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An effective kinetic resolution of racemic α-arylpropanoic acids, α-arylbutanoic acids, and β-substituted-α-arylpropanoic acids with bis(9-phenanthryl)methanol as a new achiral nucleophile in the asymmetric esterification using carboxylic anhydrides and the acyl-transfer catalyst

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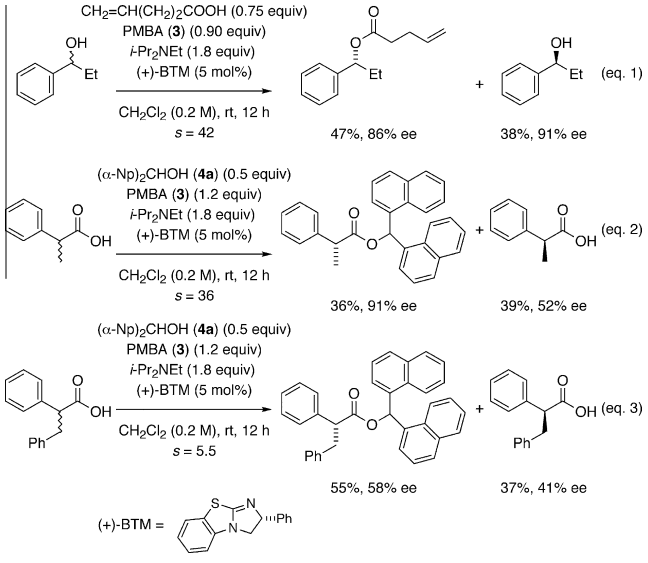
ABSTRACT

A general method for the kinetic resolution of racemic α-arylalkanoic acids with achiral alcohols is described. It was determined that bis(9-phenanthryl)methanol is a suitable nucleophile which reacts with the intermediary mixed anhydrides generated from aromatic anhydrides with α-arylpropanoic acids or β-substituted-α-arylpropanoic acids in the presence of (+)-benzotetramisole to produce the corresponding optically active esters with high ee's under very mild conditions.

We recently reported the first asymmetric esterification of achiral carboxylic acids with racemic benzylic alcohols (Scheme 1, Eq. 1)[1] via the in situ formation of the mixed anhydride using aromatic anhydrides, such as *p*-methoxybenzoic anhydride (PMBA; **3**), and the chiral acyl-transfer catalysts, such as (−)-tetramisole and (+)-benzotetramisole ((+)-BTM), which were introduced by Birman et al.[2] Because this protocol utilized the transacylation process to generate the mixed anhydride, we expected that not only racemic secondary alcohols, but also racemic carboxylic acids could be applicable for the asymmetric esterification in the same manner. In fact, we succeeded in the development of a new method for the kinetic resolution of the racemic α-arylpropanoic acids with achiral alcohols using chiral acyl-transfer catalysts (Eq. 2).[3,4] In this reaction, bis(α-naphthyl)methanol (**4a**) functions as a very effective nucleophile for producing the optically active esters from racemic α-arylpropanoic acids with high ee's in the presence of an aromatic anhydride as a coupling reagent with the benzotetramisole derivatives. Various racemic α-arylpropanoic acids and non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, ketoprofen, fenoprofen, flurbiprofen, and naproxen, were successfully resolved to produce the corresponding chiral carboxylic acids and their esters with high *s*-values[5] via the asymmetric esterification. However, there exists a limitation when applying this method to other substrates; that is, the only kinetic resolution of racemic



Scheme 1. Our previous results (Eqs. 1 and 2) and limitation (Eq. 3).

mono-substituted propanoic acids was attained to give the optically active esters with high enantioselectivities. For instance, the reaction of racemic 2,3-diphenylpropanoic acid with **4a** in the presence of **3** and (+)-BTM afforded the corresponding ester in

