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Kinetic Resolution of Racemic 1-Heteroarylalkanols by Asymmetric Esterification Using Diphenylacetic Acid with Pivalic Anhydride and a Chiral Acyl-transfer Catalyst

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A variety of optically active 1-heteroarylalkanols and their esters, which include heteroaromatic moieties, such as 2-furyl, 2-thienyl, 3-thienyl, 2-thiazoyl, 2-benzothiazoyl, and 2-benzoxazoyl groups, are efficiently produced by a novel asymmetric esterification. The transition states that form the desired (*R*)-esters from the (*R*)-1-heteroarylalkanols are determined by DFT calculations, and the structural features of these transition states are systematically discussed.

Optically active 1-heteroarylalkanols are commonly utilized as chiral building blocks in pharmaceutical and agrochemical industries to provide valuable drugs via asymmetric synthesis. Several useful enzymatic methods for preparing chiral 1-heteroarylalkanols are available today for these purposes.[1] To the best of our knowledge, however, a general nonenzymatic method for the kinetic resolution (KR) of the racemic 1-heteroarylalkanols has not yet appeared until now. In order to expand the synthetic utilities of the chiral 1-heteroarylalkanol derivatives, we planned to develop a nonenzymatic method for the production of the chiral molecules starting from racemic substrates using the KR of (*R*)- and (*S*)-1-heteroarylalkanols.

We have reported the first asymmetric esterification[2,3] of racemic benzylic alcohols with free carboxylic acids via the formation of the mixed anhydrides in situ using carboxylic anhydrides as coupling reagents and chiral acyl-transfer catalysts, such as (*S*)-tetramisole and (*R*)-benzotetramisole ((*R*)-BTM), which were introduced by Birman et al.[4] Recently, we also achieved the KR of racemic 2-hydroxyalkanoates[5] with diphenylacetic acid using pivalic anhydride in the presence of (*R*)-BTM. During our examination of solvent effects, it became apparent that diethyl ether is a suitable media for the KR of racemic alcohols to improve both the reactivity and the selectivity.

Furthermore, we successfully determined several preferable transition states to form the desired chiral (*R*)-diesters from (*R*)-2-hydroxyesters using (*R*)-BTM,[5] and the optically active bis-(1-naphthyl)methyl (*R*)-esters from (*R*)-2-arylpropanoic acids[3b] using (*R*)-BTM based on theoretical calculations from density functional theory (DFT).[6] The transition state **ts**-(*R*)-**A** in Figure 1 presents the most stable structure forming methyl (*R*)-2-acetyloxypropanoate from methyl (*R*)-lactate by reaction with acetic anhydride and (*R*)-BTM. It was revealed that this transition state is strongly stabilized by the attractive interaction between oxygen in the ester carbonyl group and the positive electronic charge on the face of the dihydroimidazolium salt during the bond-forming step. Based on our investigation of the reaction mechanism during the BTM-mediated acyl-transfer catalysis, we also disclosed the preferable transition state **ts**-(*R*)-**B** to provide (*R*)-1-phenylethyl acetate from (*R*)-1-phenylethanol

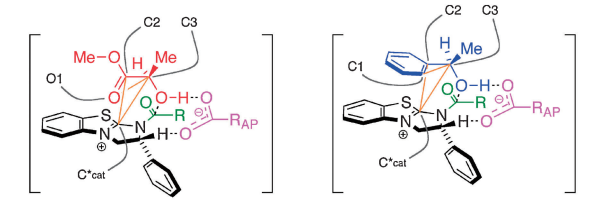


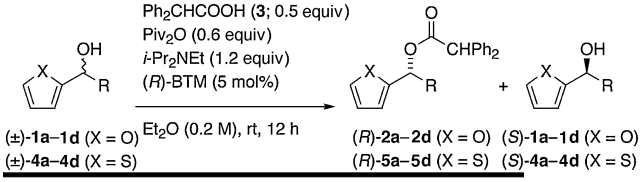
Figure 1. Transition structures **ts**-(*R*)-**A** and **ts**-(*R*)-**B** derived from methyl (*R*)-lactate and (*R*)-1-phenylethanol with the intermediary zwitterionic species (**int-II**) (See also Scheme 1, vide infra, and Supporting Information (SI)).[7]

