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Kinetic Resolution of Racemic Carboxylic Acids by an L-Histidine-Derived Sulfonamide-Induced Enantioselective Esterification Reaction

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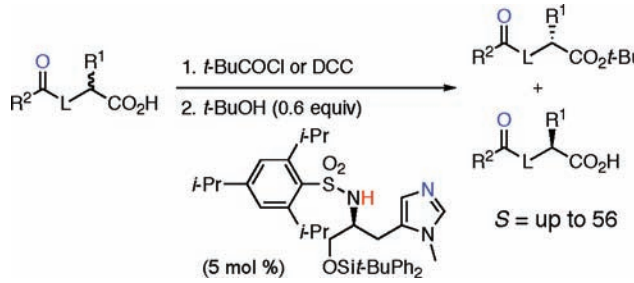
ABSTRACT



The direct and catalytic kinetic resolution of racemic carboxylic acids bearing a Brønsted base such as O-protected α-hydroxy carboxylic acids and N-protected α-amino acids has been accomplished through an L-histidine-derived sulfonamide-induced enantioselective esterification reaction with *tert*-butyl alcohol for the first time. Highly asymmetric induction [$S(k_{fast}/k_{slow})$ = up to 56] has been achieved under the equilibrium between a chiral catalyst and two diastereomeric acylammonium salts through an intramolecular hydrogen-bonding interaction.

We recently described the kinetic resolution of racemic alcohols **2** bearing a Brønsted base site such as a carbamoyl oxygen by L-histidine-derived sulfonamide (**1**)-induced enantioselective acylation with isobutyric anhydride (Scheme 1).[1–3] Compounds **1** are small artificial acylases that contain an *N*-methylimidazole moiety as a nucleophilic base and a sulfonamidyl proton as a Brønsted acid and induce the high-level kinetic resolution of (±)-**2** through hydrogen bonding between a sulfoamidyl proton of **1** and a carbonyl oxygen of **2**.

We report here the kinetic resolution of racemic carboxylic acids **4** bearing a Brønsted base site as well as (±)-**2** by **1**-induced enantioselective esterification (Scheme 2). To the best of our knowledge, this is the first successful example

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(1) (a) Ishihara, K.; Kosugi, Y.; Akakura, M. *J. Am. Chem. Soc.* **2004**, *126*, 12212. (b) Ishihara, K.; Kosugi, Y.; Akakura, M. *Tetrahedron* **2007**, *63*, 6191. For an account article, see: (c) Ishihara, K.; Sakakura, A.; Hatano, M. *Synlett* **2007**, 686.

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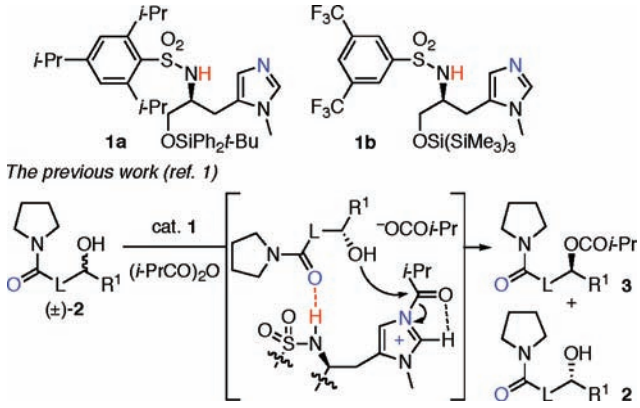
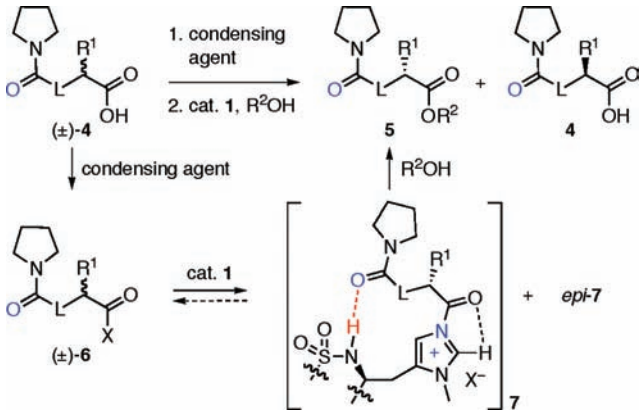
Scheme 1. Kinetic Resolution of (±)-**2**



of the *direct* kinetic resolution of racemic carboxylic acids induced by artificial enzymes. In contrast, there have been several reported examples of the enantioselective catalytic