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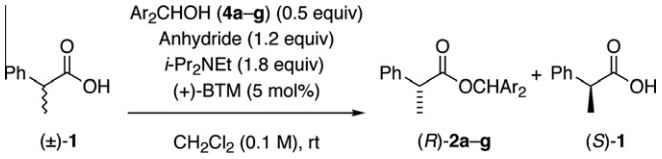
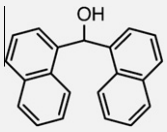
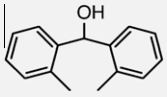
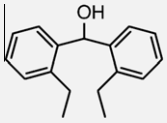
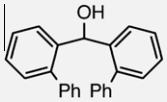
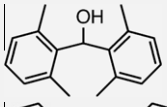
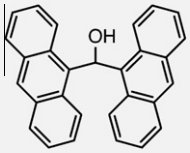
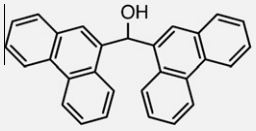
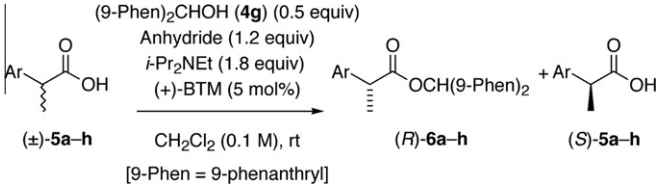
Table 1
Kinetic resolution of (±)-**1** with several kinds of achiral alcohols



Entry	Ar_2CHOH (**4**)		Conditions[a]	Yield (**2** ; **1**) [%]	ee (**2** ; **1**) [%]	*s*
1		**4a**	A	53 ; 29	87 ; 57	27
2		**4a**	B	28 ; 44	90 ; 32	25
3		**4b**	A	32 ; 39	89 ; 34	24
4		**4b**	B	21 ; 46	77 ; 17	9
5		**4c**	A	24 ; 29	89 ; 28	23
6		**4c**	B	14 ; 55	91 ; 10	23
7		**4d**	A	NR[b]	—	—
8		**4e**	A	NR[b]	—	—
9		**4f**	A	NR[b]	—	—
10		**4g**	A	42 ; 33	89 ; 48	27
11		**4g**	B	42 ; 42	91 ; 52	37

[a] Conditions A (see Ref. 6); Anhydride = Bz_2O, time = 6 h. Conditions B (see Ref. 7); Anhydride = PMBA (**3**), time = 12 h.
[b] No reaction.

Table 2
Kinetic resolution of racemic α-arylpropanoic acid derivatives **5a**–**h**, including nonsteroidal anti-inflammatory drugs (NSAIDs)



