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Kinetic Resolution of Racemic α-Arylalkanoic Acids with Achiral Alcohols via the Asymmetric Esterification Using Carboxylic Anhydrides and Acyl-Transfer Catalysts

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Abstract: A variety of optically active carboxylic esters are produced by the kinetic resolution of racemic α-substituted carboxylic acids using achiral alcohols, aromatic or aliphatic carboxylic anhydrides, and chiral acyl-transfer catalysts. The combination of 4-methoxybenzoic anhydride (PMBA) or pivalic anhydride with the modified benzotetramisole-type catalyst ((*S*)-*β*-Np-BTM) is the most effective for promotion of the enantioselective coupling reaction between racemic carboxylic acids and a novel nucleophile, bis(α-naphthyl)methanol, to give the corresponding esters with high ee's. This protocol was successfully applied to the production of nonracemic nonsteroidal anti-inflammatory drugs from racemic compounds utilizing the transacylation process to generate the mixed anhydrides from the acid components with the suitable carboxylic anhydrides.

Introduction

The synthesis of optically active carboxylic acids and esters is a very important topic due to the significant role they play in the field of medicinal and pharmaceutical chemistry.[1] Some chiral resolving agents (e.g., chiral amines) have been developed for the derivatization of racemic carboxylic acids to form pairs of diastereomers which can be separated by conventional recrystallization. However, in some cases, this process requires several repetitions of salt formation between a carboxylic acid and an amine followed by recrystallization and subsequent separation of the chiral auxiliaries from the acid component to obtain a pure enantiomer. Although a very effective method for providing chiral carboxylic esters derived from 2-arylalkanoic acids by enantioselective *C*-acylations with ketenes using planar-chiral heterocycles was reported by Fu,[2] it is alternatively desirable to develop the direct and practical kinetic resolution of racemic α-substituted carboxylic acids using achiral alcohols by the promotion of a chiral catalyst. We present here a novel and effective method for producing a variety of 2-arylalkanoic acid derivatives including nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, ketoprofen, fenoprofen, flurbiprofen, and naproxen, and their esters by the kinetic resolution of racemic α-substituted carboxylic acids using achiral alcohols with acid anhydrides and chiral acyl-transfer catalysts.[3,4]

We have recently reported the first asymmetric esterification of racemic secondary benzylic alcohols with free carboxylic acids using an aromatic anhydride[5] or a bulky aliphatic carboxylic anhydride[6] as a coupling reagent by the novel mixed-anhydride formation technology (Scheme 1). The chiral induction was realized using optically active acyl-transfer catalysts, such as (*S*)-tetramisole and (*R*)-benzotetramisole ((*R*)-BTM), which were popularized by Birman et al.[7,8] By only mixing racemic alcohols and achiral carboxylic acids with (*R*)-BTM in the presence of benzoic anhydride, 4-methoxybenzoic anhydride (PMBA), or pivalic anhydride at room temperature,

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(1) For reviews of routes to optically active arylpropanoic acids, see: (a) Sonawane, H. R.; Bellur, N. S.; Ahuja, J. R.; Kulkarni, D. G. *Tetrahedron: Asymmetry* **1992**, *3*, 163. (b) Rieu, J.-P.; Boucherle, A.; Cousse, H.; Mouzin, G. *Tetrahedron* **1986**, *42*, 4095.

(2) (a) Hodous, B. L.; Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 2637. (b) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 10006. (c) Wiskur, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 6176. (d) Schaefer, C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 4606. For accounts, see: (e) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412. (f) Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542.

(3) Preliminary communication: Shiina, I.; Nakata, K.; Onda, Y. *Eur. J. Org. Chem.* **2008**, 5887.

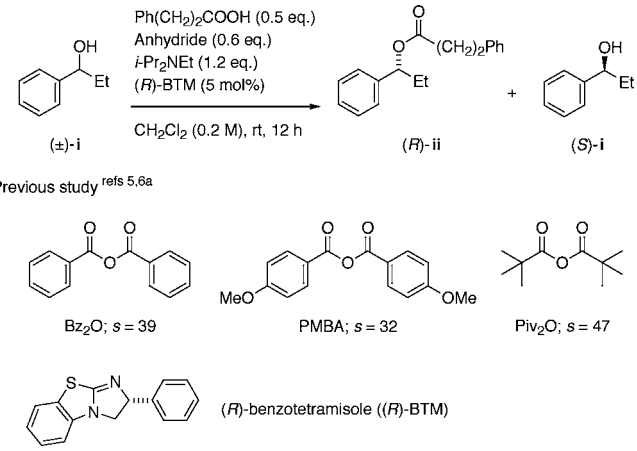
(4) For another example of asymmetric esterification of racemic carboxylic acids, see: (a) Ishihara, K.; Kosugi, Y.; Umemura, S.; Sakakura, A. *Org. Lett.* **2008**, *10*, 3191. (b) Sakakura, A.; Umemura, S.; Ishihara, K. *Synlett* **2009**, 1647. (c) Yang, X.; Birman, V. B. *Adv. Synth. Catal.* **2009**, *351*, 2301. See also other non-enzymatic enantioselective acyl transfer reactions: (d) Narasaka, K.; Kanai, F.; Okudo, M.; Miyoshi, N. *Chem. Lett.* **1989**, 1187. (e) Notte, G. T.; Sammakia, T.; Steel, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 13502. (f) Notte, G. T.; Sammakia, T. *J. Am. Chem. Soc.* **2006**, *128*, 4230. (g) Yang, X.; Lu, G.; Birman, V. B. *Org. Lett.* **2010**, *12*, 892.

(5) Shiina, I.; Nakata, K. *Tetrahedron Lett.* **2007**, *48*, 8314.

(6) (a) Shiina, I.; Nakata, K.; Sugimoto, M.; Onda, Y.; Iizumi, T.; Ono, K. *Heterocycles* **2009**, *77*, 801. See also kinetic resolution of racemic 2-hydroxyalkanoates using asymmetric esterification: (b) Shiina, I.; Nakata, K.; Ono, K.; Sugimoto, M.; Sekiguchi, A. *Chem.—Eur. J.* **2010**, *16*, 167.

(7) (a) Birman, V. B.; Li, X. *Org. Lett.* **2006**, *8*, 1351. (b) Birman, V. B.; Guo, L. *Org. Lett.* **2006**, *8*, 4859.

Scheme 1. Kinetic Resolution of Racemic Secondary Alcohol (±)-i Using Bz_2O, PMBA, and Piv_2O



the corresponding chiral carboxylic esters and the unreacted chiral alcohols were afforded in high enantiomeric excesses.[5,6]

In these reactions, carboxylic anhydrides were activated by (*R*)-BTM to react with carboxylic acids, and then the corresponding mixed anhydride (**MA**) was gradually produced during the reaction (Scheme 2). The formed **MA** (**MA-type-I**) functions as a key species for the transacylation, and the successive nucleophilic substitution of the acyloxy moiety with (*R*)-BTM followed by exchange with the chiral (*R*)-type alcohol in the racemic mixture afforded the desired (*R*)-carboxylic esters with high enantioselectivities as shown in **Case I**.

We postulated that it is possible to obtain chiral carboxylic acids from racemic carboxylic acids via kinetic resolution of the racemic mixture of **MA** (**MA-type-II**), which could be selectively activated by (*R*)-BTM to react with achiral alcohols. On the basis of the above hypothesis, we explored developing a new method for the preparation of optically active α-substituted alkanoic acid derivatives, starting from racemic carboxylic acids with achiral alcohols using our mixed-anhydride formation technology.[9]

Results and Discussion

First, the reactions of racemic 2-phenylpropanoic acid ((±)-**1**) with a variety of achiral alcohols were chosen as model cases for the optimization of nucleophile structure (Table 1). In the presence of benzoic anhydride as a coupling reagent, (*R*)-BTM was employed for chiral induction according to the standard reaction conditions established in our earlier paper.[5] As shown in entries 1 and 2, the esterification did not proceed at all when tertiary alcohols were used as nucleophiles. The reaction of

Scheme 2. Proposed Asymmetric Esterification Using Carboxylic Anhydrides as Coupling Reagents To Form the Corresponding Mixed Anhydrides, **MA-type-I** and **MA-type-II**. (Case I) Kinetic Resolution of Racemic Alcohols via **MA-type-I**. (Case II) Kinetic Resolution of Racemic Carboxylic Acids via **MA-type-II**

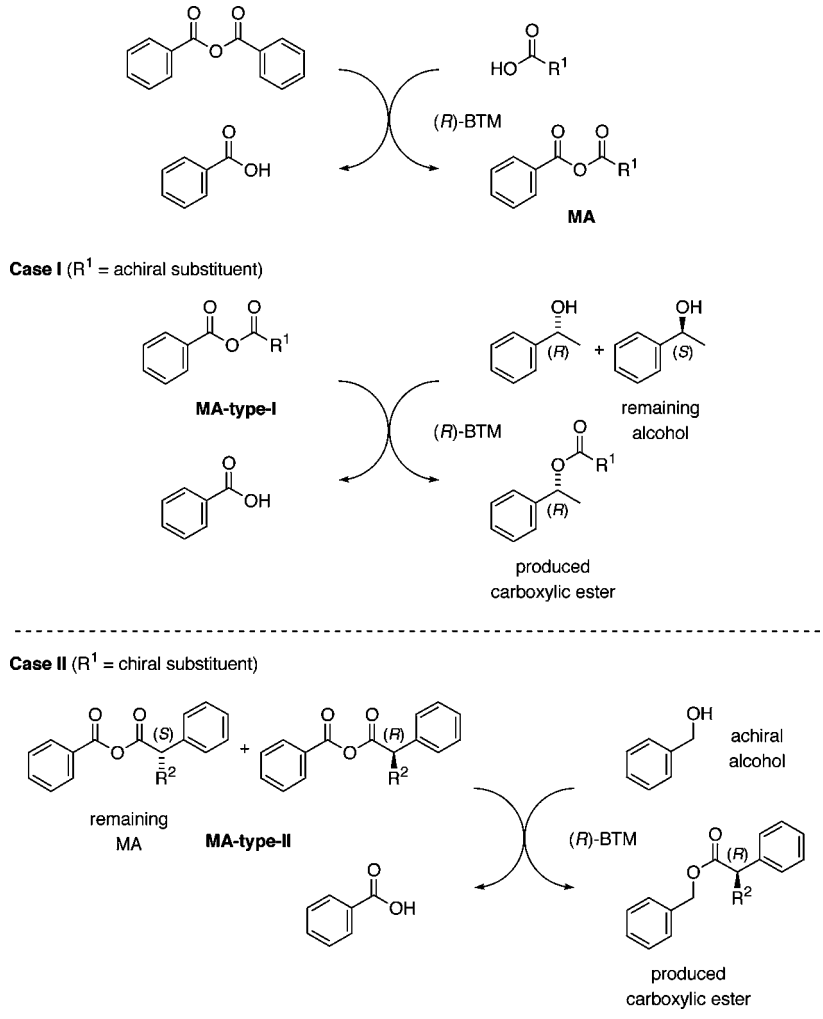
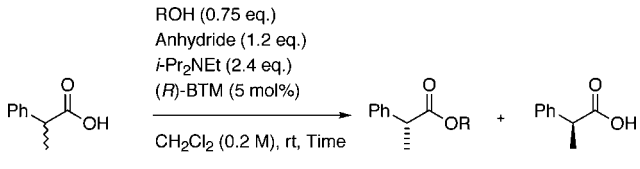
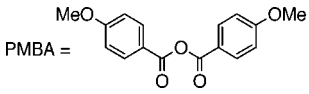
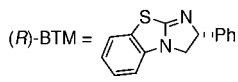


