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Kinetic Resolution of Racemic Carboxylic Acids Using Achiral Alcohols by the Promotion of Benzoic Anhydrides and Tetramisole Derivatives: Production of Chiral Nonsteroidal Anti-Inflammatory Drugs and Their Esters

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A variety of optically active carboxylic esters were produced by kinetic resolution of racemic carboxylic acids by using achiral alcohols, benzoic anhydrides, and Birman's tetramisole-type catalysts. Bis(α-naphthyl)methanol is a very effective reagent for producing the corresponding esters with high *ee* values in the presence of 4-methoxybenzoic anhydride (PMBA) as the coupling reagent by promotion of benzotetramisole derivatives (BTM, α-Np-BTM, and β-Np-BTM). This protocol directly provides chiral carboxylic esters from free carboxylic acids and achiral alcohols by utilizing a transacylation process to generate the mixed anhydrides from the acid components with benzoic anhydride derivatives in the presence of chiral catalysts.

Introduction

The synthesis of optically active carboxylic acids and esters is of utmost importance due to the significant roles that these compounds play in the fields of medicinal and pharmaceutical chemistry.[1] Some chiral resolving agents (e.g., chiral amines) were developed for the derivatization of racemic carboxylic acids to form pairs of diastereomers that can be separated by conventional recrystallization. However, 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. Recently, a very effective method for providing chiral carboxylic esters derived from α-arylalkanoic acid by the enantioselective *C*-acylations of ketenes by using planar chiral heterocycles was pioneered by Fu.[2] However, to the best of our knowledge, direct and practical kinetic resolution of racemic 2-arylalkanoic acids by using achiral alcohols by the promotion of a chiral catalyst has not yet been reported. Here we present the first effective method for producing a variety of nonsteroidal anti-inflammatory drugs such as ibuprofen, ketoprofen, fenoprofen, flurbiprofen, naproxen, and their esters by the kinetic resolution of racemic 2-arylalkanoic acids with the use of achiral alcohols, benzoic anhydride, and Birman's tetramisole-type catalysts.

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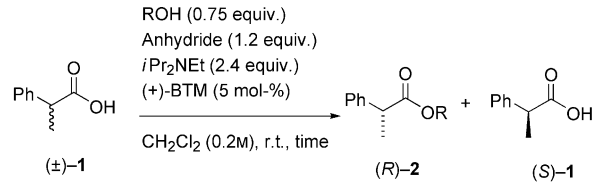
Results and Discussion

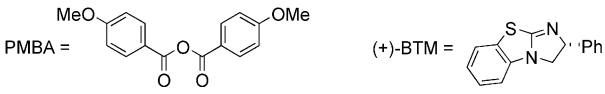
In recent years, we established effective esterification and lactonization by using benzoic anhydride derivatives as a condensation reagent to produce the desired coupling products from free carboxylic acids and alcohols (or ω-hydroxycarboxylic acids).[3] Furthermore, a novel and useful kinetic resolution reaction of racemic secondary alcohols by using free and achiral carboxylic acids by the promotion of benzoic anhydrides and chiral catalysts has successfully been developed.[4] In this reaction, the tetramisole-type chiral reagents created by Birman[5] effectively promoted the kinetic resolution of racemic 1-phenyl alkanols. These results prompted us to explore a new method for the preparation of optically active α-substituted alkanoic acid derivatives by starting from racemic carboxylic acids with achiral alcohols and by using our mixed anhydride formation technology.[6]

First, the reactions of racemic 2-phenylpropionic acid (**1**) with several achiral alcohols were chosen as model cases for the optimization of the structure of the nucleophile (Table 1). In the presence of benzoic anhydride as a coupling reagent, (+)-benzotetramisole (BTM)[5] was used for chiral induction according to the standard reaction conditions established in our preceding paper.[4] As shown in Entry 1 of Table 1, the esterification did not proceed at all when a tertiary alcohol was used as the nucleophile, and the reaction of cyclohexanol afforded the desired ester **2** in good yield, but **2** was found to be an absolutely racemic compound (Table 1, Entry 2). In contrast, it was revealed that benzyl alcohol and diphenylmethanol produced a relatively improved enantioselectivity of the corresponding carboxylic esters (33% *ee*; Table 1, Entries 3 and 4, respectively).

Table 1. Kinetic resolution of (±)-2-phenylpropionic acid.