Scheme 2. Our Proposal for the Kinetic Resolution of (±)-**4**

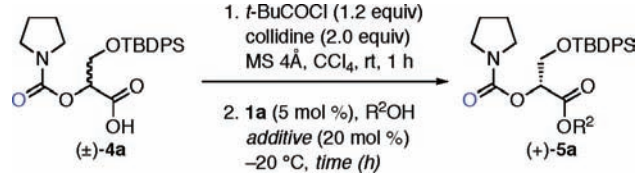


alcoholysis or thiolysis of racemic or prochiral 2-pyridinethiol esters,[4] oxazolidinethiones,[5] and cyclic carboxylic acid derivatives or anhydrides.[6,7] However, such activated derivatives of racemic carboxylic acids must be used as isolated substrates for kinetic resolution.

Our proposal is shown in Scheme 2. If (±)-**4** can be activated as (±)-**6** with a suitable condensing agent in situ, the subsequent kinetic resolution of (±)-**6** may occur at the generation step of acylammonium salts **7** and *epi*-**7** with or without an enantioselective hydrogen bonding interaction between (±)-**6** and **1** regardless of alcohols (R^2OH) (*the first kinetic control*). However, if the conversion of (±)-**6** to **7** and/or *epi*-**7** is reversible, the enantioselectivity would be determined by the rate difference of the esterification of **7** and *epi*-**7** with R^2OH (*the second kinetic control*).

First, the esterification of (±)-**4a**, which was derived from (±)-glyceric acid with alcohols, was attempted in the presence of 5 mol % of **1a** in carbon tetrachloride at −20 °C (Table 1). **4a** was activated as a mixed anhydride **6a** (X = *t*-$BuCO_2$) with pivaloyl chloride (1.2 equiv) in the presence of 2,4,6-collidine and MS 4Å in situ before the addition of **1a** (5 mol %) and alcohols (0.5∼0.7 equiv).[8] Although the esterification of **6a** with benzyl alcohol proceeded even at −20 °C, kinetic resolution was observed at quite a low level (entry 1). The reactivity of benzyl alcohol is high enough to react with the mixed anhydride in the absence of **1a** (entry 1). This is one of the reasons why the esterification with benzyl alcohol showed poor enantioselectivity. The reaction with isopropyl alcohol in the presence of pivaloyl chloride (1.0 equiv) showed low reactivity and gave moderate enantioselectivity [Selective factor: $S(k_{\text{fast-reacting enantiomer}}/k_{\text{slow-}}$

Table 1. Kinetic Resolution of (±)-**4a** Induced by **1a**[a]



entry	R^2OH (equiv)	additive[b]	*t* (h)[b]	yield (%)[c] of **5a**	*ee* (%)[d] of **5a**, **4a**	*S*[e]
1[f]	BnOH, 0.5	-	6	14	-, -	-
2	BnOH, 0.5	-	6	31	6, 0	1
3[g]	*i*-PrOH, 0.7	-	24	34	23, -	1.8
4	*i*-PrOH, 0.7	-	22	55	27, -	2.3
5	*i*-PrOH, 0.7	*t*-$BuCO_2H$	19	69 [66]	28, 55	3.1 [2.9]
6[h]	*i*-PrOH, 0.5	*t*-$BuCO_2H$	25	50 [44]	69, 54	11 [9.3]
7	*t*-BuOH, 0.6	-	48	16	92, -	27
8	*t*-BuOH, 0.6	*t*-$BuCO_2H$	52	39	89, -	31
9[i]	*t*-BuOH, 0.6	*t*-$BuCO_2H$	24	29 [26]	73, 25	8.6 [8.3]

[a] Unless otherwise noted, (±)-**4a** (0.50 mmol) was used in CCl_4 (1.5 mL). TBDPS = Si*t*-$BuPh_2$. [b] For step 2. [c] Isolated yield. The conversion, which was calculated by using the ee's of **5a** and **4a**, is shown in brackets. [d] HPLC analysis. [e] The *S* was calculated by using the yield and ee of (+)-**5a**. The *S*, which was calculated by using the ee's of (+)-**5a** and (−)-**4a**, is shown in brackets. See ref 9. [f] The reaction was conducted in the absence of **1a**. [g] 1.0 equiv of *t*-BuCOCl was used. [h] After a solution of *i*-PrOH in CCl_4 (1.0 mL) was added dropwise to a solution of **6a** in CCl_4 (0.5 mL) for 24 h, the reaction mixture was stirred for 1 h. [i] **1b** was used instead of **1a**.