Table 1. Kinetic Resolution of Racemic 2-Phenylpropanoic Acid ((±)-**1**) Using Various Nucleophiles



entry	ROH	anhydride	time	ester **2** yield [%] (% ee)	acid **1** yield [%] (% ee)
1	TrOH	Bz_2O	18 h	0 (nd)	0 (nd)
2	*t*-BuOH	Bz_2O	15 h	0 (nd)	0 (nd)
3	*c*-HexOH	Bz_2O	3 d	39 (0)	31 (3)
4	Bn_2CHOH	Bz_2O	16 h	12 (3)	11 (0)
5	$PhCH_2OH$	Bz_2O	12 h	40 (33)	60 (23)
6	Ph_2CHOH	Bz_2O	12 h	42 (33)	37 (19)
7	$(4\text{-}MeOC_6H_4)_2CHOH$	Bz_2O	12 h	15 (12)	26 (0)
8	$(4\text{-}FC_6H_4)_2CHOH$	Bz_2O	12 h	60 (27)	27 (35)
9	$(\beta\text{-Np})_2CHOH$	Bz_2O	11 h	67 (31)	16 (41)
10	$(\alpha\text{-Np})_2CHOH$ (**3**)	Bz_2O	4 h	56 (81)	19 (80)
11	$(\alpha\text{-Np})_2CHOH$ (**3**)	PMBA	4 h	46 (86)	46 (60)
12	$(\alpha\text{-Np})_2CHOH$ (**3**)	Piv_2O	4 h	42 (89)	51 (27)
13	PhOH	Bz_2O	1 h	56 (24)	14 (28)
14	$2,6\text{-}Me_2C_6H_3OH$	Bz_2O	12 h	12 (44)	5 (9)
15	$2,6\text{-}Ph_2C_6H_3OH$	Bz_2O	15 h	19 (58)	36 (8)
16	$2,6\text{-}(\beta\text{-Np})_2C_6H_3OH$	Bz_2O	2.5 h	29 (64)	43 (23)
17	$2,6\text{-}(\beta\text{-Np})_2C_6H_3OH$	PMBA	2.5 h	15 (67)	71 (11)
18	$2,6\text{-}(\alpha\text{-Np})_2C_6H_3OH$	Bz_2O	7.5 h	14 (77)	31 (15)
19	$2,6\text{-}(\alpha\text{-Np})_2C_6H_3OH$	PMBA	4 h	21 (86)	58 (17)





secondary alcohols (entries 3 and 4) afforded the desired esters in 39% and 12% yields, respectively, but the produced carboxylates and the recovered carboxylic acids proved to be almost racemic compounds. On the other hand, it was revealed that benzyl alcohol and diphenylmethanol produced a relatively improved enantioselectivity of the corresponding carboxylic esters (33% ee in each case) as shown in entries 5 and 6.

Next, several achiral diphenylmethanol derivatives were examined as nucleophiles for the kinetic resolution of (±)-**1** as depicted in entries 7−10. Substitution of the aryl ring of diphenylmethanol diminished the selectivities (entries 7 and 8), and the use of bis(β-naphthyl)methanol afforded relatively better results compared with those of the reaction using bis(4-fluorophenyl)methanol (entry 9; cf. entry 8). Fortunately, we determined that the kinetic resolution of (±)-**1** could be attained effectively by employing bis(α-naphthyl)methanol (**3**) as the achiral nucleophile, which produced the corresponding ester (*R*)-**2** and the recovered acid (*S*)-**1** with good enantiomeric excesses (81% ee; 80% ee) as shown in entry 10. Similar to the kinetic resolution of racemic secondary alcohols in the previous paper,[5,6] PMBA as well as pivalic anhydride also proved to be suitable coupling reagents, and the desired ester (*R*)-**2** was obtained in 86% and 89% ee's, respectively (entries 11 and 12).

Furthermore, we screened phenol and several substituted phenol derivatives for the kinetic resolution of (±)-**1** as listed in entries 13−19. Although phenol itself provided poor ee's in the present reaction, it was determined that introduction of bulky substituents at the *o*- and *o*′-positions on the aromatic rings was effective in attaining good enantioselectivity of the formed carboxylic ester **2**. For example, the combined use of 2,6-bis(α-naphthyl)phenol and PMBA produced the optically active ester **2** in 86% ee as demonstrated in entry 19. We succeeded in discovering that there were two suitable nucleophiles, **3** and 2,6-bis(α-naphthyl)phenol, in this asymmetric esterification, and the former was clearly superior to the latter in both chemical yields and selectivities of the desired products based on the above experimental results (compare entries 11 and 19).

We then tried to optimize the suitable structure of the chiral acyl-transfer catalysts, and the results, including chemical yields and selectivities of the produced esters and recovered carboxylic acids, are listed in Table 2. New catalysts, (*S*)-α-Np-BTM and (*S*)-β-Np-BTM used in entries in 9 and 10, were easily generated from 2-amino-2-(α-naphthyl)-1-ethanol and 2-amino-2-(β-naphthyl)-1-ethanol, respectively. These amino alcohol derivatives had already been utilized for the synthesis of chiral ligands,[10] which were applied to the asymmetric cyclopropanation of 2,5-dimethyl-2,4-hexadiene to produce several chrysanthemic acid derivatives including pyrethroid chemicals. Other benzotetramisole-type catalysts, such as (*S*)-*i*-Pr-BTM, (*S*)-*t*-Bu-BTM, and (*S*)-Bn-BTM, were prepared from the corresponding 1,2-amino alcohols or α-amino acids according to the synthetic protocol reported by Birman et al.[7]

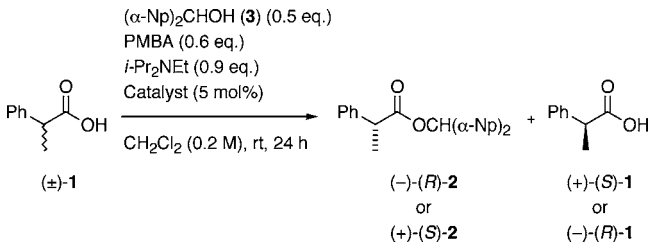
When the reaction was carried out using 5 mol % of (*R*)-BTM or (*S*)-BTM in the presence of 0.5 equiv of **3**, 0.6 equiv of PMBA, and 0.9 equiv of diisopropylethylamine, the enantioselective esterification proceeded smoothly at room temperature, and the corresponding chiral carboxylic ester **2** was obtained in good yield (33% for (*R*)-**2**, 34% for (*S*)-**2**) with a fairly good enantioselectivity (89% ee for (*R*)-**2**, 87% ee for (*S*)-**2**). Furthermore, nearly half the amount of the unreacted carboxylic acid (*S*)-**1** or (*R*)-**1** (49% or 58%) was also recovered in moderate optical purity (41% or 38% ee) as shown in entry 1 or 2. On the other hand, the modified BTM derivatives, such as (*S*)-*i*-Pr-BTM, (*S*)-*t*-Bu-BTM, and (*S*)-Bn-BTM, which have aliphatic substituents instead of a phenyl group on the dihydroimidazole moiety of BTM, afforded poor results as depicted

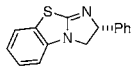
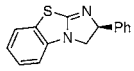
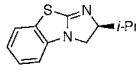
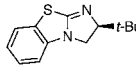
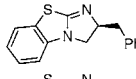
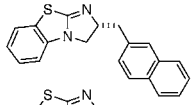
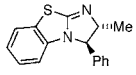
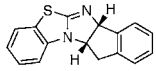
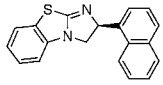
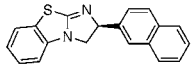
(8) Other related studies by Birman et al. for the kinetic resolution of racemic alcohols: (a) Birman, V. B.; Uffman, E. W.; Jiang, H.; Li, X.; Kilbane, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 12226. (b) Birman, V. B.; Jiang, H. *Org. Lett.* **2005**, *7*, 3445. (c) Birman, V. B.; Jiang, H.; Li, X.; Guo, L.; Uffman, E. W. *J. Am. Chem. Soc.* **2006**, *128*, 6536. (d) Birman, V. B.; Li, X.; Jiang, H.; Uffman, E. W. *Tetrahedron* **2006**, *62*, 285. (e) Birman, V. B.; Li, X.; Han, Z. *Org. Lett.* **2007**, *9*, 37. (f) Zhang, Y.; Birman, V. B. *Adv. Synth. Catal* **2009**, *351*, 2525. Carboxy group transfer reaction of azlactones using tetramisole derivatives: (g) Joannesse, C.; Johnston, C. P.; Concellón, C.; Simal, C.; Philp, D.; Smith, A. D. *Angew. Chem., Int. Ed.* **2009**, *48*, 8914. See also: (h) Kobayashi, M.; Okamoto, S. *Tetrahedron Lett.* **2006**, *47*, 4347. (i) Zhou, H.; Xu, Q.; Chen, P. *Tetrahedron* **2008**, *64*, 6494.

(9) (a) Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M. *J. Org. Chem.* **2004**, *69*, 1822. (b) Shiina, I. *Chem. Rev.* **2007**, *107*, 239. (c) Shiina, I.; Katoh, T.; Nagai, S.; Hashizume, M. *Chem. Rec.* **2009**, *9*, 305, and references therein.

(10) (a) Masumoto, K.; Itagaki, M. *Jpn. Kokai Tokkyo Koho 2004 067,671*, 2004; *Chem. Abstr.* **2004**, *140*, 217396. (b) Masumoto, K.; Itagaki, M. *Jpn. Kokai Tokkyo Koho 2004 051,604*, 2004; *Chem. Abstr.* **2004**, *140*, 181222. (c) Itagaki, M.; Masumoto, K.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 3292. See also other references for the reduction of α-amino acids: (d) van Lingen, H. L.; van de Mortel, J. K. W.; Hekking, K. F. W.; van Delft, F. L.; Sonke, T.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **2003**, 317. (e) van Lingen, H. L.; van Delft, F. L.; Storcken, R. P. M.; Hekking, K. F. W.; Klaassen, A.; Smits, J. J. M.; Ruskowska, P.; Frelek, J.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **2005**, 4975.

