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A NEW METHOD FOR PRODUCTION OF CHIRAL 2-ARYLOXYPROPANOIC ACIDS USING EFFECTIVE KINETIC RESOLUTION OF RACEMIC 2-ARYLOXYCARBOXYLIC ACIDS

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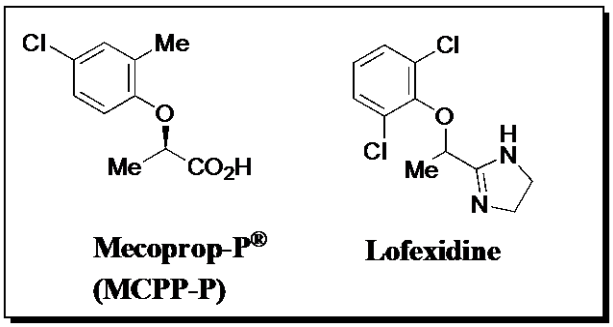
Abstract – We report a novel method for the preparation of 2-aryloxypropanoic acids by kinetic resolution of racemic 2-aryloxypropanoic acids using enantioselective esterification. The usage of pivalic anhydride (Piv_2O) as an activating agent, bis(α-naphthyl)methanol ($(\alpha\text{-Np})_2CHOH$) as an achiral alcohol, and (+)-benzotetramisole ((+)-BTM) as a chiral acyl-transfer catalyst enables the effective separation of various racemic 2-aryloxypropanoic acids to afford optically active carboxylic acids and the corresponding esters with high enantioselectivities. Furthermore, theoretical calculations of the transition states required to form the chiral esters successfully proved the enantiomer recognition mechanism of the asymmetric esterification.

INTRODUCTION

Optically pure 2-aryloxypropanoic acids and their derivatives are important moieties that are widely used in the agrochemical and pharmaceutical industries (Scheme 1). In the case of the herbicide Mecoprop®, 2-(4-chloro-2-methylphenoxy)propanoic acid, only the (*R*)-(+)-enantiomer exhibits herbicidal activity and is manufactured in the optically pure form, Mecoprop-P® (MCPP-P).[1] In addition, although the α_2-adrenergic receptor agonist Lofexidine, which can be derived from 2-aryloxypropanoic acids, is on the market as a racemic mixture, it was reported that the (*S*)-(–)-enantiomer has 10-fold more potency than the (*R*)-(+)-enantiomer.[2] Therefore, synthetic strategies to afford chiral 2-aryloxypropanoic acids or their derivatives are essential to afford beneficial enantiomers, and have attracted the interest of many research groups.

The authors dedicate this paper to Professor Dr. Ei-ichi Negishi on the celebration of his 77th birthday.



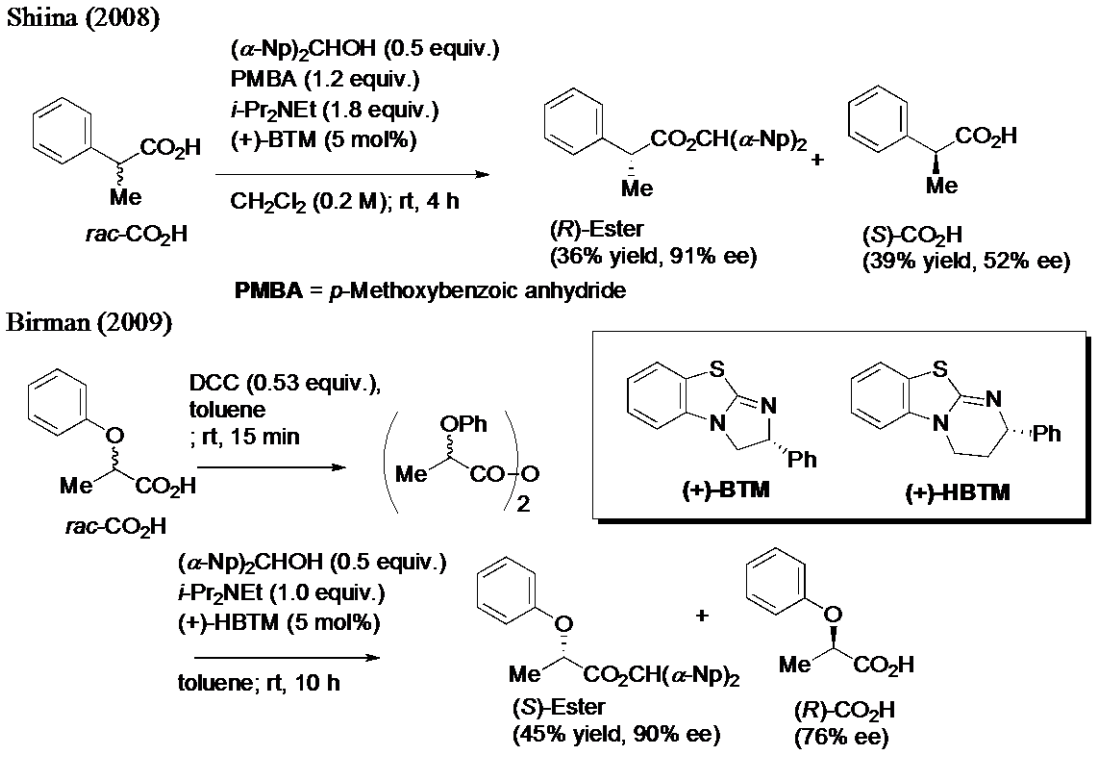
Scheme 1. Related bioactive compounds of 2-aryloxypropanoic acids

Chiral 2-aryloxypropanoic acid derivatives can be obtained by S_N2 reaction at the 2-positon of the corresponding chiral lactic acid derivatives produced by fermentation.[3] However, because of concerns about the loss of precious chiral substrates[4] and unexpected racemization in the 2-substitution step, it may be an effective approach to configure directly the chiral center of 2-aryloxypropanoic acids after introducing the 2-aryloxy groups.

There are several straightforward routes to the preparation of optically active 2-aryloxypropanoic acids from prochiral or racemic aryloxy compounds, such as asymmetric hydrogenation of 2-aryloxypropenoic acids,[5] microbial deracemization,[6] and optical resolution.[7] Of these, the optical resolution system is thought to be the most valuable in terms of usability for the enhancement of enantiomeric excess in the synthesized products. However, to the best of our knowledge, reported optical resolutions to date have been limited to those involving enzymatic hydrolysis. As the enzymatic approach requires strict validation, development of an effective and non-enzymatic optical resolution of racemic 2-aryloxy carboxylic acids would be highly beneficial in process chemistry.

Several non-enzymatic kinetic resolution systems of racemic 2-arylpropanoic acids have been developed in recent years (Scheme 2). Initially, we introduced an effective system of kinetic resolution by applying asymmetric esterification of racemic carboxylic acids, and demonstrated that various racemic 2-arylpropanoic acids could be kinetically separated to afford the optically active carboxylic acids and corresponding esters.[8] This kinetic resolution system consists of carboxylic acid anhydride as an activating agent, bis(α-naphthyl)methanol ($(\alpha\text{-Np})_2\text{CHOH}$) as an achiral nucleophile, and commercially available (+)-benzotetramisole ((+)-BTM)[9] as a chiral acyl-transfer catalyst. Simply by mixing racemic carboxylic acids with these reagents and chiral BTM, the corresponding chiral carboxylic esters and unreacted chiral carboxylic acids could be obtained in high enantiomeric excesses. Moreover, based on our knowledge of activating carboxylic acids in macrolactonization using 2-methyl-6-nitrobenzoic anhydride (MNBA),[10] we have developed activating agents using suitable carboxylic acid anhydrides such as *p*-methoxybenzoic anhydride (PMBA),[8] followed by pivalic anhydride (Piv_2O).[11] Furthermore, in a mechanistic study, it was revealed that this enantioselective esterification proceeds through a mixed

anhydride (MA), a reactive intermediate formed *in situ* from the substrate and the activating reagent, followed by formation of a transition state with the achiral alcohol and the chiral BTM.[11]



Scheme 2. Previously reported kinetic resolution of racemic carboxylic acids by asymmetric esterification

Subsequently, Birman *et al.* disclosed a novel procedure of high-enantioselective esterification by switching from the carboxylic acid anhydride to DCC and from BTM to homobenzotetramisole (HBTM), respectively.[12] They also showed that this kinetic resolution system is applicable to a variety of racemic 2-substituted propanoic acids including 2-aryl, 2-aryloxy, and 2-arylthiopropanoic acids. However, as this procedure is a two-stage treatment, involving generation of the symmetrical carboxylic acid anhydride (SA) by DCC followed by completion of esterification by adding nucleophile, base, and catalyst, it can still be further improved.

In this study, a one-stage treatment based on *in situ* MA-formation was applied to the kinetic resolution of 2-aryloxypropanoic acids using Piv_2O. We aimed to investigate further the substrate scope and elucidate its transition state and chiral recognition mechanism.

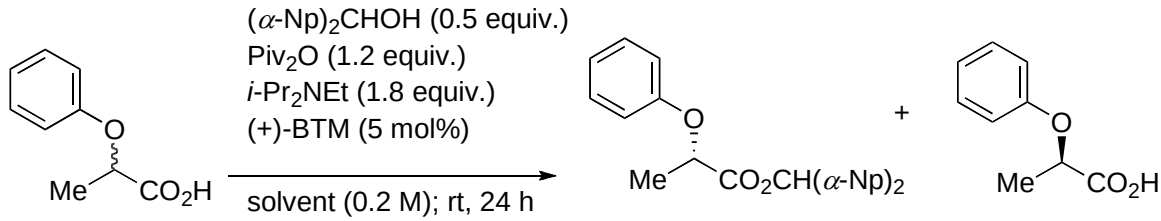
RESULTS AND DISCUSSION

In our previous study on the kinetic resolution of racemic 2-arylpropionic acids, we were able to identify the equivalent amounts of each reagent required as 0.5 equiv. of $(\alpha\text{-Np})_2CHOH$, 1.2 equiv. of Piv_2O, 1.8

equiv. of *i*-Pr_2NEt, and 5 mol% of (+)-BTM. Therefore, in the current study, we used these optimized conditions as the initial reaction conditions for the screening of suitable solvents.

2-Phenoxypropanoic acid (**1a**), a simple 2-aryloxypropanoic acid, was selected as the model substrate, and six commonly-used solvents were employed in our initial screening (Table 1).

Table 1. Screening of solvents to optimize reaction conditions for the kinetic resolution of 2-aryloxypropanoic acids



rac-**1a** (*S*)-**2a** (*R*)-**1a**

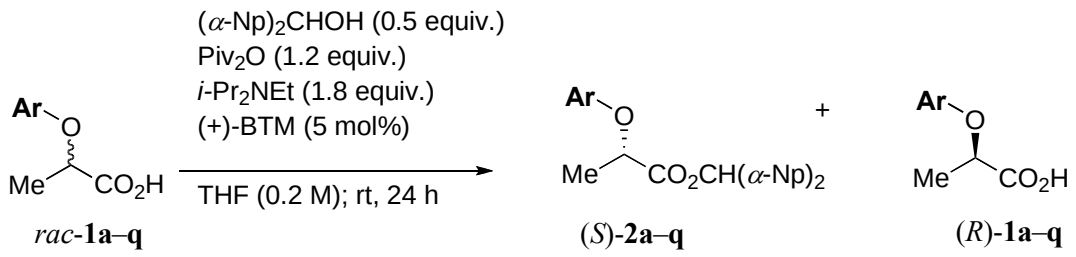
Entry	Solvent	Yield[a] of (*S*)-**2a**/(*R*)-**1a** (%)	ee of (*S*)-**2a**/(*R*)-**1a** (%)	*s*
1	CH_2Cl_2	42/46	75/54	12
2	THF	49/43	75/76	16
3	DMF	47/46	74/63	12
4	Et_2O	47/41	59/61	7.1
5	toluene	50/43	58/61	6.8
6	MeCN	46/50	58/49	6.0

[a]isolated yield.

To evaluate the effectiveness of the kinetic resolution, we used a selectivity factor (*s*-value), which indicates the ratio of reactivities of the (*R*)- and (*S*)-carboxylic acids.[13] In all entries except CH_2Cl_2 (Entry 1, 42% yield), 0.5 equiv. of (α-Np)$_2$CHOH was converted to the ester almost quantitatively, while the enantiomeric excesses of the esters produced and *s*-values greatly depended on the solvent used. Diethyl ether (Entry 4), toluene (Entry 5), and MeCN (Entry 6) gave diminished enantiomeric excesses of esters below 60% ee. Tetrahydrofuran (THF) gave the best enantiomeric excess and *s*-value, as shown in Entry 2 (75% ee, $s = 16$).

Having optimized the reaction conditions, a variety of 2-aryloxypropanoic acids bearing various substituted phenyls or bicyclic aromatic rings were applied to the investigation of the substrate scope (Table 2).

Table 2. Kinetic resolution of racemic 2-aryloxypropanoic acids



rac-**1a**–**q** (*S*)-**2a**–**q** (*R*)-**1a**–**q**

Entry	**Ar**	Yield[a] of (*S*)-**2**/(*R*)-**1** (%)	ee of (*S*)-**2**/(*R*)-**1** (%)	*s*
1[b]	C_6H_5 (**a**)	49/43	75/76	16
2	*o*-Cl-C_6H_4 (**b**)	46/45	93/90	82
3	*m*-Cl-C_6H_4 (**c**)	49/43	75/78	16
4	*p*-Cl-C_6H_4 (**d**)	49/50	72/68	12
5	*o*-Me-C_6H_4 (**e**)	46/45	88/86	45
6	*m*-Me-C_6H_4 (**f**)	46/39	76/77	17
7	*p*-Me-C_6H_4 (**g**)	50/45	73/76	14
8	*p*-Cl-*o*-Me-C_6H_3 (**h**)	49/46	84/88	34
9	α-Naphthyl (**i**)	50/47	87/83	36
10	β-Naphthyl (**j**)	50/49	75/73	15
11	2,6-Cl_2-C_6H_3 (**k**)	46/51	78/69	16
12	2,4-Cl_2-C_6H_3 (**l**)	47/44	90/90	60
13	*o*-F-C_6H_4 (**m**)	48/45	86/85	35
14	*o*-Br-C_6H_4 (**n**)	48/49	95/88	110
15	*o*-MeO-C_6H_4 (**o**)	49/43	88/76	38
16	*o*-NO_2-C_6H_4 (**p**)	47/53	92/79	58
17	*o*-Ph-C_6H_4 (**q**)	47/50	96/89	131

[a]isolated yield, [b]Table 1, Entry 2.

