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Kinetic Resolution of the Racemic 2-Hydroxyalkanoates Using the Enantioselective Mixed-Anhydride Method with Pivalic Anhydride and a Chiral Acyl-Transfer Catalyst

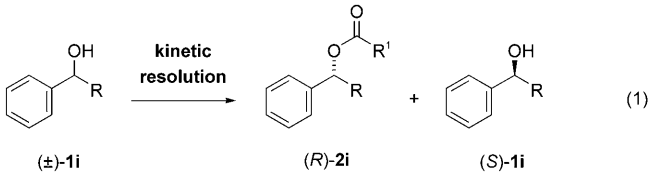
Isamu Shiina,* Kenya Nakata, Keisuke Ono, Masuhiro Sugimoto, and Akihiro Sekiguchi[a]

Abstract: A variety of optically active 2-hydroxyalkanoates and the corresponding 2-acyloxyalkanoates are produced by the kinetic resolution of racemic 2-hydroxyalkanoates by using achiral 2,2-diarylacetic acid with hindered carboxylic anhydrides as the coupling reagents. The combined use of diphenylacetic acid, pivalic anhydride, and (+)-(*R*)-benzotetramisole ((*R*)-BTM) effectively produces (*S*)-2-hydroxyalkanoates and (*R*)-2-acyloxyalkanoates from the racemic 2-hydroxyalkanoates (*s*-values = 47–202). This protocol directly provides the desired chiral 2-hydroxyalkanoate derivatives from achiral diarylacetic acid and racemic secondary alcohols that do not include the *sec*-phenethyl alcohol moiety by using the transacylation process to generate the mixed anhydrides from the acid components with bulky carboxylic anhydrides under the influence of the chiral acyl-transfer catalyst. The transition state that provides the desired (*R*)-2-acyloxyalkanoate from (*R*)-2-hydroxyalkanoate included in the racemic mixture is disclosed by DFT calculations, and the structural features of the transition form are also discussed.

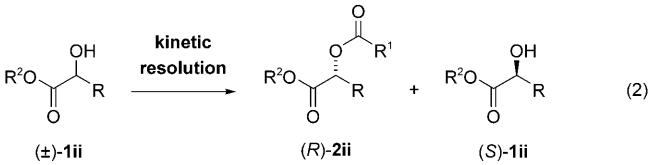
Keywords: anhydrides · chirality · density functional calculations · enantioselectivity · kinetic resolution

Introduction

Optically active 2-hydroxy- and 2-acyloxyalkanoates[1] are frequently utilized as fundamental synthons for the production of chiral molecules, such as medicines, biologically active chemicals, and advanced functionalized polymers. Recently, several effective methods for the kinetic resolution of racemic *sec*-phenethyl alcohol derivatives were developed that afforded the corresponding chiral secondary alcohols with high enantiomeric excesses [Eq. (1)]:[2] however, to the best of our knowledge a general artificial method for the kinetic resolution of 2-hydroxyalkanoates [Eq. (2)] has not yet appeared until now. Because of the extensive synthetic utility of the chiral 2-hydroxyalkanoate derivatives, it is strongly desired to establish a facile protocol to prepare these valuable materials through the resolution of the racemic substrates.



(1)



(2)

We have recently reported the first asymmetric esterification of achiral carboxylic acids with racemic benzylic alcohols[3] through the formation of mixed anhydrides in situ by using aromatic or pivalic anhydrides with chiral acyl-transfer catalysts, such as (−)-(*S*)-tetramisole and (+)-(*R*)-benzotetramisole ((*R*)-BTM), which were introduced by Birman et al.[4] The asymmetric esterification also directly provides