(4) Narasaka, K.; Kanai, F.; Okudo, M.; Miyoshi, N. *Chem. Lett.* **1989**, 1187.

(5) (a) Notte, G. T.; Sammakia, T.; Steel, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 13502. (b) Notte, G. T.; Sammakia, T. *J. Am. Chem. Soc.* **2006**, *128*, 4230.

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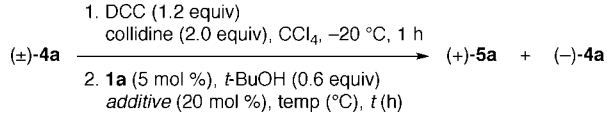
(7) For the enantioselective dynamic kinetic resolution of azalactones, see: (a) Liang, J.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 3154. (b) Berkessel, A.; Mukherjee, S.; Müller, T. N.; Cleemann, F.; Roland, K.; Brandenburg, M.; Neudörfl, J.-M.; Lex, J.-M. J. *Org. Biomol. Chem.* **2006**, *4*, 4319.

(8) It was ascertained that a mixed anhydride **6** was quantitatively obtained from **4** and pivaloyl chloride under the conditions for step 1 shown in Table 1. Dried MS 4Å was effective at preventing the hydrolysis of pivaloyl chloride during the reaction of step 1.

reacting enantiomer)[9] = 1.8] (entry 3). The use of 1.2 equiv of pivaloyl chloride increased the reactivity without loss of enantioselectivity (entry 4). Interestingly, the addition of pivalic acid (20 mol %) improved the reactivity and enantioselectivity (S = 3.1, entry 5). Pivalic acid would probably serve as a Brønsted acid (ammonium proton) to activate **6a** or a nucleophilic base[10] or Brønsted base (pivalate anion) to assist the equilibrium between **6a** and its acylammonium salt **7a** in the presence of collidine.[11] However, the enantioselectivity was still moderate. Surprisingly, the use of *tert*-butyl alcohol gave high enantioselectivity (S = 31, entry 8). Pivalic acid promoted the esterification with *tert*-butyl alcohol as well as that with isopropyl alcohol (entry 4 vs entry 5, entry 7 vs entry 8). The dramatic improvement in enantioselectivity upon switching from isopropyl alcohol to *tert*-butyl alcohol suggests that equilibrium between **4a** and **7a** may be important for attaining a high level of kinetic resolution.[12] These experimental results suggest that *the first kinetic resolution*at the generation step of **7a** would occur at a low level. However, when the esterification step was much slower than the generation step of **7a**, such as in entry 5, higher enantioselectivity was observed with *the second kinetic control*.In fact, higher asymmetric induction was observed with the dropwise addition of isopropyl alcohol (entry 5 vs entry 6). Catalyst **1b** was inferior to **1a** with regard to enantioselectivity (entry 9).

Next, other condensing agents were examined for the above reaction. As shown in Table 2, the esterification of

Table 2. Kinetic Resolution of (±)-**4a** Induced by **1a**[a]



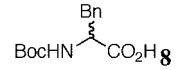
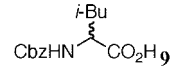
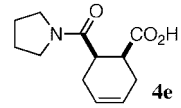
entry	additive	temp (°C), t (h)[b]	yield (%)[c] of (+)-**5a**	ee (%)[d] of (+)-**5a**, (−)-**4a**	S[e]
1	t-$BuCO_2H$	−20, 17	41	89, -	28
2	-	−20, 3	[35]	92, 49	[37]
3[f]	-	−40, 38	38 [37]	94, 56	57 [56]

[a] Unless otherwise noted, (±)-**4a** (0.50 mmol) was used in CCl_4 (1.5 mL). [b] For step 2. [c] Isolated yield. The conversion, which was calculated by using the ee's of **5a** and **4a**, is shown in brackets. [d] HPLC analysis. [e] The S was calculated by using the yield and ee of (+)-**5a**. The S, which was calculated by using the ee's of (+)-**5a** and (−)-**4a**, is shown in brackets. See ref 9. [f] Toluene (1.0 mL) was used instead of CCl_4.