In all entries, the yields of the corresponding esters were almost quantitative. In Entries 2–7, carboxylic acids incorporating an Me or Cl substituent at the *ortho*-, *meta*-, or *para*-position of the 2-phenoxy group were investigated. The substituent of the phenoxy group was found to affect the stereochemistry, with carboxylic acids bearing the *ortho*-substituted phenoxy group giving good enantiomeric excesses and high *s*-values, while substituents at the *meta*- (Entry 3, $s = 16$ and Entry 6, $s = 17$) or *para*- (Entry 4, $s = 12$ and Entry 7, $s = 14$) positions having little effect relative to unsubstituted 2-phenoxypropanoic acid (**1a**) (Entry 1, $s = 16$). By exploiting this tendency, racemic 2-(*p*-chloro-*o*-methylphenoxy)propanoic acid (*rac*-**1h**), MCPP, was successfully separated to provide the potent (*R*)-(+)-carboxylic acid ((*R*)-**1h**), MCPP-P (Entry 8, 46% yield, 88% ee). A similar tendency was also observed in carboxylic acids incorporating a naphthoxy group. For example, 2-(α-naphthoxy)propanoic acid (**1i**) (Entry 9, $s = 36$) gave a good *s*-value compared with 2-(β-naphthoxy)propanoic acid (**1j**) (Entry 10, $s = 15$).

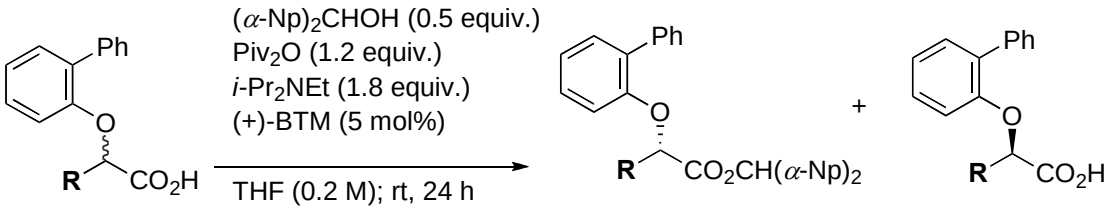
In addition, the carboxylic acid bearing substituents at both *ortho*-positions of the phenoxy group, 2-(2,6-dichlorophenoxy)propanoic acid (**1k**) (Entry 11, s = 16), gave diminished selectivity compared with an *ortho*-monosubstituted (Entry 2, s = 82) or *ortho*, *para*-disubstituted phenoxy group on the carboxylic acid (Entry 12, s = 60).

Furthermore, a series of carboxylic acids incorporating an *ortho*-substituent such as a halogen (Entries 2, 13, and 14), methoxy (Entry 15), nitro (Entry 16), or phenyl (Entry 17) substituent in the phenoxy group were examined. Therefore, irrespective of the electric properties of the substituents, bulky *ortho*-substituents in the phenoxy group have a tendency to enhance the enantioselectivity as represented by the *o*-bromophenoxy group (Entry 14, s = 110) and *o*-phenylphenoxy group (Entry 17, s = 131).

Regarding the absolute configuration of these products, it was experimentally confirmed that the obtained esters (**2**) take *S* configuration in entries 1, 2, and 12 (see experimental section). In a similar fashion, it is easy to consider that the other produced chiral esters take *S* configuration.

We then considered whether other extended 2-aryloxyalkanoic acids are applicable to our procedure. The *o*-phenylphenoxy group that showed the best selectivity in Table 2 was applied to the screening of alkanoic acids (Table 3). Contrary to our expectations, conversion yields of 2-aryloxybutanoic acid (**1r**) (Entry 2) and 2-aryloxypentanoic acid (**1s**) (Entry 3) into the corresponding esters were dramatically reduced to approximately 20%. Doubling of the catalyst loading led to some improvement in the yield of the corresponding ester (*R*)-**2s**, but only up to 34% (Entry 4). As shown in Entry 5, it is clear that 2-aryloxyalkanoic acids that branch at the 3-position are not suitable for this kinetic resolution system.

Table 3. Kinetic resolution of racemic 2-(*o*-phenylphenoxy)alkanoic acids

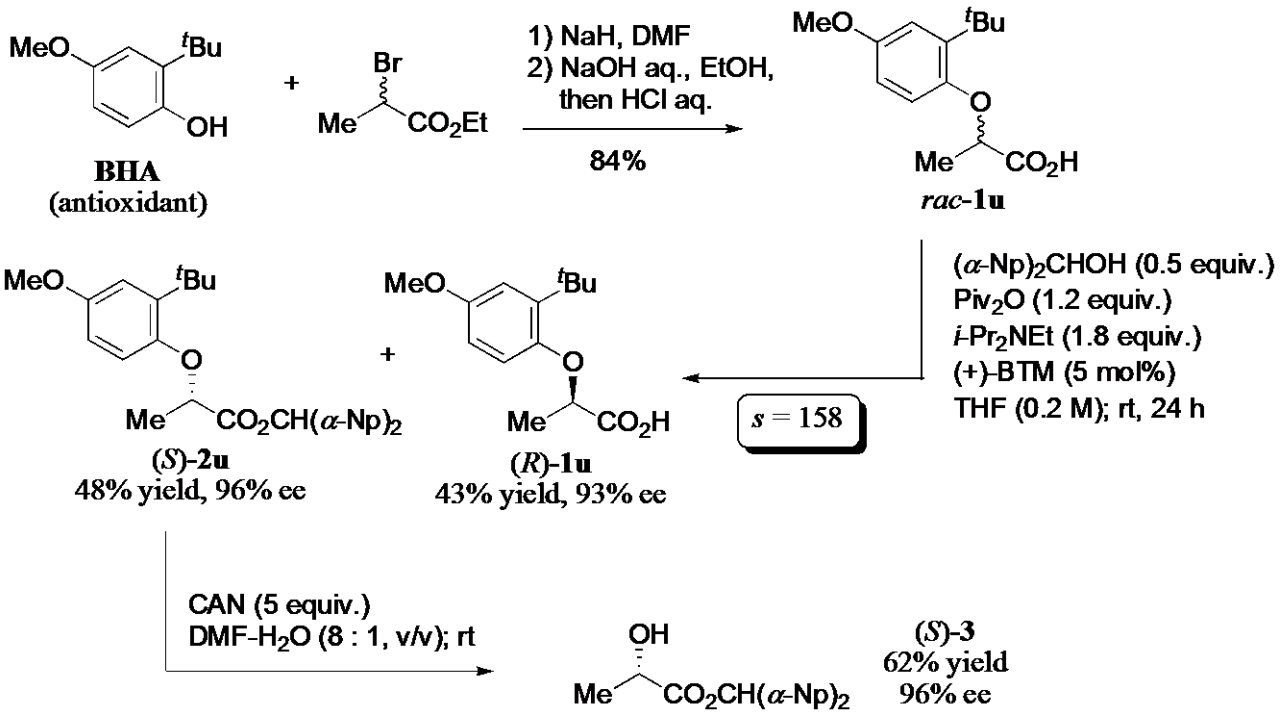


rac-**1q**–**t** (*S*)-**2q**–**t** (*R*)-**1q**–**t**

Entry	**R**	Yield[a] of (*S*)-**2**/(*R*)-**1** (%)	ee of (*S*)-**2**/(*R*)-**1** (%)	s
1[b]	Me (**q**)	47/50	96/89	131
2	Et (**r**)	22/76	94/30	45
3	*n*-Pr (**s**)	18/80	93/21	33
4[c]	*n*-Pr (**s**)	34/53	91/51	36
5	*i*-Pr (**t**)	0/68	-/-	-

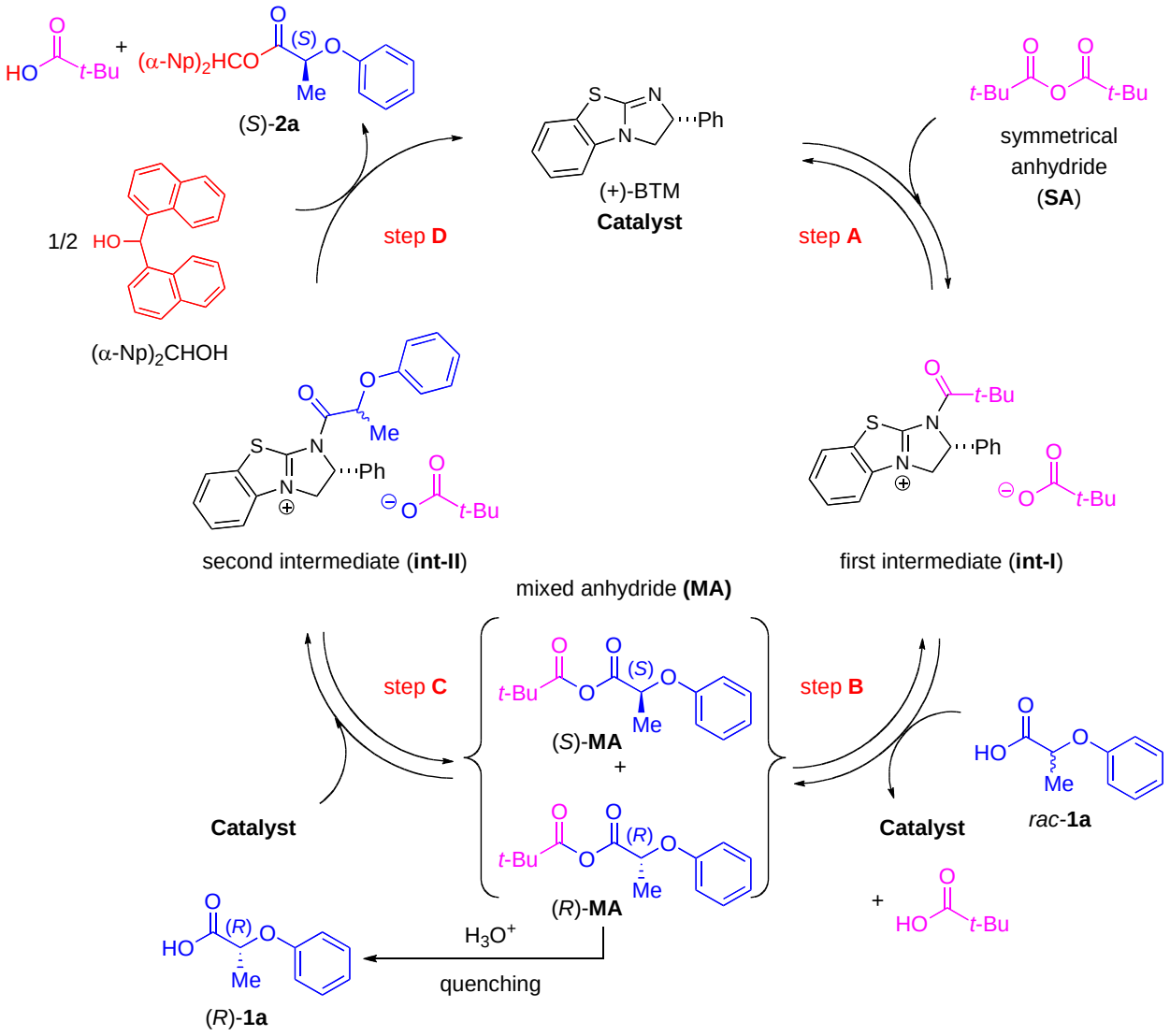
[a]isolated yield, [b]Table 2, Entry 17, [c](+)-BTM (10 mol%).

Subsequently, we anticipated that removing the aryl group of the separated chiral 2-aryloxypropionic acid esters would offer a novel approach to provide optically active 2-hydroxypropanoic acid esters, applicable for further syntheses. Specifically, based on the preference of substituents in the phenoxy group as described above, an *o*-*tert*-butyl-*p*-methoxyphenoxy group was selected as the aryloxy group incorporating both a bulky substituent in the *ortho*-position and a *p*-methoxy substituent that are oxidatively removable by cerium ammonium nitrate (CAN).[14] As shown in Scheme 3, racemic 2-(*o*-*tert*-butyl-*p*-methoxyphenoxy)propanoic acid (*rac*-**1u**) was readily prepared from racemic ethyl 2-bromopropanoate and an inexpensive antioxidant, butylated hydroxy anisole (BHA), and then kinetic resolution of *rac*-**1u** was successfully accomplished to provide the desired optically active ester (*S*)-**2u** in 48% yield with an excellent selectivity (96% ee, s = 158). Finally, the oxidative deprotection of the *p*-methoxy aryl group in (*S*)-**2u** afforded the corresponding 2-hydroxypropanoic acid ester ((*S*)-**3**) in 62% yield with maintenance of optical purity (96% ee).



Scheme 3. Kinetic resolution of racemic 2-(*o*-*tert*-butyl-*p*-methoxyphenoxy)propanoic acid (*rac*-**1u**) and deprotection of the aryloxy group

To explain these experimental findings, theoretical aspects including the transition state and the chiral recognition mechanism of the asymmetric esterification were considered next. Given the perspectives described in our previous work,[11] we propose a catalytic cycle for this reaction as depicted in Scheme 4.