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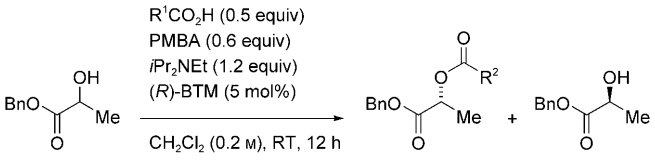
the chiral 2-arylpropionic acid derivatives from the corresponding racemic 2-arylpropionic acids by using kinetic resolution with achiral secondary alcohols through the formation of the mixed anhydrides derived from the acid components and aromatic anhydrides under the influence of (*R*)-BTM or (*S*)-β-Np-BTM.[5] Because these protocols utilized rapid transacylation to form the suitable mixed anhydrides from free carboxylic acids in situ, we expected that the present asymmetric esterification could be applicable for not only preparation of chiral *sec*-phenethyl alcohol derivatives, but also for the production of optically active 2-hydroxyalkanoates. Herein, we report the novel and useful kinetic resolution of racemic 2-hydroxyalkanoates that do not contain an aryl alkyl carbinol moiety, by using the present mixed-anhydride technology with free achiral carboxylic acids and hindered carboxylic anhydrides.

Results and Discussion

First, the reactions of racemic benzyl lactate ((±)-**1**) with several achiral carboxylic acids were chosen as model cases for optimization of electrophile structure (Table 1). In the presence of 4-methoxybenzoic anhydride (PMBA) as a coupling reagent, (*R*)-BTM was used for chiral induction according to the standard reaction conditions established in our preceding papers.[3] As shown in entries 1 and 2 in Table 1, the esterification provides the chiral lactate ((*S*)-**1**) and the corresponding 2-acyloxypropanoates ((*R*)-**2a** and (*R*)-**2b**) with medium selectivities ($s=14$ and 20).[6] We next increased the bulkiness around the carbonyl group of the intermediary mixed anhydrides by introducing several substituents to the 2-positions of the electrophiles. The results are shown in entries 3–7 of Table 1. Fortunately, we discovered that diphenylacetic acid is a very effective electrophile and it afforded the desired chiral benzyl 2-(diphenylacetoxy)propanoate ((*R*)-**2e**) and benzyl lactate ((*S*)-**1**) in good enantiomeric excesses (95 and 62% *ee*, respectively) with high chemical conversion (35% yield of (*R*)-**2e** and 48% recovery of (*S*)-**1**) as depicted in entry 5 in Table 1. Because an excellent *s*-value ($s=70$) and medium chemoselectivity (**2e**/**2′** = 80/20) were attained in this case in which the kinetic resolution was carried out in the presence of PMBA as shown above, we further attempted to improve the chemoselectivity of the desired ester **2e** over the undesired byproduct **2′** for practical use of this reaction.

Several carboxylic anhydrides including two aromatic anhydrides and four other kinds of aliphatic anhydrides were next examined as coupling reagents for the kinetic resolution of (±)-**1** with diphenylacetic acid (**3**) in order to prevent the formation of **2′** (Table 2). Surprisingly, all of the reactions afforded very good enantioselectivities, and the corresponding carboxylic ester (*R*)-**2e** and the resulting alcohol (*S*)-**1** were obtained in high enantiomeric excesses ($s=>62$). It was found that the use of bulky anhydrides, such as pivalic anhydride, provided the optically active ester **2e** with almost no formation of the undesirable ester **2′** as shown in entries 3–6 in Table 2.[3b] The solvent effect was further examined in the above reaction and we found that diethyl ether functions as a suitable medium for the kinetic resolution of (±)-**1** to produce the desired ester (*R*)-**2e** in good yield (44%) with an excellent enantiomeric excess (97% *ee*), so that the *s*-value dramatically increased to 146 (Table 2, entry 7).

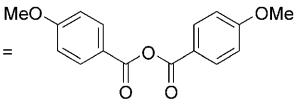
Table 1. Kinetic resolution of racemic benzyl lactate ((±)-**1**) by using the mixed-anhydride method.



(±)-**1** — R² = R¹; (*R*)-**2a**–**g**; R² = 4-MeOC$_6$H$_4$; **2′** — (*S*)-**1**

Entry	R¹	Yield of **2** [%][a]	**2**/**2′**[b]	*ee* (**2**) [%]	Yield of **1** [%][a]	*ee* (**1**) [%]	*s*
1	Ph(CH$_2$)$_2$ (**a**)	33	86/14	80	54	42	14
2	*p*TolCH$_2$ (**b**)	35	86/14	85	42	46	20
3	*i*Pr (**c**)	50	95/5	85	47	78	29
4	*c*Hex (**d**)	38	87/13	88	34	56	27
5	Ph$_2$CH (**e**)	35	80/20	95	48	62	70
6	(α-Np)$_2$CH (**f**)	8	84/16	94	86	6	35
7	(β-Np)$_2$CH (**g**)	31	89/11	95	52	51	63

[a] Isolated yield. [b] Determined by ^{1}H NMR spectroscopy.

