7 mL min^{-1}, 254 nm, t_R = 11.6 min (*R*) and 12.8 min (*S*)].

(*S*)-2-(2-Methylphenoxy)butanoic acid (7b): 100% conversion, 91% yield, 65% *ee* [Chiralcel OD-H (25 cm × 0.46 cm ID), hexane/2-propanol = 95:5, 0.8 mL min^{-1}, 254 nm, t_R = 16.5 min (*R*) and 18.2 min (*S*)].

(*S*)-2-(2-Methoxyphenoxy)butanoic acid (7c): 100% conversion, 92% yield, 91% *ee* [Chiralcel OD-H (25 cm × 0.46 cm ID), hexane/2-propanol = 93:7, 0.8 mL min^{-1}, 254 nm, t_R = 10.3 min (*R*) and 11.6 min (*S*)].

(*S*)-2-(2-Chlorophenoxy)butanoic acid (7d): 100% conversion, 93% yield, 85% *ee* [Chiralcel OD-H (25 cm × 0.46 cm ID), hexane/2-propanol = 93:7, 0.8 mL min^{-1}, 254 nm, t_R = 7.3 min (*R*) and 8.2 min (*S*)].

(*S*)-2-(4-Methylphenoxy)butanoic acid (7e): 99% conversion, 90% yield, 95% *ee* [Chiralcel OD-H (25 cm × 0.46 cm ID), hexane/2-propanol = 93:7, 0.8 mL min^{-1}, 254 nm, t_R = 10.0 min (*R*) and 11.1 min (*S*)].

(*S*)-2-(4-Chlorophenoxy)butanoic acid (7f): 100% conversion, 91% yield, 95% *ee* [Chiralcel OD-H (25 cm × 0.46 cm ID), hexane/2-propanol = 93:7, 0.8 mL min^{-1}, 254 nm, t_R = 9.4 min (*R*) and 11.0 min (*S*)].

(*S*)-2-(4-Bromophenoxy)butanoic acid (7g): 100% conversion, 93% yield, 81% *ee* [Chiralcel OD-H, hexane/2-propanol = 93:7, 0.8 mL min^{-1}, 254 nm, t_R = 14.7 min (*R*) and 16.1 min (*S*)].

(*S*)-2-(4-*tert*-Butylphenoxy)butanoic acid (7h): 100% conversion, 91% yield, 95% *ee* [Chiralcel OD-H (25 cm × 0.46 cm ID), hexane/2-propanol = 93:7, 0.8 mL min^{-1}, 254 nm, t_R = 6.7 min (*R*) and 8.2 min (*S*)].

(*S*)-2-(3-Methylphenoxy)butanoic acid (7i): 100% conversion, 90% yield, 94% *ee* [Chiralcel OD-H (25 cm × 0.46 cm ID), hexane/2-propanol = 93:7, 0.8 mL min^{-1}, 254 nm, t_R = 9.5 min (*R*) and 10.5 min (*S*)].

(*S*)-2-[3,5-Di-(trifluoromethyl)phenoxy]butanoic acid (7j): 100% conversion, 91% yield, 80% *ee* [Chiralpak AD-H (25 cm × 0.46 cm ID), hexane/2-propanol = 93:7, 0.8 mL min^{-1}, 254 nm, t_R = 5.3 min (*R*) and 6.9 min (*S*)].

(*S*)-2-(3,5-Difluorophenoxy)butanoic acid (7k): 100% conversion, 92% yield, 91% *ee* [Chiralpak AD-H (25 cm × 0.46 cm ID), hexane/2-propanol = 93:7, 0.8 mL min^{-1}, 254 nm, t_R = 9.2 min (*R*) and 11.4 min (*S*)].

(*S*)-2-(2-Naphthyloxy)butanoic acid (7l): 100% conversion, 91% yield, 80% *ee* [Chiralcel OD-H (25 cm × 0.46 cm ID), hexane/2-propanol = 93:7, 0.8 mL min^{-1}, 254 nm, t_R = 12 min (*R*) and 16 min (*S*)].

(***S*)-2-Methoxy-3-phenylpropanoic acid (9)**: 94% conversion, 81% *ee* [Chiralcel OD-H (25 cm × 0.46 cm ID), hexane/2-propanol = 93:7, 0.8 mL min^{-1}, 254 nm, t_R = 15.5 min (*R*) and 23.3 min (*S*)].

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References

[1] a) T. Y. Shen, *Angew. Chem.* **1972**, *84*, 512; *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 460; b) D. Lednicer, L. A. Mitscher, *The Organic Chemistry of Drug Synthesis* Wiley, New York, **1977** and **1980**, Vols. 1 and 2; c) C. Botteghi, S. Paganelli, A. Schinato, M. Marchetti, *Chirality* **1991**, *3*, 355.

[2] For reviews, see: a) E. N. Jacobsen, A. Pfaltz, H. Yamamoto (Eds.), *Comprehensive Asymmetric Catalysis*, Springer, Berlin, **1999**, Vols. I-III; b) W.-J. Tang, X.-M. Zhang, *Chem. Rev.* **2003**, *103*, 3029.

[3] a) T. Ohta, H. Takaya, M. Kitamura, K. Nagai, R. Noyori, *J. Org. Chem.* **1987**, *52*, 3174; b) T. Ohta, H. Takaya, R. Noyori, *Tetrahedron Lett.* **1990**, *31*, 7189; c) K. Mashima, K. Kusano, N. Sato, Y. Matsumura, K. Nozaki, H. Kumobayashi, N. Sayo, Y. Hori, T. Ishizaki, S. Akutagawa, H. Takaya, *J. Org. Chem.* **1994**, *59*, 3064.