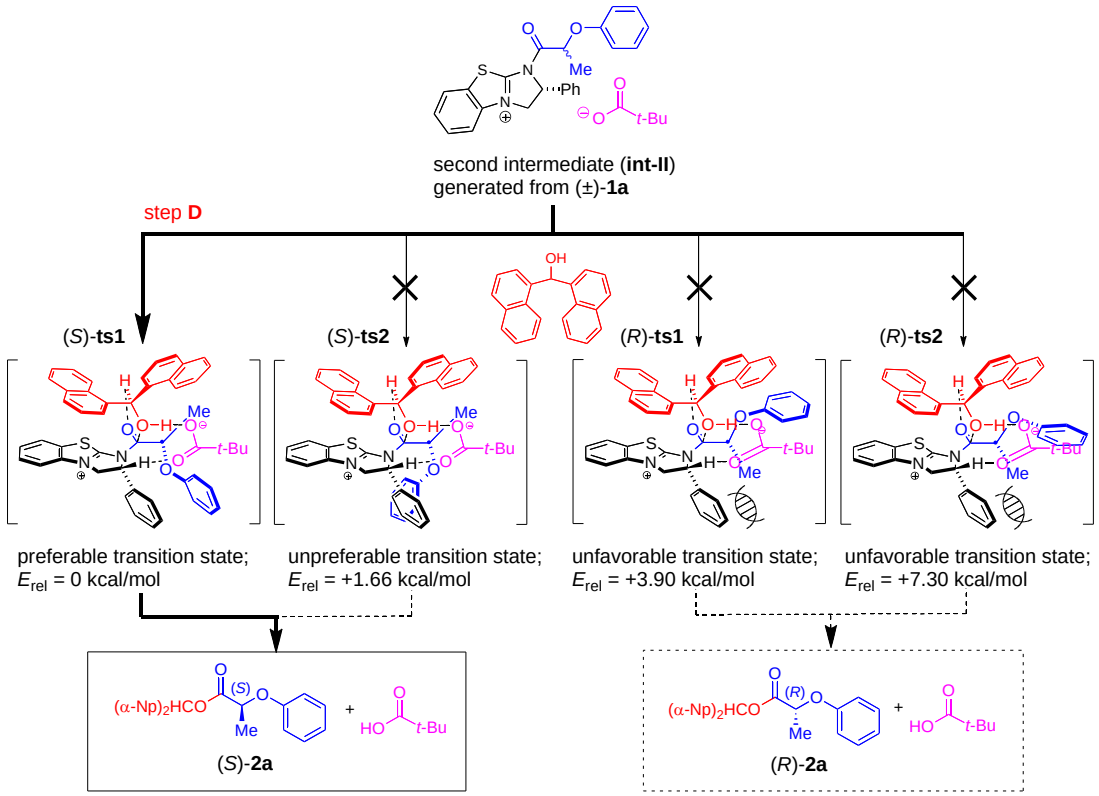
Scheme 4. Proposed reaction pathway for the kinetic resolution of *rac*-**1a**

First, a **MA** forms as the key intermediate *in situ* from Piv_2O with racemic 2-phenoxypropanoic acid (*rac*-**1a**) via generation of a zwitterion (**int-I**) through steps **A** and **B** by promotion of the acyl-transfer catalyst, (+)-BTM. In the next step **C**, (*S*)-, and (*R*)-**MA** would be activated again by (+)-BTM to form the corresponding zwitterionic species (**int-II**), and half the amount of **int-II** generated from (*S*)-**MA** would selectively react with $(\alpha\text{-Np})_2CHOH$ to afford the desired (*S*)-**2a** with high enantiomeric excess through step **D**. The remaining mixed anhydride ((*R*)-**MA**) would be hydrolyzed to produce unreacted (*R*)-**1a** as a recovered optically active starting material with good enantiopurity. It is anticipated step **D** would be the key enantio-determining step during this multiple transacylation process.

Based on these considerations, determination of the transition state forming the optically active (*S*)-**2a** from (*S*)-**1a** with $(\alpha\text{-Np})_2CHOH$, (+)-BTM, and Piv_2O via the dihydroimidazolium salt (**Int-II**) was carried out using density functional theory (DFT) calculations at the B3LYP/6-31G*//B3LYP/6-31G* level of theory according to the method previously reported.[11,15]

We successfully obtained two predominant transition states ((*S*)-**ts1** and (*S*)-**ts2**) to produce the desired ester (*S*)-**2a** as depicted in Scheme 5. These transition states differed in orientation of the 2-phenoxy groups of (*S*)-**1a**, with the 2-phenoxy group of the (*S*)-**ts1** overlapping the phenyl ring at the C-2 position of the dihydroimidazolium salt, while the 2-phenoxy group of (*S*)-**ts2** faces the opposite side. (*S*)-**ts1** is lower in energy than (*S*)-**ts2** by 1.66 kcal/mol owing to the stable stacking structure of aromatic rings as illustrated in Scheme 5 and Figure 1. Consequently, it was supposed that esterification of (*S*)-**1a** proceeds through (*S*)-**ts1**.

The high selectivity in the present kinetic resolution could be explained by the rapid transformation of (*S*)-**1a** into (*S*)-**2a** via this stabilized transition structure consisting of the $(\alpha\text{-Np})_2$CHOH and the dihydroimidazolium salt (**int-II**) derived from the mixed anhydride (*S*)-**MA** and (+)-BTM. In the case of the preferred (*S*)-**ts1**, the distance of the forming carbon–oxygen bond (between the carbonyl carbon of the acid component and oxygen of the hydroxyl group) is 2.169 Å, accompanied by the coordination of oxygen in the carbonyl moiety onto the hydrogen at the C-1 position of alcohol at a distance of 2.401 Å, as shown in Figure 1. It is further observed that the distance of the cleaving oxygen–hydrogen bond (between oxygen and hydrogen in the hydroxyl group) is 1.277 Å.



Scheme 5. Calculated transition state of the kinetic resolution of *rac*-**1a**

A frequency analysis of (*S*)-**ts1** revealed that the nucleophilic attack of the alcohol to the carbonyl group and the deprotonation of the hydroxyl group with the pivalate anion proceeded under a concerted reaction

mechanism because the carbon–oxygen bond-forming step and the oxygen–hydrogen bond-cleaving process occurred synchronously. The diarylalcohol moiety of (α-Np)$_2$CHOH in (*S*)-**ts1** has a rigid structure, in which the conformation is restricted by the attractive interaction between one of the naphthalene rings and the positive electronic charge on the face of the dihydroimidazolium salt as well as coordination of the oxygen atoms in the pivalate anion onto the hydrogen atom in the hydroxyl group (1.151 Å) and the hydrogen atom at the C-2 position of the dihydroimidazolium salt (2.100 Å).

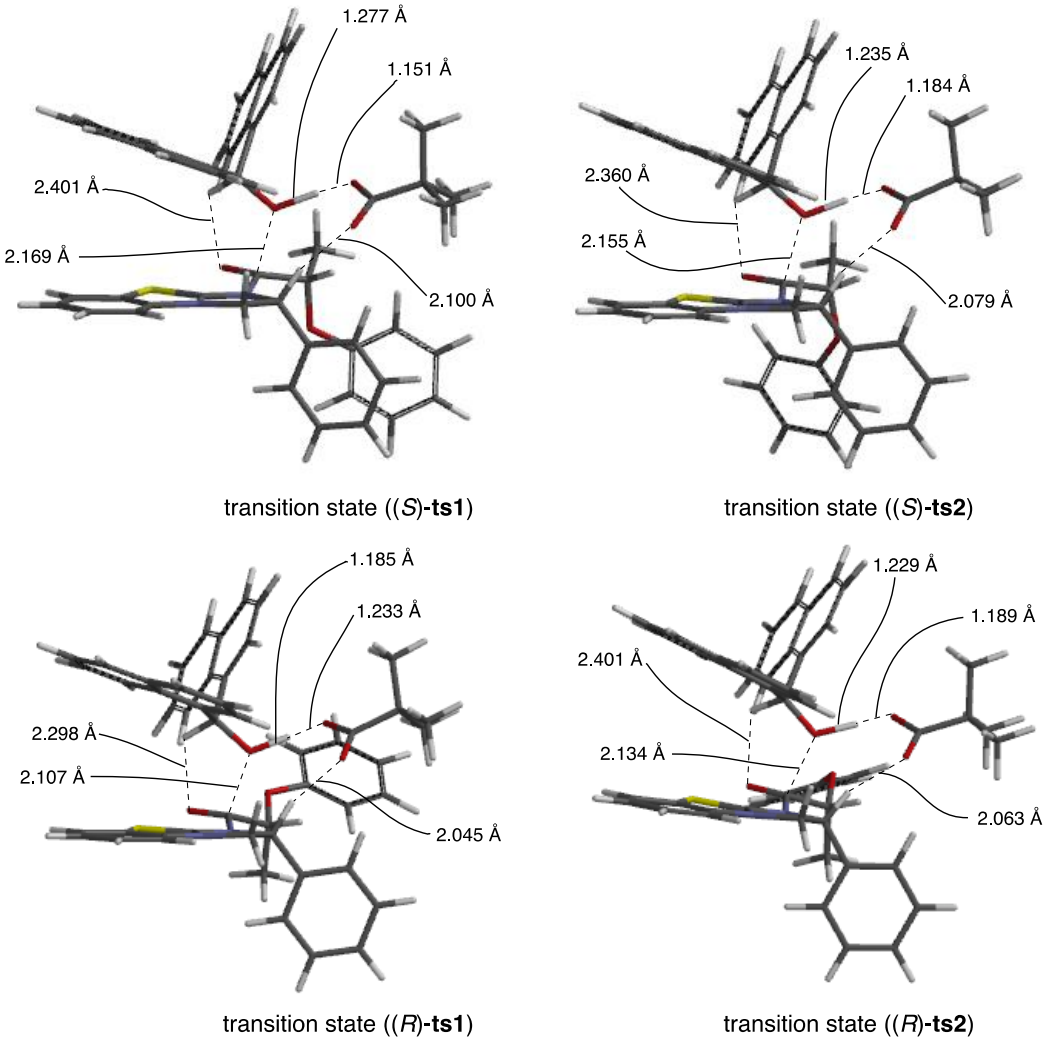
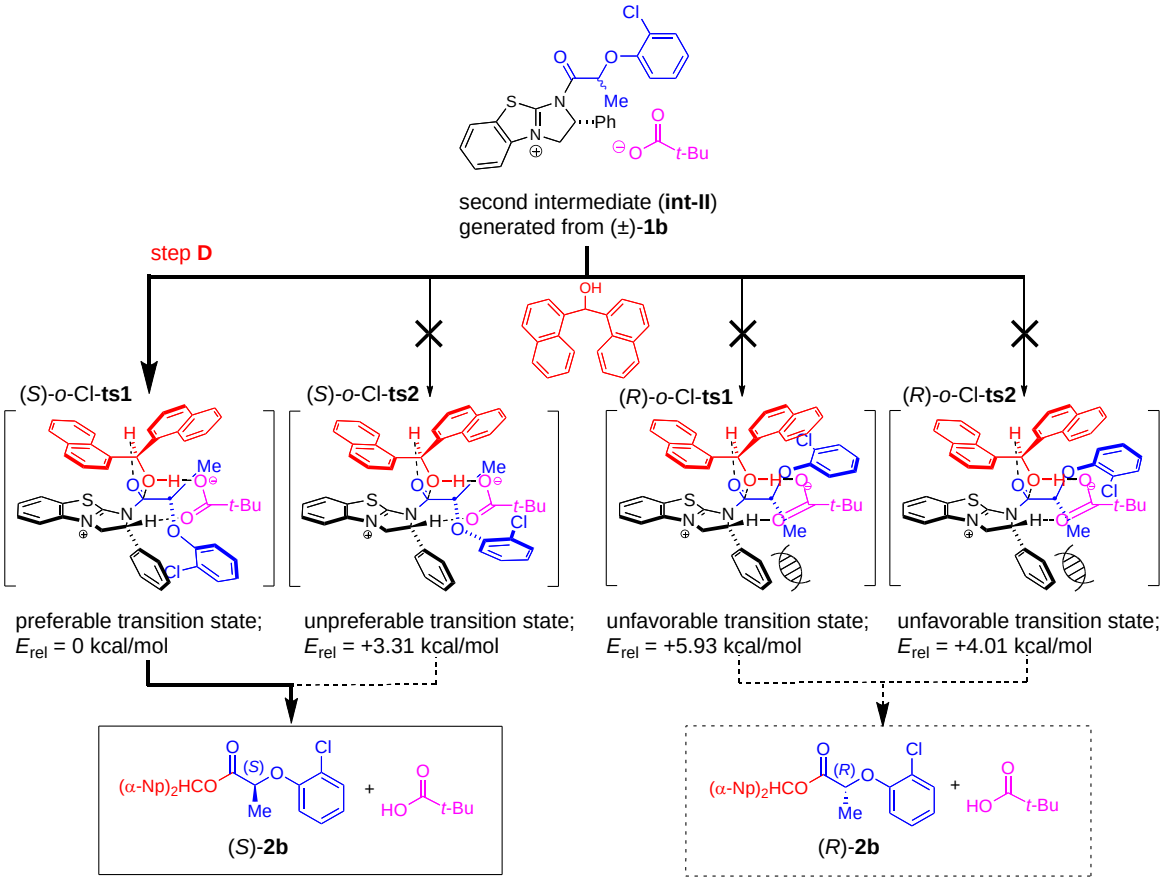


Figure 1. Structure of calculated transition state ((*S*)-**ts1**, (*S*)-**ts2**, (*R*)-**ts1**, and (*R*)-**ts2**)

Conversely, complexation of (α-Np)$_2$CHOH with the dihydroimidazolium salt (**int-II**) including (*R*)-**MA** and (+)-BTM, an enantiomer of (*S*)-**MA**, produced two transition states, (*R*)-**ts1** and (*R*)-**ts2**, with a high energy relative to (*S*)-**ts1**, E_{rel} = +3.90 kcal/mol and +7.30 kcal/mol, respectively (Scheme 5). Thus, it is supposed that transformation of (*R*)-**1a** into (*R*)-**2a** proceeds mainly through the former transition state, (*R*)-**ts1**. These high-energy transition states derived from the steric repulsion between the methyl substituent at the 2-position of (*R*)-**1a** and the phenyl group at the C-2 position of the dihydroimidazolium

salt to afford the corresponding (*R*)-**2a**. In addition, it is considered that the strained conformation of the 2-phenoxy group necessary to avoid the steric hindrance of $(\alpha\text{-Np})_2$CHOH destabilizes its transition state. On the basis of theoretical calculations, it is certain that the desired chiral (*S*)-**2a** was selectively obtained by the rapid transformation of (*S*)-**MA** through the most stable transition state (*S*)-**ts1**, while the esterification of (*R*)-**1a** via (*R*)-**ts1** proceeded very slowly according to the energy gap of 3.90 kcal/mol.