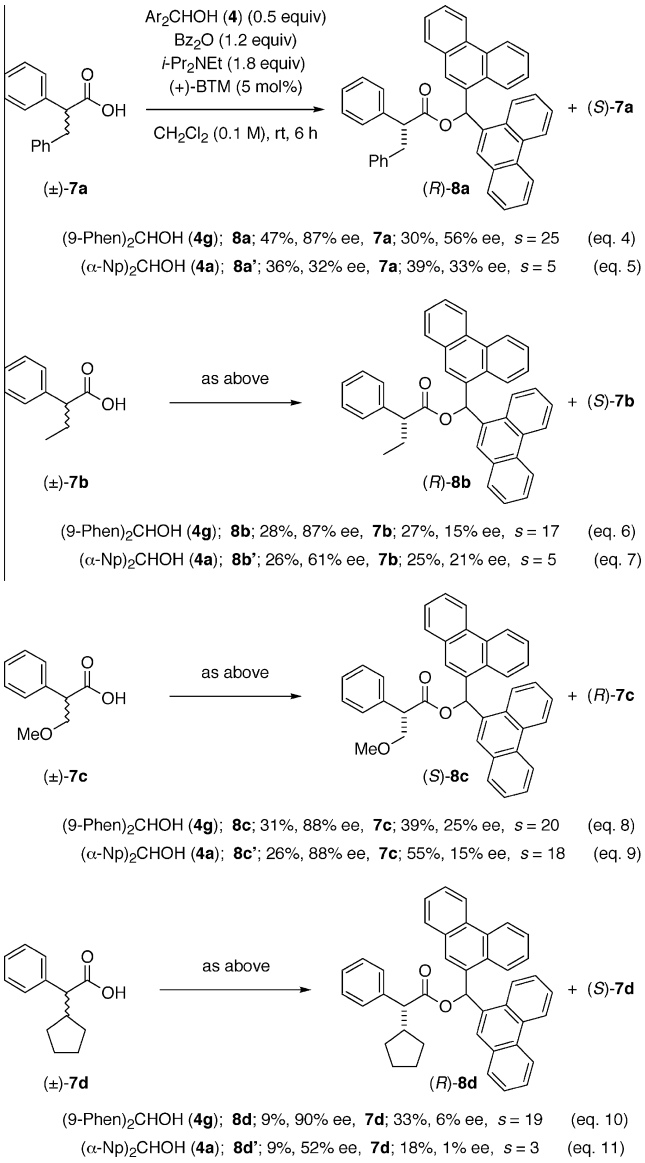
Entry	Ar	Acid (**5**)	Conditions[a]	Yield (**6** ; **5**) [%]	ee (**6** ; **5**) [%]	*s*
1	4-MeC_6H_4	**5a**	A	42 ; 19	87 ; 54	24
2		**5a**	B	41 ; 44	85 ; 44	19
3	4-MeOC_6H_4	**5b**	A	36 ; 25	78 ; 48	13
4		**5b**	B	39 ; 42	82 ; 49	16
5	4-ClC_6H_4	**5c**	A	53 ; 24	80 ; 54	15
6		**5c**	B	47 ; 43	80 ; 57	16
7	$4\text{-}i\text{-BuC}_6H_4$	Ibuprofen (**5d**)	A	36 ; 33	90 ; 42	27
8		**5d**	B	39 ; 30	89 ; 49	27
9	3-BzC_6H_4	Ketoprofen (**5e**)	A	49 ; 19	75 ; 43	11
10		**5e**	B	53 ; 43	72 ; 60	11
11	3-PhOC_6H_4	Fenoprofen **(5f)**	A	54 ; 36	78 ; 50	14
12		**5f**	B	47 ; 39	78 ; 60	15
13	3-F-4-PhC_6H_3	Flurbiprofen **(5g)**	A	41 ; 28	88 ; 44	23
14		**5g**	B	48 ; 32	81 ; 64	18
15	2-(6-MeO-Np)	Naproxen **(5h)**	A	50 ; 27	88 ; 61	30
16		**5h**	B	49 ; 42	87 ; 61	26

[a] Conditions A (see Ref. 6); Anhydride = Bz_2O, time = 6 h. Conditions B (see Ref. 7); Anhydride = PMBA (**3**), time = 12 h.

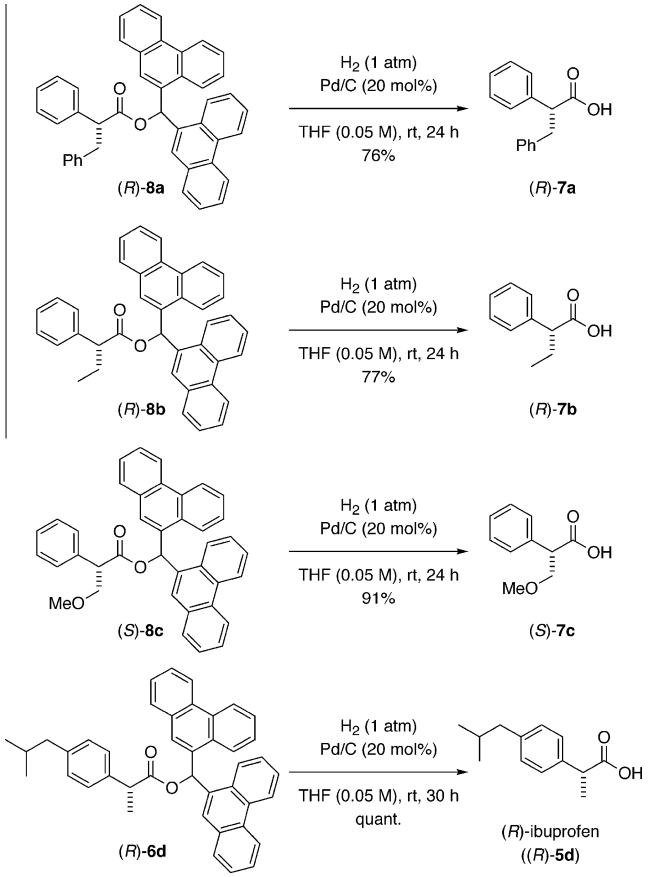
55% yield with a moderate selectivity (58% ee) as shown by Eq. 3 (s = 5.5), therefore, further improvements are required for establishing a reliable and more useful synthetic technology to produce the chiral β-substituted-α-arylpropanoic acid derivatives. We now report a widely applicable mixed-anhydride method for producing the optically active α-arylalkanoic acids and those esters starting from the racemic materials by the combined use of aromatic anhydrides, achiral alcohols, and the chiral acyl-transfer catalyst.