Table 2. . Kinetic Resolution of Racemic 2-Phenylpropanoic Acid ((±)-**1**) Using Various Catalysts

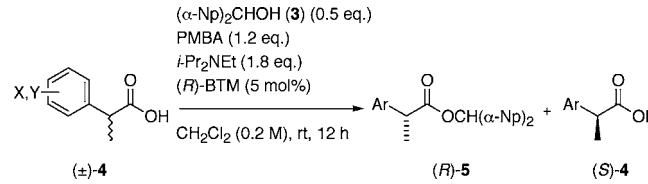


entry	catalyst		ester **2** yield [%] (% ee)	acid **1** yield [%] (% ee)
1		(*R*)-BTM	33 (–89% ee)	49 (41 % ee)
2		(*S*)-BTM	34 (87% ee)	58 (–38% ee)
3		(*S*)-*i*-Pr-BTM	42 (64% ee)	35 (–46% ee)
4		(*S*)-*t*-Bu-BTM	6 (–10% ee)	61 (1% ee)
5		(*S*)-Bn-BTM	44 (55% ee)	42 (–42% ee)
6		(*R*)-β-NpCH2-BTM	44 (–50% ee)	40 (35 % ee)
7		(*R,R*)-noref-BTM	22 (12% ee)	52 (–8% ee)
8		(*R,S*)-fused-BTM	23 (–12% ee)	54 (5% ee)
9		(*S*)-α-Np-BTM	29 (88% ee)	67 (–23% ee)
10		(*S*)-β-Np-BTM	40 (91% ee)	56 (–44% ee)

in entries 3−7. The use of a penta-fused type novel catalyst ((*R,S*)-fused-BTM) unfortunately showed unacceptable selectivity for the produced carboxylic ester **2** and the recovered carboxylic acid **1** (entry 8); however, we successfully revealed that the use of (*S*)-α-Np-BTM or (*S*)-*β*-Np-BTM is very effective in this reaction to afford the desired ester with high ee's (entries 9 and 10, respectively). It is especially worth noting that the reaction mediated with (*S*)-*β*-Np-BTM (entry 10) could be carried out by a facile protocol to provide the optically active carboxylic ester (*S*)-**2** (91% ee) in good yield with the highest selectivity.

A variety of examples of the kinetic resolution of racemic 2-arylpropanoic acid derivatives (**4a**−**h**) with **3** by promotion with PMBA and (*R*)-BTM is demonstrated in Table 3. The selectivity factor (*s*-value) principally shows the ratio of reactivities of (*R*)- and (*S*)-carboxylic acids; however, our reaction system includes multiple transacylation stages so that the conversion value obtained from HPLC analysis of the products does not accurately correspond to the conversion value obtained by ^{1}H NMR integration of the crude reaction mixture. Therefore, we introduce an apparent selective factor (s_{app}-value) instead of the formal *s*-value in this paper in order to evaluate the efficiency of the kinetic resolution of racemic carboxylic

Table 3. Kinetic Resolution of Racemic 2-Phenylpropanoic Acid Derivatives Including Nonsteroidal Anti-inflammatory Drugs (NSAIDs) Using (*R*)-BTM and PMBA



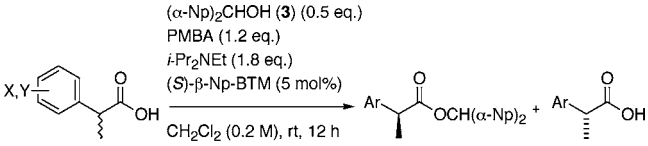
entry	X, Y	acid	ester **5** yield [%] (% ee)	acid **4** yield [%] (% ee)	s_{app}
1	H, H	**4a**	36 (91)	39 (52)	36
2	4-Me, H	**4b**	37 (83)	31 (44)	17
3	4-MeO, H	**4c**	44 (86)	35 (47)	21
4	4-Cl, H	**4d**	48 (83)	33 (46)	17
5	4-*i*-Bu, H	ibuprofen (**4e**)	39 (92)	33 (36)	34
6	3-Bz, H	ketoprofen (**4f**)	55 (77)	36 (58)	14
7	3-PhO, H	fenoprofen (**4g**)	46 (82)	42 (53)	17
8	3-F, 4-Ph	flurbiprofen (**4h**)	53 (83)	34 (37)	15

acids. The s_{app}-values were determined according to the equation $s_{app} = \ln((1 - C_{HPLC})(1 - ee_A))/\ln((1 - C_{HPLC})(1 + ee_A))$. The conversion C_{HPLC} used in the above equation was calculated as $C_{HPLC} = ee_A/(ee_E + ee_A)$, where ee_E is the enantiomeric excess of the optically active carboxylic ester and ee_A is the enantiomeric excess of the unreacted carboxylic acid.[11,8a] As shown by entries 1−4, all kinetic resolutions of racemic 2-phenylpropanoic acid (**4a**), 2-(4-methylphenyl)propanoic acid (**4b**), 2-(4-methoxyphenyl)propanoic acid (**4c**), and 2-(4-chlorophenyl)-propanoic acid (**4d**) provided the optically active carboxylic esters (*R*)-**5a**−**d** in good enantiomeric excesses (83−91% ee), therefore it is postulated that there is not a very large electronic effect on the aromatic ring of the substrates. Several derivatives of 2-phenylpropanoic acid, such as ibuprofen (**4e**), ketoprofen (**4f**), fenoprofen (**4g**), and flurbiprofen (**4h**), are used clinically as NSAIDs; thus the kinetic resolutions of these valuable compounds were next examined. As shown in entries 5−8, the optically active ibuprofen ester (**5e**, 92% ee), ketoprofen ester (**5f**, 77% ee), fenoprofen ester (**5g**, 82% ee), and flurbiprofen ester (**5h**, 83% ee) were easily prepared by the reaction of (±)-**4e**−**h** with the nucleophile **3** in the presence of PMBA and (*R*)-BTM under the standard reaction conditions (s_{app} = 14−34).

Table 4 displays a variety of examples of the kinetic resolution of racemic 2-arylpropanoic acid derivatives **4a**−**h** with **3** using the combination of PMBA and (*S*)-*β*-Np-BTM. All of the reactions using the 2-phenylpropanoic acid derivatives substituted at the 4-position on the aromatic rings produced the corresponding esters (*S*)-**5a**−**d** in good enantiomeric excesses (4-H; 91% ee, 4-Me; 81% ee, 4-MeO; 85% ee, 4-Cl; 86% ee), irrespective of the substituents at the 4-position on the aromatic rings of the 2-arylalkanoic acid derivatives. The (*S*)-*β*-Np-BTM-mediated asymmetric acyl-transfer reaction was also successfully applied to the preparation of the chiral NSAIDs esters (*S*)-**5e**−**h** in high ee's (78−92% ee) with good s_{app}-values (entries 5−8, s_{app} = 14−45). It is worth noting that the effective kinetic resolutions of racemic **4a**−**h** were achieved using (*S*)-*β*-Np-BTM to give better selectivities compared with the reactions in which the original (*R*)-BTM catalyst was used (cf. Table 3, except for entry 6). Additionally, further improved selectivities were observed by the combined use of (*S*)-*β*-Np-BTM with pivalic anhydride for the coupling between the racemic α-sub-

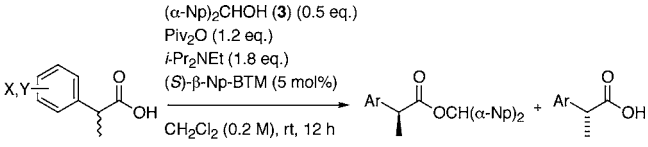
(11) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.

Table 4. Kinetic Resolution of Racemic 2-Phenylpropanoic Acid Derivatives Including Nonsteroidal Anti-inflammatory Drugs (NSAIDs) Using (*S*)-*β*-Np-BTM and PMBA



entry	X, Y	acid	ester **5** yield [%] (% ee)	acid **4** yield [%] (% ee)	s_{app}
1	H, H	**4a**	41 (91)	35 (55)	38
2	4-Me, H	**4b**	44 (81)	45 (67)	19
3	4-MeO, H	**4c**	46 (85)	30 (68)	25
4	4-Cl, H	**4d**	51 (86)	33 (37)	19
5	4-*i*-Bu, H	ibuprofen (**4e**)	42 (92)	41 (66)	45
6	3-Bz, H	ketoprofen (**4f**)	49 (78)	39 (51)	14
7	3-PhO, H	fenoprofen (**4g**)	46 (86)	42 (59)	25
8	3-F, 4-Ph	flurbiprofen (**4h**)	48 (85)	41 (45)	19

Table 5. Kinetic Resolution of Racemic 2-Phenylpropanoic Acid Derivatives Including Nonsteroidal Anti-inflammatory Drugs (NSAIDs) Using (*S*)-*β*-Np-BTM and Piv_2O

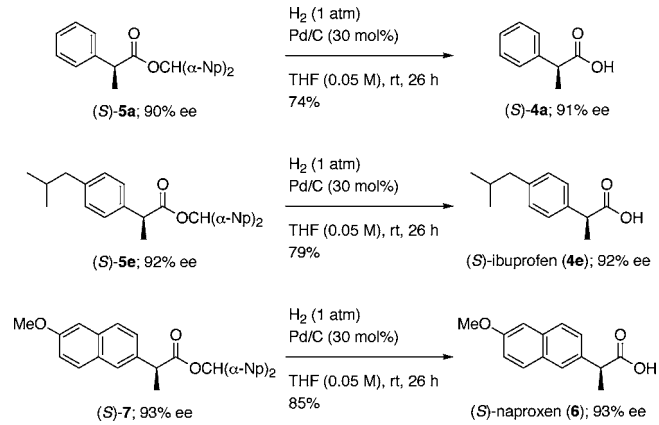


entry	X, Y	acid	ester **5** yield [%] (% ee)	acid **4** yield [%] (% ee)	s_{app}
1	H, H	**4a**	45 (92)	51 (59)	44
2	4-Me, H	**4b**	48 (86)	39 (62)	26
3	4-MeO, H	**4c**	50 (89)	33 (77)	41
4	4-Cl, H	**4d**	49 (82)	34 (68)	20
5	4-*i*-Bu, H	ibuprofen (**4e**)	42 (93)	32 (67)	55
6	3-Bz, H	ketoprofen (**4f**)	48 (85)	48 (62)	23
7	3-PhO, H	fenoprofen (**4g**)	46 (88)	39 (67)	32
8	3-F, 4-Ph	flurbiprofen (**4h**)	46 (87)	42 (67)	29

stituted carboxylic acids **4a**−**h** with **3** as listed in Table 5 (entries 1−4, s_{app} = 20−44; entries 5−8, s_{app} = 23−55).