Using this established protocol for proving transition states, we then tried to account theoretically for the enhanced selectivity by substitution at the *ortho*-position in the phenoxy group, as depicted in Table 2. 2-(*o*-Chlorophenoxy)propanoic acid (**1b**) (Table 2, Entry 2, s = 82) was selected as a model substrate for further computational calculations to determine the transition states and their energies. Successful calculations of **1b** disclosed four possible transition states that afford the corresponding esters; (*S*)-*o*-Cl-**ts1** and (*S*)-*o*-Cl-**ts2** derived from (*S*)-**1b**, and (*R*)-*o*-Cl-**ts1** and (*R*)-*o*-Cl-**ts2** derived from (*R*)-**1b**, respectively (Scheme 6).



Scheme 6. Calculated transition state of the kinetic resolution of *rac*-**1b**

Calculations of the energy of each transition state revealed the enhancement of the relative energy of the unfavorable (*R*)-*o*-Cl-**ts2** ($E_{rel(o\text{-}Cl)}$ = +4.01 kcal/mol, Scheme 6) compared with the corresponding relative energy of (*R*)-**ts1** derived from (*R*)-**1a** (E_{rel} = +3.90 kcal/mol, Scheme 5). Therefore, it is considered that

the large energy gap because of the increased strain at the 2-phenoxy group by *ortho*-substitution causes the observed high ee shown in Table 2.

CONCLUTIONS

In summary, we have developed an effective kinetic resolution system to provide optically active 2-aryloxypropanoic acids and the corresponding esters. By screening the reaction media, it was found that THF was the most suitable solvent to achieve high enantiomeric excesses of the recovered carboxylic acids and the formed esters. Investigation of a series of substituents on the 2-phenoxy groups showed the preference of *ortho*-substituted bulky groups. This perception was also utilized for the production of the optically pure 2-hydroxypropanoic acid ester using the *o*-*tert*-butyl-*p*-methoxyphenyl group as a functional protecting group.

In addition, we succeeded in disclosing the reaction mechanism to afford high enantioselectivity using theoretical calculations, and expounded on the substituent effect in the 2-phenoxy group. Further investigation will be focused on different racemic carboxylic acids bearing other hetero atoms at the 2-position.

EXPERIMENTAL

All melting points were uncorrected. IR spectra were taken on a JASCO FT/IR-6100 spectrometer. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ with a Bruker AM400 (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR) instrument, and the chemical shifts were reported in ppm from tetramethylsilane (0.00 ppm) for ^{1}H NMR and $CDCl_3$ (77.0 ppm) for ^{13}C NMR as an internal standard, respectively. HRMS were recorded by Bruker ESI-TOF MS. Column chromatography was performed on Silica gel 60 (Merck) or Wakogel B5F. Thin layer chromatography was performed on Wakogel B5F. All reactions were carried out under argon atmosphere in dried glassware, unless otherwise noted. Diethyl ether was distilled from sodium and benzophenone, dichloromethane was distilled from diphosphorus pentoxide, then calcium hydride, and dried over MS 4A, and THF and DMF were distilled from calcium hydride, and dried over MS 4A.

Racemic 2-aryloxypropanoic acids, *rac*-**1a**–**c** and *rac*-**1l**, were purchased from Tokyo Kasei Kogyo Co., Ltd (TCI). *Rac*-**1d**–**k**, *rac*-**1m**–**r**, and *rac*-**1u** were prepared from racemic ethyl 2-bromopropanoate or methyl 2-bromobutanoate and the corresponding hydroxyaryl compounds according to literature method.[6] Methyl (*R*)-lactate that was used for the preparation of the authentic (*S*)-**2b** was also purchased from TCI.

Racemic ethyl 2-([1,1'-biphenyl]-2-yloxy)pentanoate (*rac*-4s).

To a mixture of racemic ethyl 2-hydroxypentanoate (1.46 g, 10.0 mmol), 2-phenylphenol (1.70 g, 10.0 mmol), and triphenylphosphine (3.15 g, 12.0 mmol) in THF (35 mL) at 0 °C was added 40% diisopropyl

azodicarboxylate in toluene (7.37 mL, 14.0 mmol). After the reaction mixture had been stirred for 2 h at room temperature, 40% diisopropyl azodicarboxylate in toluene (2.11 mL, 4.00 mmol) was added. The reaction mixture was stirred for 14 h at room temperature, and then diluted with hexane. After filtration of the slurry mixture and evaporation of the solvent, the crude product was purified by silica gel column chromatography (EtOAc/hexane = 1/40) to afford *rac*-**4s** (1.12 g, 38% yield) as a colorless oil: IR (neat): 2961, 1732, 1598, 1584, 1503, 1480, 770, 751, 732, 698 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.63-7.56 (m, 2H, Ar), 7.42-7.20 (m, 5H, Ar), 7.07-7.00 (m, 1H, Ar), 6.86-6.80 (m, 1H, Ar), 4.60 (t, *J* = 6.2 Hz, 1H, 2-H), 4.18 (q, *J* = 7.2 Hz, 2H, OEt), 1.82 (dt, *J* = 6.2, 7.6 Hz, 2H, 3-H), 1.37 (qt, *J* = 7.2, 7.6 Hz, 2H, 4-H), 1.22 (t, *J* = 7.2 Hz, 3H, OEt), 0.85 (t, *J* = 7.2 Hz, 3H, 5-CH_3); ^{13}C NMR ($CDCl_3$): δ 171.9 (1), 154.8, 138.4, 131.5, 131.2, 129.7, 128.4, 127.8, 126.8, 121.7, 113.1, 76.7 (2), 61.0 (Et), 34.7 (3), 18.3 (4), 14.1 (Et), 13.7 (5); HR MS: calcd for $C_{19}H_{22}O_3Na$ ($M + Na^+$) 321.1461, found 321.1468.

Racemic 2-((1,1'-biphenyl)-2-yloxy)pentanoic acid (*rac*-1s).

To a solution of *rac*-**4s** (1.08 g, 3.62 mmol) in ethanol (20 mL) at 0 °C was added aqueous sodium hydroxide (4.2 M, 5.0 mL, 21 mmol). The reaction mixture was stirred at room temperature for 4 h, and then it was acidified with 1 M hydrochloric acid (50 mL). The mixture was extracted with EtOAc, and the organic layer was dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was crystallized from CH_2Cl_2 and hexane to afford *rac*-**1s** (879 mg, 90% yield) as a white solid: Mp 131-133 °C (CH_2Cl_2/hexane); IR (KBr): 2972, 1704, 1599, 1583, 1502, 1479, 772, 748, 728, 701 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.42 (br s, 1H, CO_2H), 7.59-7.50 (m, 2H, Ar), 7.45-7.23 (m, 5H, Ar), 7.12-7.05 (m, 1H, Ar), 6.93-6.86 (m, 1H, Ar), 4.65 (t, *J* = 6.0 Hz, 1H, 2-H), 1.94-1.78 (m, 2H, 3-H), 1.46-1.31 (m, 2H, 4-H), 0.86 (t, *J* = 7.2 Hz, 3H, 5-CH_3); ^{13}C NMR ($CDCl_3$): δ 175.2 (1), 154.2, 138.1, 131.9, 131.3, 129.5, 128.6, 128.0, 127.1, 122.4, 113.5, 76.7 (2), 34.4 (3), 18.1 (4), 13.6 (5); HR MS: calcd for $C_{17}H_{18}O_3Na$ ($M + Na^+$) 293.1148, found 293.1152.

Racemic ethyl 2-[(1,1'-biphenyl)-2-yloxy]-3-methylbutanoate (*rac*-4t).

To a solution of ethyl 3-methyl-2-oxobutanoate (290 mg, 2.0 mmol) in Et_2O (4 mL) at 0 °C was added sodium borohydride (150 mg, 4.0 mmol) in water (2 mL). After the reaction mixture had been stirred for 1 h at 0 °C, sodium borohydride (38 mg, 1.0 mmol) was added. The reaction mixture was stirred for 2 h at 0 °C, and then diluted with water. The mixture was extracted with CH_2Cl_2, and the organic layer was dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, ethyl 2-hydroxy-3-methylbutanoate was obtained as a colorless oil. This crude product was used in the next reaction without further purification.

To a solution of ethyl 2-hydroxy-3-methylbutanoate (2.0 mmol) and 2,6-lutidine (290 μL, 2.5 mmol) in CH_2Cl_2 (6 mL) at –78 °C was added trifluoromethanesulfonic anhydride (420 μL, 2.5 mmol). The

reaction mixture had been stirred for 5 min at –78 °C, and then gradually raised to room temperature for 2 h. After cooling to 0 °C, the reaction mixture was diluted with water. The mixture was extracted with CH_2Cl_2, and the organic layer was dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was diluted with CH_2Cl_2-hexane (1:1, v/v) and filtered through silica gel. The filtrate was concentrated to afford ethyl 3-methyl-2-{[(trifluoromethyl)sulfonyl]oxy}butanoate (470 mg, 84% yield) as a pale yellow oil. This crude product was used in the next reaction without further purification.

To a solution of 3-methyl-2-{[(trifluoromethyl)sulfonyl]oxy}butanoate (284 mg, 1.67 mmol) and 2-phenylphenol (464 mg, 1.67 mol) in DMF (4 mL) at 0 °C was added sodium hydride (55% in paraffin liquid, 87 mg, 2.0 mmol). After the reaction mixture had been stirred for 25 min at room temperature, water was added. The mixture was extracted with hexane-EtOAc (1:1, v/v), and the organic layer was dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by preparative thin layer chromatography on silica (EtOAc/hexane = 1/3) to afford *rac*-**4t** (411 mg, 82% yield) as a colorless oil: IR (neat): 2961, 1732, 1598, 1584, 1503, 1480, 770, 751, 732, 698 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.64-7.58 (m, 2H, Ar), 7.43-7.19 (m, 5H, Ar), 7.12-7.05 (m, 1H, Ar), 6.93-6.86 (m, 1H, Ar), 4.43 (d, *J* = 4.8 Hz, 1H, 2-H), 4.19 (q, *J* = 7.2 Hz, 2H, OEt), 2.19 (dqq, *J* = 4.8, 6.8, 6.8 Hz, 1H, 3-H), 1.22 (t, *J* = 7.2 Hz, 3H, OEt), 0.92 (d, *J* = 6.8 Hz, 3H, 4-CH_3), 0.91 (d, *J* = 6.8 Hz, 3H, 4-CH_3); ^{13}C NMR ($CDCl_3$): δ 171.1 (1), 154.9, 138.5, 131.5, 131.1, 129.8, 128.3, 127.7, 126.7, 121.4, 112.3, 81.3 (2), 60.9 (Et), 31.7 (3), 18.7 (4), 17.5 (4), 14.2 (Et); HR MS: calcd for $C_{19}H_{22}O_3Na$ ($M + Na^+$) 321.1461, found 321.1452.

Racemic (*R*)-2-[(1,1'-biphenyl)-2-yloxy]-3-methylbutanoic acid (*rac*-1t).

Rac-**4t** (377 mg, 1.26 mmol) was hydrolyzed in accordance with the preparation of *rac*-**3s**, and then crystallized from CH_2Cl_2 and hexane to afford *rac*-**1t** (257 mg, 75% yield) as a white solid: Mp 82-84 °C (CH_2Cl_2/hexane); IR (KBr): 2967, 1702, 1601, 1585, 1503, 1479, 766, 748, 727, 697 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.58 (br s, 1H, CO_2H), 7.59-7.51 (m, 2H, Ar), 7.46-7.18 (m, 5H, Ar), 7.11-7.03 (m, 1H, Ar), 6.89-6.80 (m, 1H, Ar), 4.43 (d, *J* = 4.0 Hz, 1H, 2-H), 2.31-2.18 (m, 1H, 3-H), 0.95 (d, *J* = 6.8 Hz, 3H, 4-CH_3), 0.94 (d, *J* = 6.8 Hz, 3H, 4-CH_3); ^{13}C NMR ($CDCl_3$): δ 174.6 (1), 154.5, 138.1, 131.8, 131.3, 129.7, 128.6, 127.9, 127.1, 122.1, 112.8, 81.3 (2), 31.6 (3), 18.6 (4), 17.2 (4); HR MS: calcd for $C_{17}H_{18}O_3Na$ ($M + Na^+$) 293.1148, found 293.1158.

General procedure for kinetic resolution of racemic 2-aryloxypropanoic acid (Tables 1–3, Scheme 3).