First, we examined the kinetic resolution of racemic 2-phenylpropanoic acid ((±)-**1**) with several achiral alcohols in the presence of benzoic anhydride and a catalytic amount of (+)-BTM in order to determine the suitable structure of the nucleophiles (Table 1). When the reaction was carried out using bis(α-naphthyl)methanol (**4a**) under the modified standard reaction conditions established in a preceding paper,[3] the asymmetric esterification smoothly proceeded and a good s-value (s = 27) was obtained (entry 1). We further investigated the use of benzhydrols **4b** and **4c** having alkyl substituents at the o- and o'-positions on the aromatic rings and relatively good stereoselectivities were also observed (entries 3 and 5: cf. entry 1). On the other hand, the reactions with very bulky alcohols **4d–f** possessing large substituents on the o- and o'-positions did not take place at all (entries 7–9). Fortunately, it was found that the kinetic resolution of (±)-**1** with bis(9-phenanthryl)methanol (**4g**) successfully proceeded to afford the desired optically active ester (*R*)-**2g** in good yield with a high enantioselectivity as shown in entry 10 (s = 27). Similar to the preceding results,[3] PMBA (**3**) also functions as an effective coupling reagent for the reaction of (±)-**1** with **4a**, **4c**, and **4g** by the combined use of (+)-BTM, and almost all the resolutions demonstrated in Table 1 produced satisfactory s-values as shown by entries 2, 6, and 11 except for entry 4 (s = 25, 23, and 37).

Table 2 displays a variety of examples of the kinetic resolution of α-arylpropanoic acid derivatives **5a–h** with **4g** under the above optimized conditions A[6] (Table 1, entry 10) and B[7] (Table 1, entry 11). As shown by entries 1–6, all the kinetic resolutions of 2-(4-methylphenyl)propanoic acid (**5a**), 2-(4-methoxyphenyl)propanoic acid (**5b**), and 2-(4-chlorophenyl)propanoic acid (**5c**) provided the optically active carboxylic esters in good enantiomeric excesses (78–87% ee), irrespective of the substituents at the 4-position on the aromatic rings of the 2-arylpropanoic acid derivatives. Furthermore, we examined the asymmetric acyl-transfer reaction of several NSAIDs, such as ibuprofen (**5d**), ketoprofen (**5e**), fenoprofen (**5f**), flurbiprofen (**5g**), and naproxen (**5h**), as listed in entries 7–16. Although the kinetic resolution of **5e** under both conditions, A and B, gave medium enantioselectivities (entries 9 and 10, s = 11, in each case), other reactions produced the corresponding chiral NSAIDs esters in high ee's (78–90% ee) with good s-values (s = 14–30) in every case (entries 7, 8, 11–16).



