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# The first asymmetric esterification of free carboxylic acids with racemic alcohols using benzoic anhydrides and tetramisole derivatives: an application to the kinetic resolution of secondary benzylic alcohols

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**Abstract**—A variety of optically active carboxylic esters are produced by the kinetic resolution of racemic secondary benzylic alcohols using free carboxylic acids with benzoic anhydride and tetramisole derivatives. 4-Methoxybenzoic anhydride (PMBA) is the best reagent to use in producing the corresponding esters in high ee when the reaction is catalyzed by (+)-benzotetramisole (BTM); by contrast, when non-substituted benzoic anhydride is used as a coupling reagent, the resulting optically active alcohols are obtained with high selectivities. This protocol directly produces chiral carboxylic esters from free carboxylic acids and racemic secondary alcohols by utilizing the trans-acylation process to generate mixed anhydrides from acid components and benzoic anhydride derivatives under the influence of chiral catalysts.


Synthesis of optically active secondary alcohols and their derivatives is one of the most important topics in the field of basic science.[1] Recently, some acylation methods have been developed for the kinetic resolution of racemic alcohols that use acyl halides or carboxylic anhydrides to produce the corresponding chiral esters in high ee.[2] As far as we know, however, the kinetic resolution of racemic alcohols using free carboxylic acids has not yet been achieved. A reaction using carboxylic acids as acyl donors would have great general and synthetic utility if achieved.

In recent years, we developed an effective method for esterification and lactonization that uses benzoic anhydride derivatives as condensation reagents to produce the desired coupling products from free carboxylic acids and alcohols (or $\omega$-hydroxycarboxylic acids).[3] In this report, we study the novel and useful kinetic resolution of racemic secondary benzylic alcohols using free carboxylic acids by the promotion of benzoic anhydride derivatives and a chiral nucleophilic catalyst developed recently by Birman et al.[4]

First, 1-phenyl-1-propanol ((±)-**1**) and 3-phenylpropionic acid were chosen as model substrates for optimization of the structure of the substituted benzoic anhydrides (Table 1).[5] As a nucleophilic catalyst, (–)-tetramisole (commercially available as a hydrochloride salt) was used for chiral induction according to the reported kinetic resolution procedure with propionic anhydride.[4c] As shown in entry 1, benzoic anhydride afforded relatively good enantioselectivity of the corresponding carboxylic ester **2** (90% ee), and the *s*-value[6] of the reaction was excellent ($s = 22$). Furthermore, 4-methoxybenzoic anhydride (PMBA) afforded the desired ester with good enantioselectivity (88% ee), and the *s*-value was also over 20 (entry 5). As shown in entries 8–12, we found that all substituted benzoic anhydrides with electron-withdrawing groups gave poor results. For example, the desired ester was obtained in only 4% yield when 2-methyl-6-nitrobenzoic anhydride (MNBA) was used in this model system (entry 12), even though MNBA is a very powerful reagent for the production of lactones, including highly-oxygenated medium- and large-sized ring compounds.[3] On the other hand, substituted benzoic anhydrides with

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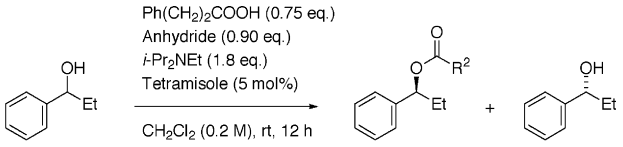
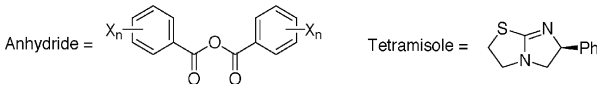
**Table 1.** Kinetic resolution of secondary benzylic alcohols using benzoic anhydride esterification with tetramisole