To a mixture of racemic 2-aryloxypropanoic acid (*rac*-**1**) (0.200 mmol), pivalic anhydride (48.7 μL, 0.240 mmol), and bis(α-naphthyl)methanol (28.4 mg, 0.100 mmol) in solvent (1.0 mL) at room

temperature were successively added diisopropylethylamine (62.7 μL, 0.360 mmol) and (+)-BTM (2.5 mg, 10 μmol). The reaction mixture was stirred for 24 h at room temperature, and then quenched with 1 M hydrochloric acid. The mixture was extracted with EtOAc, and the organic layer was dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by preparative thin layer chromatography on silica (toluene/hexane = 90/10) to afford the corresponding (*S*)-**2**. The polar fraction including carboxylic acid was further purified by preparative thin layer chromatography on silica (EtOAc/hexane/formic acid = 10/40/1) to afford the recovered optically active (*R*)-**1**.

(*R*)-2-Phenoxypropanoic acid ((*R*)-1a). [Table 1, Entry 2 (Table 2, Entry 1), 43% yield, 76% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane/TFA = 1/50/0.05, flow rate = 1.0 mL/min): t_R = 16.3 min (12.0%), t_R = 22.0 min (88.0%); The absolute configuration was determined as *R* by the comparison of the retention time with the literature data.[12a]

Di(1-naphthyl)methyl (*S*)-2-phenoxypropanoate ((*S*)-2a). [Table 1, Entry 2 (Table 2, Entry 1), 49% yield, 75% ee] Spectroscopic data were previously reported.[12a] HPLC (CHIRALCEL OD-H, *i*-PrOH/hexane = 1/9, flow rate = 0.5 mL/min): t_R = 12.2 min (12.4%), t_R = 27.0 min (87.6%).

(*R*)-2-(2-Chlorophenoxy)propanoic acid ((*R*)-1b). [Table 2, Entry 2, 45% yield, 90% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane/TFA = 1/50/0.05, flow rate = 0.75 mL/min): t_R = 20.5 min (4.9%), t_R = 25.7 min (95.1%). The absolute configuration was determined as *R* by the comparison of the retention time with that of the authentic sample (*S*)-**1b** derived from methyl (*R*)-lactate (*vide infra*).

Di(1-naphthyl)methyl (*S*)-2-(2-chlorophenoxy)propanoate ((*S*)-2b). [Table 2, Entry 2, 46% yield, 93% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/50, flow rate = 0.75 mL/min): t_R = 19.3 min (96.4%), t_R = 24.0 min (3.6%); ^{1}H NMR ($CDCl_3$): δ 8.47 (s, 1H, 1'-H), 8.10-7.75 (m, 6H, Ar), 7.57-7.17 (m, 9H, Ar), 6.96-6.78 (m, 2H, Ar), 6.75-6.62 (m, 1H, Ar), 4.86 (q, *J* = 6.8 Hz, 1H, 2-H), 1.68 (d, *J* = 6.8 Hz, 3H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 170.8 (1), 153.2, 134.2, 134.1, 133.9, 133.8, 131.1, 130.9, 130.5, 129.3, 129.1, 129.0, 128.8, 127.4, 126.8, 126.6, 126.2, 125.93, 125.85, 125.8, 125.2, 125.1, 123.7, 123.30, 123.28, 122.5, 115.0, 74.0 (2), 71.9 (1'), 18.4 (3); HR MS: calcd for $C_{30}H_{23}ClO_3Na$ ($M + Na^+$) 489.1228, found 489.1210; Analytical data on racemic compound: Mp 163-164 °C (hexane); IR (KBr): 3064, 1749, 1589, 1510, 1481, 1185, 1122, 803, 786, 780, 758 cm^{-1}. The absolute configuration was determined as *S* by the comparison of the retention time with that of the authentic sample (*R*)-**2b** derived from methyl (*R*)-lactate (*vide infra*).

(*R*)-2-(3-Chlorophenoxy)propanoic acid ((*R*)-1c). [Table 2, Entry 3, 43% yield, 78% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane/TFA = 1/50/0.05, flow rate = 1.0 mL/min): t_R = 14.4 min (10.8%), t_R = 17.8 min (89.2%).

Di(1-naphthyl)methyl (*S*)-2-(3-chlorophenoxy)propanoate ((*S*)-2c). [Table 2, Entry 3, 49% yield, 75%

ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/50, flow rate = 1.0 mL/min): t_R = 17.5 min (87.3%), t_R = 21.9 min (12.7%); ^{1}H NMR ($CDCl_3$): δ 8.45 (s, 1H, 1'-H), 8.06-7.73 (m, 6H, Ar), 7.58-7.18 (m, 8H, Ar), 7.06-6.95 (m, 1H, Ar), 6.94-6.81 (m, 2H, Ar), 6.69-6.61 (m, 1H, Ar), 4.83 (q, *J* = 6.8 Hz, 1H, 2-H), 1.61 (d, *J* = 6.8 Hz, 3H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 171.0 (1), 158.2, 134.9, 134.1, 134.0, 133.9, 133.8, 131.1, 130.9, 130.2, 129.4, 129.2, 129.0, 128.8, 126.9, 126.6, 126.2, 126.0, 125.9, 125.7, 125.2, 125.1, 123.3, 123.2, 121.8, 115.7, 113.3, 72.8 (2), 72.1 (1'), 18.5 (3); HR MS: calcd for $C_{30}H_{23}ClO_3Na$ (M + Na^+) 489.1228, found 489.1213; Analytical data on racemic compound: Mp 127-128 °C (hexane); IR (KBr): 3060, 1743, 1625, 1595, 1580, 1510, 1476, 1183, 1131, 800, 783 cm^{-1}.

(*R*)-2-(4-Chlorophenoxy)propanoic acid ((*R*)-1d). [Table 2, Entry 4, 50% yield, 68% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane/TFA = 1/50/0.05, flow rate = 1.0 mL/min): t_R = 19.8 min (15.9%), t_R = 25.9 min (84.1%); IR (KBr): 2995, 1717, 1595, 1490, 825 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.27-7.15 (m, 2H, Ar), 6.85-6.75 (m, 2H, Ar), 4.74 (q, *J* = 7.5 Hz, 1H, 2-H), 1.64 (d, *J* = 7.5 Hz, 3H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 177.0 (1), 155.8, 129.6, 127.0, 116.6, 72.4 (2), 18.3 (3); HR MS: calcd for $C_9H_9ClO_3Na$ (M + Na^+) 223.0132, found 223.0143; Analytical data on racemic compound: Mp 115-116 °C (CH_2Cl_2/hexane); IR (KBr): 3065, 1717, 1600, 1510, 1123, 777, 698 cm^{-1}.

Di(1-naphthyl)methyl (*S*)-2-(4-chlorophenoxy)propanoate ((*S*)-2d). [Table 2, Entry 4, 49% yield, 72% ee] HPLC (CHIRALCEL OD-H, *i*-PrOH/hexane = 1/300, flow rate = 1.0 mL/min): t_R = 33.6 min (14.2%), t_R = 38.1 min (85.8%); ^{1}H NMR ($CDCl_3$): δ 8.45 (s, 1H, 1'-H), 8.03-7.75 (m, 1H, Ar), 7.93-7.75 (m, 5H, Ar), 7.56-7.41 (m, 3H, Ar), 7.38-7.19 (m, 5H, Ar), 7.07-7.00 (m, 2H, Ar), 6.73-6.64 (m, 2H, Ar), 4.79 (q, *J* = 6.8 Hz, 1H, 2-H), 1.61 (d, *J* = 6.8 Hz, 3H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 171.1 (1), 156.0, 134.2, 133.93, 133.92, 133.8, 131.1, 130.8, 129.4, 129.3, 129.3, 129.2, 129.0, 128.8, 126.8, 126.6, 126.5, 126.3, 126.0, 125.9, 125.6, 125.2, 125.0, 123.3, 123.2, 116.4, 116.4, 73.0 (2), 72.0 (1'), 18.5 (3); HR MS: calcd for $C_{30}H_{23}ClO_3Na$ (M + Na^+) 489.1228, found 489.1223; Analytical data on racemic compound: Mp 123-125 °C (hexane); IR (KBr): 3063, 1746, 1598, 1511, 1490, 1186, 1133, 825, 783, 775 cm^{-1}.

(*R*)-2-(*o*-Tolyloxy)propanoic acid ((*R*)-1e). [Table 2, Entry 5, 45% yield, 86% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane/TFA = 1/50/0.05, flow rate = 0.75 mL/min): t_R = 15.5 min (6.9%), t_R = 14.3 min (93.1%); ^{1}H NMR ($CDCl_3$): δ 7.17-7.08 (m, 2H, Ar), 6.92-6.87 (m, 1H, Ar), 6.74-6.68 (m, 1H, Ar), 4.78 (q, *J* = 6.8 Hz, 1H, 2-H), 2.26 (s, 3H, $ArCH_3$), 1.65 (d, 3H, *J* = 6.8 Hz, 3H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 177.8 (1), 155.4, 131.2, 127.5, 126.8, 121.7, 112.0, 72.4 (2), 18.5 (3), 16.2 ($ArCH_3$); HR MS: calcd for $C_{10}H_{12}O_3Na$ (M + Na^+) 203.0679, found 203.0670; Analytical data on racemic compound: Mp 92-94 °C (CH_2Cl_2/hexane); IR (KBr): 2990, 1713, 1601, 1591, 1494, 759 cm^{-1}.

Di(1-naphthyl)methyl (*S*)-2-(*o*-tolyloxy)propanoate ((*S*)-2e). [Table 2, Entry 5, 46% yield, 88% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/50, flow rate = 0.75 mL/min): t_R = 14.8 min (94.2%), t_R

= 18.5 min (5.8%); ^{1}H NMR ($CDCl_3$): δ 8.52 (s, 1H, 1'-H), 8.05-7.97 (m, 1H, Ar), 7.93-7.77 (m, 5H, Ar), 7.55-7.19 (m, 8H, Ar), 7.13-7.05 (m, 1H, Ar), 6.96-6.80 (m, 2H, Ar), 6.66-6.58 (m, 1H, Ar), 4.88 (q, J = 6.8 Hz, 1H, 2-H), 2.19 (s, 3H, $ArCH_3$), 1.63 (d, J = 6.8 Hz, 3H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 171.6 (1), 155.7, 134.4, 134.2, 133.9, 133.8, 131.2, 131.0, 130.9, 129.3, 129.0, 128.9, 128.8, 127.4, 126.8, 126.60, 126.57, 126.3, 125.9, 125.8, 125.6, 125.2, 125.1, 123.4, 123.3, 121.3, 111.9, 72.7 (2), 71.7 (1'), 18.6 (3), 16.2 ($ArCH_3$); HR MS: calcd for $C_{31}H_{26}O_3Na$ (M + Na^+) 469.1774, found 469.1758; Analytical data on racemic compound: Mp 142-144 °C (hexane); IR (KBr): 3062, 1749, 1601, 1592, 1510, 1494, 1179, 1135, 803, 785, 756 cm^{-1}.

(*R*)-2-(*m*-Tolyloxy)propanoic acid ((*R*)-1f). [Table 2, Entry 6, 39% yield, 77% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane/TFA = 1/50/0.05, flow rate = 0.75 mL/min): t_R = 19.2 min (11.4%), t_R = 24.9 min (88.6%); ^{1}H NMR ($CDCl_3$): δ 7.18-7.08 (m, 1H, Ar), 6.84-6.75 (m, 1H, Ar), 6.75-6.61 (m, 2H, Ar). 4.78 (q, J = 6.8 Hz, 1H, 2-H), 2.30 (s, 3H, $ArCH_3$), 1.63 (d, J = 6.8 Hz, 3H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 176.8 (1), 157.1, 139.9, 129.4, 122.9, 116.2, 111.9, 72.1 (2), 21.5 ($ArCH_3$), 18.4 (3); HR MS: calcd for $C_{10}H_{12}O_3Na$ (M + Na^+) 203.0679, found 203.0681; Analytical data on racemic compound: Mp 106-108 °C (CH_2Cl_2/hexane); IR (KBr): 2993, 1709, 1610, 1585, 1488, 770 cm^{-1}.

Di(1-naphthyl)methyl (*S*)-2-(*m*-tolyloxy)propanoate ((*S*)-2f). [Table 2, Entry 6, 46% yield, 76% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/50, flow rate = 0.75 mL/min): t_R = 22.3 min (87.9%), t_R = 31.8 min (12.1%); ^{1}H NMR ($CDCl_3$): δ 8.47 (s, 1H, 1'-H), 8.06-7.97 (m, 1H, Ar), 7.93-7.75 (m, 5H, Ar), 7.56-7.18 (m, 8H, Ar), 7.08-6.90 (m, 1H, Ar), 6.77-6.70 (m, 1H, Ar), 6.65-6.58 (m, 2H, Ar), 4.85 (q, J = 6.8 Hz, 1H, 2-H), 2.17 (s, 3H, $ArCH_3$), 1.61 (d, J = 6.8 Hz, 3H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 171.6 (1), 157.5, 139.6, 134.4, 134.1, 133.9, 133.8, 131.2, 130.9, 129.3, 129.2, 129.0, 128.9, 128.8, 126.8, 126.6, 126.3, 125.9, 125.8, 125.7, 125.2, 125.1, 123.35, 123.28, 122.4, 115.8, 112.0, 72.5 (2), 71.7 (1'), 21.4 ($ArCH_3$), 18.6 (3); HR MS: calcd for $C_{31}H_{26}O_3Na$ (M + Na^+) 469.1774, found 469.1760; Analytical data on racemic compound: Mp 147-149 °C (hexane); IR (KBr): 3059, 1745, 1699, 1591, 1510, 1489, 1170, 1131, 801, 784 cm^{-1}.

