AN EFFECTIVE KINETIC RESOLUTION OF RACEMIC SECONDARY BENZYLIC ALCOHOLS USING 3-PYRIDINECARBOXYLIC ANHYDRIDE AND A CHIRAL ACYL-TRANSFER CATALYST IN THE ABSENCE OF TERTIARY AMINE

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Abstract – 3-Pyridinecarboxylic anhydride (3-PCA) was found to function as an efficient coupling reagent for the kinetic resolution of racemic secondary benzylic alcohols with achiral carboxylic acids in the presence of a catalytic amount of (+)-BTM. A variety of optically active carboxylic esters are produced with high enantiomeric excesses by this new chiral induction system without using a tertiary amine.

We have recently reported the first asymmetric esterification of racemic secondary benzylic alcohols with free carboxylic acids using an aromatic anhydride[1] or bulky aliphatic carboxylic anhydride[2] as a coupling reagent by the novel mixed-anhydride formation technology (**Scheme 1**). The chiral induction was realized using the optically active acyl-transfer catalysts, such as (–)-tetramisole and (+)-benzotetramisole ((+)-BTM), which were introduced by Birman et al.[3] By only mixing racemic alcohols and achiral carboxylic acids with (+)-BTM in the presence of benzoic anhydride, 4-methoxybenzoic anhydride (PMBA), or pivalic anhydride at room temperature, the corresponding chiral carboxylic esters and the unreacted chiral alcohols were afforded in high enantiomeric excesses.

We have also achieved the kinetic resolution of racemic 2-arylpropionic acid derivatives with achiral alcohols using PMBA in the presence of (+)- and (–)-BTM or (–)-β-Np-BTM in a similar manner (**Scheme 2**).[4,5] This protocol directly provides chiral carboxylic esters from racemic carboxylic acids and achiral alcohols by utilizing the transacylation process to generate the mixed-anhydrides from the
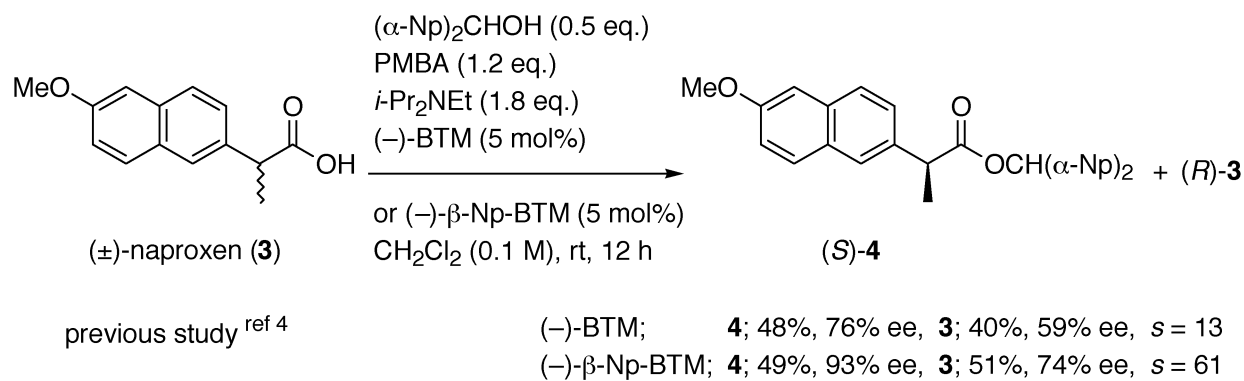

The authors dedicate this paper to Professor Akira Suzuki on the celebration of his 80th birthday.