PMBA = 

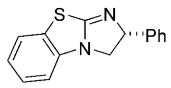
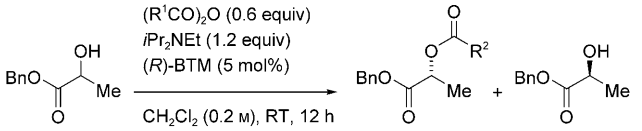
(*R*)-BTM = 

Table 2. Kinetic resolution of racemic benzyl lactate ((±)-**1**) with diphenylacetic acid (**3**).



(±)-**1** — R² = Ph$_2$CH; (*R*)-**2e**; R² = R¹; **2′** — (*S*)-**1**

Entry	R¹	Yield of **2** [%][a]	**2**/**2′**[b]	*ee* (**2**) [%]	Yield of **1** [%][a]	*ee* (**1**) [%]	*s*
1	Ph	46	87/13	92	43	84	64
2	4-MeOC$_6$H$_4$[PMBA]	35	80/20	95	48	62	70
3	*t*Bu	44	98/2	94	55	68	62
4	PhMe$_2$C	27	98/2	95	43	75	92
5	Ph$_2$MeC	37	>99/<1	96	44	62	87
6	Ph$_3$C	11	>99/<1	97	75	12	72
7[c]	*t*Bu	44	98/2	97	55	82	146

[a] Isolated yield. [b] Determined by ^{1}H NMR spectroscopy. [c] Diethyl ether was used as a solvent instead of dichloromethane.

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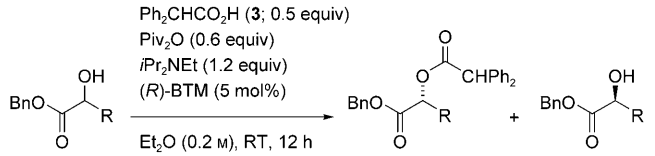
Eventually, esterification of a variety of racemic 2-hydroxyalkanoates ((±)-**4a–j**) with diphenylacetic acid (**3**) by promotion with pivalic anhydride and (*R*)-BTM was demonstrated in order to assess the generality of this novel method (Table 3). All the reactions with 2-hydroxyalkanoates that have linear alkyl substituents R next to the carbonyl group produced the corresponding esters (*R*)-**5a–c**, **5e**, **5f**, and **5h** in good enantiomeric excesses (Table 3, entries 1–3, 5, 6, and 8; R = Me, Et, *n*Pr, *n*Bu, *i*Bu, and $Ph(CH_2)_2$; 94–97% *ee*) with excellent *s*-values (*s* = 126–202). It is noteworthy that this protocol was successfully applied for the preparation of chiral dihydroxy ester equivalents (*R*)-**5i** (93% *ee*) and (*S*)-**4i** (87% *ee*) in the same manner by the asymmetric coupling reaction starting from the racemic benzyl 3-(*tert*-butyldimethylsiloxy)-2-hydroxypropanoate ((±)-**4i**) with the achiral electrophile **3**, as shown in entry 9 in Table 3 (R = $TBSOCH_2$, *s* = 80). Furthermore, the kinetic resolution of racemic benzyl 4-(*tert*-butyldimethylsiloxy)-2-hydroxybutanoate ((±)-**4j**) with **3** also effectively produced the optically active malic acid derivatives (*R*)-**5j** (96% *ee*) and (*S*)-**4j** (87% *ee*) in 45% and 52% yields, respectively (Table 3, entry 10; R = $TBSO(CH_2)_2$, *s* = 146).

Table 3. Kinetic resolution of racemic benzyl 2-hydroxyalkanoates ((±)-**4a–j**) by the mixed-anhydride method.