The kinetic resolution of naproxen (**6**), a widely used anti-inflammatory drug, by the present method with achiral alcohol was next examined, and the results are summarized in Scheme 3. The reaction of racemic naproxen with **3** in the presence of PMBA and (*R*)- or (*S*)-BTM afforded the corresponding ester (*R*)- or (*S*)-**7** in 53% or 48% yield with moderate enantioselectivity (77% or 76% ee), and nearly 40% of the resulting (*S*)- or (*R*)-naproxen was recovered with 62% or 59% ee, respectively (s_{app} = 15 or 13). We found that the reaction using (*S*)-α-Np-BTM produced (*S*)-**7** with a relatively better enantiomeric excess (88% ee, s_{app} = 25); moreover, the best result was also obtained when (*S*)-*β*-Np-BTM was applied to the kinetic resolution of (±)-**6** by the combined use of the nucleophile **3** with PMBA or pivalic anhydride to provide the chiral naproxen ester (*S*)-**7** in good yield with a high enantiomeric excess (49% yield, 93% ee, s_{app} = 61 for PMBA; 43% yield, 93% ee, s_{app} = 59 for Piv_2O).

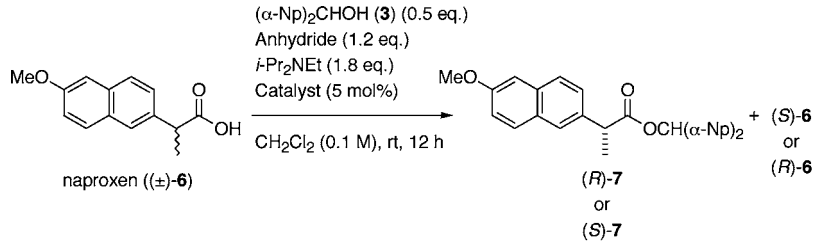
Scheme 4. Deprotection of Bis(α-naphthyl)methyl Esters To Form (*S*)-2-Phenylpropanoic Acid ((*S*)-**4a**), (*S*)-Ibuprofen (**4e**), and (*S*)-Naproxen (**6**)



We then attempted the transformation of the optically active bis(α-naphthyl)methyl esters into free carboxylic acids in order to obtain the corresponding 2-arylalkanoic acid derivatives including several NSAIDs (Scheme 4). Under the conventional hydrogenation conditions to remove the benzyl ester moiety, the cleavage of the bis(α-naphthyl)methyl ester group was successfully carried out to give the chiral 2-phenylpropanoic acid (*S*)-**4a**, (*S*)-ibuprofen (**4e**), and (*S*)-naproxen (**6**) without any loss of the optical purity of the starting esters (*S*)-**5a**, (*S*)-**5e**, and (*S*)-**7**, respectively.

Next, we prepared deuterated 2-phenylpropanoic acid (Me-d_3) ((*R*)-**8**) for the determination of the reaction pathway of the present mixed-anhydride method. Kinetic resolution of racemic carboxylic acid (±)-**8** was carried out using alcohol

Scheme 3. Kinetic Resolution of Racemic Naproxen ((±)-**6**)



(*R*)-BTM, PMBA; (*R*)-**7**; 53%, 77% ee, (*S*)-**6**; 37%, 62% ee, s_{app} = 15

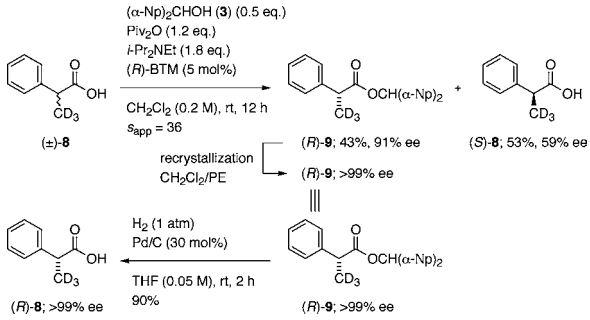
(*S*)-BTM, PMBA; (*S*)-**7**; 48%, 76% ee, (*R*)-**6**; 40%, 59% ee, s_{app} = 13

(*S*)-α-Np-BTM, PMBA; (*S*)-**7**; 43%, 88% ee, (*R*)-**6**; 48%, 44% ee, s_{app} = 25

(*S*)-β-Np-BTM, PMBA; (*S*)-**7**; 49%, 93% ee, (*R*)-**6**; 51%, 74% ee, s_{app} = 61

(*S*)-β-Np-BTM, Piv_2O; (*S*)-**7**; 43%, 93% ee, (*R*)-**6**; 37%, 69% ee, s_{app} = 59

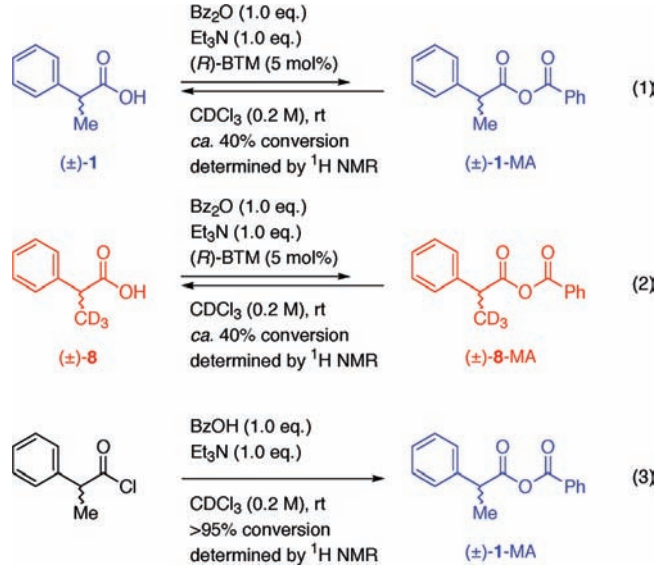
Scheme 5. Preparation of Optically Pure Deuterated (*R*)-2-Phenylpropanoic Acid (Me-d_3) ((*R*)-**8**) by the Kinetic Resolution of Racemic Deuterated 2-Phenylpropanoic Acid (Me-d_3) ((±)-**8**)



3 in the presence of pivalic anhydride and (*R*)-BTM to afford the corresponding ester (*R*)-**9** in 43% with high enantioselectivity (91% ee) as shown in Scheme 5. First recrystallization of the optically active (*R*)-**9** increased the enantiomeric excess of (*R*)-**9** to over 99% ee, and the following hydrogenation of the produced bis(α-naphthyl)methyl ester (*R*)-**9** cleaved the ester linkage in (*R*)-**9** to afford the optically pure carboxylic acid (*R*)-**8**.

Formation of the mixed anhydride consisting of aliphatic carboxylic acid and benzoic acid parts was determined on the basis of several ^{1}H NMR experiments as depicted in Charts 1−3 (Figure 1). Chart 1 shows the ^{1}H NMR of the mixture of racemic carboxylic acid (±)-**1** and benzoic anhydride in the presence of Et_3N with 5 mol % of (*R*)-BTM at room temperature (reaction 1 in Scheme 6). An equilibrium was observed to exist between (±)-**1** and (±)-**1**-MA in this transacylation process, and nearly 40% of the starting material ((±)-**1**) was facilely converted to the corresponding mixed anhydride ((±)-**1**-MA). Next, a deuterated mixed anhydride (±)-**8**-MA, which includes residues of the racemic deuterated 2-phenylpropanoic acid (Me-d_3) ((±)-**8**) and benzoic acid components, was also prepared from (±)-**8** with benzoic anhydride under the same reaction conditions (reaction 2), and the required ^{1}H NMR spectrum of (±)-**8**-MA was obtained as described in Chart 2. The structure of the mixed anhydride (±)-**1**-MA formed in Chart 1 was confirmed by comparison of this ^{1}H NMR chart (Chart 1) with that of an authentic sample (Chart 3), which was independently generated

Scheme 6. Formation of Mixed Anhydrides from Racemic 2-Phenylpropanoic Acid ((±)-**1**) and Racemic Deuterated 2-Phenylpropanoic Acid (Me-d_3) ((±)-**8**) with Benzoic Anhydride



from 2-phenylpropanoyl chloride and benzoic acid with Et_3N as shown in reaction 3 in Scheme 6.

In order to determine the ratio of the formed enantiomers of the mixed anhydride generated in situ in the present transacylation system, a stoichiometric mixture of (*S*)-**1** and (*R*)-**8** was treated with benzoic anhydride in the presence of Et_3N with 5 mol % of (*R*)-BTM at room temperature (reaction 4 in Scheme 7). Conversion of ca. 40% of the mixture of the starting carboxylic acids (*S*)-**1** and (*R*)-**8** was observed by a ^{1}H NMR experiment (Chart 4) as shown in the bottom diagram in Figure 2, and it was clarified that nearly equimolar amounts of (*S*)-**1**-MA and (*R*)-**8**-MA (51:49) were formed in the reaction mixture (cf. Charts 1 and 2 in Figure 2).

From the results of the above ^{1}H NMR experiment, we estimated the catalytic cycle of this reaction as illustrated in Scheme 8. First, a mixed anhydride (**MA**) forms as a key intermediate in situ from aromatic or pivalic anhydride (**SA**) with the racemic α-substituted carboxylic acid via generation of the zwitterion (**int-I**) through steps **A** and **B** by the promotion

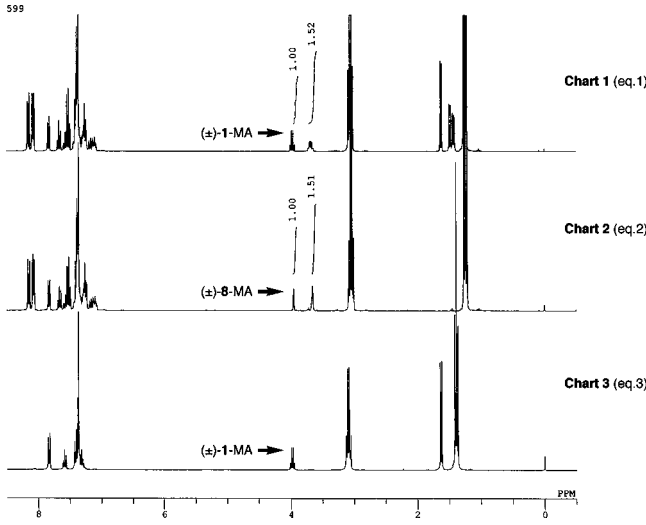


Figure 1. Comparison of ^{1}H NMR spectra obtained in reactions 1−3 (Charts 1−3).