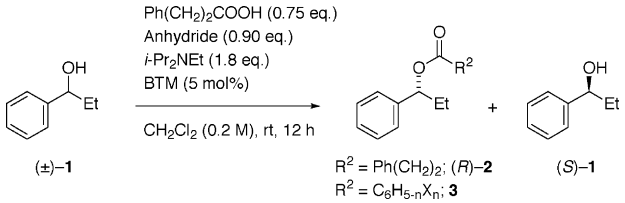

| Entry | $X_n$ | Yield of **2** (%) | **2/3** | Yield of **1** (%) | ee (**2**/**1**) (%) | *s* |
|---|---|---|---|---|---|---|
| 1 | H | 14 | 94/6 | 68 | 90/17 | 22 |
| 2 | 4-Me | 38 | 98/2 | 42 | 77/66 | 15 |
| 3 | 2-Me | 5 | 96/4 | 66 | 67/17 | 6 |
| 4 | 3,5-$Me_2$ | 39 | 97/3 | 37 | 81/73 | 21 |
| 5 | 4-MeO [PMBA] | 29 | 98/2 | 63 | 88/36 | 22 |
| 6 | 3,5-$(MeO)_2$ | 23 | 98/2 | 72 | 87/26 | 18 |
| 7 | 3,4,5-$(MeO)_3$ | 35 | 96/4 | 51 | 81/63 | 18 |
| 8 | 4-Cl | 60 | 97/3 | 25 | 16/31 | 2 |
| 9 | 2,6-$Cl_2$ | 12 | 93/7 | 73 | 42/4 | 2 |
| 10 | 2,4,6-$Cl_3$ | Trace | nd | nd | nd/nd | nd |
| 11 | 2-MeO-4-Cl | 16 | 96/4 | 72 | 79/15 | 10 |
| 12 | 2-Me-6-$NO_2$ [MNBA] | 4 | nd | nd | nd/nd | nd |



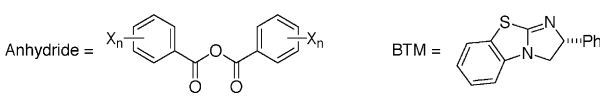

electron-donating groups, such as PMBA, produced comparatively better chemical yields and enantioselectivities for **2**, as shown in entries 2–7. Although a small amount of the undesired benzoates **3** was obtained in every case, the chemoselectivities of **2** versus **3** were generally satisfactory (>96/4 in entries 2–8, 11).

Next, (+)-benzotetramisole (BTM), an advanced acylation catalyst developed by Birman[4c] was used as a chiral promoter in further studies (Table 2). Benzoic anhydride and five other kinds of substituted derivatives, which produced the high *s*-values shown in Table 1, were used in combination with BTM, as shown in Table 2. Almost all of these reactions produced very good results, and the corresponding carboxylic esters **2** and alcohols **1** were produced in high ee ($s = >30$). When the reaction was carried out using non-substituted benzoic anhydride (entry 1), the desired ester was obtained in 48% yield with good enantioselectivity (89% ee) and an excellent *s*-value ($s = 46$).[7] Furthermore, we also found that PMBA functions as a suitable coupling reagent that gives the desired products with high enantioselectivities (entry 4; $s = 43$).[8] We subsequently examined other factors such as reaction temperature and solvent by changing the reaction conditions, but we obtained poor results. For instance, when the reaction was carried out using benzoic anhydride coupled with BTM at 5 °C for 48 h, the corresponding ester **2** was produced in 55% yield with 57% ee ($s = 8$). Furthermore, the use of a DMF solvent at room temperature afforded the desired ester in 58% yield, and the ee of the product decreased to 76% ($s = 11$).

**Table 2.** Kinetic resolution of secondary benzylic alcohols using benzoic anhydride esterification with BTM

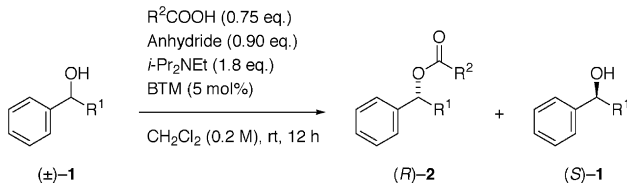



| Entry | $X_n$ | Yield of **2** (%) | **2/3** | Yield of **1** (%) | ee (**2**/**1**) (%) | *s* |
|---|---|---|---|---|---|---|
| 1 | H | 48 | 98/2 | 47 | 89/85 | 46 |
| 2 | 4-Me | 49 | 99/1 | 45 | 83/94 | 38 |
| 3 | 3,5-$Me_2$ | 31 | 99/1 | 61 | 90/48 | 30 |
| 4 | 4-MeO [PMBA] | 41 | 98/2 | 46 | 90/75 | 43 |
| 5 | 3,5-$(MeO)_2$ | 34 | 98/2 | 52 | 90/48 | 30 |
| 6 | 3,4,5-$(MeO)_3$ | 46 | 98/2 | 39 | 84/90 | 35 |