by the reaction with acetic anhydride and (*R*)-BTM. It is apparently observed that the aromatic ring in (*R*)-1-phenylethanol is almost parallel to the horizontal plane of the conjugated aromatics in the dihydroimidazolium salt. The spontaneous formation of this stable stacking structure due to π–cation interaction is easily anticipated according to the pioneering theoretical analysis of the transition state to provide (*R*)-1-phenylethyl acetate using (*R*)-CF_3-PIP, a chiral acyl-transfer catalyst, reported by Houk, Birman, et al.[8] The dihedral angle $\theta_{(O1–C2–C3–C^*cat)}$ in **ts**-(*R*)-**A** is $-12.5°$ and it clearly suggests that the C=O group in the ester moiety and the plane surface of the conjugated aromatics in the dihydroimidazolium salt nearly cross at right angles.[5] On the other hand, the dihedral angle $\theta_{(C1–C2–C3–C^*cat)}$ in **ts**-(*R*)-**B** is 89.6°, so that the structure of **ts**-(*R*)-**B** includes the stacking correlation between the aromatic ring in (*R*)-1-phenylethanol and the plane surface of the conjugated aromatics in the dihydroimidazolium salt.

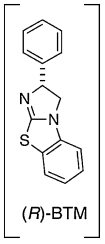
In this communication, we report the novel KR of a variety of racemic 1-heteroarylalkanols using diphenylacetic acid by the promotion of pivalic anhydride and (*R*)-BTM, as an application of our mixed anhydride formation technology for enantioselective esterification. The peculiar transition structures of several 1-heteroarylalkanols that will be converted into the corresponding chiral esters in the stereo-discriminating reactions are also discussed.

We first examined the KR of racemic 1-(2-furyl)ethanol ((±)-**1a**) with diphenylacetic acid (**3**) using pivalic anhydride and a catalytic amount of (*R*)-BTM in diethyl ether at room temperature for 12 h,[5] which was the standard reaction conditions established in our preliminary study (Table 1, Entry 1). Fortunately, the reaction smoothly proceeded to afford the corresponding ester (*R*)-**2a** (42% yield, 90% ee) and the recovered alcohol (*S*)-**1a** (42% yield, 57% ee) with a good *s*-value[9] ($s = 34$). This desirable result encouraged us to expand the scope of the substrate for the reaction, and we next examined

Table 1. Kinetic resolution of the racemic 1-(2-furyl)alkanols (±)-**1a**–**1d** and 1-(2-thienyl)alkanols (±)-**4a**–**4d**



Entry	X	R		Yield/% (**2**/**5**; **1**/**4**)	ee/% (**2**/**5**; **1**/**4**)	*s*
1	O	Me	**1a**	42; 42	90; 57	34
2	O	Et	**1b**	39; 61	89; 62	31
3	O	*i*-Pr	**1c**	41; 47	94; 67	69
4	O	*t*-Bu	**1d**	31; 65	91; 22	28
5[a]	O	*t*-Bu	**1d**	42; 55[b]	87; 67[b]	28
6	S	Me	**4a**	45; 53	89; 69	35
7	S	Et	**4b**	42; 46	93; 81	71
8	S	*i*-Pr	**4c**	45; 46	96; 82	118
9	S	*t*-Bu	**4d**	21; 68	96; 23	69
10[a]	S	*t*-Bu	**4d**	43; 51[b]	93; 70[b]	56

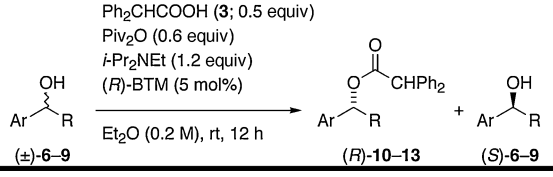


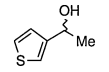
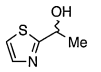
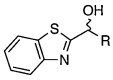
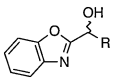
[a]Less hindered carboxylic acid ($Ph(CH_2)_2COOH$; 0.5 equiv) was used as an acyl donor instead of using $Ph_2CHCOOH$ (**3**; 0.5 equiv). [b]The corresponding 3-phenylpropanoate ((*R*)-**2e** or (*R*)-**5e**) was obtained instead of diphenylacetate ((*R*)-**2d** or (*R*)-**5d**).