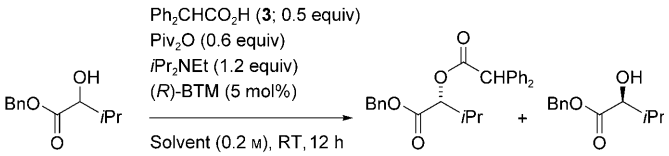
(±)-**4a–j** (*R*)-**5a–j** (*S*)-**4a–j**

Entry	R	Yield of **5** [%][a]	**5**/**5′**[b]	*ee* (**5**) [%]	Yield of **4** [%][a]	*ee* (**4**) [%]	*s*
1	Me (**a**)	44	98/2	97	55	82[c]	146
2	Et (**b**)	46	>99/<1	95	43	94	126
3	*n*Pr (**c**)	50	>99/<1	95	48	97	171
4	*i*Pr (**d**)	46	>99/<1	92	50	73	53
5	*n*Bu (**e**)	47	>99/<1	96	51	88	128
6	*i*Bu (**f**)	45	>99/<1	94	55	97	140
7	*c*Hex (**g**)	43	>99/<1	91	53	75	47
8	$Ph(CH_2)_2$ (**h**)	48	99/1	96	47	95	202
9	$TBSOCH_2$ (**i**)	47	>99/<1	93	50	87	80
10	$TBSO(CH_2)_2$ (**j**)	45	>99/<1	96	52	87	146

[a] Isolated yield. [b] Determined by ^{1}H NMR spectroscopy. [c] **5a** = **2e**, **4a** = **1**.

Several kinds of solvents were next examined in order to reveal the difference of those effects on the reaction of racemic benzyl 2-hydroxy-3-methylbutanoate ((±)-**4d**) with **3** (Table 4). The reactivity of substrate improved when dialkyl ether was used as a reaction medium (Table 4, entries 3–7).[4i] These results showed that not only diethyl ether functions as a good medium, but also other ethers such as diisopropyl ether, methyl *tert*-butyl ether (MTBE), and cyclopentyl methyl ether (CPME) facilitated the desirable selective coupling between alcohol (*R*)-**4d** and carboxylic acid **3** in the presence of (*R*)-BTM. Other solvents such as dichloromethane and toluene were rather less effective (Table 4, entries 1 and 2; *s* = 19 and 22) compared with dialkyl ethers (Table 4, entries 3–6; *s* = > 50),[7] and *N,N*-dimethylformamide (DMF) was ineffective for this reaction because only 10% of the desired ester **5d** was obtained although the enantioselectivity factor was acceptable (Table 4, entry 8; *s* = 28).

Table 4. Kinetic resolution of racemic benzyl 2-hydroxy-3-methylbutanoate ((±)-**4d**) with diphenylacetic acid (**3**).



(±)-**4d** (*R*)-**5d** (*S*)-**4d**

Entry	Solvent	Yield of **5d** [%][a]	**5d**/**5d′**[b]	*ee* (**5d**) [%]	Yield of **4d** [%][a]	*ee* (**4d**) [%]	*s*
1	CH_2Cl_2	32	>99/<1	84	47	49	19
2	toluene	26	>99/<1	84	58	65	22
3	Et_2O	46	>99/<1	92	50	73	53
4	iPr_2O	44	>99/<1	92	54	77	57
5	MTBE[c]	40	>99/<1	93	54	69	52
6	CPME[d]	36	>99/<1	93	58	53	50
7	THF[e]	38	>99/<1	90	61	57	33
8	DMF[f]	10	>99/<1	92	82	22	28

[a] Isolated yield. [b] Determined by ^{1}H NMR spectroscopy. [c] Methyl *tert*-butyl ether. [d] Cyclopentyl methyl ether. [e] Tetrahydrofuran. [f] *N,N*-Dimethylformamide.

