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PAPER

**(*R*)-(+)-*N*-Methylbenzoguanidine ((*R*)-NMBG) catalyzed kinetic resolution of racemic secondary benzylic alcohols with free carboxylic acids by asymmetric esterification†**

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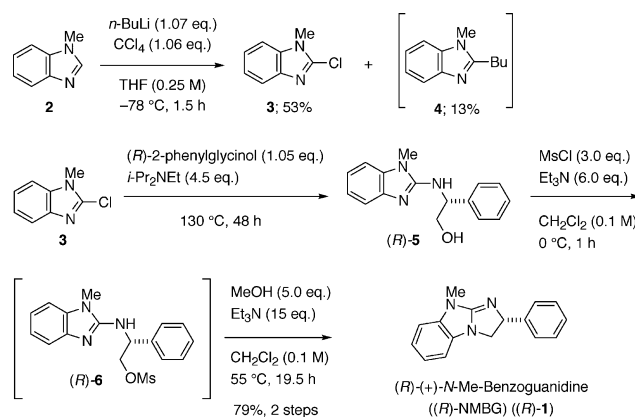
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(*R*)-(+)-*N*-Methylbenzoguanidine ((*R*)-NMBG) was found to function as an efficient acyl-transfer catalyst for the kinetic resolution of racemic secondary benzylic alcohols in the presence of achiral carboxylic acids and pivalic anhydride. The use of a tertiary amine in this reaction is not necessary to attain good chemical yields of the products. It was determined that diphenylacetic acid could be employed as the most suitable acyl donor for achieving a high enantioselectivity for the kinetic resolution of the racemic secondary benzylic alcohols having *normal aliphatic alkyl chains* at the C-1 positions. On the other hand, a less-hindered carboxylic acid, such as 3-phenylpropanoic acid, functioned as a better acyl donor for the kinetic resolution of racemic secondary benzylic alcohols having *branched aliphatic alkyl chains* at the C-1 positions.

Since Nájera *et al.* first attempted to use chiral guanidine as a basic catalyst for asymmetric syntheses in 1994,<sup>1</sup> numerous efforts have been devoted to develop useful chiral guanidine-type catalysts for this purpose.<sup>2</sup> To the best of our knowledge, however, almost all chiral guanidines have been used for the deprotonation stages in the asymmetric catalyses, and nucleophilic chiral guanidine species have still not yet been designed. Recently, we reported new methods for the kinetic resolution (KR) of not only racemic secondary alcohols<sup>3,4</sup> but also racemic  $\alpha$ -arylpropanoic acids<sup>5,6</sup> using carboxylic anhydride as a condensation reagent in the presence of the chiral acyl-transfer catalysts, such as (*S*)-tetramisole,<sup>7</sup> (*R*)-BTM,<sup>7</sup> and (*S*)- $\beta$ -Np-BTM<sup>5b</sup> (Fig. 1). In this communication, we first used the chiral *N*-methylbenzoguanidine (*R*)-**1** as a new nucleophilic catalyst for the KR of the racemic secondary benzylic alcohols by the asymmetric esterification with achiral carboxylic acids *via* the *in situ* formation of mixed anhydrides using pivalic anhydride as a coupling reagent.

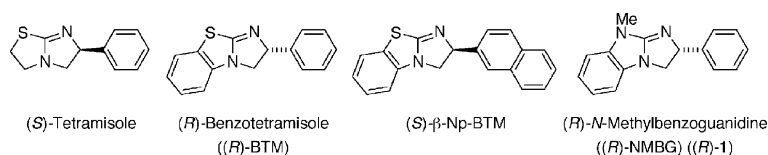
The hydrochloric acid salt of the racemic 9-methyl-2-phenyl-9-hydro-2-imidazolino[1,2-*a*]benzimidazole (**1**) was produced by Anisimova *et al.* in 1986,<sup>8</sup> but there has been no literature reference for the preparation of the chiral *N*-methylbenzoguanidine ((*R*)-NMBG) ((*R*)-**1**) until now, therefore, we decided to develop an alternative route for the synthesis of the chiral catalyst (*R*)-**1** as shown in Scheme 1.