other various racemic 1-(2-furyl)alkanols (±)-**1b**–**1d** and 1-(2-thienyl)alkanols (±)-**4a**–**4d** involving several aliphatic substituents at the C-1 positions. As shown in Entries 2–4, the KR of the 1-(2-furyl)alkanol derivatives (±)-**1b**–**1d** effectively took place to produce a variety of the optically active carboxylic esters (*R*)-**2b**–**2d** with high selectivities ($s = 28$–69). When 1-(2-furyl)-2-methylpropanol ((±)-**1c**; R = *i*-Pr, Entry 3) was employed under the above conditions, the chemical yield and enantiopurity of the desired ester (*R*)-**2c** reached the highest values (41% yield, 94% ee, $s = 69$). On the other hand, the reaction of 1-(2-furyl)-2,2-dimethylpropanol ((±)-**1d**; R = *t*-Bu, Entry 4) provided a relatively lower yield of (*R*)-**2d** with a high enantiopurity. We could obtain an improved yield of the desired ester (*R*)-**2e** with the same *s*-value when using 3-phenylpropanoic acid as a less hindered acyl donor for (±)-**1d** instead of using diphenylacetic acid (**3**) in this case (Entry 5). We observed better selectivities for the KR of 1-(2-thienyl)alkanol derivatives (±)-**4a**–**4d** compared to those of the KR of the racemic 1-(2-furyl)alkanols (±)-**1a**–**1d** (Entries 6–10; $s = 35$–118 versus Entries 1–5; $s = 28$–69).

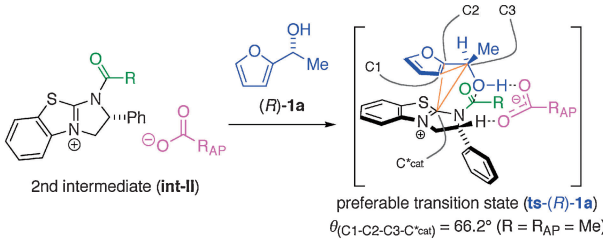
We further examined a variety of examples of the KR of 1-heteroarylalkanols **6**–**9** under the standard reaction conditions, and the generality of this protocol is demonstrated as shown in Table 2. The reaction of 1-(3-thienyl)ethanol ((±)-**6**), a positional isomer of 1-(2-thienyl)ethanol ((±)-**4a**), afforded nearly the same good *s*-value as that of the reaction of (±)-**4a** irrespective of the substitution pattern (Entry 1). It was revealed that the reaction of the racemic 1-(1,3-thiazol-2-yl)ethanol ((±)-**7**) and 1-(benzothiazol-2-yl)ethanol ((±)-**8a**) showed almost the same reactivity, whether or not an extra aromatic ring on (±)-**7** exists (Entries 2 and 3). On the other hand, we found that the selectivities depend on the structures of the ring systems of the aromatic moieties of (±)-**7** and (±)-**8a**, and a better result was

Table 2. Kinetic resolution of the racemic 1-heteroarylalkanols (±)-**6**–**9**



Entry	Substrate	R		Yield/% (**10**–**13**; **6**–**9**)	ee/% (**10**–**13**; **6**–**9**)	*s*
1			**6**	47; 44	85; 88	37
2			**7**	48; 52	87; 81	37
3		Me	**8a**	49; 48	91; 86	57
4		Et	**8b**	44; 52	96; 71	93
5		*i*-Pr	**8c**	47; 53	96; 86	142
6		Me	**9a**	50; 46	92; 99	122
7		Et	**9b**	48; 51	94; 91	100
8[a]		*i*-Pr	**9c**	48; 51	93; 94	96

[a]Reaction time; 18 h.