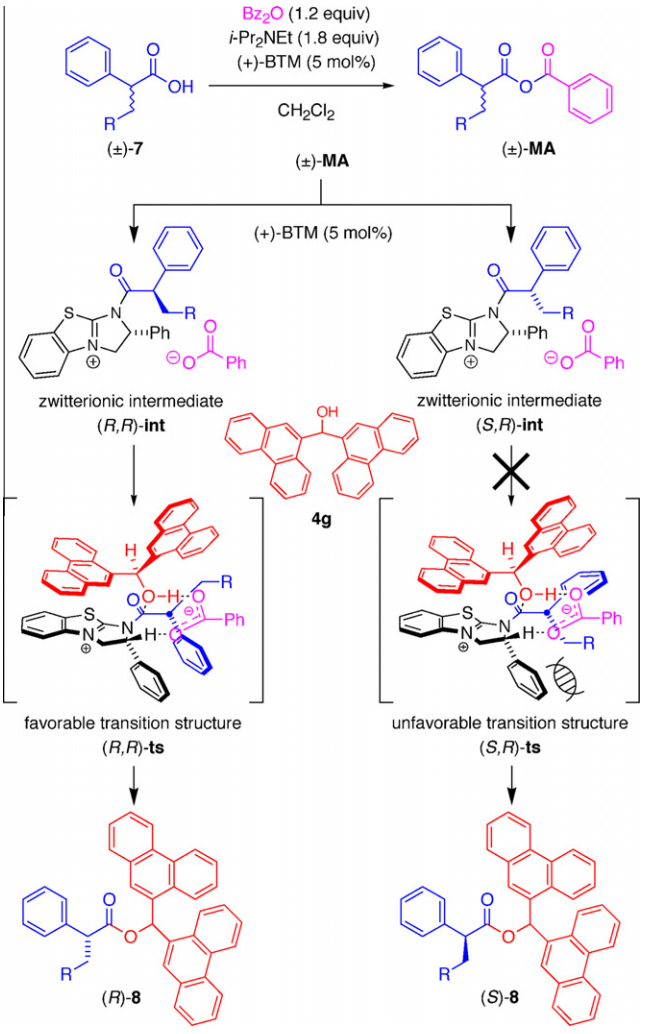
Scheme 2. Improved kinetic resolution of a variety of racemic β-substituted-α-arylpropanoic acid derivatives (**7a–d**) (Eqs. 4, 6, 8, and 10).



Scheme 3. Deprotection of bis(9-phenanthryl)methyl esters to form the chiral β-substituted-α-arylpropanoic acid derivatives ((*R*)-**7a**, (*R*)-**7b**, and (*S*)-**7c**) and (*R*)-ibuprofen ((*R*)-**5d**).

Next, the present protocol was applied to the kinetic resolution of the racemic 2,3-diphenylpropanoic acid (**7a**), 2-phenylbutanoic acid (**7b**), 3-methoxy-2-phenylpropanoic acid (tropic acid methyl ether) (**7c**), and 2-cyclopentyl-2-phenylacetic acid (**7d**) using alcohol **4g** as a nucleophile (Scheme 2). As demonstrated by Eqs. 4, 6, 8, and 10, the combined use of benzoic anhydride and (+)-BTM afforded the corresponding optically active esters (*R*)-**8a**, (*R*)-**8b**, (*S*)-**8c**, and (*R*)-**8d** with high enantioselectivities (87%, 87%, 88%, and 90% ee, respectively) under the established conditions A, and fairly good *s*-values were observed for the reactions of the alcohol **4g** with **7a–d** ($s = 25$, 17, 20, and 19, respectively). It is worth noting that the effective kinetic resolutions of **7a–d** have not been achieved when the reaction was carried out in the presence of alcohol **4a** as a nucleophile (Eqs. 5, 7, 9, and 11), which was explored in our preliminary studies on this project ($s = 5$, 5, 18, and 3, respectively).

We then attempted the transformation of the optically active bis(9-phenanthryl)methyl esters into free carboxylic acids in order to obtain the corresponding 2-arylalkanoic acid derivatives (Scheme 3). Under the conventional hydrogenation conditions to remove the benzyl ester moiety, the cleavage of bis(9-phenanthryl)methyl esters (*R*)-**8a**, (*R*)-**8b**, (*S*)-**8c**, and (*R*)-**6d** was successfully carried out to give the chiral β-substituted-α-arylpropanoic acids (*R*)-**7a**, (*R*)-**7b**, (*S*)-**7c**, and (*R*)-ibuprofen ((*R*)-**5d**), respectively.