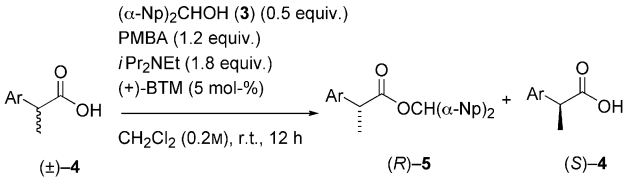
Entry	ROH	Anhydride	Time	Yield (**2** ; **1**) [%]	*ee* (**2** ; **1**) [%]	*s*
1	*t*BuOH	Bz_2O	15 h	0 ; 0	nd ; nd	nd
2	*c*HexOH	Bz_2O	3 d	39 ; 31	0 ; 3	1
3	$PhCH_2OH$	Bz_2O	12 h	40 ; 60	33 ; 23	2
4	Ph_2CHOH	Bz_2O	12 h	42 ; 37	33 ; 19	2
5	$(4\text{-}MeOC_6H_4)_2CHOH$	Bz_2O	12 h	15 ; 26	12 ; 0	1
6	$(4\text{-}FC_6H_4)_2CHOH$	Bz_2O	12 h	60 ; 27	27 ; 35	2
7	$(\beta\text{-Np})_2CHOH$	Bz_2O	11 h	67 ; 16	31 ; 41	3
8	$(\alpha\text{-Np})_2CHOH$ (**3**)	Bz_2O	4 h	56 ; 19	82 ; 80	24
9	$(\alpha\text{-Np})_2CHOH$ (**3**)	PMBA	4 h	46 ; 46	86 ; 60	25



Next, several achiral diphenylmethanol derivatives were examined as nucleophiles for the kinetic resolution of **1** (Table 1, Entries 5–8). Substitution of the aryl ring of diphenylmethanol diminished the selectivities (Table 1, Entries 5 and 6), and the use of bis(β-naphthyl)methanol afforded results similar to those obtained when diphenylmethanol was used (Table 1, Entry 7; cf. Entry 4). 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 resulted in the corresponding ester and the recovery of (*S*)-2-phenylpropionic acid with good enantiomeric excesses (82 and 80% *ee*, respectively); the *s*-value also dramatically increased to 24 (Table 1, Entry 8). Similar to the kinetic resolution of secondary alcohols in the previous paper,[4] 4-methoxybenzoic anhydride (PMBA) also proved to be a suitable coupling reagent and the *s*-value reached 25 (Table 1, Entry 9).

A variety of examples of the resolution of 2-arylpropionic acid derivatives **4** with bis(α-naphthyl)methanol (**3**) by promotion with PMBA and BTM is listed in Table 2. All the reactions using the 2-phenylpropionic acid derivatives substituted at the 4-position on the aromatic ring produced the corresponding esters in good enantiomeric excess (4-H, 91% *ee*; 4-Me, 83% *ee*; 4-MeO, 86% *ee*; 4-Cl, 83% *ee*); therefore, it is postulated that there is not a very large electronic effect on the aromatic ring of the substrates (Table 2, Entries 1–4). Several derivatives of 2-phenylpropionic acid, such as ibuprofen (**4e**), ketoprofen (**4f**), fenoprofen (**4g**), and flurbiprofen (**4h**), are used as nonsteroidal anti-inflammatory drugs for clinical treatment, so that the kinetic resolution of these valuable compounds was next examined (Table 2, Entries 5–8). The optically active ibuprofen ester (92% *ee*), ketoprofen ester (77% *ee*), fenoprofen ester (82% *ee*), and flurbiprofen ester (83% *ee*) were easily prepared by the reaction with **3** in the presence of PMBA and BTM under the standard reaction conditions.

Table 2. Kinetic resolution of (±)-2-phenylpropionic acid derivatives.



Entry	Ar	Acid	Yield (**5** ; **4**) [%]	*ee* (**5** ; **4**) [%]	*s*
1	Ph	**4a**	36 ; 39	91 ; 52	36
2	$4\text{-}MeC_6H_4$	**4b**	37 ; 31	83 ; 45	17
3	$4\text{-}MeOC_6H_4$	**4c**	44 ; 35	86 ; 47	21
4	$4\text{-}ClC_6H_4$	**4d**	48 ; 33	83 ; 46	17
5	$4\text{-}i\text{Bu}C_6H_4$	ibuprofen (**4e**)	39 ; 33	92 ; 36	34
6	$3\text{-}BzC_6H_4$	ketoprofen (**4f**)	55 ; 36	77 ; 58	14
7	$3\text{-}PhOC_6H_4$	fenoprofen (**4g**)	46 ; 42	82 ; 53	17
8	$3\text{-F-4-Ph}C_6H_3$	flurbiprofen (**4h**)	53 ; 34	83 ; 37	15

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 Figure 1. The reaction of racemic naproxen with **3** in the presence of PMBA and (–)-BTM afforded the corresponding ester **7** in 48% yield with moderate enantioselectivity (76% *ee*), and 40% of the resulting (*R*)-naproxen was recovered in 59% *ee* (*s* = 13). Furthermore, we prepared several BTM derivatives including novel compounds and applied them to the kinetic resolution of **6** by combining PMBA and **3**. We found that the reaction using (*S*)-α-Np-BTM produced **7** with a relatively better enantiomeric excess (88% *ee*, *s* = 25), and it was also found that (*S*)-β-Np-BTM was a very effective catalyst to promote the kinetic resolution of the racemic naproxen, which afforded the desired ester **7** in good yield with a high enantiomeric excess (49% yield, 93% *ee*, *s* = 61).