Scheme 1. Transition structure **ts**-(*R*)-**1a** derived from (*R*)-1-(2-furyl)ethanol ((*R*)-**1a**) with the intermediary zwitterionic species (**int-II**) (See also SI).[7]

obtained in the latter case (Entry 2; $s = 37$ versus Entry 3; $s = 57$). As shown in Entry 6, the reaction of 1-(benzoxazol-2-yl)ethanol ((±)-**9a**) provided the desired chiral ester (*R*)-**13a** in quantitative yield with good selectivity (50%, 92% ee), and the remaining alcohol (*S*)-**9a** was also recovered in very high yield and selectivity (46%, 99% ee) to afford an overall excellent selectivity ($s = 122$). It is noteworthy that all the derivatives of benzothiazoles **8a**–**8c** and benzoxazoles **9a**–**9c** in Table 2 (Entries 3–8) were successfully converted into the corresponding chiral esters (*R*)-**12a**–**12c**/**13a**–**13c** with excellent selectivities ($s = 57$–142) regardless of the aliphatic substituent R (R = Me; **8a**/**9a**, R = Et; **8b**/**9b**, R = *i*-Pr; **8c**/**9c**).

Determination of the transition state forming the optically active (*R*)-ester from (*R*)-1-(2-furyl)ethanol ((*R*)-**1a**) with the intermediary zwitterionic species (**int-II**), which was generated from acetic anhydride and (*R*)-BTM, was carried out using DFT calculations according to the former report on the KR of the racemic 2-hydroxyalkanoates.[5,10] Among the several calculated transition state models forming the desired ester from the alcohol (*R*)-**1a** with **int-II**, the most stable structure **ts**-(*R*)-**1a** is depicted in Scheme 1. All of the three-dimensional structures of the transition states in Scheme 1 and Figure 2 are shown in the SI.[7] We noted the stacking correlation between the furan ring and the plane surface of the conjugated aromatics in the dihydro-

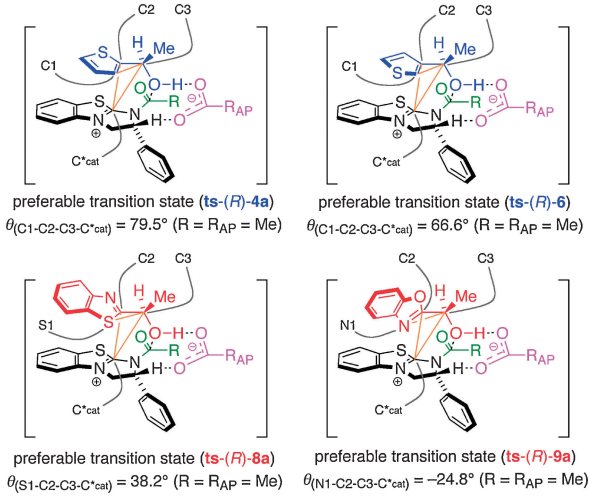


Figure 2. Transition structures **ts**-(*R*)-**4a**, **ts**-(*R*)-**6**, **ts**-(*R*)-**8a**, and **ts**-(*R*)-**9a** derived from (*R*)-1-(2-thienyl)ethanol ((*R*)-**4a**), (*R*)-1-(3-thienyl)ethanol ((*R*)-**6**), (*R*)-1-(benzothiazol-2-yl)ethanol ((*R*)-**8a**), and (*R*)-1-(benzoxazol-2-yl)ethanol ((*R*)-**9a**) with the intermediary zwitterionic species (**int-II**).

imidazolium salt because the value of the dihedral angle $\theta_{(C1–C2–C3–C^*cat)}$ in **ts**-(*R*)-**1a** is very large ($\theta = 66.2°$). This transition structure belongs to the **ts**-(*R*)-**B** type category similar to the reaction of the benzylic alcohols (cf. Figure 1 and SI);[7] and therefore, the strong coordination of oxygen in the furan ring to the positive electronic charge on the face of dihydroimidazolium salt is not observed in **ts**-(*R*)-**1a**.