acid components and the suitable aromatic carboxylic anhydrides.
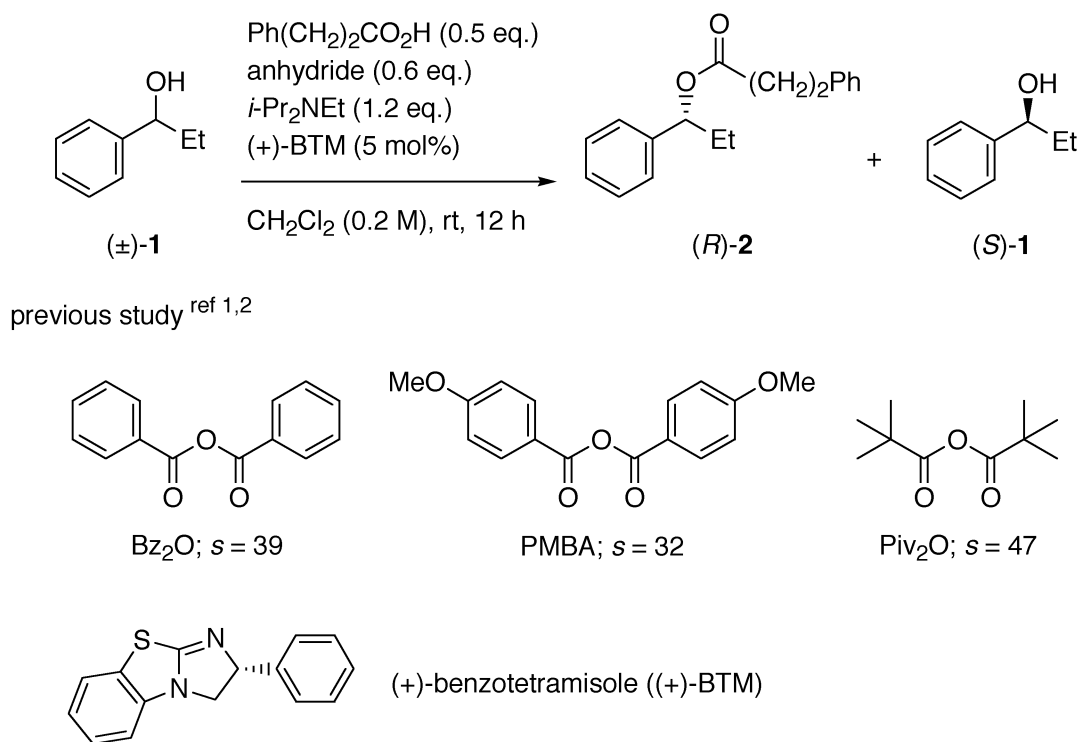
**Scheme 1.** Kinetic Resolution of (±)-1 Using Bz$_2$O, PMBA, and Piv$_2$O (Our Previous Study)

Scheme 2. Kinetic Resolution of (±)-Naproxen (Our Previous Study)

Recently, Mukaiyama et al. reported 3-pyridinecarboxylic anhydride (3-PCA) promoted the coupling reaction between various carboxylic acids and alcohols to form the corresponding carboxylic esters in high yields without using any base.[6] The nicotinic acid residue in 3-PCA functions as a strong electron

withdrawing group, so that the successive acyl-transfer reaction giving the mixed-anhydride and the desired carboxylic esters might be successfully performed in the absence of tertiary amines during the above transformation. In the present study, we further applied this useful reagent for the asymmetric synthesis of chiral carboxylic esters by the enantioselective mixed-anhydride method for the kinetic resolution of racemic secondary benzylic alcohols with achiral carboxylic acids.

First, we tried to optimize the temperature for the kinetic resolution of the racemic 1-phenyl-1-propanol ((±)-**1**) with 3-phenylpropionic acid in the presence of 3-PCA and (+)-BTM (**Table 1**). When the reaction was carried out at room temperature, the esterification smoothly proceeded and the corresponding chiral carboxylic ester (R)-**2** was obtained in good yield (44%) with a high selectivity (90% ee). Nearly half the amount of the unreacted alcohol (S)-**1** (46%) was also recovered in good optical purity (80% ee) showing a very good selectivity factor (s-value)[7] as shown in Entry 1 (s = 47). It is worth remarking that the reaction could be carried out at 0 °C to afford the optically active carboxylic ester and alcohol in good yields with the highest selectivities (s = 63, Entry 2). On the other hand, even lower temperatures were not effective for this kinetic resolution and both the reactivity and the ee's of the products diminished with the decreasing temperature (Entries 3 and 4). The use of a tertiary amine in this reaction is not necessary to obtain good chemical yields of the products, but it works as an inhibitor for providing the chiral carboxylic esters and alcohols in high ee's. For example, the addition of 1.1 equivalents of diisopropylethylamine to the above model reaction under the optimized conditions afforded the lowest selectivity factor (s = 2, Entry 5).