**Scheme 1** Synthesis of (*R*)-(+)-*N*-methylbenzoguanidine ((*R*)-NMBG) ((*R*)-**1**).

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**Fig. 1** Structures of (*S*)-tetramisole, (*R*)-benzotetramisole ((*R*)-BTM), (*S*)- $\beta$ -Np-BTM, and (*R*)-*N*-methylbenzoguanidine ((*R*)-NMBG) ((*R*)-**1**).

**Table 1** Examination of the effect of the solvents and co-bases for the KR of ( $\pm$ )-**7**

Entry	Solvent	<i>i</i> -Pr <sub>2</sub> NEt	Yield ( <b>8a</b> ; <b>7</b> ) (%)	ee ( <b>8a</b> ; <b>7</b> ) (%)	<i>s</i>
1	CH <sub>2</sub> Cl <sub>2</sub>	— <sup>a</sup>	20; 70	91; 51	31
2	CH <sub>2</sub> Cl <sub>2</sub>	○ <sup>b</sup>	22; 58	88; 51	26
3	Et <sub>2</sub> O	— <sup>a</sup>	45; 45	88; 84	40
4	Et <sub>2</sub> O	○ <sup>b</sup>	47; 48	90; 77	43
5	AcOEt	— <sup>a</sup>	43; 51	93; 70	54
6	AcOEt	○ <sup>b</sup>	48; 51	90; 69	40

<sup>a</sup> Without *i*-Pr<sub>2</sub>NEt. <sup>b</sup> With *i*-Pr<sub>2</sub>NEt.

First, treatment of *N*-methylbenzimidazole (**2**) with butyllithium and carbon tetrachloride was carried out according to a known literature method<sup>9</sup> and the desired 2-chloro-*N*-methylbenzimidazole (**3**) was predominantly obtained in 53% yield with a small amount of the undesired butylated product **4** (13%). The transformation of **3** into (*R*)-NMBG ((*R*)-**1**) was successfully accomplished through the coupling with (*R*)-2-phenylglycinol, mesylation of the resulting chiral amino alcohol (*R*)-**5** and the successive annulation of an intermediary (*R*)-**6** via the one-pot operation based on similar previous studies (79% yield for 2 steps).<sup>5b</sup>

With the new catalyst (*R*)-NMBG ((*R*)-**1**) in hand, we then examined the effect of the solvents and co-bases on the (*R*)-NMBG-mediated KR of the racemic 1-phenylpropanol (( $\pm$ )-**7**) with 3-phenylpropanoic acid using pivalic anhydride at room temperature for 12 h, which were the modified reaction conditions established in our preliminary research (Table 1). When the reaction was carried out in dichloromethane as the solvent in the absence or presence of *i*-Pr<sub>2</sub>NEt, the desired chiral ester (*R*)-**8a** was obtained with good *s*-values,<sup>10</sup> however, the chemical yield was moderate, as listed in Entry 1 or 2. Fortunately, we found that the acceleration of the reaction was accomplished in diethyl ether or ethyl acetate solvent and higher *s*-values were also observed in these reactions (Entries 3–6). Interestingly, almost the same *s*-values were attained whether or not *i*-Pr<sub>2</sub>NEt was used as the co-base. We decided that the conditions used in Entry 3 (in diethyl ether without using tertiary amines) would be applied for our further studies of the KR of racemic secondary benzylic alcohols.