The estimated reaction pathway is illustrated in Scheme 1. First, a mixed anhydride (**B**) forms as a key intermediate in situ from pivalic anhydride (**A**) with diphenylacetic acid (**3**) after generation of the zwitterion (**Int-I**) during steps **i** and **ii** by the promotion of the nucleophilic catalyst ((*R*)-BTM). Actually, when pivalic anhydride (**A**) was treated with **3** in the presence of triethylamine with (*R*)-BTM, the facile formation of the mixed anhydride (**B**) was observed on the basis of a ^{1}H NMR experiment. Next, the mixed anhydride (**B**) is activated again by (*R*)-BTM to form the corresponding zwitterionic species (**Int-II**), which then selectively reacts with benzyl (*R*)-2-hydroxyalkanoates ((*R*)-**4a–j**) included in the racemic mixture (±)-**4a–j** to afford the desired carboxylic esters (*R*)-**5a–j** with high enantiomeric excesses through steps **iii** and **iv**. Furthermore, the remaining half of the nucleophiles can be recovered as the unreacted optically active alcohols (*S*)-**4a–j** with high enantiopurities.

Determination of the transition state forming the optically active diester from methyl (*R*)-lactate ((*R*)-**8**) with the electrophile (**Int-II**) was carried out by using 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.[8] We obtained several transition states, and the most stable structure that produces (*S*)- or (*R*)-diester ((*S*)- or (*R*)-**9**) is depicted in Scheme 2.[9,10] It was found that

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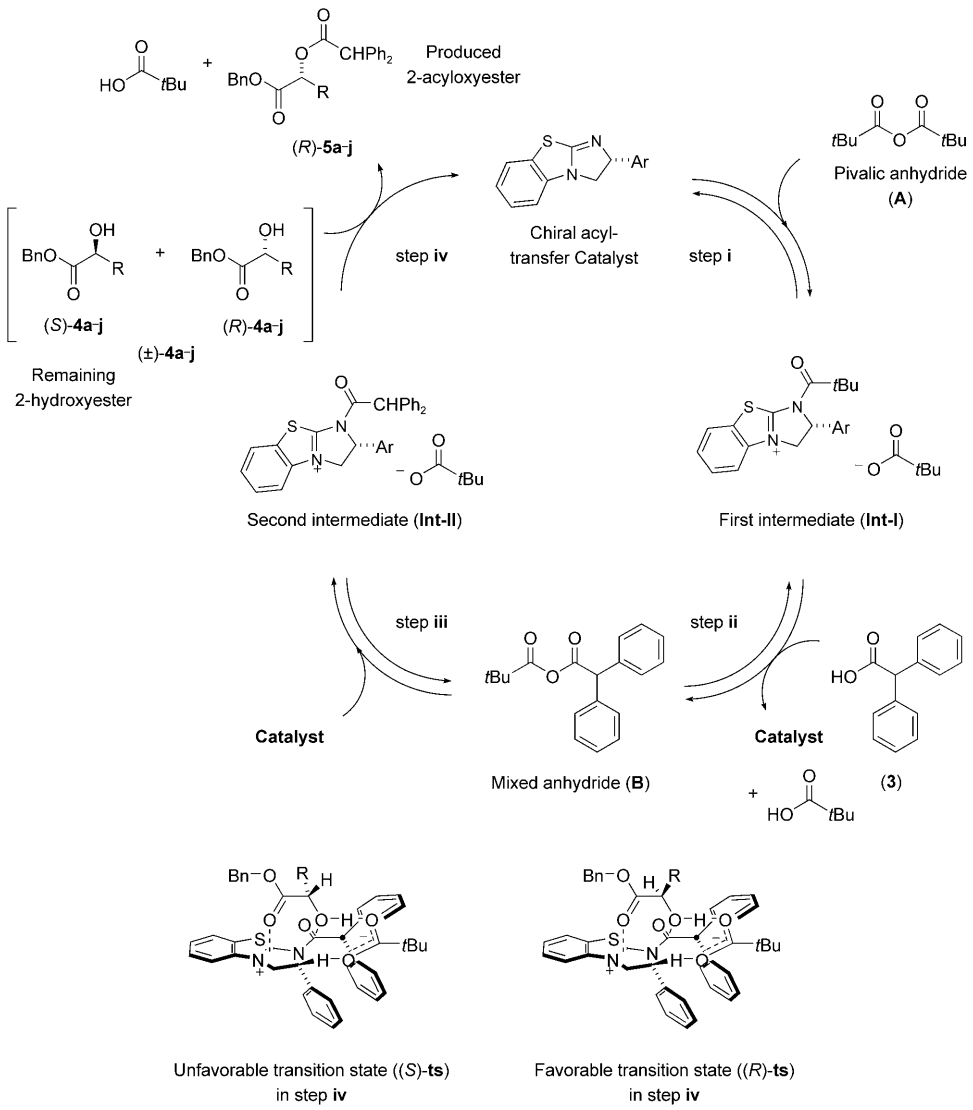