Scheme 4. Plausible reaction pathway of the kinetic resolution of racemic α-arylalkanoic acid ((±)-**7**) to form the chiral bis(9-phenanthryl)methyl ester ((*R*)-**8**) via the corresponding racemic mixed anhydride ((±)-**MA**).

The estimated reaction pathway is illustrated in Scheme 4. First, a mixed anhydride (±)-**MA** forms as a key intermediate in situ from aromatic anhydride with the racemic acid (±)-**7** by the promotion of (*R*)-(+)-BTM. In the next step, (*R*)- and (*S*)-**MA** would be activated again by (*R*)-(+)-BTM to form the corresponding zwitterionic species (*R,R*)-**int** and (*S,R*)-**int**, and then (*R,R*)-**int** generated from (*R*)-**MA** selectively reacts with **4g** to afford the desired ester (*R*)-**8** with high enantiomeric excess via the preferable transition structure (*R,R*)-**ts**. On the other hand, (*S*)-**MA** produces an unstable structure (*S,R*)-**ts**, which has a higher energy derived from steric repulsion between the substituent at the α-position of (*S*)-**7** and the phenyl group at C-2 of (*R*)-(+)-BTM. Therefore, it is assumed that the desired chiral ester (*R*)-**8** was preferentially obtained by the rapid transformation of (*R*)-**MA** through the stable transition state (*R,R*)-**ts**.

In summary, we have developed a widely applicable method for the kinetic resolution of racemic α-arylalkanoic acids with achiral alcohols. It was revealed that bis(9-phenanthryl)methanol reacted with the intermediary mixed anhydrides generated from aromatic anhydrides with α-arylpropanoic acids or β-substituted-α-arylpropanoic acids in the presence of (+)-BTM to produce the corresponding optically active esters with high ee's. Further studies of the mixed-anhydride method affording the chiral carboxylic acid derivatives are now in progress in this laboratory.

Acknowledgment

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References and notes

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5. Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.
6. Typical procedure for the esterification of 2-phenylpropanoic acid ((±)-**1**) by using Bz_2O with (+)-BTM (Table 1, entry 10, Conditions A): To a solution of (±)-**1** (29.5 mg, 0.196 mmol) and Bz_2O (54.3 mg, 0.240 mmol) in dichloromethane (2.0 mL) at room temperature were successively added diisopropylethylamine (62.9 μL, 0.360 mmol), (+)-BTM (2.5 mg, 9.9 μmol), and bis(9-phenanthryl)methanol (**4g**) (38.4 mg, 0.100 mmol). The mixture was stirred for 6 h at room temperature and then it was quenched with saturated aqueous NH_4Cl. The organic layer was separated and the aqueous layer was extracted with dichloromethane. 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 (*R*)-**2g** (42.3 mg, 42% yield, 89% ee) and a part of the recovered optically active carboxylic acid. The aqueous layer was acidified by 1 M HCl to adjust to pH 2 and then the aqueous layer was extracted with dichloromethane. 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 unreacted optically active carboxylic acid (*S*)-**1** (totally 9.9 mg, 33% yield, 48% ee). [$s = 27.3$].
7. Typical procedure for the esterification of 2-phenylpropanoic acid ((±)-**1**) by using PMBA (**3**) with (+)-BTM (Table 1, entry 11, Conditions B): To a solution of (±)-**1** (29.7 mg, 0.198 mmol) and PMBA (68.7 mg, 0.240 mmol) in dichloromethane (2.0 mL) at room temperature were successively added diisopropylethylamine (62.9 μL, 0.360 mmol), (+)-BTM (2.5 mg, 9.9 μmol), and bis(9-phenanthryl)methanol (**4g**) (38.4 mg, 0.100 mmol). The mixture was stirred for 12 h at room temperature and then it was quenched with saturated aqueous NH_4Cl. After the usual work up as described in conditions A, the corresponding ester (*R*)-**2g** (43.3 mg, 42% yield, 91% ee) and the unreacted optically active carboxylic acid (*S*)-**1** (12.4 mg, 42% yield, 52% ee) were obtained, respectively. [$s = 36.9$].