We next used a variety of carboxylic acids for the (*R*)-NMBG-catalyzed KR of ( $\pm$ )-**7** with pivalic anhydride in diethyl ether at room temperature for 24 h in order to optimize the acyl donor's structure (Table 2). As shown by Entries 1–5, several carboxylic acids possessing less-hindered substituents at the C-1 positions were applied for the KR of ( $\pm$ )-**7**, and it was found that both the reactivity and the selectivity were not so varied according to the main frameworks of the acyl donors. Among them, the highest yield of the desired ester **8a** (51%) and the highest enantioselectivity (*s* = 42) were simultaneously obtained when 3-phenylpropanoic acid was used as the acyl donor (Entry 1). It was further revealed that the employment of more hindered acyl donors, such as cyclohexanecarboxylic acid and diphenylacetic

**Table 2** (*R*)-NMBG-catalyzed KR of ( $\pm$ )-**7** using various carboxylic acids

Entry	R	Yield ( <b>8</b> ; <b>7</b> ) (%)	ee ( <b>8</b> ; <b>7</b> ) (%)	<i>s</i>
1	Ph(CH <sub>2</sub> ) <sub>2</sub>	(a) 51; 41	87; 87	42
2	Ph(CH <sub>2</sub> ) <sub>3</sub>	(b) 34; 57	90; 43	29
3	Et	(c) 40; 51	92; 53	42
4	(CH <sub>3</sub> ) <sub>2</sub> CH(CH <sub>2</sub> ) <sub>2</sub>	(d) 38; 54	92; 55	42
5	CH <sub>2</sub> =CHCH <sub>2</sub> CH <sub>2</sub>	(e) 46; 51	84; 65	22
6	<i>c</i> -C <sub>6</sub> H <sub>11</sub>	(f) 47; 47	90; 89	55
7	Ph <sub>2</sub> CH	(g) 55; 41	87; 99	73

**Table 3** (*R*)-NMBG-catalyzed KR of several racemic secondary benzylic alcohols ( $\pm$ )-**9a–d** with diphenylacetic acid or 3-phenylpropanoic acid

Entry	R	Time/h	Yield ( <b>10</b> / <b>11</b> ; <b>9</b> ) (%)	ee ( <b>10</b> / <b>11</b> ; <b>9</b> ) (%)	<i>s</i>
1 <sup>a</sup>	Me	(a) 12	48; 45	89; 80	43
2 <sup>a</sup>	Et	(b) 12	50; 50	92; 87	68
3 <sup>a</sup>	<i>i</i> -Pr	(c) 24	45; 50	88; 73	34
4 <sup>a</sup>	<i>t</i> -Bu	(d) 24	9; 91	87; 8	15
5 <sup>b</sup>	<i>i</i> -Pr	(c) 24	50; 38	90; 97	85
6 <sup>b</sup>	<i>t</i> -Bu	(d) 24	38; 46	94; 72	67

<sup>a</sup> Diphenylacetic acid was used as the acyl donor. The corresponding esters (*R*)-**10a–d** were produced. <sup>b</sup> 3-Phenylpropanoic acid was used as the acyl donor. The corresponding esters (*R*)-**11c,d** were produced.

acid, improved the enantioselectivities of the KR of ( $\pm$ )-**7** without any loss of reactivities as shown by Entries 6 and 7 (*s* = 55 and 73).

In order to explore the scope and limitation of these reactions, we further examined the asymmetric esterification of diphenylacetic acid with several racemic benzylic alcohols ( $\pm$ )-**9a–d**, which have different aliphatic substituents at the C-1 positions (R = Me, Et, *i*-Pr, and *t*-Bu) as listed in Table 3. When we carried out the KR of ( $\pm$ )-**9a** and **9b** bearing the normal aliphatic alkyl chains at the C-1 positions (R = Me and Et) under the standard reaction conditions (in diethyl ether at room temperature for 12 h), nearly half the amounts of the desired (*R*)-carboxylic esters ((*R*)-**10a** and (*R*)-**10b**) and the unreacted (*S*)-alcohols ((*S*)-**9a** and (*S*)-**9b**) were obtained in high yields with good enantiopurities (Entries 1 and 2, *s* = 43 and 68). Asymmetric esterification of the racemic 2-methyl-1-phenylpropanol (( $\pm$ )-**9c**; R = *i*-Pr) with diphenylacetic acid also produced a good enantioselectivity as shown in Entry 3 (*s* = 34), although this process required a longer reaction time (24 h) to complete conversion of half the amount of ( $\pm$ )-**9c** into the corresponding chiral ester (*R*)-**10c** because ( $\pm$ )-**9c** has a relatively large steric hindrance around the hydroxyl group.