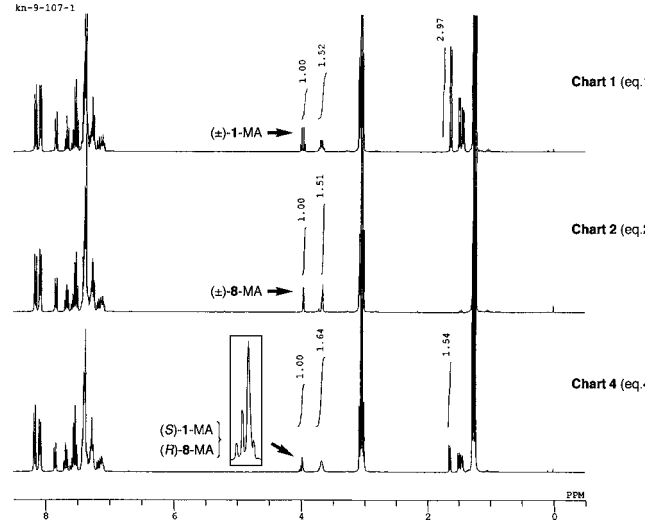
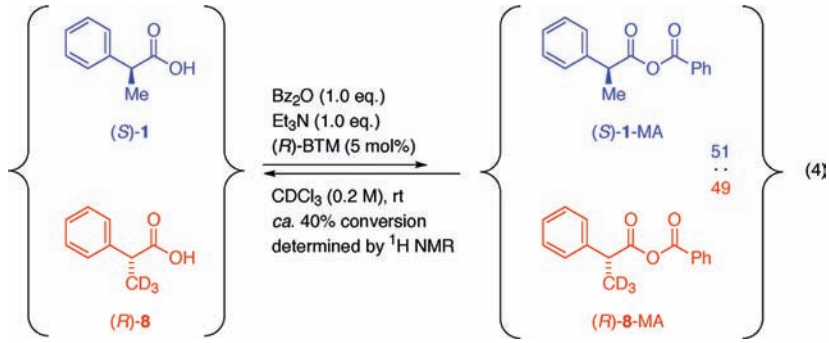
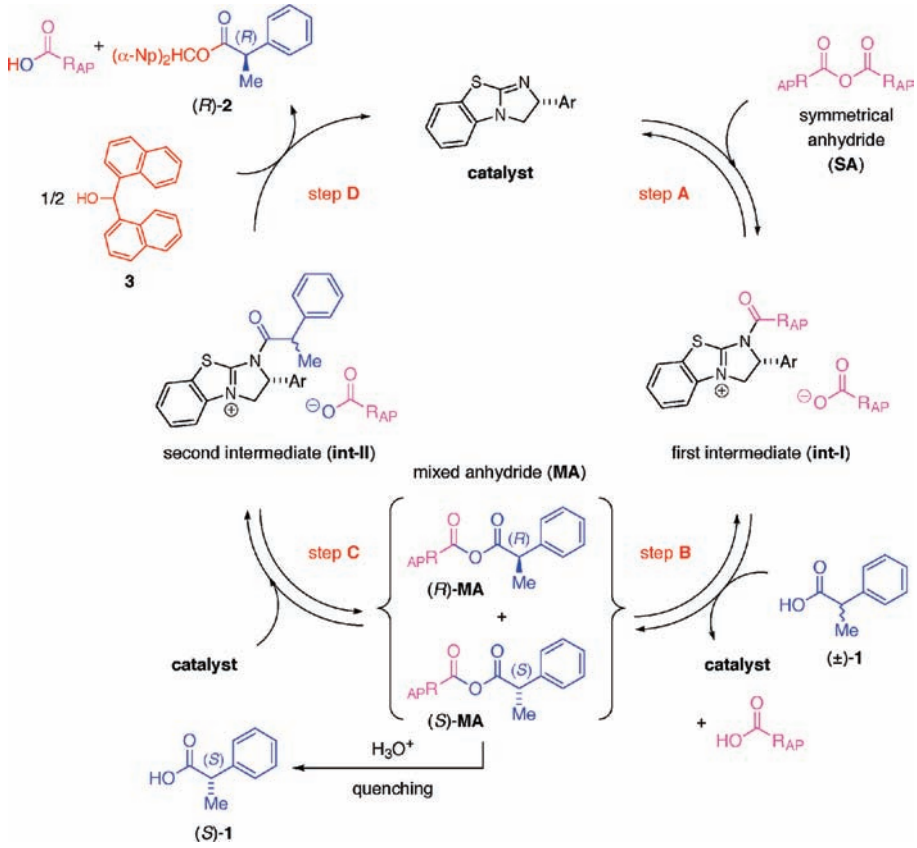


Figure 2. Comparison of ^{1}H NMR spectra obtained in reactions 1, 2, and 4 (Charts 1, 2, and 4).

Scheme 7. Formation of a Mixture of Mixed Anhydrides from a Mixture of (*S*)-2-Phenylpropanoic Acid ((*S*)-**1**) and Deuterated (*R*)-2-Phenylpropanoic Acid (Me-d_3) ((*R*)-**8**) with Benzoic Anhydride



Scheme 8. Plausible Reaction Pathway of the Kinetic Resolution of Racemic α-Substituted Carboxylic Acids



of the acyl-transfer catalyst. In the next step **C**, (*R*)- and (*S*)-**MA** would be activated again by the chiral acyl-transfer catalyst to form the corresponding zwitterionic species (**int-II**), and half the amount of **int-II** generated from (*R*)-**MA** selectively would react with a nucleophilic alcohol **3** to afford the desired (*R*)-carboxylic ester with high enantiomeric excess through step **D**. On the other hand, the remaining half of the mixed anhydride ((*S*)-**MA**) would be hydrolyzed to produce the unreacted (*S*)-carboxylic acid as a recovered optically active starting material with good enantiopurity. The efficiency of the kinetic resolution completely depends on the structure of the alcohol as shown in Table 1, and thus it is anticipated that step **D** would include the most important stage for determining the enantioselectivity during this multiple transacylation process.[12]

We further investigated the reaction mechanism forming the mixed anhydrides and the dihydroimidazolium intermediates in detail by a ^{1}H NMR experiment. It was initially observed that the formation of a small amount of the second dihydroimidazolium intermediate (**int-II** in Scheme 8) occurred in the reaction of racemic carboxylic acid (±)-**1** with an equimolar amount of benzoic anhydride and 5 mol % of (*R*)-BTM as shown in the top diagram (Chart 1) in Figure 3. It was anticipated that the intermediary species (**int-II**) consists of two stereoisomers, that is, a dihydroimidazolium intermediate (**int-II**-(*R*)/(*R*)) derived from (*R*)-**1** with benzoic anhydride and (*R*)-BTM and another intermediate (**int-II**-(*S*)/(*R*)) consisting of (*S*)-**1**, benzoic anhy-

(12) The reaction pathway and the structure of similar zwitterionic species have been discussed for the kinetic resolution of racemic 2-hydroxyalkanoates using diphenylacetic acid with BTM in ref 6b. Birman et al. also proposed the transition state model for the kinetic resolution of α-aryl, α-aryloxy, and α-arylthioalkanoic acids using homobenzotetramisole (HBTM) via formation of the corresponding zwitterionic species in ref 4c.

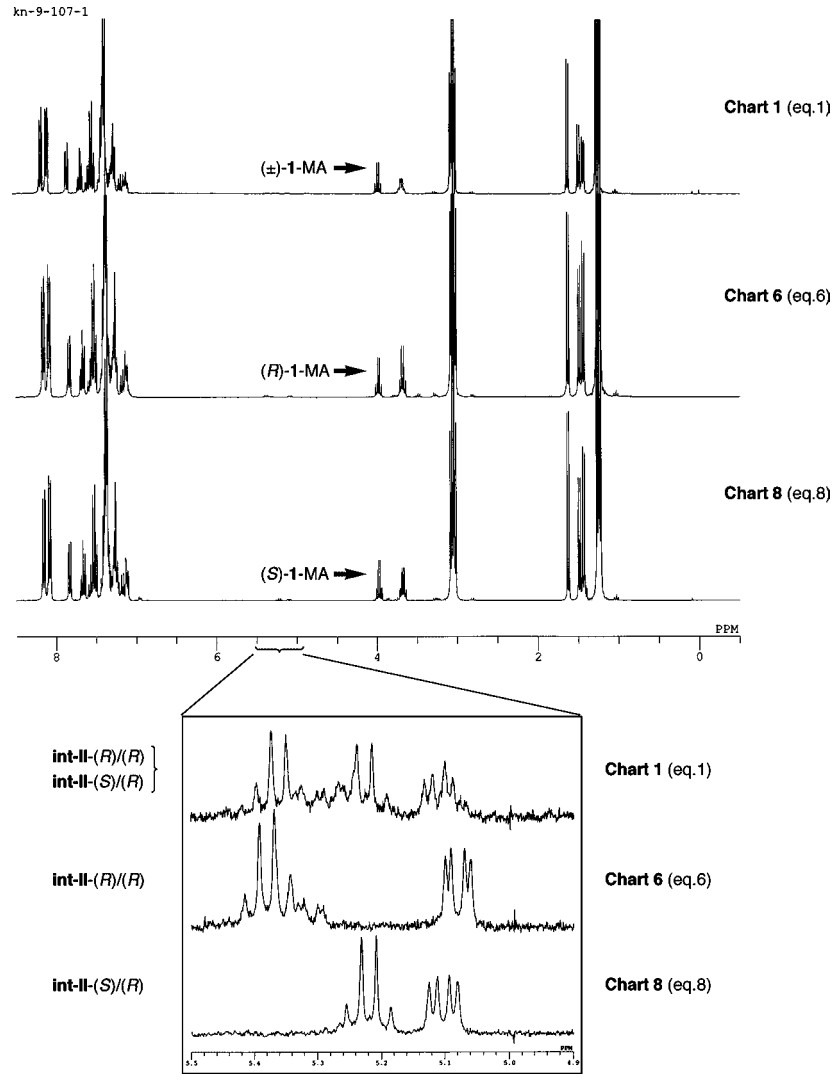


Figure 3. Comparison of ^{1}H NMR spectra obtained in reactions 1, 6, and 8 (Charts 1, 6, and 8).

dride and (*R*)-BTM. Therefore, the following control experiments were also carried out as depicted in Scheme 9.