Scheme 1. Reaction pathway to form the optically active 2-acyloxyalkanoates ((*R*)-**5a–j**) and 2-hydroxyalkanoates ((*S*)-**4a–j**).

the high selectivity attained in the present kinetic resolution can be explained by the rapid transformation of (*R*)-**8** into (*R*)-**9** through the stabilized transition state (*R*)-**8-ts**, which consists of (*R*)-**8** and the imidazolium salt (**Int-II**) derived from the mixed anhydride (**B**) and (*R*)-BTM. The distance of the forming C–O bond (between carbonyl carbon of the acid component and oxygen of hydroxy) is 2.172 Å, and the distance of the cleaved O–H bond (between oxygen and hydrogen in hydroxy) is 1.313 Å. A frequency analysis of (*R*)-**8-ts** 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 C–O bond-forming step and the O–H bond-cleaving process occurred simultaneously. The lactate moiety has a rigid structure in which the conformation is restricted by the attractive interaction between oxygen in the ester carbonyl group and the positive electronic charge on the face of the imidazolium salt as well as the coordination of oxygens in the pivalate anion onto hydrogen in hydroxy (1.132 Å) and hydrogen at C-2 of the imidazolium salt (2.103 Å). On the other hand, complexation of the imidazolium salt (**Int-II**) with methyl (*S*)-lactate ((*S*)-**8**), an enantiomer of methyl (*R*)-lactate ((*R*)-**8**), produced an unstable structure, (*S*)-**8-ts**,[11] that has a higher energy derived from steric repulsion between the alkyl substituent at the 2-position of (*S*)-**8** and one of the phenyl groups of diphenylacetic acid moiety of the imidazolium salt to afford the corresponding ester (*S*)-**9**. Therefore, the desired (*R*)-diester was selectively obtained by the rapid transformation of (*R*)-**8** into (*R*)-**9** through the transition state (*R*)-**8-ts**.

Based on the above theoretical studies of the reaction mechanism, it was revealed that the aromatic part of the benzyl ester group in 2-hydroxyalkanoates **4a–j** is not required to achieve high selectivity. Actually, the use of the racemic ethyl 2-hydroxypentanoate ((±)-**6**) as an acyl-donor instead of benzyl 2-hydroxyalkanoates for the present kinetic resolution under the standard reaction conditions also afforded the optically active diester (*R*)-**7** with a high enantiomeric excess (97% *ee*), whereas the unreacted ethyl 2-hydroxypentanoate ((*S*)-**6**) was additionally recovered with a high optical purity (89% *ee*); this gave excellent selectivity ($s=217$) as shown in Scheme 3. According to the above theoretical predictions, the reaction of racemic methyl lactate ((±)-**8**) with diphenylacetic acid (**3**) successfully proceeded to provide the desired optically active 2-acyloxyester (*R*)-**9** and the recovered 2-hydroxyester (*S*)-**8** with a high selectivity factor ($s=119$).