When the reaction of 2,2-dimethyl-1-phenylpropanol (( $\pm$ )-**9d**; R = *t*-Bu) including the hindered *t*-Bu group was carried out under the standard reaction conditions, the reactivity was drastically

**Table 4** (*R*)-NMBG-catalyzed KR of a variety of racemic secondary benzylic alcohols ( $\pm$ -**12Aa–f**) and ( $\pm$ -**12Ba–f**) with diphenylacetic acid

Entry	Ar		Yield ( <b>13</b> ; <b>12</b> ) (%)	ee ( <b>13</b> ; <b>12</b> ) (%)	<i>s</i>
1	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	( <b>Aa</b> )	45; 54	89; 78	42
2	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	( <b>Ab</b> )	44; 43	86; 85	37
3	<i>p</i> -FC <sub>6</sub> H <sub>4</sub>	( <b>Ac</b> )	47; 50	81; 75	21
4	<i>o</i> -MeC <sub>6</sub> H <sub>4</sub>	( <b>Ad</b> )	50; 50	90; 87	54
5	$\alpha$ -Np	( <b>Ae</b> )	50; 50	88; 87	44
6 <sup>a</sup>	$\beta$ -Np	( <b>Af</b> )	52; 48	85; 83	32
7	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	( <b>Ba</b> )	48; 50	93; 80	64
8	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	( <b>Bb</b> )	50; 50	89; 86	50
9 <sup>a</sup>	<i>p</i> -FC <sub>6</sub> H <sub>4</sub>	( <b>Bc</b> )	47; 53	84; 78	27
10	<i>o</i> -MeC <sub>6</sub> H <sub>4</sub>	( <b>Bd</b> )	49; 51	92; 83	66
11 <sup>a</sup>	$\alpha$ -Np	( <b>Be</b> )	47; 53	95; 82	98
12	$\beta$ -Np	( <b>Bf</b> )	50; 42	90; 91	60

<sup>a</sup> The reaction was carried out for 6 h.

reduced and a low yield of (*R*)-**10d** was attained (Entry 4; 9%). However, the yield of an alternative desired ester (*R*)-**11d** increased to an acceptable level (Entry 6; 38%) along with a high enantioselectivity (*s* = 67) by employing 3-phenylpropanoic acid as a less-hindered acyl donor for ( $\pm$ )-**9c** instead of using diphenylacetic acid (*cf.* Entry 4). The KR of ( $\pm$ )-**9c** with 3-phenylpropanoic acid, which was proved to be a suitable acyl donor for the hindered substrates, was reexamined under the above conditions, and we observed remarkable improvements in the chemical yield and enantiopurity of the desired ester (*R*)-**11c** as shown in Entry 5 (50% yield, 90% ee, *s* = 85).

Then, we performed the (*R*)-NMBG-catalyzed KR of a variety of racemic secondary benzylic alcohols ( $\pm$ -**12Aa–f**) and ( $\pm$ -**12Ba–f**) for evaluating of the generality of this novel method (Table 4). Because racemic alcohols ( $\pm$ -**12Aa–f**) and ( $\pm$ -**12Ba–f**) do not possess bulky aliphatic alkyl chains at the C-1 positions (R = Me and Et), the KRs of ( $\pm$ -**12Aa–f**) and ( $\pm$ -**12Ba–f**) were carried out using diphenylacetic acid as the optimized acyl donor for less bulky substrates. All the reactions produced very good results, and nearly half amounts of the corresponding chiral carboxylic esters ((*R*)-**13Aa–f** and (*R*)-**13Ba–f**) and the unreacted chiral alcohols ((*S*)-**12Aa–f** and (*S*)-**12Ba–f**) were produced with high enantioselectivities (*s* = >20). As shown by Entries 1–3, the KR of ( $\pm$ -**12Aa–c**) afforded good *s*-values irrespective of the electronic effect at the *para* position on the aromatic rings of the alcohols. The reaction of ( $\pm$ -**12Ad**) smoothly proceeded in spite of the steric effect at the *ortho* position on the aromatic ring and showed the best result among Entries 1–6 (*s* = 54, Entry 4). When we carried out the reaction of 2-naphthoethanols ( $\pm$ -**12Ae**) and ( $\pm$ -**12Af**), good *s*-values were also obtained in both cases irrespective of the positions of the substituted groups on the naphthalene rings (Entries 5 and 6). We observed the tendency to have better results for the reactions of ( $\pm$ -**12Ba–f**) in comparison to those of ( $\pm$ -**12Aa–f**) (*s* = 27–98 in Entries 7–12 *versus* *s* = 21–54 in Entries 1–6). For example, the enantiopurity of the desired ester (*R*)-**13Be** reached