Based on the former systematic studies of the reactions of (*R*)-**4a**, (*R*)-**6**, (*R*)-**8a**, and (*R*)-**9a** with **int-II** generated from acid anhydride with (*R*)-BTM, the corresponding transition structures were also determined as shown in Figure 2. The calculated results (upper two figures) showed that the dihedral angles $\theta_{(C1–C2–C3–C^*cat)}$ of the transition states **ts**-(*R*)-**4a** and **ts**-(*R*)-**6**, which were derived from (*R*)-1-(2-thienyl)ethanol ((*R*)-**4a**) and (*R*)-1-(3-thienyl)ethanol ((*R*)-**6**), are very large ($\theta = 79.5$ and 66.6°, respectively); consequently, it was proven that the thiophene groups function as π-electron donors to the plane surface of the conjugated aromatics in the dihydroimidazolium salt to form the **ts**-(*R*)-**B** type transition structures.

On the other hand, it was found that the sulfur in benzothiazole firmly coordinates to the cationic center in the most stable transition state **ts**-(*R*)-**8a** (Figure 2, left column, bottom figure), which was derived from (*R*)-1-(benzothiazol-2-yl)ethanol ((*R*)-**8a**) with **int-II**. The value of the dihedral angle $\theta_{(S1–C2–C3–C^*cat)}$ of the transition states **ts**-(*R*)-**8a** is relatively small ($\theta = 38.2°$), so that this structure could be classified in the **ts**-(*R*)-**A** type category, and we can observe the stabilization of **ts**-(*R*)-**8a** due to the attractive interaction between sulfur in the benzothiazole moiety and the positive electronic charge on the face of the dihydroimidazolium salt in this bond-forming step.

Furthermore, we could determine the transition structure of the reaction of (*R*)-**9a** with **int-II**.[11] The peculiar form of **ts**-(*R*)-**9a** is also depicted in Figure 2 (right column, bottom figure), in which the nitrogen in the oxazole coordinates to the cation center of **int-II**. This structure also belongs to the **ts**-(*R*)-**A** type category, because the value of the dihedral angle $\theta_{(N1–C2–C3–C^*cat)}$ of **ts**-(*R*)-**9a** is very small ($\theta = -24.8°$). The value of the dihedral angle of **ts**-(*R*)-**9a** is very close to that of **ts**-(*R*)-**A** ($\theta = -12.5°$) consisting of acetic anhydride, (*R*)-BTM, and methyl (*R*)-lactate. Hence, the observed strong coordination of nitrogen to the cationic center of **ts**-(*R*)-**9a** might be crucial to stabilizing the structure of **ts**-(*R*)-**9a**. It is deduced that the effective KR of the 1-(benzoxazol-2-yl)ethanol via **ts**-(*R*)-**9a** was attained from this structural effect in the transition state, because the similar transition state **ts**-(*R*)-**A** also includes the strong coordination of oxygen to the cationic center and the successful KR of the racemic 2-hydroxyesters was attained in prior experiments to produce remarkably high selectivity factors ($s = 47–202$).[5]

In summary, we have achieved the first efficient non-enzymatic method for providing the optically active 1-heteroarylalkanol derivatives by the KR of the racemic 1-heteroarylalkanols with diphenylacetic acid using pivalic anhydride in the presence of (*R*)-benzotetramisole ((*R*)-BTM). Further studies of the present method to provide chiral materials and other applications of this novel protocol are now in progress in our laboratory.

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10 Energy difference between transition states to form (*R*)-**2a** and (*S*)-**2a** from (*R*)-**1a** and (*S*)-**1a** with the 2nd intermediate (**int-II**), which was generated from diphenylacetic acid (**3**) and pivalic anhydride was calculated to be 3.92 kcal mol^{-1} at the B3LYP/6-311+G**//B3LYP/6-31G* level. See the SI.[7]
11 Energy difference between transition states to form (*R*)-**13a** and (*S*)-**13a** from (*R*)-**9a** and (*S*)-**9a** with the 2nd intermediate (**int-II**), which was generated from diphenylacetic acid (**3**) and pivalic anhydride was calculated to be 4.76 kcal mol^{-1} at the B3LYP/6-311+G**//B3LYP/6-31G* level. See the SI.[7]

