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Kinetic resolution of racemic α-hydroxyphosphonates by asymmetric esterification using achiral carboxylic acids with pivalic anhydride and a chiral acyl-transfer catalyst†

Isamu Shiina,* Keisuke Ono and Takayoshi Nakahara

A practical protocol is developed to directly provide chiral α-acyloxyphosphonates and α-hydroxyphosphonates from (±)-α-hydroxyphosphonates utilizing the transacylation process to generate the mixed anhydrides from acid components and pivalic anhydride in the presence of organocatalysts (*s*-value = 33–518).

Chiral α-hydroxyphosphonates and α-amino phosphonates have attracted considerable attention because of their potential biological activities, including their antitumor and enzyme inhibitory effects.[1] In addition, it has been shown that several peptide analogues, such as α-hydroxyphosphonate moieties, function as HIV protease inhibitors.[1g–j] Therefore, enzymatic methods for the preparation of chiral α-hydroxyphosphonates by the kinetic resolution (KR) of racemic α-hydroxyphosphonates have been developed.[2] Recently, Onomura reported the KR of racemic α-hydroxyphosphonates using an organometallic species;[3] however, to the best of our knowledge, organocatalytic methods for the KR of racemic α-hydroxyphosphonates have not been described to date. Thus, we planned to develop an effective route for the preparation of various chiral α-hydroxyphosphonates *via* the KR of racemic α-hydroxyphosphonates using an organocatalyst.

In 2007, we reported the first asymmetric esterification[4a] of free carboxylic acids with racemic secondary benzylic alcohols in the presence of carboxylic anhydrides as coupling reagents and optically active acyl-transfer catalysts, such as (*S*)-tetramisole and (*R*)-benzotetramisole ((*R*)-BTM), which were popularized by Birman *et al.*[5] Originally, Birman and coworkers employed propanoic anhydride or isobutyric anhydride as an acyl donor for the enantioselective acylation of racemic secondary alcohols, and several other groups have subsequently explored the use of symmetric anhydrides for the KR of racemic compounds with additional variations of the acyl-transfer catalysts.[6] We also achieved the KR of racemic 2-hyroxyalkanoates[4b] and 2-hydroxylactones[4c] using the mixed anhydride (MA) method and successfully determined the preferable transition structures required to form the desired chiral (*R*)-esters starting from diphenylacetic acid with secondary (*R*)-alcohols using density functional theory (DFT) calculations.[4b] It was revealed that the conformation of the transition structure (**ts**-(*R*)) to form methyl (*R*)-2-(diphenylacetoxy)propanoate starting from methyl (*R*)-lactate *via* the intermediary dihydroimidazolium salt **I** as shown in Fig. 1 is strongly restricted by an attractive interaction between the oxygen in the ester carbonyl group and the positive electronic charge on the face of intermediate **I** during the bond-forming step.[4b,c,7] On the basis of analysis of these calculated structures, we expected that (i) an attractive interaction between the oxygen in the phosphorus–oxygen double bond of phosphonic acid derivatives and intermediate **I** should be observed during asymmetric esterification and (ii) this strategy could be applied to the KR of racemic α-hydroxyphosphonates similar to that of racemic α-hydroxycarboxylates.

Herein, we report a novel and practical KR of racemic α-hydroxyphosphonates using free carboxylic acids. The reaction proceeds with the promotion of pivalic anhydride using a chiral acyl-transfer catalyst and is an application of our MA formation technology for enantioselective esterification.

First, we examined the KR of racemic dimethyl 1-hydroxy-3-phenylpropylphosphonate ((±)-**1**) using diphenylacetic acid in

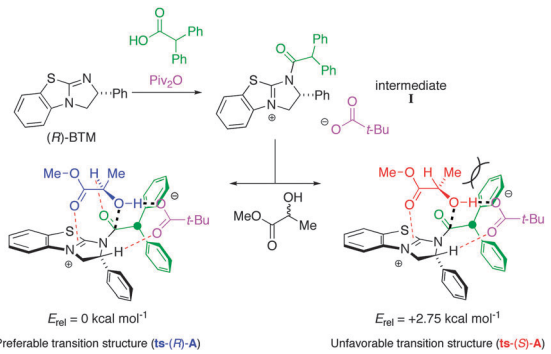

Fig. 1 Calculated transition structures (**ts**-(*R*) and **ts**-(*S*)) required to form the corresponding esters, starting from methyl (*R*)-lactate and methyl (*S*)-lactate with the ion pair intermediate **I**.