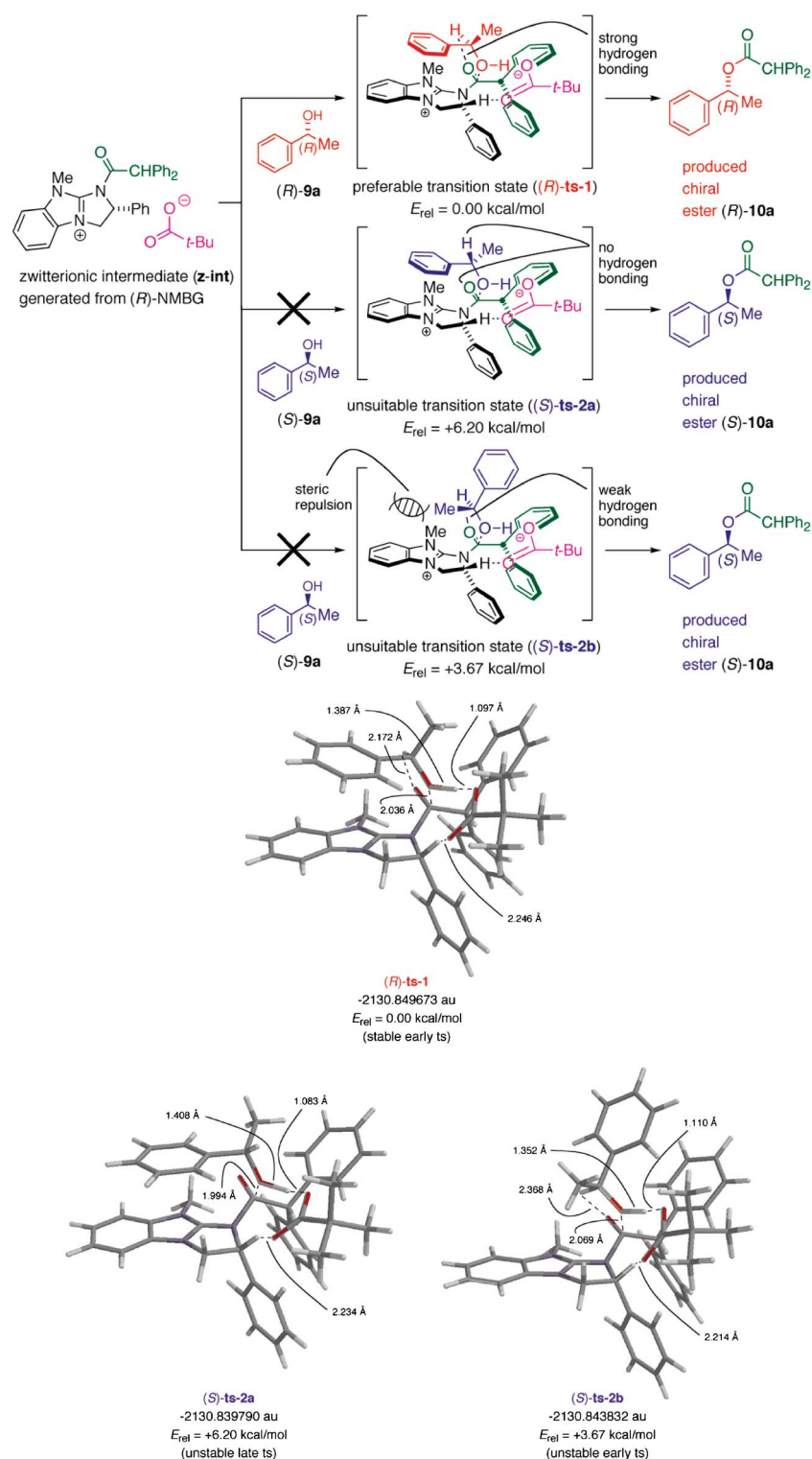
the highest value (95% ee) when ( $\pm$ )-**12Be** was employed under the above stated reaction conditions (*s* = 98, Entry 11).