Conclusions

In summary, we have developed the first practical method to provide the optically active 2-hydroxy- and 2-acyloxyalkanoates by the nonenzymatic kinetic resolution of the racemic 2-hydroxyalkanoates by using diphenylacetic acid (**3**), pivalic anhydride, and the chiral acyl-transfer catalyst. This

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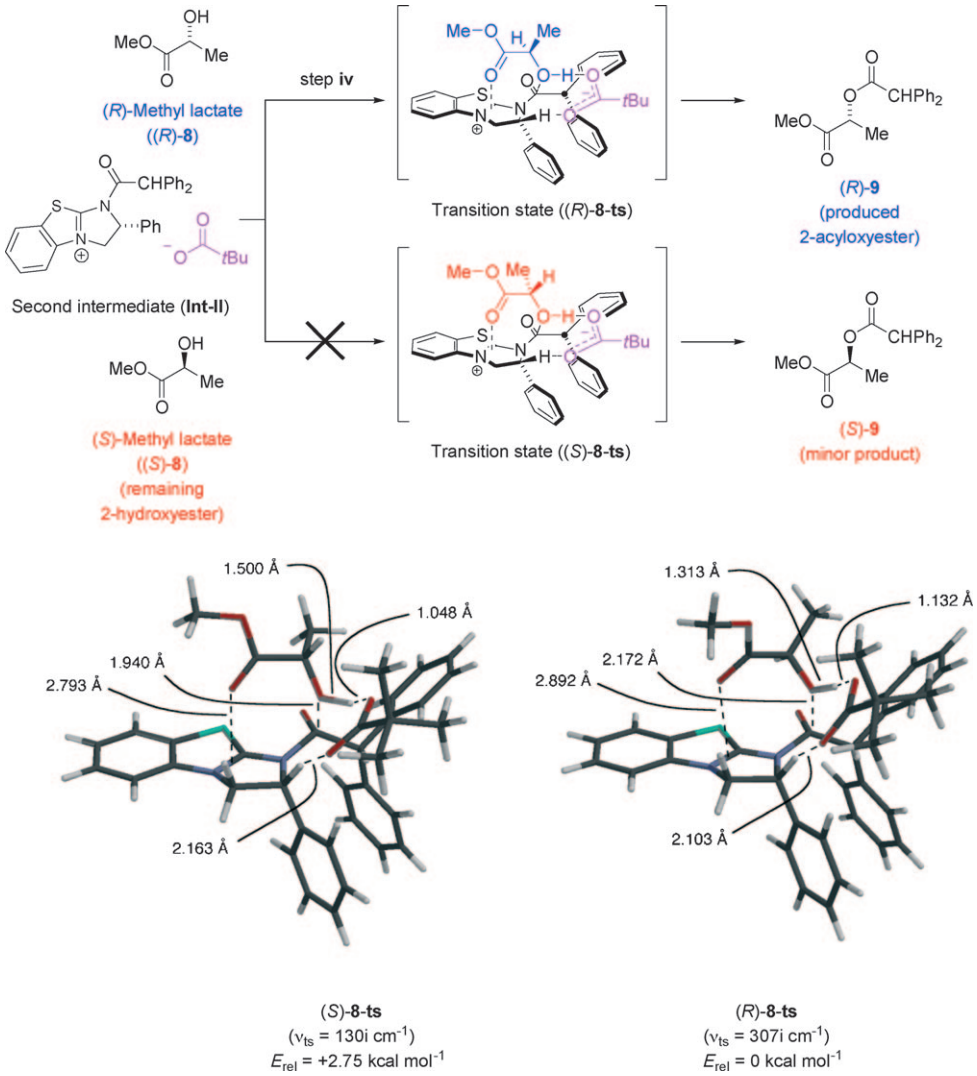
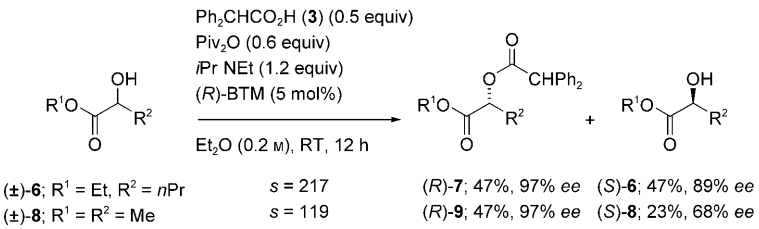


Scheme 2. Calculated transition states to form methyl 2-(diphenylacetoxy)propanoate (**9**) from methyl lactate (**8**).