[4] a) X. Zhang, T. Uemura, K. Matsumura, N. Sayo, H. Kumobayashi, H. Takaya, *Synlett* **1994**, 501; b) T. Uemura, X. Zhang, K. Matsumura, N. Sayo, H. Kumobayashi, T. Ohta, K. Nozaki, H. Takaya, *J. Org. Chem.* **1996**, *61*, 5510.

[5] P. J. Genêt, C. Pinel, V. Ratovelomanana-Vidal, S. Mallart, X. Pfister, L. Bischoff, M. C. Cano De Andrade, S. Darses, C. Galopin, J. A. Laffitte, *Tetrahedron: Asymmetry* **1994**, *5*, 675.

[6] C.-C. Pai, C.-W. Lin, C.-C. Lin, C.-C. Chen, A. S. C. Chan, *J. Am. Chem. Soc.* **2000**, *122*, 11513.

[7] T. Benincori, E. Brenna, F. Sannicolò, L. Trimarco, P. Antognazza, E. Cesarotti, F. Demartin, T. Pilati, *J. Org. Chem.* **1996**, *61*, 6244.

[8] T. Benincori, E. Cesarotti, O. Piccolo, F. Sannicolò, *J. Org.Chem.* **2000**, *65*, 2043.

[9] T. Manimaran, T.-C. Wu, W. D. Klobucar, C. H. Kolich, G. P. Stahly, *Organometallics* **1993**, *12*, 1467; see also refs.[3a,4,6]

[10] a) T. Sturm, W. Weissensteiner, F. Spindler, *Adv. Synth. Catal.* **2003**, *345*, 160; b) A. Dondoni, G. De Lathauwer, D. Perrone, *Tetrahedron Lett.* **2001**, *42*, 4819; c) R. Hoen, J. A. F. Boogers, H. Bernsmann, A. J. Minnaard, A. Meetsma, T. D. Tiemersma-Wegman, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *Angew. Chem.* **2005**, *117*, 4281; *Angew. Chem. Int. Ed.* **2005**, *44*, 4209.

[11] I. Yamaka, M. Yamaguchi, T. Yamagishi, *Tetrahedron: Asymmetry* **1996**, *7*, 3339.

[12] X. Cheng, Q. Zhang, J.-H. Xie, L.-X. Wang, Q.-L. Zhou, *Angew. Chem.* **2005**, *117*, 1142; *Angew. Chem. Int. Ed.* **2005**, *44*, 1118.

[13] F. Ozawa, A. Kubo, Y. Matsumoto, T. Hayashi, *Organometallics* **1993**, *12*, 4188.

[14] J.-H. Xie, H.-F. Duan, B.-M. Fan, X. Cheng, L.-X. Wang, Q.-L. Zhou, *Adv. Synth. Catal.* **2004**, *346*, 625.

[15] a) J. Secor, C. Cseke, W. J. Owen, in: *Biocatalysis in Agricultural Biotechnology*, (Eds: J. R. Whitaker, P. E. Sonnet), ACS Symposium Series 389, American Chemical Society, Washington, DC, **1989**, pp. 265–276; b) L. J. Haskelberg, *J. Org. Chem.* **1947**, *12*, 423; c) K. C. Joshi, S. C. Bahel, *J. Ind. Chem. Soc.*, **1960**, *37*, 365; d) H. Bekker, H. Cassebaum, W. Leitz, *Pharmazie* **1972**, *27*, 411; e) D. R. Feller, V. S. Kamanna, H. A. I. Newman, K. J. Romstedt, D. T. Witiak, G. Bettoni, S. H. Bryant, D. Conte-Camerino, F. Loiodice, V. Tortorella, *J. Med. Chem.* **1987**, *30*, 1265; f) F. Gualtieri, C. Bottalico, A. Calandrella, S. Dei, M. P. Giovannoni, S. Maelli, M. N. Romanelli, S. Scapecchi, E. Teodori, N. Galeotti, C. Ghelardini, A. Giotti, A. Bartolini, *J. Med. Chem.* **1994**, *37*, 1712; g) N. Mathew, S. Subramanian, M. Kalyanasundaram, *Ind. J. Chem.* **1996**, *35*, 40; h) O. Tværmose-Nielsen, S. Rachlin, H. Dannacher, F. Björkling, D. Kirstein, E. Bramm, C. K. Nielsen, J. T. Mortensen, L. Binderup, *Bioorg. Med. Chem.* **1997**, *5*, 415.

[16] P. E. Maligres, S. W. Krska, G. R. Humphrey, *Org. Lett.* **2004**, *6*, 3147.

[17] I. N. Houpis, L. E. Patterson, C. A. Alt, J. R. Rizzo, T. Y. Zhang, M. Huarez, *Org. Lett.* **2005**, *7*, 1947.

[18] a) H. Hagiwara, F. Abe, H. Uda, *J. Chem. Soc., Perkin. Trans. 1*, **1993**, 2651; b) T. Padmanathan, U. S. Sultanbawa, *J. Chem. Soc., Perkin. Trans. 2*, **1963**, 4210.

[19] B. Deevi, K. Marimganti, S. H. Rachakonda, K. S. S. Pakala, K. Nagaswamy, *J. Org. Chem.* **1999**, *64*, 1197.

[20] a) E. Wenkert, N. F. Glob, R. P. Hatch, D. Wenkert, *Helv. Chim. Acta.* **1977**, *60*, 1; b) C. Didier, D. Christian, D. Alain, *Tetrahedron* **1996**, *52*, 6665.

[21] M. Kitamura, M. Tokunaga, R. Noyori, *J. Org. Chem.* **1992**, *57*, 4053.