Determination of the transition state forming the optically active (*R*)-ester ((*R*)-**10a**) from (*R*)-1-phenyl-1-ethanol ((*R*)-**9a**) using the zwitterionic intermediate (**z-int**), which was generated from the mixed anhydride and (*R*)-NMBG, was carried out using DFT calculations at the B3LYP/6-31G\*//B3LYP/6-31G\* level according to the former report on the KR of the racemic 2-hydroxyalkanoates<sup>3d</sup> and 2-arylpropanoic acids.<sup>5b,11</sup> Among several calculated transition states forming the desired ester (*R*)-**10a** from (*R*)-**9a**, the most stable structure (*R*)-**ts-1** is depicted in Scheme 2. The Cartesian coordinates of the three-dimensional structures of the transition states in Scheme 2 are shown in the ESI.†

We noted the stacking correlation between the benzene ring and the plane surface of the conjugated aromatics in the *N*-methylbenzoguanidinium salt. The alcohol (*R*)-**9a** has a rigid structure in which the conformation is restricted by the coordination of oxygen in the acyl donor moiety onto hydrogen at the C-1 position in (*R*)-**9a** (2.172 Å). The distance of the forming C–O bond (between the carbonyl carbon of the acid component and the oxygen of hydroxy) is 2.036 Å, and the distance of the cleaved O–H bond (between oxygen and hydrogen in hydroxy) is 1.387 Å. By the calculated bond distances of these elements, it is supported that (i) the nucleophilic attack of the alcohol on the carbonyl group and (ii) the deprotonation of the hydroxyl group with the carboxylate anion simultaneously proceeded under the concerted reaction mechanism to form the desired chiral ester (*R*)-**10a**.

On the other hand, two different structures ((*S*)-**ts-2a** and (*S*)-**ts-2b**) derived from (*S*)-1-phenyl-1-ethanol ((*S*)-**9a**) with **z-int** were found to produce the opposite stereoisomer (*S*)-**10a** *via* similar transacylation processes. The coordination of oxygen in the acyl donor moiety onto hydrogen at the C-1 position in (*S*)-**9a** is not observed in the structure (*S*)-**ts-2a**, therefore, the relative energy of the (*S*)-**ts-2a** considerably increases ( $E_{\text{rel}} = +6.20$  kcal mol<sup>-1</sup>) compared with the value of the stable transition state (*R*)-**ts-1** ( $E_{\text{rel}} = 0.00$  kcal mol<sup>-1</sup>). Another transition state (*S*)-**ts-2b** is the rotamer of (*S*)-**ts-2a**, and (*S*)-**ts-2b** has a conformation in which the coordination of oxygen in the acyl donor moiety onto hydrogen at the C-1 position in (*S*)-**9a** exists. However, the structure (*S*)-**ts-2b** has a higher energy ( $E_{\text{rel}} = +3.67$  kcal mol<sup>-1</sup>) compared to that of (*R*)-**ts-1** ( $E_{\text{rel}} = 0.00$  kcal mol<sup>-1</sup>) because the methyl group at the C-1 position in (*S*)-**9a** should be very close to the plane surface of the conjugated aromatics in the *N*-methylbenzoguanidinium salt.<sup>12</sup> This steric effect considerably increases the structural energy of (*S*)-**ts-2b**, and the reaction pathway to give the undesired ester (*S*)-**10a** is effectively prevented in the key transacylation process.