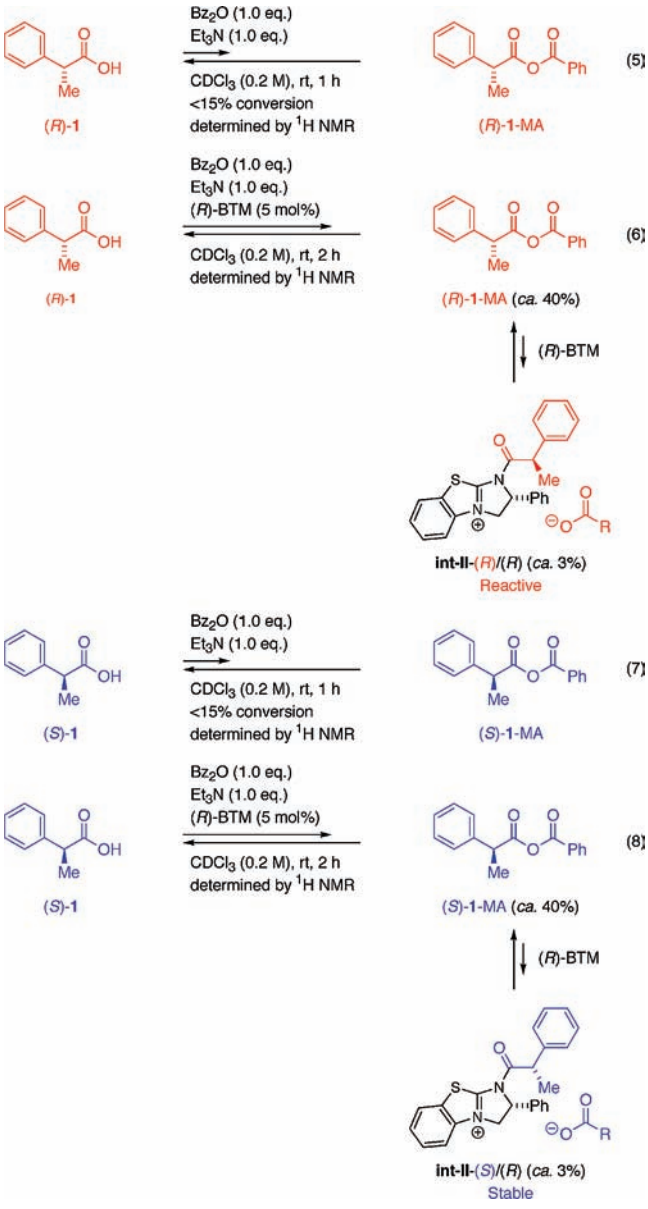
First, we obtained the ^{1}H NMR spectrum of a solution of stoichiometric amounts of carboxylic acid (*R*)-**1**, benzoic anhydride, and Et_3N without (*R*)-BTM in $CDCl_3$. This procedure is represented in reaction 5 in Scheme 9, and the ^{1}H NMR spectrum of the mixture is shown in the top diagram (Chart 5) in Figure 4. An addition of 5 mol % of (*R*)-BTM to the above reaction mixture resulted in forming ca. 30% (*R*)-**1**-MA and a small amount of **int-II**-(*R*)/(*R*) (ca. 2%) after 1 h (Chart 6 [1 h] in Figure 4) and forming ca. 40% (*R*)-**1**-MA and ca. 3% of **int-II**-(*R*)/(*R*) after 2 h based on the ^{1}H NMR analysis as shown in the bottom diagram (Chart 6) in Figure 4. Transformation of carboxylic acid (*R*)-**1** with benzoic anhydride and (*R*)-BTM into the intermediate (**int-II**-(*R*)/(*R*)) via (*R*)-**1**-MA is illustrated as reaction 6 in Scheme 9.

Next, we added 5 mol % of (*R*)-BTM to the reaction mixture of equimolar amounts of carboxylic acid (*S*)-**1**, benzoic anhydride, and Et_3N, and the corresponding several spectra were obtained as shown in Figure 5. The top diagram (Chart 7) in Figure 5 shows the spectrum without any (*R*)-BTM, and the other diagrams (Chart 8 [5 min], Chart 8 [1 h], and Chart 8) in Figure 5 display spectra with an additional 5 mol % of (*R*)-BTM. It was observed that ca. 40% (*S*)-**1**-MA and a small amount of **int-II**-(*S*)/(*R*) (ca. 3%) were formed after 2 h on the basis of ^{1}H NMR analysis of the last spectrum. This interconversion process among carboxylic acid (*S*)-**1**, mixed anhydride (*S*)-**1**-MA, and the intermediate (**int-II**-(*S*)/(*R*)) with or without (*R*)-BTM is depicted in reactions 7 and 8 in Scheme 9.

Three important spectra of the dihydroimidazolium intermediates (Chart 1, Chart 6, and Chart 8) are collected in Figure 3, namely, the top diagram (Chart 1) shows the ^{1}H NMR of a diastereomeric mixture of **int-II** derived from racemic carboxylic acid (±)-**1** (reaction 1 in Scheme 6), the middle one (Chart 6) is the ^{1}H NMR of **int-II**-(*R*)/(*R*) derived from carboxylic acid (*R*)-**1** (reaction 6 in Scheme 9), and the bottom one (Chart 8) is the ^{1}H NMR of **int-II**-(*S*)/(*R*) derived from carboxylic acid (*S*)-**1** (reaction 8 in Scheme 9). These observations indicated that the top diagram of **int-II** (Chart 1) derived from racemic carboxylic acid (±)-**1** includes nearly equimolar amounts of **int-II**-(*R*)/(*R*) and **int-II**-(*S*)/(*R*); therefore, both the intermediates **int-II**-(*R*)/(*R*) and **int-II**-(*S*)/(*R*) could be simultaneously produced by the treatment of racemic carboxylic acid (±)-**1** with equimolar amounts of benzoic anhydride and Et_3N in the presence of a catalytic amount of (*R*)-BTM.

The reactivity of **int-II**-(*R*)/(*R*) should be higher than that of **int-II**-(*S*)/(*R*) because (*R*)-**2** was selectively produced from **int-II**-(*R*)/(*R*) by the rapid nucleophilic addition of alcohol **3** to **int-**

Scheme 9. Formation of Mixed Anhydrides and Dihydroimidazolium Intermediates from (*R*)-2-Phenylpropanoic Acid ((*R*)-**1**) and (*S*)-2-Phenylpropanoic Acid ((*S*)-**1**) with Benzoic Anhydride and (*R*)-BTM



II-(*R*)/(*R*), although a mixture of both species, **int-II**-(*R*)/(*R*) and **int-II**-(*S*)/(*R*), was formed in this reaction system. At the quenching stage of the present kinetic resolution of racemic carboxylic acids, nearly half the amount of the starting carboxylic acid was recovered from the mixed anhydrides by the hydrolysis of (*S*)-MA and (*R*)-MA; however, a small amount of the starting carboxylic acid should also be recovered from the mixture of the reactive **int-II**-(*R*)/(*R*) and the remaining stable **int-II**-(*S*)/(*R*) in situ. Therefore, it is assumed that the enantiomeric excess of the recovered (*S*)-carboxylic acid might be lowered to some extent by the preferable hydrolysis of **int-II**-(*R*)/(*R*) over **int-II**-(*S*)/(*R*).

Determination of the transition state forming the chiral ester (*R*)-**2** from 2-phenylpropanoic acid ((±)-**1**) with **3**, (*R*)-BTM, and pivalic anhydride via **int-II** was carried out using the density functional theory (DFT) calculations at the B3LYP/6-31G*//B3LYP/6-31G* level according to the method reported by Houk and Birman et al.[13] We successfully obtained the transition state

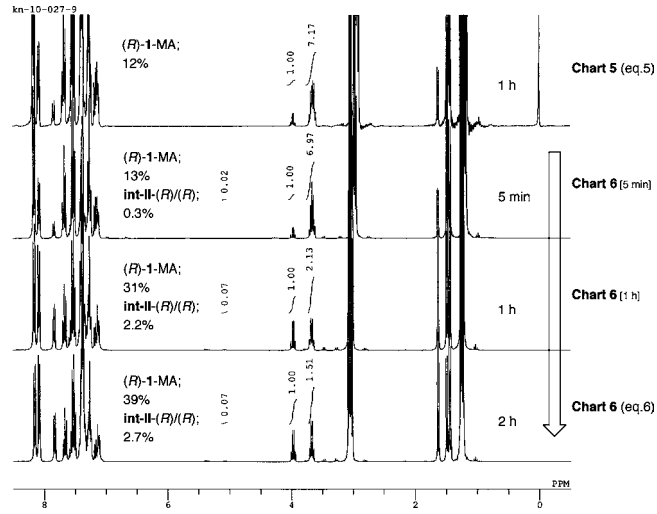


Figure 4. Comparison of ^{1}H NMR spectra obtained in reactions 5 and 6 (Charts 5 and 6).

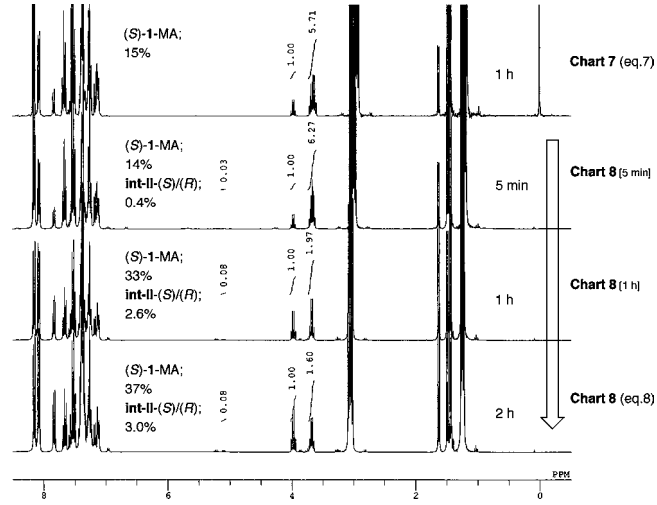
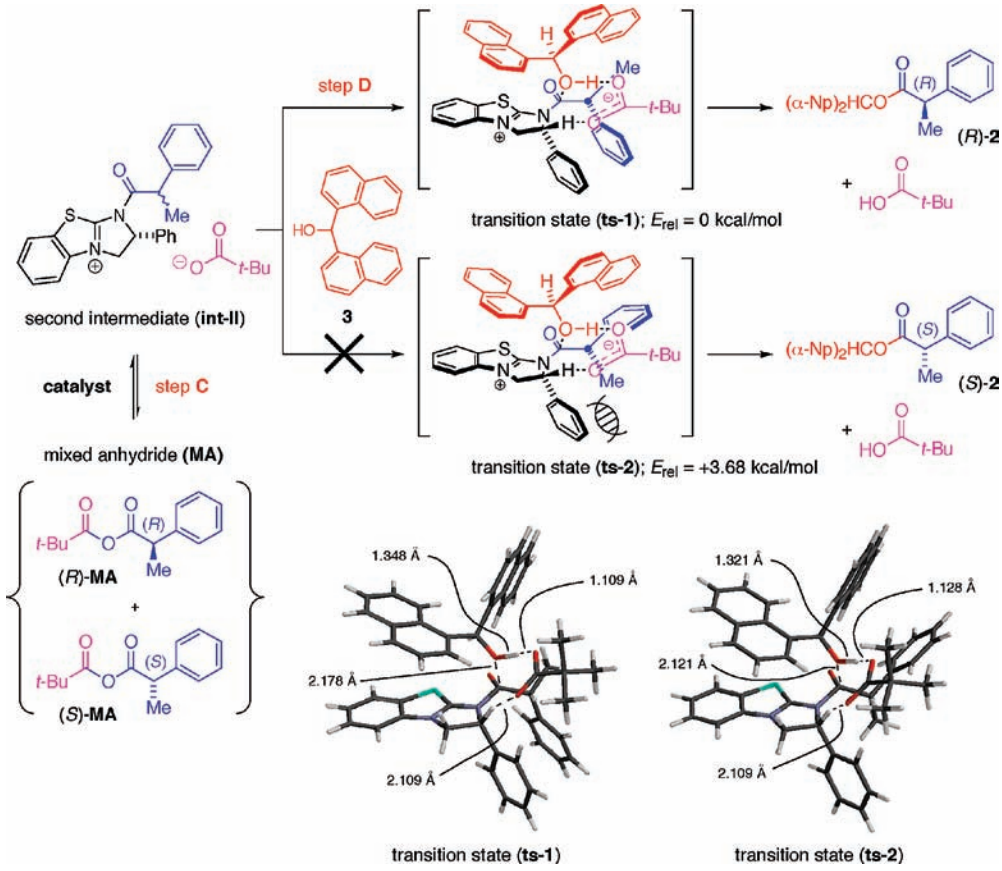


Figure 5. Comparison of ^{1}H NMR spectra obtained in reactions 7 and 8 (Charts 7 and 8).