Scheme 3. Kinetic resolution of racemic ethyl 2-hydroxypentanoate ((±)-**6**) and methyl lactate ((±)-**8**) by the enantioselective mixed-anhydride method.

protocol affords optically active compounds directly from racemic 2-hydroxyalkanoates that do not contain the *sec*-phenethyl alcohol moiety, through transacylation of the mixed anhydrides generated from **3** with bulky carboxylic anhydrides under the influence of (*R*)-BTM. One of the features of the present protocol is that it provides a very simple procedure for producing the desired chiral ester derivatives. That is, the addition of promoters to the mixture of racemic 2-hydroxyalkanoates, free acid **3**, and pivalic anhydride at room temperature affords both optically active 2-acyloxyalkanoates and 2-hydroxyalkanoates in good yields with high enantiopurities. 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.

Experimental Section

General methods, detailed experimental procedures, spectroscopic data of all compounds, and Cartesian coordinates and absolute energies for all calculated structures have been provided in the Supporting Information.

Typical procedure for the synthesis of the optically active 2-acyloxyalkanoates from the racemic 2-hydroxyalkanoates with diphenylacetic acid (3) by using pivalic anhydride and (*R*)-BTM: Diisopropylethylamine (46.4 μL, 0.266 mmol), (*R*)-BTM (2.8 mg, 0.0111 mmol) and a solution of racemic benzyl 4-(*tert*-butyldimethylsiloxy)-2-hydroxybutanoate ((±)-**4j**; 72.1 mg, 0.222 mmol) in diethyl ether (0.5 mL) were successively added to a solution of pivalic anhydride (27.0 μL, 0.133 mmol) and diphenylacetic acid (**3**; 23.6 mg, 0.111 mmol) in diethyl ether (0.6 mL) at room temperature. The mixture was stirred for 12 h at room temperature and then quenched with saturated aqueous $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4. After filtration of the mixture and evaporation of the solvent, the crude product was purified by preparative thin layer chromatography on silica (hexane/ethyl acetate 5:1) to afford the corresponding diester (*R*)-**5j** (51.7 mg, 45%, 96% *ee*) and the recovered optically active hydroxyester (*S*)-**4j** (37.2 mg, 52%, 87% *ee*) as colorless oils [Table 3, entry 10, $s = 146$].

Acknowledgements

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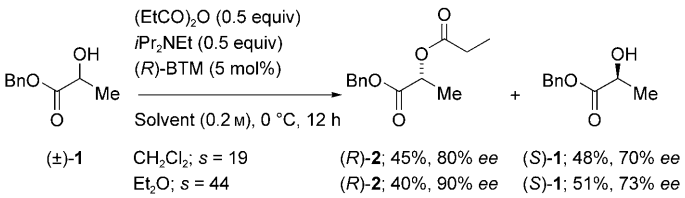
[6] The *s* values were determined according to the literature method:[2b,4c] $s=\ln[(1-C_{HPLC})(1-ee_A)]/\ln[(1-C_{HPLC})(1+ee_A)]$. The conversion C_{HPLC} used in the above equation was calculated as $C_{HPLC}=ee_A/(ee_E+ee_A)$, in which ee_E is the enantiomeric excess of 2-acyloxyalkanoate and ee_A is the enantiomeric excess of the unreacted 2-hydroxyalkanoate. The conversion values thus obtained were generally within 1–2% of the values obtained by ^{1}H NMR integration of the crude reaction mixture.

[7] A similar solvent effect was observed in the present study for the reaction of racemic benzyl lactate ((±)-**1**) with propionic anhydride as shown below.



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[10] Cartesian coordinates and absolute energies for all reported structures are included in the Supporting Information.

[11] Another transition state (*S*)-**8**-**ts**-**2** to afford (*S*)-**9** was determined. This structure has earlier transition form compared with (*S*)-**8**-**ts** and the energy is higher than that of (*S*)-**8**-**ts** ($E_{rel((S)\text{-}8\text{-}ts)}=2.75$ kcal mol^{-1}, $E_{rel((S)\text{-}8\text{-}ts\text{-}2)}=7.66$ kcal mol^{-1}). Cartesian coordinates of the second stable transition state (*S*)-**8**-**ts**-**2** to afford (*S*)-**9** are described in the Supporting Information.

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