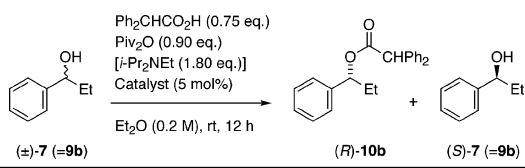
We finally reexamined the efficiency of the asymmetric esterification catalyzed by the representative three nucleophilic catalysts, (*S*)-tetramisole, (*R*)-BTM, and (*R*)-NMBG (Table 5). When the racemic alcohol ( $\pm$ )-**7** (= **9b**) was treated with diphenylacetic acid in the absence or presence of *i*-Pr<sub>2</sub>NEt in diethyl ether under the identical reaction conditions, the corresponding diphenylacetate **10b** and the recovered alcohol **7** were produced with good to high enantioselectivities (**10b**; 81–95% ee, **7**; 48–87% ee). The use of (*S*)-tetramisole without *i*-Pr<sub>2</sub>NEt afforded the lower yield of the desired ester **10b** compared to the reaction which was carried out using *i*-Pr<sub>2</sub>NEt (Entries 1 (**10b**; 38%) *versus* 2 (**10b**; 41%)). The



**Scheme 2** Optimized transition state geometries to form (*R*)-1-phenylethyl diphenylacetate ((*R*)-**10a**) or (*S*)-1-phenylethyl diphenylacetate ((*S*)-**10a**) from (*R*)-1-phenyl-1-ethanol ((*R*)-**9a**) or (*S*)-1-phenyl-1-ethanol ((*S*)-**9a**) Using DFT calculations at the B3LYP/6-31G\*\*/B3LYP/6-31G\* level.

same tendency was also observed in the (*R*)-BTM-mediated KR (Kinetic Resolution) of the racemic **7** with diphenylacetic acid using pivalic anhydride; that is, the desired diphenylacetate **10b** was formed in a relatively lower yield (44%) with a fairly good selectivity ( $s = 96$ ) by the reaction in the absence of *i*-Pr<sub>2</sub>NEt of

Entry 3, and the better yield of **10b** (47%) with a lower selectivity ( $s = 35$ ) was attained by the reaction in the presence of *i*-Pr<sub>2</sub>NEt as shown in Entry 4. A most ideal result occurred with Entry 5 in which (*R*)-NMBG was used as a nucleophilic catalyst without *i*-Pr<sub>2</sub>NEt, and the quantitative yields of the desired ester (**10b**; 50%)

**Table 5** Examination of the nucleophilic catalysts and co-bases for the KR of ( $\pm$ )-**7**


Entry	Catalyst	<i>i</i> -Pr <sub>2</sub> NEt	Yield ( <b>10b</b> ; <b>7</b> ) (%)	ee ( <b>10b</b> ; <b>7</b> ) (%)	<i>s</i>
1	( <i>S</i> )-Tetramisole	— <sup>a</sup>	38; 62	91 <sup>c</sup> ; 48 <sup>d</sup>	33
2	( <i>S</i> )-Tetramisole	○ <sup>b</sup>	41; 59	81 <sup>c</sup> ; 51 <sup>d</sup>	16
3	( <i>R</i> )-BTM	— <sup>a</sup>	44; 53	95; 81	96
4	( <i>R</i> )-BTM	○ <sup>b</sup>	47; 53	89; 71	35
5	( <i>R</i> )-NMBG	— <sup>a</sup>	50; 50	92; 87	68
6	( <i>R</i> )-NMBG	○ <sup>b</sup>	51; 48	82; 79	24

<sup>a</sup> Without *i*-Pr<sub>2</sub>NEt. <sup>b</sup> With *i*-Pr<sub>2</sub>NEt. <sup>c</sup> (*S*)-**10b** was obtained instead of forming (*R*)-**10b**. <sup>d</sup> (*R*)-**7** (= **9b**) was obtained instead of forming (*S*)-**7** (= **9b**).