The assumed reaction pathway is illustrated in Figure 2. First, a mixed anhydride (MA) forms in situ as a key intermediate from the racemic carboxylic acid and benzoic anhydride by the promotion of basic catalysts. Actually, when racemic 2-phenylpropionic acid (**1**) was treated with benzoic anhydride in the presence of triethylamine with (+)-BTM, facile formation of the mixed anhydrides [(*R*)- and (*S*)-MA] was observed by ^1H NMR spectroscopy. In the second cycle, half of the mixed anhydride [(*R*)-MA] will be selectively activated by (+)-BTM, which then reacts with a half an equivalent of the nucleophilic alcohol to afford the desired (*R*)-carboxylic ester with a high *ee*. The remaining half of the mixed anhydride [(*S*)-MA] would be hydrolyzed to produce the unreacted (*S*)-carboxylic acid. The efficiency of the

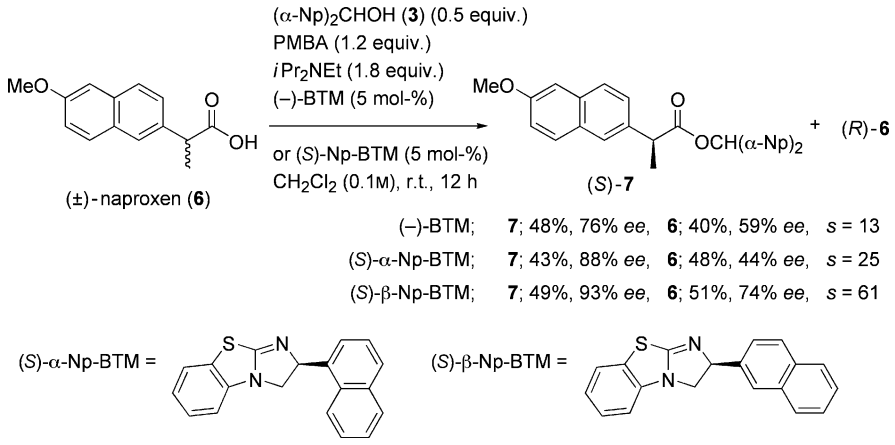


Figure 1. Kinetic resolution of (±)-naproxen.

kinetic resolution completely depends on the structure of the alcohol as shown in Table 1; thus, it is anticipated that the second cycle includes the most important stage for determining the enantioselectivity of this multiple transacylation process.

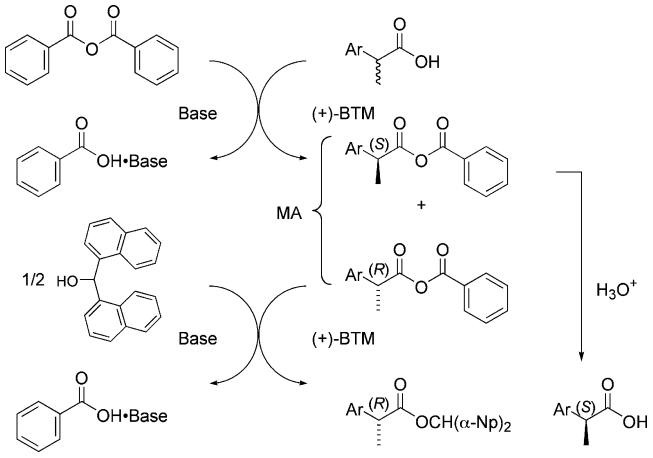


Figure 2. Proposed reaction pathway of the kinetic resolution.

Conclusions

We developed a new practical method for providing optically active 2-arylalkanoic acids and their esters by kinetic resolution of racemic carboxylic acids with the use of achiral alcohols, benzoic anhydride, and tetramisole derivatives. A combination of PMBA, 1,1-diarylmethanol, and a BTM-type catalyst is best to produce the corresponding esters from 2-arylpropionic acid derivatives with a high *ee* under mild reaction conditions. This method was successfully utilized for the kinetic resolution of ibuprofen, ketoprofen, fenoprofen, flurbiprofen, and naproxen by modification of the structure of the nucleophiles and BTM-type catalysts. Further studies on the present method to provide chiral carboxylic acid derivatives and other applications of this novel protocol to the syntheses of useful complex molecules are now in progress.

Experimental Section

Typical Procedure for the Preparation of Optically Active Naproxen (6) and Its Ester from Racemic Naproxen (6) by Using PMBA with (*S*)-β-Np-BTM: To a solution of PMBA (68.5 mg, 0.239 mmol), (±)-naproxen (**6**) (45.8 mg, 0.199 mmol), and bis(α-naphthyl)methanol (28.4 mg, 99.9 μmol) in dichloromethane (2.0 mL) at room temperature was successively added diisopropylethylamine (62.7 μL, 0.360 mmol) and (*S*)-β-Np-BTM (2.9 mg, 9.6 μmol). The mixture was stirred for 12 h at room temperature and then quenched with saturated aqueous NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with diethyl ether. The combined organic layer was dried with 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 (*S*)-**7** (49.1 mg, 49% yield, 93% *ee*) and the recovered optically active naproxen [(*R*)-**6**] (23.4 mg, 51% yield, 74% *ee*). [*s* = 60.9, Figure 1, Run 3].

Supporting Information (see footnote on the first page of this article): Experimental procedures; characterization of the products; ^1H and ^{13}C NMR spectra of the optically active carboxylic acids and esters.

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