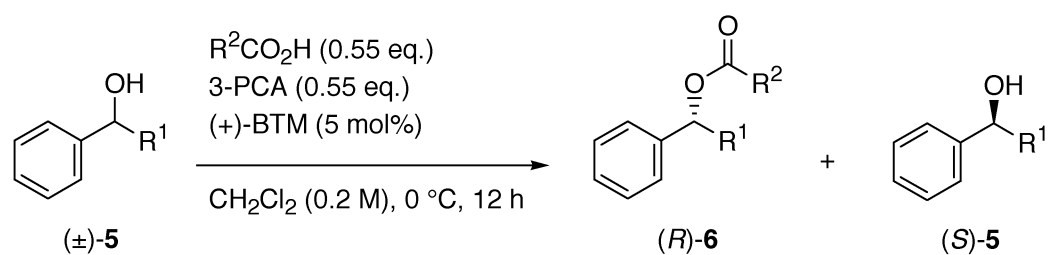**Table 1.** Temperature Effect for the Kinetic Resolution of (±)-**1**
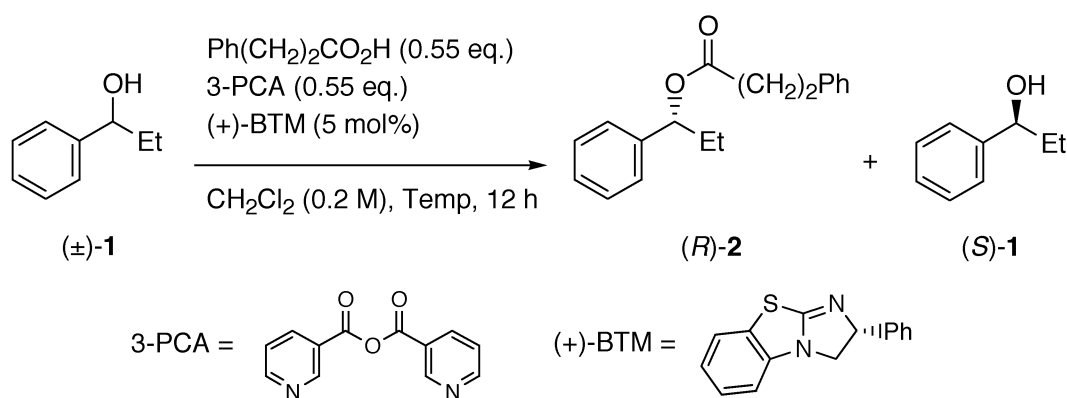
Entry	Temp [°C]	Yield (**2** ; **1**) [%]	ee (**2** ; **1**) [%]	s
1	rt	44 ; 46	90 ; 80	47
2	0	44 ; 45	93 ; 79	63
3	−23	35 ; 53	90 ; 56	35
4	−45	28 ; 61	80 ; 40	12
5 [a]	0	38 ; 54	18 ; 11	2

[a] The reaction was carried out in the presence of 1.1 eq. of i-Pr$_2$NEt (cf. Entry 2).

We then applied a variety of carboxylic acids for the kinetic resolution of the racemic benzylic alcohols possessing aliphatic substituents at the C-1 position (($\pm$)-**5**) to extend the utility of this facile method for the asymmetric synthesis. As listed in **Table 2**, all reactions effectively took place and a variety of the corresponding (*R*)-carboxylic esters **6** and the unreacted (*S*)-alcohols **5** were obtained with high *s*-values (*s* = 22–94) irrespective of the substituents (R^1 = Me, Et, *i*-Pr, and *t*-Bu) at the C-1 position in alcohols (($\pm$)-**5**). It was found that both propionic and 3-phenylpropionic acids were usable for all the resolutions of the secondary benzylic alcohols (Entries 1–4, 10–13). Several other aliphatic carboxylic acids were further examined for the asymmetric esterification with 1-phenyl-1-propanol (R^1 = Et) and excellent *s*-values (*s* = 22–50) were observed as shown in Entries 5–9, therefore, the wide-substrate generality of the present advanced kinetic resolution using 3-PCA was successfully demonstrated. It is also noteworthy that the asymmetric esterification of almost all the substrates employed in **Table 2** produced satisfactory *s*-values that were superior to the preceding results which have been attained using an aromatic anhydride[1] or bulky aliphatic anhydride[2] (See: Entries 1–6, 10, and 13).