Department of Applied Chemisty, Faculty of Science, Tokyo University of Science, 1-3 Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan.
E-mail: shiina@rs.kagu.tus.ac.jp; Fax: +81 3 3260 5609; Tel: +81 3 3260 4271

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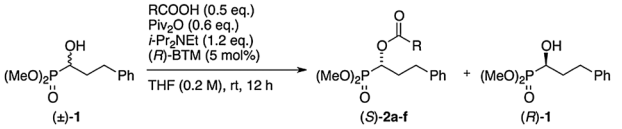
the presence of pivalic anhydride and (*R*)-BTM in diethyl ether at room temperature for 12 h, which were former optimized conditions for 2-hydroxyalkanoates.[4b] The reaction proceeded smoothly to afford the corresponding chiral diphenylacetate ((*S*)-**2a**; 46% yield, 98% ee) and the recovered alcohol ((*R*)-**1**; 52% yield, 88% ee, *s* = 266). Fortunately, the desired chiral ester (*S*)-**2a** was also obtained with an extremely high enantiopurity and *s*-value[8] when THF was used as the solvent (46% yield, 99% ee, *s* = 419).

Next, we investigated the scope of the reaction in THF with respect to the carboxylic acid (Table 1). The use of acetic acid afforded the corresponding acetate (*S*)-**2b** in good yield and selectivity (entry 1; 45% yield, 95% ee, *s* = 88). The KR using propanoic acid, 3-phenylpropanoic acid, isobutyric acid, and cyclohexanecarboxylic acid (entries 2–5) yielded (*S*)-**2c**–**2f**, respectively, also with good selectivities (*s* = 110, 96, 286, and 96, respectively). Diphenylacetic acid was found to be the preferred carboxylic acid for the enantioselective esterification of (±)-**1** to provide the corresponding chiral α-acyloxyphosphonate and α-hydroxyphosphonate (entry 6; *s* = 419).

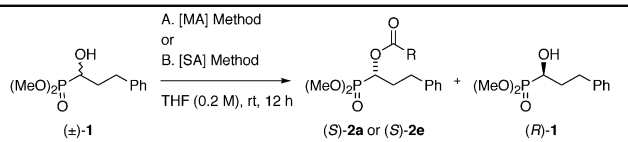
We have demonstrated additional experiments using symmetric anhydrides (SAs) for drawing a comparison between the MA method and the SA method (Table 2). In entries 1 and 2, the average *s*-values (for two runs) of the KR of (±)-**1** using diphenylacetic acid and isobutyric acid are presented (s_{av} = 427 and 246, respectively).[9] On the other hand, we carried out the KR of (±)-**1** using diphenylacetic anhydride (DPHAA)[10] or isobutyric anhydride,[5] and the average *s*-values are also shown in entries 3 and 4 (s_{av} = 362 and 122, respectively).[9] Based on these results, it was revealed that the MA method using diphenylacetic acid with pivalic anhydride is the most suitable protocol to provide the desired chiral (*S*)-ester and the recovered chiral (*R*)-alcohol with high enantioselectivities.

Table 1 Kinetic resolution of racemic 1-hydroxy-3-phenylpropylphosphonate ((±)-**1**) with a variety of carboxylic acids



Entry	R	Ester yield/% (ee/%)	Alcohol yield/% (ee/%)	*s*
1	Me (**b**)	45 (95)	55 (78)	88
2	Et (**c**)	49 (95)	51 (89)	110
3	$Ph(CH_2)_2$ (**d**)	48 (94)	50 (90)	96
4	i-Pr (**e**)	48 (98)	51 (87)	286
5	*c*-Hex (**f**)	46 (95)	54 (84)	96
6	Ph_2CH (**a**)	46 (99)	53 (89)	419

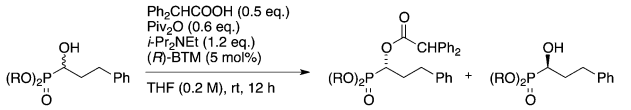
Table 2 Kinetic resolution of (±)-**1** using a mixed anhydride (MA) method and a symmetric anhydride (SA) method



Conditions A. [MA]; RCOOH (0.5 eq.), Piv_2O (0.6 eq.), *i*-Pr_2NEt (1.2 eq.), (*R*)-BTM (5 mol%)
Conditions B. [SA]; $(RCO)_2O$ (0.5 eq.), *i*-Pr_2NEt (0.6 eq.), (*R*)-BTM (5 mol%)