(**ts-1**) to produce the desired ester (*R*)-**2** as depicted in Scheme 10.[14,15] The high selectivity found to be attained in the present kinetic resolution could be explained by the rapid transformation of (*R*)-**1** into (*R*)-**2** via this stabilized transition structure consisting of the nucleophile **3** and the dihydroimidazolium salt (**int-II**) derived from the mixed anhydride (*R*)-**MA** and (*R*)-BTM. The distance of the forming carbon−oxygen bond (between carbonyl carbon of the acid component and oxygen of hydroxy) is 2.178 Å, and the distance of the cleaving oxygen−hydrogen bond (between oxygen and hydrogen in hydroxy) is 1.348 Å. A frequency analysis of **ts-1** revealed that the nucleophilic attack of the alcohol to carbonyl group and the deprotonation of the hydroxyl group with the pivalate anion proceeded under the concerted reaction mechanism because the carbon−oxygen bond-forming step and the oxygen−hydrogen bond-cleaving process synchronously occurred. The diarylcarbinol moiety of **3** in **ts-1** 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 oxygens in the pivalate anion onto hydrogen in hydroxy (1.109 Å) and hydrogen at C-2 of the dihydroimidazolium salt (2.109 Å). On the other hand, complexation of **3** with the

Scheme 10. Calculated Transition State of the Kinetic Resolution of Racemic 2-Phenylpropanoic Acid ((±)-**1**)

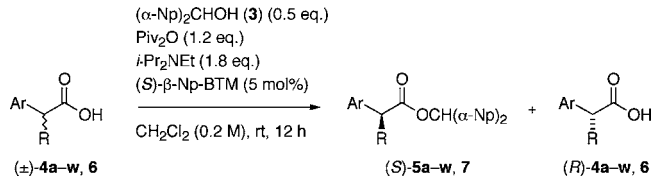


dihydroimidazolium salt (**int-II**) including (*S*)-**MA** and (*R*)-BTM, an enantiomer of (*R*)-**MA**, produced an unstable structure **ts-2**, which has a much higher energy (E_{rel} = +3.68 kcal/mol) derived from steric repulsion between the methyl substituent at the α-position of (*S*)-**1** and the phenyl group at C-2 of the dihydroimidazolium salt to afford the corresponding ester (*S*)-**2**. Therefore, the desired chiral ester (*R*)-**2** was selectively obtained by the rapid transformation of (*R*)-**MA** through the transition state **ts-1**.

From the structural features of the transition state, we speculated that a variety of 2-arylalkanoic acids having multifunctional groups on the aromatic ring could be applied to this reaction system. All the substrates, which were used in the kinetic resolution of racemic 2-arylalkanoic acids in this paper, are listed in Table 6. Racemic carboxylic acids **4a**−**w** and **6** were treated with pivalic anhydride and a catalytic amount of (*S*)-*β*-Np-BTM at room temperature. As shown in entries 10−12, kinetic resolution of *ortho*-substituted aromatic compounds **4i**−**k** produced the corresponding chiral carboxylic esters in high ee's (94−98% ee), and excellent s_{app}-values were observed (s_{app} = 89, 193, and 76, respectively). Furthermore, racemic 2,5-disubstituted aromatic compounds (**4l** and **4m**), racemic 2,4-disubstituted aromatic compounds (**4n** and **4o**), a racemic 2,3-disubstituted aromatic compound (**4p**), and a racemic 2,3,5-trisubstituted aromatic compound (**4q**) were also effectively transformed into the corresponding chiral (*S*)-carboxylic esters (91−98% ee), and the remaining (*R*)-carboxylic acids were recovered in relatively good ee's (64−99.5% ee) as shown in entries 13−18 (s_{app} = 484, 235, 55, 61, 72, and 146, respectively). Although kinetic resolution of racemic 2-phenylbutanoic acid (**4r**) showed a moderate s_{app}-value (entry 19, s_{app} = 11), racemic 3-methoxy-2-phenylpropanoic acid (**4s**), which is a methoxy-substituted compound at the C-3 position of 2-phenylpropanoic acid (cf. **4a**), afforded relatively better selectivity (entry 20, s_{app} = 24). Kinetic resolution of the fused aromatic compounds, such as racemic 2-(α-naphthyl)propanoic acid (**4t**), racemic 2-(*β*-naphthyl)propanoic acid (**4v**), and racemic 2-(9-phenanthryl)propanoic acid (**4w**) was next examined as shown in entries 21, 23, and 24, and the desired optically active carboxylic esters were produced in good yields with high enantioselectivities in all cases (90−98% ee, s_{app} = 136, 46, and 361, respectively). When racemic 2-(α-naphthyl)butanoic acid (**4u**) was employed in this reaction system, we could obtain fairly good selectivities of the products even though **4u** has a structure including an extra methyl group on the C-3 position of 2-arylpropanoic acid (entry 22, s_{app} = 57).

We then tried to realize the effect of substituents on the 2-arylpropanoic acid moiety by computational calculation according to the established protocol to evaluate the stabilities of the favorable transition state (**ts-1**) for the reaction of (*R*)-**4a** with **3** and the unfavorable transition state (**ts-2**) for the reaction of (*S*)-**4a** with **3** in Scheme 10 (vide supra). First, we successfully determined two transition structures for the reaction of 2-phenylbutanoic acid (**4r**), which corresponds to a methylated compound at the C-3 position of 2-phenylpropanoic acid (**4a**), with alcohol **3** using (*R*)-BTM as shown in Scheme 11. The transition state (**ts-1**−**4r**) was generated from alcohol **3** with the dihydroimidazolium salt (**int-II**) including the (*R*)-**4r** moiety, and another transition state (**ts-2**−**4r**) was produced from alcohol **3** with the dihydroimidazolium salt (**int-II**) including the (*S*)-**4r** moiety. The steric energy of the former transition state (**ts-1**−**4r**) is lower than that of the latter ($E_{rel(4r)}$ = +3.27 kcal/

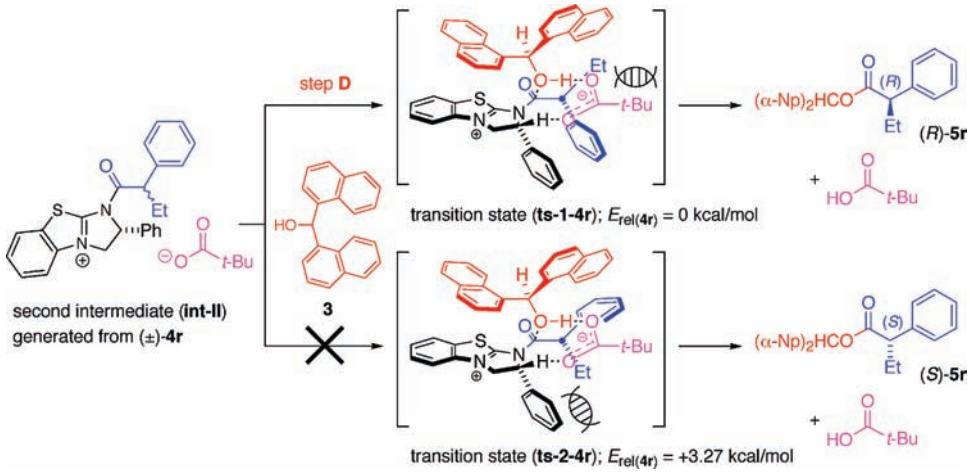
Table 6. Kinetic Resolution of a Variety of Racemic 2-Arylalkanoic Acids Using (*S*)-*β*-Np-BTM and Piv_2O



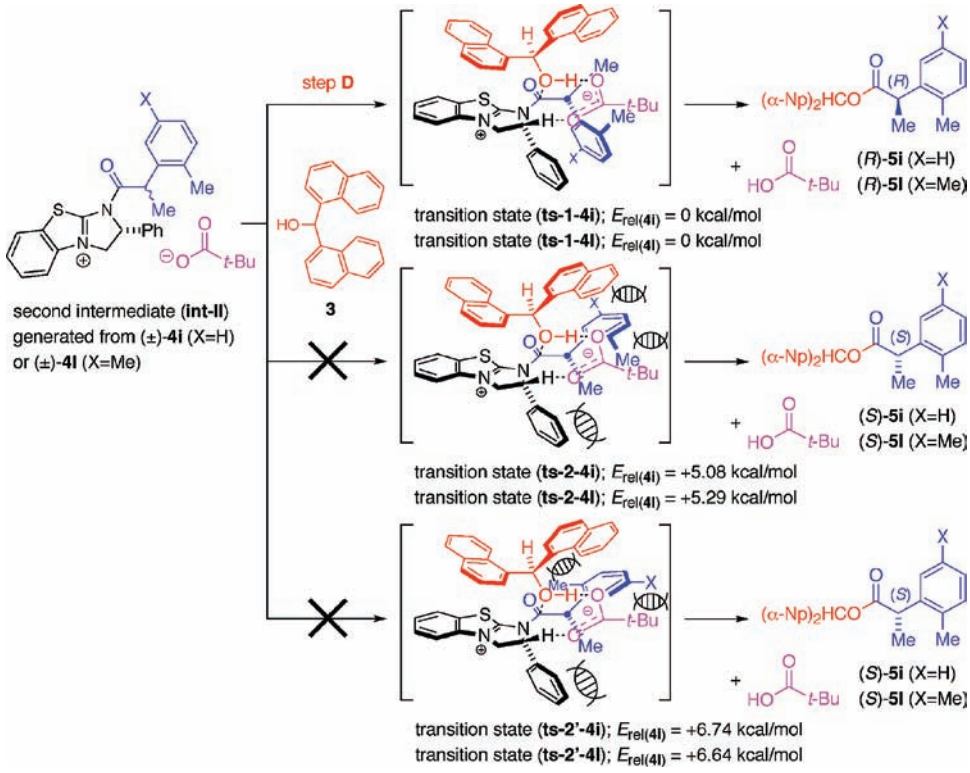
Entry	Yield of ester [%] (ee of ester)	Yield of acid [%] (ee of acid)	s_{app}
1	**5a**; 45% (92% ee)	**4a**; 51% (59% ee)	44
2	**5b**; 48% (86% ee)	**4b**; 39% (62% ee)	26
3	**5c**; 50% (89% ee)	**4c**; 33% (77% ee)	41
4	**5d**; 49% (82% ee)	**4d**; 34% (68% ee)	20
5	**5e**; 42% (93% ee)	ibuprofen (**4e**); 32% (67% ee)	55
6	**5f**; 48% (85% ee)	ketoprofen (**4f**); 48% (62% ee)	23
7	**5g**; 46% (88% ee)	fenoprofen (**4g**); 39% (67% ee)	32
8	**5h**; 46% (87% ee)	flurbiprofen (**4h**); 42% (67% ee)	29
9[a]	**7**; 43% (93% ee)	naproxen (**6**); 37% (69% ee)	59
10	**5i**; 45% (95% ee)	**4i**; 30% (71% ee)	89
11	**5j**; 48% (98% ee)	**4j**; 30% (73% ee)	193
12	**5k**; 46% (94% ee)	**4k**; 34% (75% ee)	76
13	**5l**; 40% (98% ee)	**4l**; 43% (99.5% ee)	484
14	**5m**; 47% (98% ee)	**4m**; 38% (73% ee)	235
15	**5n**; 48% (93% ee)	**4n**; 33% (68% ee)	55
16	**5o**; 49% (91% ee)	**4o**; 45% (85% ee)	61
17	**5p**; 50% (93% ee)	**4p**; 39% (85% ee)	72
18	**5q**; 41% (97% ee)	**4q**; 32% (64% ee)	146
19	**5r**; 45% (75% ee)	**4r**; 35% (46% ee)	11
20[b]	**5s**; 37% (88% ee)	**4s**; 47% (39% ee)	24
21	**5t**; 48% (96% ee)	**4t**; 41% (82% ee)	136
22[c]	**5u**; 33% (95% ee)	**4u**; 52% (31% ee)	57
23	**5v**; 49% (90% ee)	**4v**; 34% (76% ee)	46
24	**5w**; 48% (98% ee)	**4w**; 49% (86% ee)	361