Table 2. Kinetic Resolution of ($\pm$)-**5** with Various Carboxylic Acids

| Entry	R^1	R^2	Yield (**6** ; **5**) [%]	ee (**6** ; **5**) [%]	*s*	(s[a]	s[b]	s[c])
1	Me	Et	35 ; 41	91 ; 63	42	(–	–	26)
2	Me	$Ph(CH_2)_2$	41 ; 42	91 ; 71	45	(–	–	33)
3	Et	Et	40 ; 55	93 ; 64	56	(38	39	43)
4	Et	$Ph(CH_2)_2$	44 ; 45	93 ; 79	63	(46	43	47)
5	Et	$Ph(CH_2)_3$	44 ; 51	93 ; 57	49	(31	39	41)
6	Et	$Me_2CH(CH_2)_2$	43 ; 50	92 ; 70	50	(22	23	40)
7	Et	$CH_2=CHCH_2CH_2$	43 ; 54	91 ; 55	38	(28	42	39)
8	Et	$MeOCH_2$	45 ; 50	82 ; 70	22	(14	15	26)
9	Et	$c\text{-}C_6H_{11}$	36 ; 59	93 ; 59	50	(8	12	73)
10	*i*-Pr	Et	40 ; 53	95 ; 69	84	(34	47	53)
11	*i*-Pr	$Ph(CH_2)_2$	45 ; 55	91 ; 73	49	(33	46	1580)
12	*t*-Bu	Et	22 ; 78	93 ; 25	36	(20	42	101)
13	*t*-Bu	$Ph(CH_2)_2$	37 ; 63	96 ; 55	94	(22	88	81)

[a] The number in parentheses shows the *s*-value when using Bz_2O at rt (ref 1).

[b] The number in parentheses shows the *s*-value when using PMBA at rt (ref 1).

[c] The number in parentheses shows the *s*-value when using Piv_2O at rt (ref 2).

Usually, it is necessary to employ tertiary amines, such as triethylamine and diisopropylethylamine, for the rapid formation of the mixed-anhydride (MA) derived from the carboxylic anhydrides and carboxylic acids, and for the completed production of the desired carboxylic esters from the intermediary MA with alcohols via transacylation in the effective ester-synthesis. However, the kinetic resolution of the racemic alcohols with achiral carboxylic acids using 3-PCA and (+)-BTM does not require the existence of the tertiary amines.

The assumed reaction pathway is illustrated in **Scheme 3**. First, 3-PCA was activated by (+)-BTM to react with carboxylic acids (R^1CO_2H) and then the corresponding MA was gradually produced during the reaction. The formed MA has a 3-pyridyloyloxy moiety which has a strong negative electronic charge on the aromatic ring, so that nitrogen in the pyridine ring coordinates with the protic parts of the starting aliphatic carboxylic acids or nicotinic acid generated from 3-PCA in situ. The successive nucleophilic substitution of the 3-pyridyloyloxy moiety with (+)-BTM followed by the exchange with the chiral (*R*)-type alcohol in the racemic mixture afforded the desired (*R*)-carboxylic esters and the recovery of the unreacted (*S*)-type alcohol with high enantioselectivities. It is postulated that the higher activity of the MA in this new reaction system provided the favorable transacylation process for the synthesis of the desired chiral compounds without using tertiary amines.
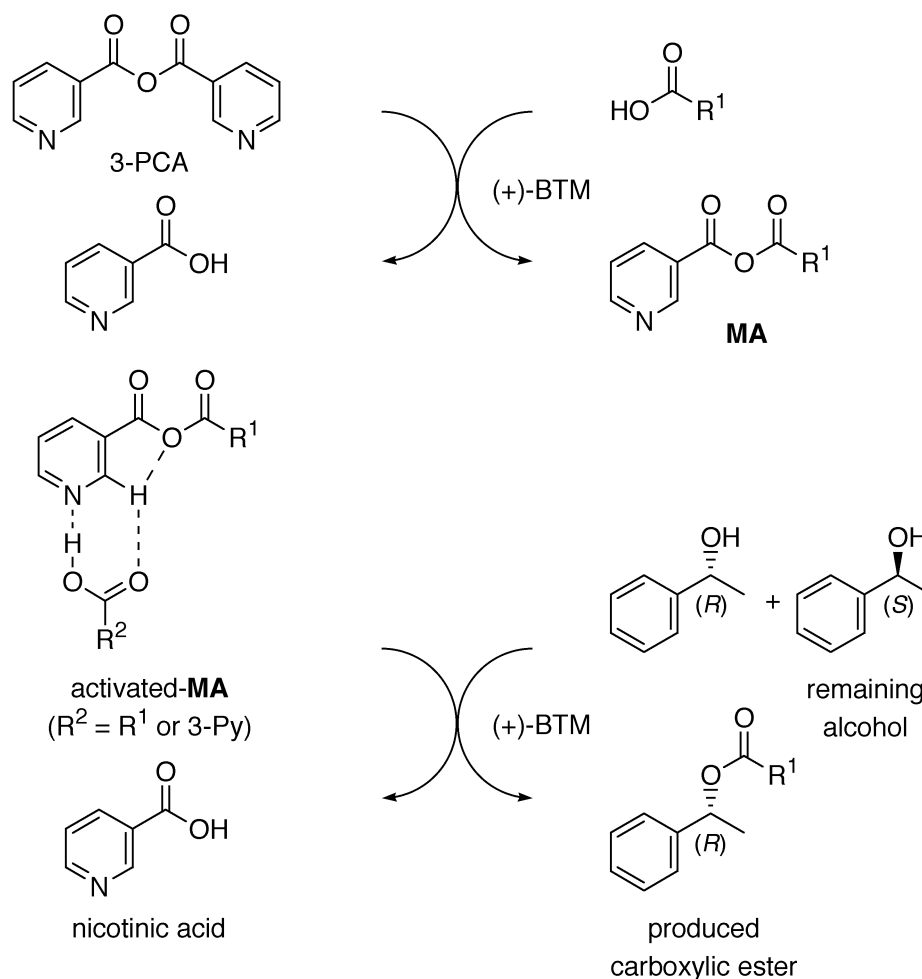
Scheme 3. Proposed Reaction Pathway of the Kinetic Resolution