(±)-**4a** with *tert*-butyl alcohol proceeded more smoothly with the use of *N*,*N*′-dicyclohexylcarbodiimide (DCC) instead of pivaloyl chloride at −20 °C under the same conditions as for entry 5 in Table 1 (entry 1). When DCC was used in the absence of pivalic acid and dried MS 4Å, the enantioselectivity and reactivity were further increased (entry 3). Thus, the esterification proceeded even at −40 °C with the use of DCC without the addition of pivalic acid to give (+)-**5a** in 38% yield with 94% ee (S = 56, entry 3).[13]

To explore the generality and scope of the above **1**-induced kinetic resolution, the esterification of several structurally diverse carboxylic acids was examined according to method A (conditions in entry 8 in Table 1) or method B (conditions in entry 2, Table 2) which were optimized for (±)-**4a** (Table 3). The esterification of not only **4a** but also other O-protected α-hydroxycarboxylic acids **4b**−**d** gave high S values (entries 1−6). (±)-*N*-Boc phenylalanine (**8**),[15] (±)-*N*-Cbz leucine (**9**), and (±)-*syn*-6-(pyrrolidine-1-carbonyl) cyclohex-3-enecarboxylic acid (**4e**) were also suitable substrates (entries 7−11). Although the reaction conditions were not optimized for each substrate, methods A and B were both effective for racemic carboxylic acids bearing a Brønsted base site. On the other hand, the present protocol was not effective for simple racemic carboxylic acids such as 2-phenylpropanoic acid (**10**) (entry 12). Nevertheless, the kinetic resolution of **10** was observed in the condensation

Table 3. Generality and Scope of the **1**-Induced Kinetic Resolution of Racemic Carboxylic Acids (Method A or B)[a]

entry	(±)-carboxylic acid	***Method*** (cat. **1**)	t (h)[b]	yield (%)[c]	ee (%)[d] of esters, acids	S[e]
1	**4b** [R^1 = Bn, L = O]	***A*** **(1a)**	48	34	86, –	21
2	**4b** [R^1 = Bn, L = O]	***B*** **(1a)**	6	39 [39]	88, 57	29 [29]
3	**4c** [R^1 = *i*-Pr, L = O]	***A*** **(1a)**	48	10	83, –	11
4	**4d** [R^1 = Ph, L = O]	***A*** **(1a)**	48	34	79(*R*), –	12
5	**4d** [R^1 = Ph, L = O]	***A*** **(1b)**	24	10	91(*R*), –	24
6	**4d** [R^1 = Ph, L = O]	***B*** **(1a)**	10	[52]	63(*R*), 68(*S*)	[8.9]
7	 **8**	***A*** **(1a)**	48	32	68(*R*), –	7.0
8	**8**	***B*** **(1a)**	20	[41]	39(*R*), 27(*S*)	[2.9]
9[f]	 **9**	***B*** **(1a)**	24	12	75, –	7.5
10	 **4e**	***A*** **(1a)**	25	0	–, –	–
11[g]	**4e**	***A*** **(1a)**	25	42	76, –	13
12	PhMeCHCO$_2$H **10**	***A*** **(1a)**	24	[43]	<5, <5	1.0
13[h]	**10**	***A'*** **(1a)**	2	17	60, –	4.4
14[h]	**10**	***B'*** **(1a)**	2	54	50, –	5.2

[a] Unless otherwise noted, (±)-carboxylic acids (0.25 mmol) were in CCl_4[14] (1.5 mL) according to method A or B (see text). [b] For step 2. [c] Isolated yield of esters. The conversion, which was calculated by using the ee's of esters and acids, is shown in brackets. [d] HPLC analysis. [e] The S was calculated by using the yield and ee of esters. The S, which was calculated by using the ee's of esters and acids, is shown in brackets. See ref 9. [f] Toluene was used as solvent. [g] *i*-PrOH (0.6 equiv) was used at 0 °C. [h] The condensation of **8** (0.25 mmol) with 2-oxazolidinone (0.6 equiv) in CCl_4 (1 mL) was carried out in the presence of *N*,*N*-diisopropylethylamine (2 equiv) and *t*-BuCOCl (1.2 equiv, method A′) or DCC (1.2 equiv, method B′) at room temperature for 2 h.