Entry	Conditions	R	Ester $yield_{av}$/% (ee_{av}/%)	Alcohol $yield_{av}$/% (ee_{av}/%)	s_{av}
1	A [MA]	Ph_2CH (**a**)	46 (99)	54 (86)	427
2	A [MA]	i-Pr (**e**)	46 (98)	54 (80)	246
3	B [SA]	Ph_2CH (**a**)	44 (99)	55 (78)	362
4	B [SA]	i-Pr (**e**)	40 (97)	59 (70)	122

Table 3 Kinetic resolution of racemic 1-hydroxy-3-phenylpropylphosphonates (±)-**1**, **3**, and **5**

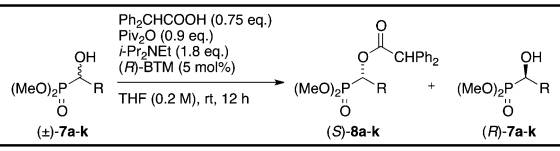


Entry	R	Ester yield/% (ee/%)	Alcohol yield/% (ee/%)	*s*
1	Me (**1**)	46 (99)	53 (89)	419
2	Et (**3**)	46 (98)	52 (87)	337
3	Ph (**5**)	47 (94)	50 (93)	106

We further examined the effect of changing the substituents in the phosphonate moiety of the 1-hydroxy-3-phenylpropylphosphonates reacting with diphenylacetic acid (Table 3). The asymmetric esterification of diethyl 1-hydroxy-3-phenylpropylphosphonate ((±)-**3**) rapidly occurred to afford the corresponding diphenylacetic acid ester (*S*)-**4** (entry 2; R = Et, 46% yield, 98% ee) and the recovered alcohol (*R*)-**3** (52% yield, 87% ee) with an excellent *s*-value (*s* = 337). The reaction of diphenyl 1-hydroxy-3-phenylpropylphosphonate ((±)-**5**) provided nearly the same yield of the ester (*S*)-**6** but with slightly lower enantiomeric excess (entry 3; R = Ph, 47% yield, 94% ee, *s* = 106).

Finally, the esterification of various racemic dimethyl 1-hydroxyphosphonates was examined to assess the generality of this method. The reactions were performed using 0.75 equivalents of diphenylacetic acid to obtain the recovered alcohols (*R*)-**7a**–**k** with higher enantiopurity (Table 4). In entry 1, racemic dimethyl 1-hydroxypropylphosphonate ((±)-**7a**; R = Et) was successfully resolved to the corresponding ester (*S*)-**8a** (51% yield) and the recovered alcohol (*R*)-**7a** (41% yield) with extremely high enantiomeric excesses (95% ee for (*S*)-**8a**, >99% ee for (*R*)-**7a**). When the reaction was carried out using racemic dimethyl 1-hydroxyalkylphosphonates bearing linear alkyl substituents R next to the phosphonate group such as (±)-**7b**, **7c**, **7g**, **7i**, and **7k**, the recovered alcohols (*R*)-**7b**, **7c**, **7g**, **7i**, and **7k** were obtained in good yields with high enantiomeric excesses (entries 2, 3, 9, 12, and 15; 43–49% yield, >99% ee for all cases). Using 3-phenylpropanoic acid as a less bulky acyl donor instead of diphenylacetic acid was very effective for the asymmetric esterification of the hindered alcohols such as (±)-**7d** (entry 5; R = i-Pr, 51% yield, 91% ee, *s* = 74) and (±)-**7f** (entry 8; R = *t*-Bu, 46% yield, 89% ee, *s* = 43). Next, the reaction of the substrate (±)-**7h** (R = $TBDPSOCH_2$) with a β-silyloxy functional group was investigated, and a fairly good result was obtained when using 0.5 equivalents of diphenylacetic acid (entry 11; *s* = 463). Although the reaction of the β-amino-functionalized substrate (±)-**7j** (R = $BocNHCH_2$) with 0.75 equivalents of diphenylacetic acid gave the desired α-acyloxyphosphonates (*S*)-**8j** in over 50% yield but with unsatisfactory selectivity (entry 13; 55% yield, 73% ee), as with (±)-**7h**, the use of 0.5 equivalents of diphenylacetic acid improved the enantiopurity of the product (*S*)-**8j** (entry 14; 50% yield, 85% ee). We further found that the KR of

Table 4 Kinetic resolution of various dimethyl 1-hydroxyphosphonates (±)-**7a–k**