The esterification of several free carboxylic acids with secondary benzylic alcohols was examined to assess the generality of this new method. The results are summarized in Table 3. As shown in entries 1–11, high *s*-values were attained for the reaction using benzoic anhydride, and the resulting alcohols (*S*)-**1** were recovered with high ee because the reaction proceeded at a good rate. On the other hand, the reaction using PMBA afforded the corresponding esters (*R*)-**2** with high enantioselectivities because the rates of the reactions in entries 12–22 are relatively low as compared to those of the reactions accelerated by the non-substituted benzoic anhydride. All of the *s*-values of reactions using PMBA, shown in entries 12–22, are excellent ($s = 12$–$88$); as a result, the desired carboxylic esters, derived from a variety

**Table 3.** Synthesis of a variety of the optically active carboxylic esters and alcohols using the asymmetric esterification




| Entry | $R^1$ | $R^2$ | Anhydride | Yield (**2**/**1**) (%) | ee (**2**/**1**) (%) | *s* |
|---|---|---|---|---|---|---|
| 1 | Et | Et | $Bz_2O$ | 47/30 | 86/87 | 38 |
| 2 | Et | $Ph(CH_2)_2$ | $Bz_2O$ | 48/47 | 89/85 | 46 |
| 3 | Et | $Ph(CH_2)_3$ | $Bz_2O$ | 49/40 | 82/90 | 31 |
| 4 | Et | $Me_2CH(CH_2)_2$ | $Bz_2O$ | 43/33 | 82/72 | 22 |
| 5 | Et | $CH_2{=}CH(CH_2)_2$ | $Bz_2O$ | 52/35 | 77/95 | 28 |
| 6 | Et | $MeOCH_2$ | $Bz_2O$ | 55/29 | 55/98 | 14 |
| 7 | Et | *c*-$C_6H_{11}$ | $Bz_2O$ | 45/41 | 63/64 | 8 |
| 8 | *i*-Pr | Et | $Bz_2O$ | 50/43 | 83/91 | 34 |
| 9 | *i*-Pr | $Ph(CH_2)_2$ | $Bz_2O$ | 54/46 | 83/90 | 33 |
| 10 | *t*-Bu | Et | $Bz_2O$ | 30/58 | 86/43 | 20 |
| 11 | *t*-Bu | $Ph(CH_2)_2$ | $Bz_2O$ | 34/55 | 86/50 | 22 |
| 12 | Et | Et | PMBA | 40/40 | 89/76 | 39 |
| 13 | Et | $Ph(CH_2)_2$ | PMBA | 41/46 | 90/75 | 43 |
| 14 | Et | $Ph(CH_2)_3$ | PMBA | 39/45 | 90/69 | 39 |
| 15 | Et | $Me_2CH(CH_2)_2$ | PMBA | 43/38 | 83/71 | 23 |
| 16 | Et | $CH_2{=}CH(CH_2)_2$ | PMBA | 47/38 | 86/91 | 42 |
| 17 | Et | $MeOCH_2$ | PMBA | 32/51 | 82/38 | 15 |
| 18 | Et | *c*-$C_6H_{11}$ | PMBA | 40/53 | 76/51 | 12 |
| 19 | *i*-Pr | Et | PMBA | 39/43 | 90/81 | 47 |
| 20 | *i*-Pr | $Ph(CH_2)_2$ | PMBA | 38/53 | 92/64 | 46 |
| 21 | *t*-Bu | Et | PMBA | 32/67 | 93/44 | 42 |
| 22 | *t*-Bu | $Ph(CH_2)_2$ | PMBA | 36/54 | 96/58 | 88 |

of carboxylic acids, were effectively obtained in high enough purity for application to the asymmetric synthesis of chiral compounds.

Typical procedure for the synthesis of optically active esters from racemic secondary alcohols using benzoic anhydride with BTM is described: To a solution of benzoic anhydride (61.0 mg, 0.270 mmol) and 3-phenylpropionic acid (34.1 mg, 0.226 mmol) in dichloromethane (1.5 mL) at room temperature were added diisopropylethylamine (94.0 μL, 0.540 mmol), BTM (3.8 mg, 0.015 mmol) and (±)-1-phenyl-1-propanol (40.8 μL, 0.300 mmol). 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 (three times). 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 ester (39.7 mg, 48%, 89% ee) and the recovered optically active secondary alcohol (19.4 mg, 47%, 85% ee), (Table 3, $s = 45.6$, entry 2).