(9) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.
(10) Pivalate anion might promote the conversion of **7a** to **6a**.
(11) The results of entries 3 and 4 indicated that unreacted pivaloyl chloride did not inactivate **1a**.
(12) (a) Spivey, A. C.; Arseniyadis, S. *Angew Chem. Int. Ed.* **2004**, *43*, 5436. (b) Xu, S.; Held, I.; Kempf, B.; Mayr, H.; Steglish, W.; Zipse, H. *Chem.−Eur. J.* **2005**, *11*, 4751.
(13) A mixed anhydride of **4a** and *t*-$BuCO_2H$ was formed in situ (entry 1). However, anhydride of **4a** was not formed as a major species under conditions of entries 2 and 3.

with a nucleophile bearing a Brønsted base site such as 2-oxazolidinone instead of *tert*-butyl alcohol (entries 13 and 14).

Since the equilibrium between **1a**, (±)-**6d**, **7d**, and *epi*-**7d** is fast relative to esterification with *tert*-butyl alcohol to **5d**, the Curtin−Hammett principle applies, and the relative free energies of activation for the reaction of **7d** and *epi*-**7d** with *tert*-butyl alcohol will determine the enantioselectivity (*selectivity factor*). If intramolecular hydrogen bonding exists between the sulfonamidyl proton and the carbamoyl oxygen in **7d**, **7d** would be thermodynamically more stable than *epi*-**7d** because of the steric hindrance between R^b and the pyrrolidinyl group (Figure 1). Furthermore, when *tert*-butyl

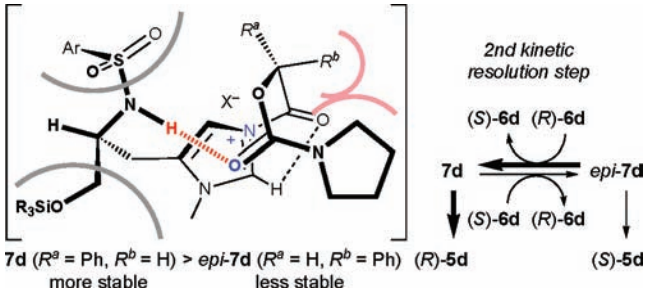
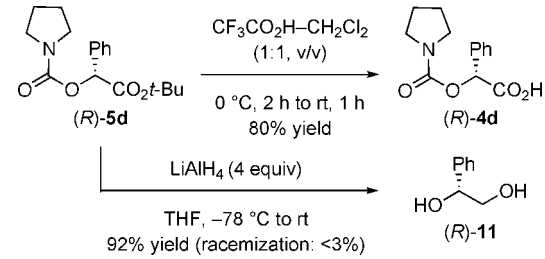


Figure 1. Predictable diastereomeric acylammonium salts **7d** and *epi*-**7d** and the second kinetic resolution step.

alcohol attacks the carbonyl carbon of **7d**, the carbonyl carbon changes hybridization to sp^3, and the interaction between R^b and the pyrrolidinyl group gets more severe, whereas less change occurs in the steric environment of R^a. Thus, the relative free energy of activation for the reaction of **7d** would be lower than that of *epi*-**7d** to give (*R*)-**5d** predominantly.

(*R*)-*tert*-Butyl α-(carbamoyloxy)carboxylate **5d**, which was produced by the asymmetric esterification, was chemoselectively transformed to (*R*)-**4d** under acidic conditions without any epimerization (Scheme 3).[16] In contrast, it was difficult

Scheme 3. Deprotection of Optically Active (*R*)-**5d** without Epimerization



to hydrolyze the carbamoyloxy group of (*R*)-**5** or (*R*)-**4** without epimerization. However, the reduction of (*R*)-**5d** with lithium aluminum hydride gave (*R*)-1,2-diol **11** in high yield without epimerization (Scheme 3).

In summary, we achieved a catalytic and direct kinetic resolution of racemic carboxylic acids for the first time under the equilibrium between a chiral catalyst and two diastereomeric acylammonium salts through an intramolecular hydrogen-bonding interaction.

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Supporting Information Available: Experimental procedures, spectroscopic data for all new compounds, $^1H/^{13}C$ NMR spectra, and HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Carbon tetrachloride was more suitable than toluene to dissolve substrates.

(15) Unfortunately, the ureas derived from reacting (±)-α-amino acids with 1-pyrrolidine-1-carbonyl chloride were decomposed by treatment with condensing agents.

(16) *tert*-Butyl group of **5a** (R^2 = *t*-Bu) was also chemoselectively cleaved under acidic conditions (CF_3CO_2H−CH_2Cl_2 (1:1(v/v)), 0 °C, 2 h) to give (+)-**4a** in >99% yield.