(*R*)-2-(*p*-Tolyloxy)propanoic acid ((*R*)-1g). [Table 2, Entry 7, 45% yield, 76% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane/TFA = 1/50/0.05, flow rate = 0.75 mL/min): t_R = 26.7 min (12.0%), t_R = 34.6 min (88.0%); ^{1}H NMR ($CDCl_3$): δ 7.10-7.04 (m, 2H, Ar), 6.82-6.77 (m, 2H, Ar), 4.74 (q, J = 6.8 Hz, 1H, 2-H), 2.27 (s, 3H, $ArCH_3$), 1.62 (d, J = 6.8 Hz, 3H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 177.0 (1), 155.0, 131.5, 130.1, 115.2, 72.5 (2), 20.5 ($ArCH_3$), 18.4 (3); HR MS: calcd for $C_{10}H_{12}O_3Na$ (M + Na^+) 203.0679, found 203.0669; Analytical data on racemic compound: Mp 101-102 °C (CH_2Cl_2/hexane); IR (KBr): 2997, 1715, 1613, 1584, 1509, 808 cm^{-1}.

Di(1-naphthyl)methyl (*S*)-2-(*p*-tolyloxy)propanoate ((*S*)-2g). [Table 2, Entry 7, 50% yield, 73% ee]

HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/50, flow rate = 0.75 mL/min): t_R = 26.5 min (86.5%), t_R = 31.2 min (13.5%); ^{1}H NMR ($CDCl_3$): δ 8.45 (s, 1H, 1'-H), 8.03-7.97 (m, 1H, Ar), 7.93-7.77 (m, 5H, Ar), 7.56-7.40 (m, 3H, Ar), 7.39-7.18 (m, 5H, Ar), 6.97-6.90 (m, 2H, Ar), 6.74-6.67 (m, 2H, Ar), 4.83 (q, *J* = 6.8 Hz, 1H, 2-H), 2.26 (s, 3H, $ArCH_3$), 1.61 (d, *J* = 6.8 Hz, 3H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 171.6 (1), 155.3, 134.3, 134.1, 133.9, 133.7, 131.2, 130.8, 130.7, 129.9, 129.9, 129.3, 129.0, 128.9, 128.77, 126.79, 126.5, 126.3, 125.9, 125.8, 125.6, 125.2, 125.1, 123.4, 123.3, 114.9, 114.9, 72.7 (2), 71.7 (1'), 20.5 ($ArCH_3$), 18.6 (3); HR MS: calcd for $C_{31}H_{26}O_3Na$ (M + Na^+) 469.1774, found 469.1764; Analytical data on racemic compound: Mp 133-136 °C (hexane); IR (KBr): 3064, 1746, 1600, 1510, 1181, 1132, 822, 799, 784, 775 cm^{-1}.

(*R*)-2-(4-Chloro-2-methylphenoxy)propanoic acid ((*R*)-1h). [16] [Table 2, Entry 8, 46% yield, 88% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane/TFA = 1/50/0.05, flow rate = 0.75 mL/min): t_R = 18.2 min (6.1%), t_R = 26.2 min (93.9%); ^{1}H NMR ($CDCl_3$): δ 7.13 (d, *J* = 2.6 Hz, 1H, Ar), 7.06 (dd, *J* = 8.8, 2.6 Hz, 1H, Ar), 6.64 (d, *J* = 8.8 Hz, 1H, Ar), 4.74 (q, *J* = 6.8 Hz, 1H, 2-H), 2.23 (s, 3H, $ArCH_3$), 1.65 (d, *J* = 6.8 Hz, 3H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 177.1 (1), 154.1, 130.9, 129.6, 126.5, 126.4, 113.2, 72.7 (2), 18.4 (3), 16.1 ($ArCH_3$); HR MS: calcd for $C_{10}H_{11}ClO_3Na$ (M + Na^+) 237.0289, found 237.0289; Analytical data on racemic compound: Mp 92-94 °C (CH_2Cl_2/hexane); IR (KBr): 2988, 1705, 1601, 1493, 880, 793, 662 cm^{-1}.

Di(1-naphthyl)methyl (*S*)-2-(4-chloro-2-methylphenoxy)propanoate ((*S*)-2h). [Table 2, Entry 8, 49% yield, 84% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/50, flow rate = 0.75 mL/min): t_R = 17.0 min (92.2%), t_R = 19.8 min (7.8%); ^{1}H NMR ($CDCl_3$): δ 8.43 (s, 1H, 1'-H), 7.99-7.77 (m, 6H, Ar), 7.55-7.42 (m, 3H, Ar), 7.39-7.26 (m, 4H, Ar), 7.23-7.17 (m, 1H, Ar), 7.01 (d, *J* = 2.6 Hz, 1H, Ar), 6.81 (dd, *J* = 8.8, 2.6 Hz, 1H, Ar), 6.49 (d, *J* = 8.8 Hz, 1H, Ar), 4.83 (q, *J* = 6.8 Hz, 1H, 2-H), 2.11 (s, 3H, $ArCH_3$), 1.64 (d, *J* = 6.8 Hz, 3H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 171.2 (1), 154.2, 134.2, 134.0, 133.9, 133.7, 131.1, 130.8, 130.7, 129.41, 129.40, 129.1, 129.0, 128.83, 126.84, 126.6, 126.14, 126.13, 126.00, 125.96, 125.9, 125.6, 125.1, 125.0, 123.22, 123.18, 113.0, 73.0 (2), 71.8 (1'), 18.5 (3), 16.1 ($ArCH_3$); HR MS: calcd for $C_{31}H_{25}ClO_3Na$ (M + Na^+) 503.1384, found 503.1377; Analytical data on racemic amorphous compound: IR (KBr): 3062, 1740, 1597, 1510, 1489, 1180, 1127, 800, 781, 767, 755, 738 cm^{-1}.

(*R*)-2-(1-Naphthoxy)propanoic acid ((*R*)-1i). [Table 2, Entry 9, 47% yield, 83% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane/TFA = 1/50/0.05, flow rate = 0.75 mL/min): t_R = 29.5 min (8.5%), t_R = 32.9 min (91.5%); ^{1}H NMR ($CDCl_3$): δ 10.81 (br s, 1H, CO_2H), 8.36-8.27 (m, 1H, Ar), 7.83-7.75 (m, 1H, Ar), 7.53-7.42 (m, 3H, Ar), 7.36-7.29 (m, 1H, Ar), 6.77-6.69 (m, 1H, Ar), 4.98 (q, *J* = 6.8 Hz, 1H, 2-H), 1.78 (d, *J* = 6.8 Hz, 3H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 177.6 (1), 153.1, 134.7, 127.5, 126.6, 125.7,

125.55, 125.49, 122.1, 121.6, 105.8, 72.5 (2), 18.5 (3); HR MS: calcd for $C_{13}H_{12}O_3Na$ (M + Na^+) 239.0679, found 239.0681; Analytical data on racemic compound: Mp 158-160 °C (CH_2Cl_2/hexane); IR (KBr): 2959, 1706, 1628, 1596, 1580, 1506, 794, 769 cm^{-1}.

Di(1-naphthyl)methyl (*S*)-2-(1-naphthoxy)propanoate ((*S*)-2i). [Table 2, Entry 9, 50% yield, 87% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/9, flow rate = 0.75 mL/min): t_R = 13.2 min (93.3%), t_R = 16.8 min (6.7%); ^{1}H NMR ($CDCl_3$): δ 8.48 (s, 1H, 1'-H), 8.33-8.01 (m, 2H, Ar), 7.93-7.71 (m, 6H, Ar), 7.57-7.05 (m, 12H, Ar), 6.63-6.56 (m, 1H, Ar), 5.04 (q, *J* = 6.8 Hz, 1H, 2-H), 1.74 (d, *J* = 6.8 Hz, 3H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 171.4 (1), 153.3, 134.6, 134.3, 134.0, 133.9, 133.7, 131.2, 130.8, 129.4, 128.98, 128.96, 128.8, 127.3, 126.9, 126.51, 126.51, 126.47, 126.0, 125.8, 125.7, 125.5, 125.4, 125.3, 125.2, 125.1, 123.4, 123.3, 122.3, 121.2, 105.8, 73.0 (2), 71.8 (1'), 18.5 (3); HR MS: calcd for $C_{34}H_{26}O_3Na$ (M + Na^+) 505.1774, found 505.1789; Analytical data on racemic compound: Mp 169-172 °C (hexane); IR (KBr): 3060, 1745, 1628, 1598, 1579, 1508, 1177, 1132, 801, 792, 775, 730 cm^{-1}.

(*R*)-2-(2-Naphthoxy)propanoic acid ((*R*)-1j). [Table 2, Entry 10, 49% yield, 73% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane/TFA = 1/50/0.05, flow rate = 0.75 mL/min): t_R = 40.3 min (13.6%), t_R = 54.1 min (86.4%); ^{1}H NMR ($CDCl_3$): δ 9.24 (br s, 1H, CO_2H), 7.80-7.61 (m, 3H, Ar), 7.49-7.38 (m, 1H, Ar), 7.38-7.29 (m, 1H, Ar), 7.22-7.14 (m, 1H, Ar), 7.10-7.04 (m, 1H, Ar), 4.94 (q, *J* = 6.8 Hz, 1H, 2-H), 1.71 (d, *J* = 6.8 Hz, 3H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 177.0 (1), 155.1, 134.2, 129.9, 129.5, 127.6, 126.9, 126.6, 124.2, 118.7, 108.0, 72.1 (2), 18.4 (3); HR MS: calcd for $C_{13}H_{12}O_3Na$ (M + Na^+) 239.0679, found 239.0676; Analytical data on racemic compound: Mp 107-108 °C (CH_2Cl_2/hexane); IR (KBr): 2986, 1713, 1630, 1601, 1513, 838, 807, 743 cm^{-1}.

Di(1-naphthyl)methyl (*S*)-2-(2-naphthoxy)propanoate ((*S*)-2j). [Table 2, Entry 10, 50% yield, 75% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/9, flow rate = 0.75 mL/min): t_R = 16.7 min (87.3%), t_R = 23.6 min (12.7%); ^{1}H NMR ($CDCl_3$): δ 8.47 (s, 1H, 1'-H), 8.07-7.60 (m, 8H, Ar), 7.55-7.00 (m, 12H, Ar), 6.97-6.90 (m, 1H, Ar), 5.00 (q, *J* = 6.8 Hz, 1H, 2-H), 1.65 (d, *J* = 6.8 Hz, 3H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 171.5 (1), 155.4, 134.3, 134.2, 134.0, 133.9, 133.7, 131.2, 130.8, 129.6, 129.38, 129.36, 129.0, 128.9, 128.7, 127.5, 127.03, 126.97, 126.5, 126.3, 126.2, 126.0, 125.7, 125.6, 125.2, 125.0, 124.0, 123.24, 123.16, 118.9, 107.8, 72.7 (2), 71.9 (1'), 18.6 (3); HR MS: calcd for $C_{34}H_{26}O_3Na$ (M + Na^+) 505.1774, found 505.1754; Analytical data on racemic compound: Mp 184-186 °C (hexane); IR (KBr): 3060, 1751, 1629, 1600, 1579, 1511, 1177, 1132, 832, 801, 780, 756 cm^{-1}.

(*R*)-2-(2,6-Dichlorophenoxy)propanoic acid ((*R*)-1k). [Table 2, Entry 11, 51% yield, 69% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane/TFA = 1/50/0.05, flow rate = 1.0 mL/min): t_R = 17.2 min (84.4%), t_R = 19.1 min (15.6%); ^{1}H NMR ($CDCl_3$): δ 8.24 (br s, 1H, CO_2H), 7.36-7.26 (m, 2H, Ar), 7.06-6.98 (m,

1H, Ar), 4.95 (q, J = 6.8 Hz, 1H, 2-H), 1.61 (d, J = 6.8 Hz, 3H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 174.6 (1), 149.2, 129.4, 129.2, 125.7, 77.4 (2), 17.9 (3); HR MS: calcd for $C_9H_8Cl_2O_3Na$ (M + Na^+) 256.9743, found 256.9733. Analytical data on racemic compound: Mp 108-110 °C (CH_2Cl_2/hexane); IR (KBr): 2932, 1710, 1567, 1460, 1450, 1441, 786, 773 cm^{-1}.

Di(1-naphthyl)methyl (*S*)-2-(2,6-dichlorophenoxy)propanoate ((*S*)-2k). [Table 2, Entry 11, 46% yield, 78% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/50, flow rate = 0.75 mL/min): t_R = 18.6 min (88.8%), t_R = 22.5 min (11.2%); ^{1}H NMR ($CDCl_3$): δ 8.52 (s, 1H, 1'-H), 8.00-7.94 (m, 2H, Ar), 7.92-7.80 (m, 4H, Ar), 7.52-7.33 (m, 8H, Ar), 7.19-7.11 (m, 2H, Ar), 6.89-6.81 (m, 1H, Ar), 5.04 (q, J = 6.4 Hz, 1H, 2-H), 1.63 (d, J = 6.4 Hz, 3H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 170.1 (1), 150.1, 134.32, 134.30, 133.81, 133.79, 131.0, 129.2, 129.2, 128.9, 128.9, 128.9, 128.8, 128.8, 126.7, 126.7, 126.0, 125.9, 125.9, 125.9, 125.2, 125.2, 125.0, 123.45, 123.36, 77.9 (2), 71.7 (1'), 18.7 (3); HR MS: calcd for $C_{30}H_{22}Cl_2O_3Na$ (M + Na^+) 523.0838, found 523.0849; Analytical data on racemic amorphous compound: IR (KBr): 3061, 1731, 1599, 1565, 1510, 1163, 1107, 800, 775, 729 cm^{-1}.