Typical procedure for the synthesis of optically active esters from racemic secondary alcohols using PMBA with BTM is described: To a solution of PMBA (77.4 mg, 0.270 mmol) and 3-phenylpropionic acid (33.9 mg, 0.225 mmol) in dichloromethane (1.5 mL) at room temperature were added diisopropylethylamine (94.0 μL, 0.540 mmol), BTM (3.8 mg, 0.015 mmol) and (±)-1-phenyl-1-propanol (40.8 μL, 0.300 mmol). 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 (three times). 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 ester (33.7 mg, 41%, 90% ee) and the recovered optically active alcohol (18.7 mg, 46%, 75% ee) (Table 3, $s$=42.8, entry 13). (*R*)-1-*Phenylpropyl 3-phenylpropanoate*: HPLC (CHIRALCEL AD-H, *i*-PrOH/hexane = 1/50, flow rate = 0.5 mL/min); $t_R = 14.5$ min (95.1%), $t_R = 20.3$ min (4.9%); IR (neat): 3031, 1741, 1604, 1496, 752, 700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 7.27–7.14 (m, 7H, Ph), 7.13–7.07 (m, 3H, Ph), 5.59 (t, $J = 7.0$ Hz, 1H, 1-H), 2.90–2.83 (m, 2H, 2′-H), 2.61 (ddd, $J = 16.0$, 9.0, 9.0 Hz, 1H, 3′-H), 2.57 (ddd, $J = 16.0$, 9.6, 9.0 Hz, 1H, 3′-H), 1.86–1.66 (m, 2H, 2-H), 0.76 (t, $J = 7.5$ Hz, 3H, 3-H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 172.2, 140.48, 140.46, 128.4, 128.3, 128.2, 127.7, 126.5, 126.2, 77.4, 36.1, 30.9, 29.3, 9.8; HR MS: calcd for $C_{18}H_{20}O_2Na$ ($M+Na^+$) 291.1356, found 291.1344.

In summary, we have developed a novel method for producing optically active secondary alcohols and their carboxylic esters: in other words, the kinetic resolution of racemic benzylic secondary alcohols, using free

carboxylic acids coupled with benzoic anhydride and tetramisole derivatives. We found that the reaction using 4-methoxybenzoic anhydride (PMBA) produced the corresponding esters in high ee under mild conditions, whereas the resulting optically active alcohols were obtained with high selectivity when non-substituted benzoic anhydride was used as a coupling reagent. This protocol produces chiral carboxylic esters directly from free carboxylic acids and racemic secondary alcohols by using the trans-acylation process to generate mixed anhydrides from acid components coupled with benzoic anhydride derivatives under the influence of chiral catalysts. Further studies on the reaction using benzoic anhydrides, as well as other applications of this protocol to the synthesis of optically active compounds, are now in progress.

## Acknowledgements

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5. For the systematic studies on the substituent effects of the aromatic ring of benzoic anhydrides, see Ref. 3c.
6. The *s*-values were determined according to the literature method:[2a,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 $C_{HPLC} = ee_A/(ee_E + ee_A)$, where $ee_E$ is the enantiomeric excess of ester and $ee_A$ is the enantiomeric excess of unreacted alcohol. 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. The BTM-catalyzed reaction of (±)-**1** with benzoic anhydride in the absence of 3-phenylpropionic acid produced the corresponding benzoate in 3% yield with 11% ee, accompanied by 97% recovery of the unreacted alcohol (1.5% ee), as shown by Birman and Li[4c] The sense of the optical rotation of the recovered alcohol is opposite to that of **1** produced in Table 2; therefore, the ee of (*S*)-**1** in entry 1 was somewhat reduced (ca. 3–4%) by this effect.
8. The BTM-catalyzed reaction of (±)-**1** with PMBA in the absence of 3-phenylpropionic acid produced the corresponding 4-methoxybenzoate in 3% yield with 4.4% ee, accompanied by 80% recovery of the unreacted alcohol (1.5% ee). The sense of the optical rotation of the recovered alcohol is opposite to that of **1** produced in Table 2; therefore, the ee of (*S*)-**1** in entry 4 was somewhat reduced (ca. 3–4%) by this effect.