and the recovered alcohol (**7**; 50%) were achieved with a good selectivity ( $s = 68$ ). It was found that the addition of *i*-Pr<sub>2</sub>NEt to this reaction system decreased the enantioselectivity of the KR of racemic **7** as shown in Entry 6 ( $s = 24$ ). Regarding the yields and the ee's of not only the desired diphenylacetate **10b**, but also the recovered alcohol **7**, the (*R*)-NMBG-catalyzed KR of the racemic alcohol **7** without *i*-Pr<sub>2</sub>NEt has been determined as the most effective protocol for the simultaneous formation of the two desired chiral compounds **10b** (92% ee) and **7** (87% ee). It is noteworthy that the tertiary amine-free reaction conditions in Entry 5 have the advantage of atom-economy to produce both the chiral ester **10b** and the chiral alcohol **7** in very high yields without using an excess amount of the basic reagent.

In conclusion, (*R*)-(+)-*N*-methylbenzoguanidine ((*R*)-NMBG) was found to be a new and efficient acyl-transfer catalyst for the KR of racemic secondary benzylic alcohols with free carboxylic acids in the presence of pivalic anhydride. This reaction does not require the use of additional co-bases, such as tertiary amines, to produce the desired chiral esters in high yields. A variety of optically active secondary alcohols and their carboxylic esters were efficiently produced in high ee's by this novel asymmetric esterification. Further studies of other utilities of (*R*)-NMBG are now in progress in this laboratory.

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- All calculations were performed with the program package Spartan '08 V1.2.0 of Wavefunction Inc. (<http://www.wavefun.com>).
- Transition state energies of (*R*)-**ts-1**, (*S*)-**ts-2a**, and (*S*)-**ts-2b** were also calculated using a polarization function including p functions on hydrogen atoms (6-31G\*\*), a diffuse function (6-31+G\*), and an advanced combination (6-31+G\*\*), and the following similar results were obtained.  $E(R)\text{-ts-1}(B3LYP/6-31G^{**}/B3LYP/6-31G^*) = -2130.9227176$  au ( $E_{rel} = 0.00$  kcal mol<sup>-1</sup>),  $E(S)\text{-ts-2a}(B3LYP/6-31G^{**}/B3LYP/6-31G^*) = -2130.9126403$  au ( $E_{rel} = +6.32$  kcal mol<sup>-1</sup>),  $E(S)\text{-ts-2b}(B3LYP/6-31G^{**}/B3LYP/6-31G^*) = -2130.9166457$  au ( $E_{rel} = +3.81$  kcal mol<sup>-1</sup>);  $E(R)\text{-ts-1}(B3LYP/6-31+G^*/B3LYP/6-31G^*) = -2130.9146371$  au ( $E_{rel} = 0.00$  kcal mol<sup>-1</sup>),  $E(S)\text{-ts-2a}(B3LYP/6-31+G^*/B3LYP/6-31G^*) = -2130.9044371$  au ( $E_{rel} = +6.40$  kcal mol<sup>-1</sup>),  $E(S)\text{-ts-2b}(B3LYP/6-31+G^*/B3LYP/6-31G^*) = -2130.9083136$  au ( $E_{rel} = +3.97$  kcal mol<sup>-1</sup>);  $E(R)\text{-ts-1}(B3LYP/6-31+G^{**}/B3LYP/6-31G^*) = -2130.9862929$  au ( $E_{rel} = 0.00$  kcal mol<sup>-1</sup>),  $E(S)\text{-ts-2a}(B3LYP/6-31+G^{**}/B3LYP/6-31G^*) = -2130.9759809$  au ( $E_{rel} = +6.47$  kcal mol<sup>-1</sup>),  $E(S)\text{-ts-2b}(B3LYP/6-31+G^{**}/B3LYP/6-31G^*) = -2130.9802310$  au ( $E_{rel} = +3.80$  kcal mol<sup>-1</sup>).