(*R*)-2-(2,4-Dichlorophenoxy)propanoic acid ((*R*)-1l). [Table 2, Entry 12, 44% yield, 90% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane/TFA = 1/50/0.05, flow rate = 0.75 mL/min): t_R = 19.9 min (5.2%), t_R = 28.6 min (94.8%); The absolute configuration was determined as *R* by the comparison of the retention time with the literature data.[12a]

Di(1-naphthyl)methyl (*S*)-2-(2,4-dichlorophenoxy)propanoate ((*S*)-2l). [Table 2, Entry 12, 47% yield, 90% ee] Spectroscopic data were previously reported.[12a] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/50, flow rate = 0.5 mL/min): t_R = 27.4 min (95.2%), t_R = 33.8 min (4.8%); The absolute configuration was determined as *S* by the comparison of the retention time with the literature data.[12a]

(*R*)-2-(2-Fluorophenoxy)propanoic acid ((*R*)-1m). [Table 2, Entry 13, 45% yield, 85% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane/TFA = 1/50/0.05, flow rate = 0.75 mL/min): t_R = 22.1 min (7.7%), t_R = 27.0 min (92.3%); ^{1}H NMR ($CDCl_3$): δ 9.99 (br s, 1H, CO_2H), 7.13-6.91 (m, 4H, Ar), 4.79 (q, J = 6.8 Hz, 1H, 2-H), 1.67 (d, J = 6.8 Hz, 3H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 176.6 (1), 153.3 (d, J = 245.0 Hz), 145.1 (d, J = 10.2 Hz), 124.4 (d, J = 4.4 Hz), 123.2 (d, J = 6.5 Hz), 117.9 (d, J = 1.4 Hz), 116.8 (d, J = 18.9 Hz), 74.3 (2), 18.3 (3); HR MS: calcd for $C_9H_9FO_3Na$ (M + Na^+) 207.0428, found 207.0437; Analytical data on racemic compound: Mp 85-87 °C (CH_2Cl_2/hexane); IR (KBr): 2998, 1721, 1614, 1591, 1503, 754 cm^{-1}.

Di(1-naphthyl)methyl (*S*)-2-(2-fluorophenoxy)propanoate ((*S*)-2m). [Table 2, Entry 13, 48% yield, 86% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/50, flow rate = 0.75 mL/min): t_R = 19.9 min (93.0%), t_R = 25.4 min (7.0%); ^{1}H NMR ($CDCl_3$): δ 8.46 (s, 1H, 1'-H), 7.99-7.79 (m, 6H, Ar), 7.56-7.22 (m, 8H, Ar), 7.07-6.97 (m, 1H, Ar), 6.90-6.72 (m, 3H, Ar), 4.88 (q, J = 6.8 Hz, 1H, 2-H), 1.67 (d, J = 6.8

Hz, 3H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 171.0 (1), 152.9 (d, J = 245.7 Hz), 145.4 (d, J = 10.3 Hz), 134.2, 134.1, 133.9, 133.8, 131.1, 130.9, 129.3, 129.1, 128.9, 128.8, 126.8, 126.6, 126.1, 125.93, 125.86, 125.7, 125.2, 125.1, 124.1 (d, J = 3.7 Hz), 123.29, 123.27, 122.3 (d, J = 7.4 Hz), 116.8 (d, J = 1.5 Hz), 116.5 (d, J = 18.3 Hz), 74.2 (2), 71.9 (1'), 18.5 (3); HR MS: calcd for $C_{30}H_{23}FO_3Na$ (M + Na^+) 473.1523, found 473.1536; Analytical data on racemic compound: Mp 139-143 °C (hexane); IR (KBr): 3071, 1733, 1612, 1504, 1180, 1131, 803, 788, 780, 747 cm^{-1}.

(*R*)-2-(2-Bromophenoxy)propanoic acid ((*R*)-1n). [Table 2, Entry 14, 49% yield, 88% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane/TFA = 1/50/0.05, flow rate = 0.75 mL/min): t_R = 20.8 min (5.9%), t_R = 25.8 min (94.1%); ^{1}H NMR ($CDCl_3$): δ 7.60-7.54 (m, 1H, Ar), 7.28-7.22 (m, 1H, Ar), 6.95-6.85 (m, 1H, Ar), 4.81 (q, J = 6.8 Hz, 1H, 2-H), 1.72 (d, J = 6.8 Hz, 3H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 174.9 (1), 153.6, 133.8, 128.6, 123.7, 115.4, 113.3, 74.0 (2), 18.2 (3); HR MS: calcd for $C_9H_9BrO_3Na$ (M + Na^+) 266.9933, found 266.9621; Analytical data on racemic compound: Mp 139-142 °C (CH_2Cl_2/hexane); IR (KBr): 2870, 1709, 1589, 1573, 1478, 749, 666 cm^{-1}.

Di(1-naphthyl)methyl (*S*)-2-(2-bromophenoxy)propanoate ((*S*)-2n). [Table 2, Entry 14, 48% yield, 95% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/50, flow rate = 0.75 mL/min): t_R = 20.8 min (2.6%), t_R = 25.9 min (97.4%); ^{1}H NMR ($CDCl_3$): δ 8.47 (s, 1H, 1'-H), 8.03-7.78 (m, 6H, Ar), 7.57-7.22 (m, 9H, Ar), 6.99-6.90 (m, 1H, Ar), 6.82-6.74 (m, 1H, Ar), 6.70-6.62 (m, 1H, Ar), 4.88 (q, J = 6.8 Hz, 1H, 2-H), 1.70 (d, J = 6.8 Hz, 3H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 170.8 (1), 154.1, 134.2, 134.0, 133.9, 133.8, 133.6, 131.1, 130.8, 129.4, 129.1, 129.0, 128.8, 128.2, 126.8, 126.6, 126.3, 125.95, 125.85, 125.76, 125.2, 125.1, 123.29, 123.28, 122.9, 114.7, 112.8, 74.0 (2), 71.9 (1'), 18.4 (3); HR MS: calcd for $C_{30}H_{23}FO_3Na$ (M + Na^+) 533.0723, found 533.0733; Analytical data on racemic compound: Mp 165-168 °C (hexane); IR (KBr): 3061, 1745, 1626, 1599, 1587, 1510, 1180, 1138, 803, 784, 780, 749 cm^{-1}.

(*R*)-2-(2-Methoxyphenoxy)propanoic acid ((*R*)-1o). [Table 2, Entry 15, 43% yield, 76% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane/TFA = 1/50/0.05, flow rate = 1.0 mL/min): t_R = 29.5 min (11.8%), t_R = 33.1 min (88.2%); ^{1}H NMR ($CDCl_3$): δ 7.10-7.01 (m, 1H, Ar), 7.00-6.85 (m, 3H, Ar), 4.63 (q, J = 6.8 Hz, 1H, 2-H), 3.87 (s, 3H, OCH_3), 1.66 (d, J = 6.8 Hz, 3H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 174.1 (1), 150.4, 146.7, 124.4, 121.4, 119.0, 112.3, 76.9 (2), 55.9 (OCH_3), 18.5 (3); HR MS: calcd for $C_{10}H_{12}O_4Na$ (M + Na^+) 219.0628, found 219.0620; Analytical data on racemic compound: Mp 79-80 °C (CH_2Cl_2/hexane); IR (KBr): 2953, 1719, 1592, 1505, 753, 740 cm^{-1}.

Di(1-naphthyl)methyl (*S*)-2-(2-methoxyphenoxy)propanoate ((*S*)-2o). [Table 2, Entry 15, 49% yield, 88% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/9, flow rate = 0.75 mL/min): t_R = 13.8 min (94.2%), t_R = 19.3 min (5.8%); ^{1}H NMR ($CDCl_3$): δ 8.46 (s, 1H, 1'-H), 8.01-7.79 (m, 6H, Ar), 7.55-7.23

(m, 8H, Ar), 6.96-6.82 (m, 2H, Ar), 6.77-6.64 (m, 2H, Ar), 4.88 (q, 1H, J = 6.8 Hz, 2-H), 3.74 (s, 3H, OCH_3), 1.66 (d, 3H, J = 6.8 Hz, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 171.5 (1), 149.9, 147.0, 134.3, 134.2, 133.84, 133.76, 131.1, 130.9, 129.3, 129.0, 128.9, 128.8, 126.8, 126.6, 126.2, 125.9, 125.8, 125.7, 125.2, 125.1, 123.4, 123.3, 122.5, 120.7, 116.0, 112.4, 74.0 (2), 71.6 (1'), 55.9 (OCH_3), 18.7 (3); HR MS: calcd for $C_{31}H_{26}O_4Na$ (M + Na^+) 485.1723, found 485.1723; Analytical data on racemic compound: Mp 164-165 °C (hexane); IR (KBr): 3061, 1745, 1592, 1502, 1180, 1135, 800, 780, 741 cm^{-1}.

(*R*)-2-(2-Nitrophenoxy)propanoic acid ((*R*)-1p). [Table 2, Entry 16, 53% yield, 79% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane/TFA = 1/10/0.01, flow rate = 0.75 mL/min): t_R = 11.1 min (10.4%), t_R = 15.3 min (89.6%); ^{1}H NMR ($CDCl_3$): δ 8.57 (br s, 1H, CO_2H), 7.96-7.89 (m, 1H, Ar), 7.62-7.52 (m, 1H, Ar), 7.19-7.11s (m, 1H, Ar), 7.09-7.02 (m, 1H, Ar), 4.97 (q, J = 6.8 Hz, 1H, 2-H), 1.76 (d, J = 6.8 Hz, 3H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 172.9 (1), 150.4, 134.6, 126.29, 126.28, 122.3, 115.8, 74.6 (2), 18.1 (3); HR MS: calcd for $C_9H_9NO_5Na$ (M + Na^+) 234.0373, found 234.0385; Analytical data on racemic compound: Mp 157-159 °C (CH_2Cl_2/hexane); IR (KBr): 2870, 1736, 1605, 1585, 1524, 1486, 1358, 741 cm^{-1}.

Di(1-naphthyl)methyl (*S*)-2-(2-nitrophenoxy)propanoate ((*S*)-2p). [Table 2, Entry 16, 47% yield, 92% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/9, flow rate = 0.75 mL/min): t_R = 16.6 min (96.0%), t_R = 18.5 min (4.0%); ^{1}H NMR ($CDCl_3$): δ 8.47 (s, 1H, 1'-H), 7.99-7.78 (m, 6H, Ar), 7.74-7.66 (m, 1H, Ar), 7.55-7.23 (m, 8H, Ar), 7.13-7.04 (m, 1H, Ar), 6.95-6.86 (m, 1H, Ar), 6.77-6.70 (m, 1H, Ar), 4.94 (q, J = 6.8 Hz, 1H, 2-H), 1.70 (d, J = 6.8 Hz, 3H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 170.2 (1), 150.6, 134.0, 133.9, 133.8, 133.7, 133.5, 133.5, 130.9, 130.8, 129.4, 129.3, 129.0, 128.9, 126.8, 126.7, 126.1, 126.0, 125.91, 125.88, 125.5, 125.3, 125.1, 123.18, 123.17, 121.3, 115.3, 74.2 (2), 72.2 (1'), 18.3 (3); HR MS: calcd for $C_{30}H_{23}NO_5Na$ (M + Na^+) 500.1468 found 500.1467; Analytical data on racemic compound: Mp 156-160 °C (hexane); IR (KBr): 3062, 1736, 1607, 1586, 1521, 1483, 1346, 1168, 1103, 801, 787, 773, 744 cm^{-1}.

(*R*)-2-[(1,1'-Biphenyl)-2-yloxy]propanoic acid ((*R*)-1q). [Table 2, Entry 17 (Table 3, Entry 1), 50% yield, 89% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane/TFA = 1/50/0.05, flow rate = 0.75 mL/min): t_R = 20.3 min (5.5%), t_R = 26.5 min (94.5%); ^{1}H NMR ($CDCl_3$): δ 7.58-7.52 (m, 2H, Ar), 7.45-7.38 (m, 2H, Ar), 7.38-7.26 (m, 3H, Ar), 7.14-7.08 (m, 1H, Ar), 6.97-6.92 (m, 1H, Ar), 4.70 (q, J = 6.8 Hz, 1H, 2-H), 1.53 (d, J = 6.8 Hz, 3H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 175.4 (1), 153.8, 138.0, 132.1, 131.4, 129.4, 128.7, 128.2, 127.2, 122.7, 114.4, 73.3 (2), 18.2 (3); HR MS: calcd for $C_{15}H_{14}O_3Na$ (M + Na^+) 265.0602, found 265.0607; Analytical data on racemic compound: Mp 138-141 °C (CH_2Cl_2/hexane); IR (KBr): 2986, 1706, 1601, 1587, 1504, 1481, 754, 725, 700 cm^{-1}.

Di(1-naphthyl)methyl (*S*)-2-[(1,1'-biphenyl)-2-yloxy]propanoate ((*S*)-2q). [Table 2, Entry 17 (Table 3,

Entry 1), 47% yield, 96% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/50, flow rate = 0.75 mL/min): t_R = 20.2 min (97.8%), t_R = 26.7 min (2.2%); ^{1}H NMR ($CDCl_3$): δ 8.45 (s, 1H, 1'-H), 8.07-7.73 (m, 6H, Ar), 7.61-6.95 (m, 16H, Ar), 6.85-6.70 (m, 1H, Ar), 4.85 (q, *J* = 6.8 Hz, 1H, 2-H), 1.49 (d, *J* = 6.8 Hz, 3H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 171.5 (1), 154.2, 138.3, 134.3, 134.1, 133.9, 133.8, 131.5, 131.3, 131.2, 130.8, 129.5, 129.5, 129.3, 129.02, 128.95, 128.8, 128.4, 127.8, 127.8, 126.8, 126.7, 126.6, 126.4, 126.0, 125.8, 125.6, 125.2, 125.1, 123.31, 123.29, 121.9, 113.4, 72.9 (2), 71.8 (1'), 18.4 (3); HR MS: calcd for $C_{36}H_{28}O_3Na$ (M + Na^+) 531.1931, found 531.1955; Analytical data on racemic amorphous compound: IR (KBr): 3059, 1737, 1599, 1584, 1509, 1480, 1180, 1135, 801, 778, 754, 734, 699 cm^{-1}.