Entry	R	Ester yield/% (ee/%)	Alcohol yield/% (ee/%)	*s*
1	Et (**7a**)	51 (95)	41 (>99)	225
2[a]	$Ph(CH_2)_2$ (**7b**)	48 (98)	49 (>99)	518
3	*n*-Pr (**7c**)	53 (94)	43 (>99)	204
4	i-Pr (**7d**)	27 (95)	67 (28)	51
5[b]	i-Pr	51 (91)	47 (93)	74
6	*c*-Hex (**7e**)	43 (98)	52 (76)	191
7	*t*-Bu (**7f**)	4 (96)	96 (3)	53
8[b]	*t*-Bu	46 (89)	47 (83)	43
9	Bn (**7g**)	49 (95)	46 (>99)	243
10	$TBDPSOCH_2$ (**7h**)	50 (91)	48 (99)	112
11[c]	$TBDPSOCH_2$	46 (99)	54 (89)	463
12	$BnO(CH_2)_2$ (**7i**)	52 (94)	48 (>99)	203
13	$BocNHCH_2$ (**7j**)	55 (73)	43 (99)	30
14[c]	$BocNHCH_2$	50 (85)	47 (87)	33
15	$CbzNH(CH_2)_2$ (**7k**)	53 (87)	46 (>99)	84

[a] **7b** = **1**, **8b** = **2a**. [b] Reaction conditions: 0.75 eq. of $Ph(CH_2)_2COOH$ was used instead of $Ph_2CHCOOH$, and the corresponding 3-phenylpropanoates (**9d** and **9f**) were obtained instead of diphenylacetates (**8d** and **8f**). [c] Reaction conditions: 0.5 eq. of $Ph_2CHCOOH$, 0.6 eq. of Piv_2O, 1.2 eq. of i-Pr_2NEt.

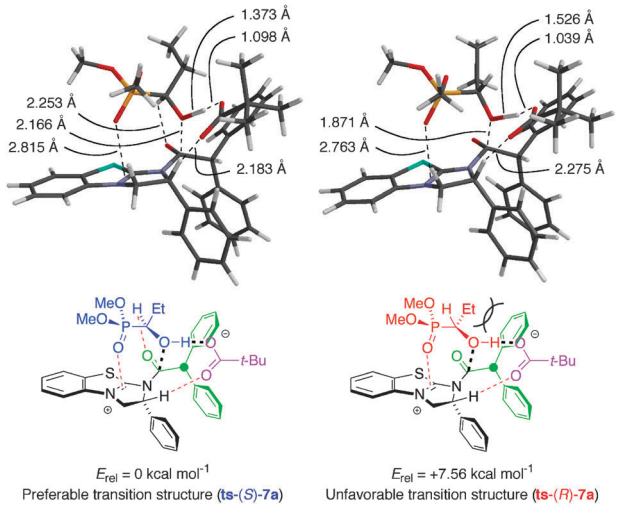


Fig. 2 Calculated transition structures (**ts**-(*S*)-**7a** and **ts**-(*R*)-**7a**) derived from intermediate **I** and (*S*)-**7a** or (*R*)-**7a**.

the γ-amino-functionalized substrate (±)-**7k** (R = $CbzNH(CH_2)_2$) with 0.75 equivalents of diphenylacetic acid afforded the desired α-acyloxyphosphonate (*S*)-**8k** with good enantiomeric excess (entry 15; 53% yield, 87% ee) along with the recovered enantiomerically pure alcohol (*R*)-**7k** (46% yield, >99% ee).

Determination of the transition states involved in the formation of the chiral (*S*)-ester from dimethyl (*S*)-1-hydroxypropylphosphonate ((*S*)-**7a**) with intermediate **I** was carried out using DFT calculations at the B3LYP/6-31G*//B3LYP/6-31G* level of theory, as previously reported for the KR of 2-hydroxyalkanoates.[4b] Among the several calculated transition states, the most stable structure (**ts**-(*S*)-**7a**) is depicted in Fig. 2. The theoretical calculations clearly show that **ts**-(*R*)-**7a** (for formation of the (*R*)-ester) has a higher energy compared with that of **ts**-(*S*)-**7a** (for formation of the (*S*)-ester); therefore, the desired (*S*)-ester was selectively obtained by the rapid transformation through the transition state **ts**-(*S*)-**7a**.

In summary, we have developed an efficient method for preparing chiral α-hydroxyphosphonates in good yields with high selectivities by the kinetic resolution of the racemic substrates in the presence of diphenylacetic acid, pivalic anhydride, and (*R*)-BTM.

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