[a] The reaction was carried out in dichloromethane (0.1 M). [b] Absolute configuration of **5s** is *R*. Absolute configuration of **4s** is *S*. [c] Ten mol % of catalyst was used.

Scheme 11. Calculated Transition State of the Kinetic Resolution of Racemic 2-Phenylbutanoic Acid ((±)-**4r**)



Scheme 12. Calculated Transition States of the Kinetic Resolution of Racemic 2-(2-Methylphenyl)propanoic Acid ((±)-**4i**) and Racemic 2-(2,5-Dimethylphenyl)propanoic Acid ((±)-**4l**)



mol); therefore, fast consumption of (*R*)-**4r** preferentially occurs to afford the desired ester (*R*)-**5r** with good enantioselectivity. However, the stability of the former transition state (**ts-1**−**4r**) is somewhat decreased based on the steric repulsion between the large ethyl group and the counteranion of the dihydroimidazolium salt as illustrated in the upper equation in Scheme 11. It is assumed that this effect increases the energy of the structure of **ts-1**−**4r**; thus, the diminished difference in the stabilities of **ts-1**−**4r** and **ts-2**−**4r** resulted in a lower selectivity of the kinetic resolution of racemic carboxylic acid (±)-**4r** in Table 6 (entry 19, s_{app} = 11) compared with that of racemic carboxylic acid (±)-**4a** (entry 1, s_{app} = 44) to afford the corresponding chiral ester **5a** via the formation of a very stable transition state (**ts-1**) in Scheme 10.

Next, the transition structures of the reaction of (*R*)-**4i** and (*S*)-**4i** with **3** were determined by the same theoretical approach. The most stable structure (**ts-1**−**4i**) derived from the intermediate (**int-II**) including (*R*)-**4i** gives the desired (*R*)-**5i** by the transacylation process with alcohol **3** as shown in Scheme 12 (X = H). On the other hand, two different structures (**ts-2**−**4i** and **ts-2′**−**4i**) derived from **int-II** including (*S*)-**4i** produce the opposite stereoisomer (*S*)-**5i** via a similar transacylation process. Apparently, the large energy gap of the two transition states between **ts-1**−**4i** and **ts-2**−**4i** ($E_{rel(4i)}$ = +5.08 kcal/mol) causes the observed high ee of the produced optically active ester **5i** (Table 6, entry 10, s_{app} = 89) based on the additional steric hindrance of the methyl group at the *o*-position on the aromatic ring toward the carboxylate anion of the dihydroimidazolium salt in **ts-2**−**4i**. Another transition state (**ts-2′**−**4i**) is merely the rotamer of **ts-2**−**4i**; however, **ts-2′**−**4i** has a more unstable structure ($E_{rel(4i)}$ = +6.74 kcal/mol) compared with **ts-2**−**4i** ($E_{rel(4i)}$ = +5.08 kcal/mol) because the methyl group at the

o-position on the aromatic ring in **ts-2′−4i** should be very close to one of the naphthalene rings included in alcohol **3**.

The present kinetic resolution of **4j**−**4q** (Table 6, entries 11−18), which possess an *ortho*-functionalized structure, afforded high ee's of the produced chiral esters (91−98% ee) and relatively good ee's of the recovered carboxylic acids (64−99.5% ee). These preferable results would arise from the same steric effect of the repulsion of the *o*-substituents toward its surroundings in the transition structures. The reaction of racemic 2-(α-naphthyl)propanoic acid (**4t**) afforded the corresponding optically active ester **5t** in high ee (96% ee) with good selectivity (entry 21, $s_{app} = 136$) due to the same effect of the α-naphthyl group, which has a structural similarity to that of an *o*-substituted benzene ring. Similarly the 2-phenylbutanoic acid (**4r**) is the equivalent of the methylated compound at the C-3 position of 2-phenylpropanoic acid (**4a**), 2-(α-naphthyl)butanoic acid (**4u**) also corresponds to the methylated compound at the C-3 position of 2-(α-naphthyl)propanoic acid (**4t**). Therefore, the selectivity of the kinetic resolution of **4u** (entry 22, $s_{app} = 57$) is lower than that of the kinetic resolution of **4t** (entry 21, $s_{app} = 136$); however, the *o*-substituted effect of the aromatic ring in **4u** induced better selectivity (entry 22, $s_{app} = 57$) compared with that observed in the reaction using another butanoic acid derivative **4r** without any substituent at the *ortho*-position on the phenyl group (entry 19, $s_{app} = 11$).

Finally, the origin of the remarkably high selectivities obtained in the racemic 2,5-disubstituted aromatic compounds (**4l**, **4m**, and **4q**) and 2-(9-phenanthryl)propanoic acid (**4w**) is surveyed by the theoretical calculation (Table 6, entries 13, 14, 18, and 24). The most preferable transition state (**ts-1**−**4l**) to give the desired chiral ester (*R*)-**5l** from racemic carboxylic acid (±)-**4l** is illustrated in Scheme 12 (X = Me), and it is noticed that the steric repulsion of the two methyl groups at the *ortho*- and *meta*′-positions on the aromatic ring toward their surroundings in this structure is not very large. On the other hand, two rotamers (**ts-2**−**4l** and **ts-2′**−**4l**) have unstable structures because of the severe steric repulsion of the two methyl groups toward their surroundings. In the unfavorable transition states (**ts-2**−**4l** and **ts-2′**−**4l**), one of the two methyl groups must locate near the counteranion of the dihydroimidazolium salt, and another methyl group must exist near one of the naphthalene rings included in alcohol **3**. These two effects simultaneously increase the steric energies of **ts-2**−**4l** and **ts-2′**−**4l**, and these reaction pathways to give the undesired ester (*S*)-**5l** are effectively prevented in the key transacylation process. DFT calculation clearly revealed that the second stable transition state (**ts-2**−**4l**) has a much higher energy ($E_{rel(4l)} = +5.29$ kcal/mol) compared with the value of the most stable transition state (**ts-1**−**4l**), and the significant energy difference might induce excellent stereoselectivity in the kinetic resolution of racemic carboxylic acids **4l**, **4m**, and **4q** ($s_{app} = 484$, 235, and 146, respectively).

2-(9-Phenanthryl)propanoic acid (**4w**) has a structural similarity to that of 2,5-disubstituted benzene derivatives, such as **4l**, **4m**, and **4q**; therefore, the β-Np-BTM-mediated kinetic resolution of racemic **4w** also proceeds with high selectivity due to the large difference in the transition state energies between the **ts-1**−**4l**-type one and the **ts-2**−**4l**-type one. The latter unstable transition structure must have a higher energy which arose from the bulkiness of the 9-phenanthryl group, so that the desired chiral ester **5w** was preferably obtained in almost pure form (98% ee) by the rapid consumption of one of the enantiomers in racemic (±)-**4w** through the stable transition state (entry 24, $s_{app} = 361$).

Conclusion

In summary, we have developed a new method for the preparation of the optically active 2-arylalkanoic acids and their esters via kinetic resolution. A combination of bis(α-naphthyl)-methanol (**3**) and (*S*)-β-Np-BTM with PMBA or pivalic anhydride proved to be the best to produce the corresponding chiral esters from racemic 2-arylpropanoic acid derivatives with high ee's under mild reaction conditions. This protocol was successfully utilized for the effective kinetic resolution of racemic ibuprofen, ketoprofen, fenoprofen, flurbiprofen, and naproxen to produce a variety of the optically active NSAIDs. Kinetic resolution of *ortho*-substituted aromatic compounds, 2,5-disubstituted aromatic compounds, 2,4-disubstituted aromatic compounds, a 2,3-disubstituted aromatic compound, and a 2,3,5-trisubstituted aromatic compound produced the corresponding chiral carboxylic esters with high ee's (91−98% ee) and excellent s_{app}-values ($s_{app} = 55-484$). This was further successfully applied to the kinetic resolution of fused aromatic compounds, such as racemic 2-(α-naphthyl)propanoic acid, racemic 2-(β-naphthyl)propanoic acid, and racemic 2-(9-phenanthryl)propanoic acid, to give the desired optically active carboxylic esters in good yields with high enantioselectivities (90−98% ee, $s_{app} = 136$, 46, and 361, respectively). One of the features of the present protocol is that it provides a very simple procedure for producing the desired chiral esters. That is, the addition of promoters to the mixture of α-substituted carboxylic acids, achiral alcohols, and the suitable carboxylic anhydride at room temperature affords the desired chiral carboxylic acids and those esters in good yields with high enantiopurity. The utility of the present protocol will be demonstrated by the applications of this reaction system to the syntheses of useful and complex natural molecules in the future.

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Supporting Information Available: Experimental procedures, spectroscopic data, and Cartesian coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Li, X.; Liu, P.; Houk, K. N.; Birman, V. B. *J. Am. Chem. Soc.* **2008**, *130*, 13836.
(14) All calculations were performed with the program package TITAN 1.0.5, Schrodinger Inc. and Wavefunction Inc., and the program package Spartan '08 1.1.1 of Wavefunction Inc.
(15) Cartesian coordinates and absolute energies for all reported structures are included in Supporting Information.