(*R*)-2-[(1,1'-Biphenyl)-2-yloxy]butanoic acid ((*R*)-1r). [Table 3, Entry 2, 76% yield, 30% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane/TFA = 1/50/0.05, flow rate = 0.75 mL/min): t_R = 18.3 min (35.2%), t_R = 23.2 min (64.8%); ^{1}H NMR ($CDCl_3$): δ 9.33 (br s, 1H, CO_2H), 7.58-7.51 (m, 2H, Ar), 7.45-7.23 (m, 5H, Ar), 7.13-7.04 (m, 1H, Ar), 6.92-6.85 (m, 1H, Ar), 4.62 (t, *J* = 5.6 Hz, 1H, 2-H), 1.93 (dq, *J* = 5.6, 7.6 Hz, 2H, 3-H), 0.94 (t, *J* = 7.6 Hz, 3H, 4-CH_3); ^{13}C NMR ($CDCl_3$): δ 175.5 (1), 154.2, 138.1, 131.8, 131.3, 129.6, 128.6, 128.0, 127.1, 122.3, 113.5, 77.6 (2), 25.7 (3), 9.1 (4); HR MS: calcd for $C_{16}H_{16}O_3Na$ (M + Na^+) 279.0992, found 279.0992; Analytical data on racemic compound: Mp 150-152 °C (CH_2Cl_2/hexane); IR (KBr): 2972, 1704, 1597, 1584, 1503, 1480, 773, 751, 738, 701 cm^{-1}.

Di(1-naphthyl)methyl (*S*)-2-[(1,1'-biphenyl)-2-yloxy]butanoate ((*S*)-2r). [Table 3, Entry 2, 22% yield, 94% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/50, flow rate = 0.75 mL/min): t_R = 20.4 min (97.1%), t_R = 22.1 min (2.9%); ^{1}H NMR ($CDCl_3$): δ 8.48 (s, 1H, 1'-H), 7.96-7.75 (m, 5H, Ar), 7.57-7.39 (m, 5H, Ar), 7.37-7.16 (m, 9H, Ar), 7.10-6.97 (m, 2H, Ar), 6.78-6.72 (m, 2H, Ar), 4.75 (t, *J* = 5.6 Hz, 1H, 2-H), 1.89 (dq, *J* = 5.6, 7.6 Hz, 2H, 3-H), 0.84 (t, *J* = 7.6 Hz, 3H, 4-CH_3); ^{13}C NMR ($CDCl_3$): δ 170.8 (1), 154.4, 138.3, 134.4, 134.1, 133.9, 133.7, 131.4, 131.21, 131.16, 130.8, 129.6, 129.6, 129.3, 129.0, 129.0, 128.8, 128.4, 127.7, 127.7, 126.8, 126.7, 126.54, 126.47, 126.0, 125.8, 125.5, 125.2, 125.1, 123.3, 123.3, 121.6, 112.6, 77.2 (2), 71.6 (1'), 26.0 (3), 9.3 (4); HR MS: calcd for $C_{37}H_{30}O_3Na$ (M + Na^+) 545.2087, found 545.2080; Analytical data on racemic amorphous compound: IR (KBr): 3059, 1734, 1599, 1583, 1509, 1480, 1177, 1134, 800, 794, 778, 753, 734, 700 cm^{-1}.

(*R*)-2-[(1,1'-Biphenyl)-2-yloxy]pentanoic acid ((*R*)-1s). [Table 3, Entry 3, 80% yield, 21% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane/TFA = 1/50/0.05, flow rate = 0.75 mL/min): t_R = 17.4 min (39.7%), t_R = 21.5 min (60.3%).

Di(1-naphthyl)methyl (*S*)-2-[(1,1'-biphenyl)-2-yloxy]pentanoate ((*S*)-2s). [Table 3, Entry 3, 18% yield, 93% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/50, flow rate = 0.75 mL/min): t_R = 17.7 min (96.4%), t_R = 20.6 min (3.6%); ^{1}H NMR ($CDCl_3$): δ 8.46 (s, 1H, 1'-H), 8.09-8.02 (m, 1H, Ar), 7.97-7.76 (m, 5H, Ar), 7.59-7.40 (m, 5H, Ar), 7.39-7.16 (m, 9H, Ar), 7.11-6.96 (m, 2H, Ar), 6.80-6.73 (m, 1H, Ar),

4.80 (t, J = 6.0 Hz, 1H, 2-H), 1.89-1.76 (m, 2H, 3-H), 1.39-1.24 (m, 2H, 4-H), 0.75 (t, J = 7.2 Hz, 3H, 5-CH_3); ^{13}C NMR ($CDCl_3$): δ 171.0 (1), 154.5, 138.3, 134.4, 134.1, 133.9, 133.8, 131.4, 131.23, 131.19, 130.8, 129.6, 129.6, 129.4, 128.98, 128.96, 128.8, 128.4, 127.7, 127.7, 126.8, 126.7, 126.53, 126.51, 126.0, 125.8, 125.6, 125.2, 125.1, 123.4, 123.3, 121.6, 112.6, 76.1 (2), 71.7 (1'), 34.5 (3), 18.2 (4), 13.5 (5); HR MS: calcd for $C_{38}H_{32}O_3Na$ (M + Na^+) 559.2244, found 559.2245; Analytical data on racemic amorphous compound: IR (KBr): 3060, 1748, 1599, 1583, 1505, 1481, 1176, 1138, 797, 779, 751, 736, 697 cm^{-1}.

(*R*)-2-(2-(*tert*-Butyl)-4-methoxyphenoxy)propanoic acid ((*R*)-1u). [Scheme 3, 43% yield, 93% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane/TFA = 1/50/0.05, flow rate = 0.75 mL/min): t_R = 12.5 min (3.7%), t_R = 15.8 min (96.3%); ^{1}H NMR ($CDCl_3$): δ 9.95 (br s, 1H, CO_2H), 6.94-6.89 (m, 1H, Ar), 6.66-6.56 (m, 2H, Ar), 4.79 (d, J = 6.8 Hz, 1H, 2-H), 3.75 (s, 3H, OCH_3), 1.69 (d, J = 6.8 Hz, 3H, 3-CH_3), 1.40 (s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$): δ 177.5 (1), 153.7, 149.9, 139.8, 115.0, 111.6, 109.7, 71.6 (2), 55.6 (OCH_3), 35.0 (*t*-Bu), 29.8 (*t*-Bu), 18.5 (3); HR MS: calcd for $C_{14}H_{20}O_4Na$ (M + Na^+) 275.1254, found 275.1263; Analytical data on racemic compound: Mp 108-110 °C (CH_2Cl_2/hexane); IR (KBr): 2953, 1712, 1603, 1499, 803, 767 cm^{-1}.

Di(1-naphthyl)methyl (*S*)-2-(2-*tert*-butyl-4-methoxyphenoxy)propanoate ((*S*)-2u). [Scheme 3, 48% yield, 96% ee] HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/50, flow rate = 0.75 mL/min): t_R = 12.0 min (2.1%), t_R = 14.1 min (97.9%); ^{1}H NMR ($CDCl_3$): δ 8.44 (s, 1H, 1'-H), 8.14-7.72 (m, 6H, Ar), 7.58-7.22 (m, 7H, Ar), 7.19-7.12 (m, 1H, Ar), 6.86 (d, J = 3.2 Hz, 1H, Ar), 6.52 (d, J = 8.8 Hz, 1H, Ar), 6.41 (dd, J = 8.8, 3.2 Hz, 1H, Ar), 4.90 (d, J = 6.8 Hz, 1H, 2-H), 3.75 (s, 3H, OCH_3), 1.65 (d, J = 6.8 Hz, 3H, 3-CH_3), 1.30 (s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$): δ 171.8 (1), 153.5, 150.1, 139.5, 134.4, 134.1, 133.9, 133.8, 131.2, 130.8, 129.3, 128.9, 128.9, 128.8, 126.8, 126.5, 126.4, 125.9, 125.7, 125.5, 125.2, 125.1, 123.34, 123.32, 114.7, 111.6, 109.6, 72.1 (1'), 71.6 (2), 55.6 (OCH_3), 34.9 (*t*-Bu), 29.6 (*t*-Bu), 18.6 (3); HR MS: calcd for $C_{35}H_{34}O_4Na$ (M + Na^+) 541.2349, found 541.2324; Analytical data on racemic amorphous compound: IR (KBr): 3053, 2952, 1735, 1599, 1585, 1510, 1498, 1485, 1179, 1127, 799, 793, 778 cm^{-1}.

Removal of 2-*tert*-butyl-4-methoxyphenoxy group of (*S*)-2u (Scheme 3). [14]

To a stirred solution of (*S*)-di(naphthalen-1-yl)methyl 2-(2-(*tert*-butyl)-4-methoxyphenoxy)propanoate ((*S*)-**2u**) (50.0 mg, 96.4 μmol, 96% ee) in DMF-H_2O (8:1, v/v) (1.8 mL) at room temperature was added cerium ammonium nitrate (264 mg, 0.48 mmol) in one portion, and then the reaction mixture was stirred for 50 min. After cooling at 0 °C, the reaction mixture was diluted with water (4 mL) and extracted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, and then dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was

purified by preparative thin layer chromatography on silica (EtOAc/hexane = 3/2) to afford **(*S*)-3** (21.1 mg, 62% yield, 96% ee) as a white solid.

Di(1-naphthyl)methyl (*S*)-2-hydroxypropanoate ((*S*)-3). [Scheme 3, 96% ee] Mp 142-148 °C (AcOEt/hexane); IR (KBr): 3363, 3062, 1743, 1597, 1512, 1188, 1126, 787, 741 cm^{-1}; HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/9, flow rate = 0.75 mL/min): t_R = 29.5 min (1.9%), t_R = 39.1 min (98.1%); ^1H NMR ($CDCl_3$): δ 8.46 (s, 1H, 1'-H), 8.03-7.78 (m, 6H, Ar), 7.56-7.32 (m, 8H, Ar), 4.48-4.34 (m, 1H, 2-H), 2.82 (br s, 1H, OH), 1.44 (d, J = 7.2 Hz, 3H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 174.9 (1), 134.2, 134.1, 133.9, 133.9, 131.0, 130.9, 129.4, 129.3, 129.0, 128.9, 126.9, 126.8, 126.0, 126.0, 125.9, 125.7, 125.22, 125.18, 123.2, 123.2, 72.4 (1'), 67.0 (2), 20.5 (3); HR MS: calcd for $C_{24}H_{20}O_3Na$ ($M + Na^+$) 379.1305, found 379.1322.

Preparation of the authentic sample of (*S*)-2b from Methyl (*R*)-lactate

Methyl (*S*)-2-(2-chlorophenoxy)propanoate ((*S*)-5b).

To a mixture of methyl (*R*)-lactate (191 μL, 2.00 mmol), 2-chlorophenol (207 μL, 2.00 mmol), and triphenylphosphine (577 mg, 2.20 mmol) in Et_2O (8 mL) at 0 °C was added 40% diisopropyl azodicarboxylate in toluene (1.58 mL, 3.00 mmol). After the reaction mixture had been stirred for 30 min at 0 °C followed by 2 h at room temperature, and then diluted with hexane. After filtration of the slurry mixture and evaporation of the solvent, the crude product was purified by silica gel column chromatography (EtOAc/hexane = 1/40) to afford (*S*)-**5b** (334 mg, 78% yield) as a colorless oil: IR (neat): 2954, 1751, 1589, 1481, 1450, 748 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.40-7.34 (m, 1H, Ar), 7.20-7.12 (m, 1H, Ar), 6.97-6.90 (m, 1H, Ar), 6.87-6.81 (m, 1H, Ar), 4.77 (q, J = 6.8 Hz, 1H, 2-H), 3.76 (s, 3H, OMe), 1.67 (d, J = 6.8 Hz, 3H, 3-H); ^{13}C NMR ($CDCl_3$): δ 172.1 (1), 153.4, 130.6, 127.6, 123.9, 122.7, 115.4, 74.2 (2), 52.3 (Me), 18.5 (3); HR MS: calcd for $C_{10}H_{11}ClO_3Na$ ($M + Na^+$) 237.0289, found 237.0292.

(*S*)-2-(2-Chlorophenoxy)propanoic acid ((*S*)-1b).

(*S*)-**5b** (298 mg, 1.39 mmol) was hydrolyzed in accordance with the preparation of *rac*-**3s**, and then crystallized from CH_2Cl_2 and hexane to afford (*S*)-**1b** (202 mg, 73% yield) as a white solid: HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane/TFA = 1/50/0.05, flow rate = 0.75 mL/min): t_R = 21.7 min (99.3%), t_R = 26.8 min (0.7%).

Di(1-naphthyl)methyl (*S*)-2-(2-chlorophenoxy)propanoate ((*S*)-2b).

To a mixture of (*S*)-**1b** (10.0 mg, 50.0 μmol), 2-methyl-6-nitrobenzoic anhydride (MNBA) (20.7 mg, 60.0 μmol), and bis(α-naphthyl)methanol (14.2 mg, 50.0 μmol) in CH_2Cl_2 (1.0 mL) at room temperature were successively added triethylamine (16.6 μL, 0.120 mmol) and DMAP (1.2 mg, 10 μmol). The reaction mixture was directly purified by preparative thin layer chromatography on silica (CH_2Cl_2/hexane = 1/1) to afford (*S*)-**2b** (22.4 mg, 96% yield) as a white solid: HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/50,

flow rate = 0.75 mL/min): t_R = 20.0 min (99.6%), t_R = 24.7 min (0.4%).

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