The stable structures of MA (**A**) generated from nicotinic acid and acetic acid, and the activated MA (**B** or **C**) with acetic acid or nicotinic acid were determined by the theoretical calculation at the B3LYP/6-31G*//B3LYP/6-31G* level after searching all conformations of the molecules as depicted in **Figure 1**.[8] It is found that the LUMO energy of MA (**A**) (–1.95 eV) was significantly lowered by the coordination of nitrogen in the pyridine ring onto the protic source of free carboxylic acids to give the strongly activated species **B** (LUMO energy = –2.14 eV) and **C** (LUMO energy = –2.24 eV). These results explain that the activation of MA (**B**) and MA (**C**) with (+)-BTM easily occurs in the absence of any base, such as tertiary amines, to afford the desired chiral carboxylic esters through the facile acyl-transfer reaction under the relatively lower temperature. We have already observed that tertiary amines can promote the reaction of carboxylic anhydrides with alcohols via another reaction pathway to produce the racemic materials; therefore, the present 3-PCA-mediated asymmetric esterification without using any base is ultimately preferable to afford the desirable chiral carboxylic esters and secondary benzylic alcohols in high ee's.
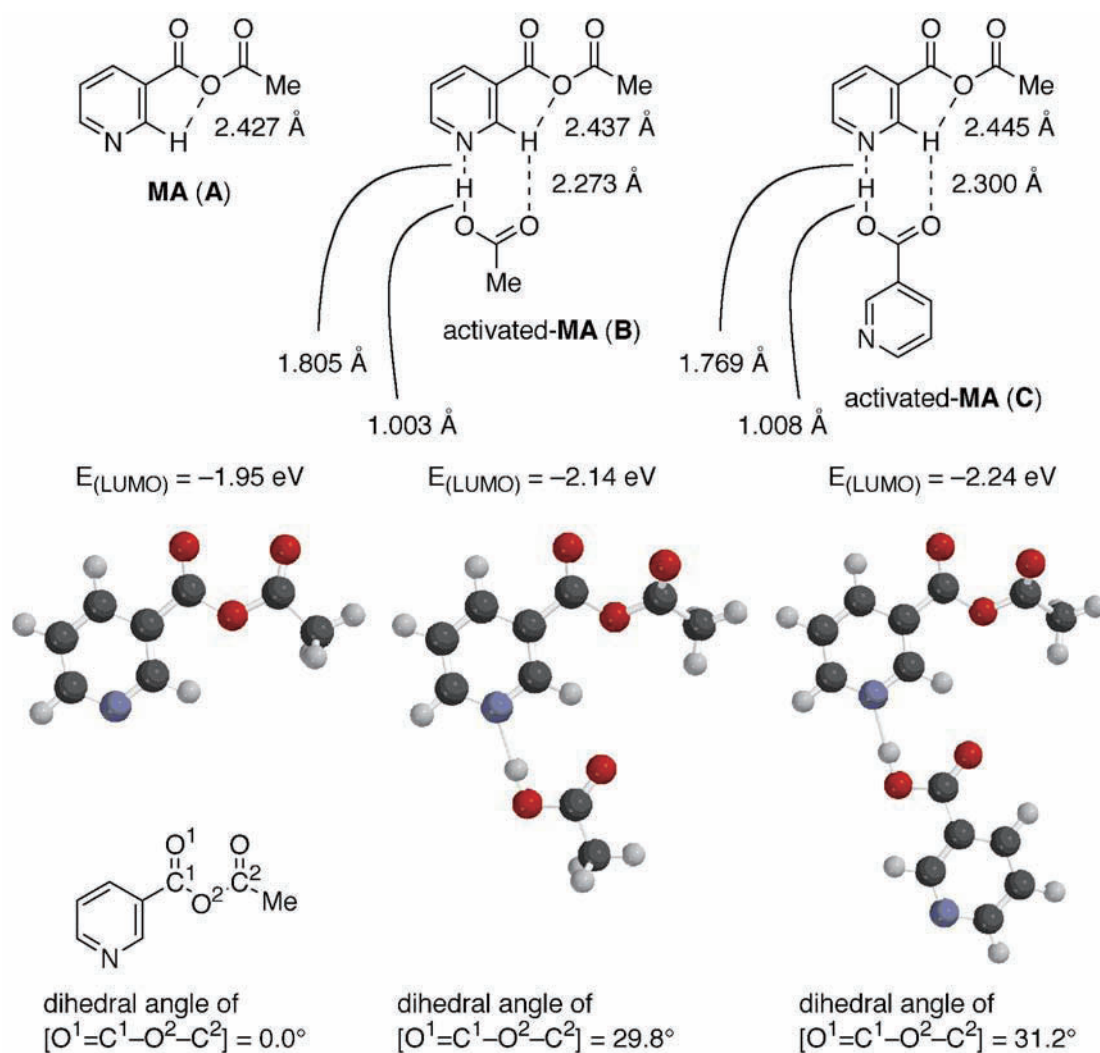
Figure 1. The Most Stable Structures and LUMO Energy Values of Mixed-Anhydride (**A**), Activated Mixed-Anhydride (**B**), and Activated Mixed-Anhydride (**C**) Calculated at B3LYP/6-31G*//B3LYP/6-31G* Level after Global Conformational Analysis

Typical procedure for the asymmetric esterification of racemic 1-phenyl-1-propanol ((±)-**1**) with 3-phenylpropionic acid by using 3-PCA in the presence of (+)-BTM was described (**Table 1**, Entry 2; **Table 2**, Entry 4): To a solution of 3-phenylpropionic acid (24.7 mg, 0.164 mmol), 3-PCA (37.8 mg, 0.166 mmol), and (+)-BTM (3.8 mg, 0.015 mmol) in dichloromethane (1.5 mL) at 0 °C was added racemic 1-phenyl-1-propanol ((±)-**1**) (40.8 µL, 0.300 µmol). After the reaction mixture had been stirred for 12 h at 0 °C, saturated aqueous $NaHCO_3$ was added at 0 °C. The organic layer was separated and the aqueous layer was extracted with diethyl ether. The combined organic layer was 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 to afford the corresponding optically active ester (*R*)-**2** (35.2 mg, 44% yield, 93% ee) and the unreacted optically active alcohol (*S*)-**1** (18.5 mg, 45% yield, 79% ee). [$s = 63.1$]

In summary, we have developed a new chiral induction protocol for the asymmetric esterification of racemic secondary benzylic alcohols with achiral carboxylic acids using 3-PCA in the presence of (+)-BTM. It was revealed that 3-PCA could be utilized as an efficient coupling reagent to produce the chiral carboxylic esters and alcohols in the total absence of tertiary amines, such as triethylamine and diisopropylethylamine. The high reactivity of the mixed-anhydride generated from 3-PCA and carboxylic acid promoted the appropriate transformation of the acylated compounds to give the desired chiral products. Further studies of the asymmetric mixed-anhydride method affording useful molecules are now in progress.

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8. All calculations were performed with the program package *Spartan '08* 1.1.1 of Wavefunction Inc. (http://www.wavefun.com).