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Kinetic Resolution of Racemic Carboxylic Acids through Asymmetric Protolactonization Promoted by Chiral Phosphonous Acid Diester

Masayuki Sakuma,[†] Akira Sakakura,[*,‡] and Kazuaki Ishihara[*,†,§]

Graduate School of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8603, Japan, Graduate School of Natural Science and Technology, Okayama University, 3-1-1 Tsushima-naka, Kita-ku, Okayama 700-8530, Japan, and JST, CREST, Japan

ishihara@cc.nagoya-u.ac.jp; sakakura@okayama-u.ac.jp

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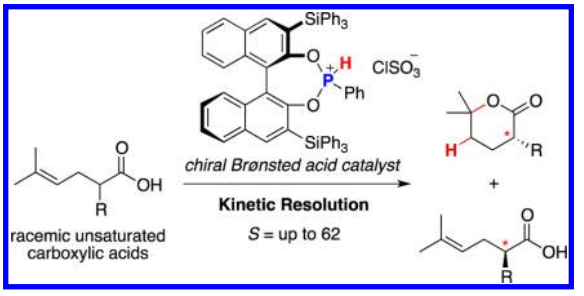
ABSTRACT



Chiral phosphonium salts induce the kinetic resolution of racemic α-substituted unsaturated carboxylic acids through asymmetric protolactonization. Both the lactones and the recovered carboxylic acids are obtained with high enantioselectivities and high S (= k_{fast}/k_{slow}) values. Asymmetric protolactonization also leads to the desymmetrization of achiral carboxylic acids. Notably, chiral phosphonous acid diester not only induced the enantioselectivity but also promoted protolactonization.

The synthesis of optically active carboxylic acids and lactones is an important subject in the field of medicinal and pharmaceutical chemistry. Intramolecular cyclization of unsaturated carboxylic acids is a useful method for the direct synthesis of lactones. However, the conventional methods, which use electrophilic reagents (EX) such as halonium compounds, organochalcogens, and transition metal complexes,[1,2] have the drawback that they require an additional step to remove the substituents (E) of the products. Although the proton-induced lactonization (protolactonization) of unsaturated carboxylic acids using a Brønsted acid is also well-known, it most often occurs with more than a stoichiometric amount of a Brønsted acid.[3] On the other hand, it has been reported that trifluoromethanesulfonic acid (TfOH) catalyzes the cyclization of unsaturated carboxylic acids to give a variety of α- or β-substituted γ- and δ-lactones in excellent yields.[4] However, it would be very difficult to apply this method to an asymmetric version, since these reactions require harsh conditions.

[†] Nagoya University.
[‡] Okayama University.
[§] JST.

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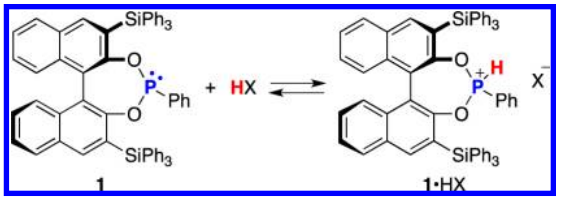
While the number of chiral Brønsted acid catalysts is increasing, the chiral protolactonization of unsaturated carboxylic acids remains rare, mainly due to the difficulty of controlling the Brønsted acidities of catalysts and the low nucleophilicity of the carboxyl group toward unactivated alkenes.[5]

Recently, we developed chiral phosphonium salts (**1**·HX), which were prepared from chiral phosphonous acid diester **1** with achiral Brønsted acids (HX), as new chiral Brønsted acid catalysts for the enantioselective polyene cyclization of 2-geranylphenols (Scheme 1).[6] With regard to asymmetric protocyclization reactions, we envisioned that the chiral phosphonium salt-promoted method could be applied to the kinetic resolution of racemic unsaturated carboxylic acids through asymmetric protolactonization. This reaction system may lead to a novel and straightforward approach for providing optically active carboxylic acids and lactones without byproduct generation derived from activating reagents. Here, we report the kinetic resolution of racemic α-substituted carboxylic acids catalyzed by chiral **1**·HX through asymmetric protolactonization.

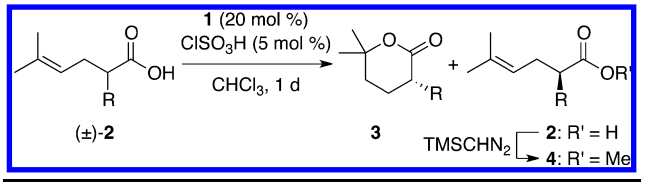
Scheme 1. Chiral Phosphonium Salts (**1**·HX)



Initially, racemic carboxylic acid (±)-**2a** was chosen as a model substrate for the chiral Brønsted acid catalyzed kinetic resolution (Table 1). Based on our previous study, we envisioned that the use of chiral **1**·HX would be important for the enantioface selection of the isoprenyl group of (±)-**2a**. First, the 6-*endo*-protolactonization of (±)-**2a** was conducted under the same conditions as those for the enantioselective cyclization of 2-geranylphenol [in the presence of **1** (40 mol %) and TfOH (10 mol %) in $CHCl_3$ at −40 °C].[6] As a result, the reaction gave the corresponding lactone **3a** with 95% ee (26% conv, entry 1). The unreacted carboxylic acid **2a** was recovered after the transformation to the methyl ester **4a** (33% ee) using $TMSCHN_2$. Therefore, these results gave a selectivity factor ($S = k_{fast}/k_{slow}$) of 54 (entry 1). When the reaction was conducted at −30 °C, the carboxylic acid was recovered with 98% ee (entry 2). The use of **1** (20 mol %) and TfOH (5 mol %) at −30 °C also gave **3a** in high enantioselectivity (95% ee) although the conversion was low (17%, entry 3).

Next, other achiral Brønsted acids (HX) were investigated under these conditions. The use of FSO_3H gave almost the same result as with the use of TfOH (95% ee, 12% conv, entry 4), although FSO_3H was the optimal Brønsted acid in the cyclization of 2-geranylphenols. On the other hand, the use of $ClSO_3H$ improved the conversion of **3a** without a significant loss of enantioselectivity (92% ee, 41% conv, entry 5). To our delight, when the **1**·$ClSO_3H$-catalyzed protolactonization was conducted at −40 °C, the enantioselectivity was increased to 94% ee without any decrease in the conversion, which gave the highest selectivity factor ($S = 62$, entry 6). Additionally, when the reaction was conducted at −20 °C, the recovered carboxylic acid was obtained with 95% ee (entry 7). These results suggested that simple control of the reaction temperature could allow easy access to optically active carboxylic acids and lactones with high enantioselectivities. Meanwhile, when the reaction was conducted in the absence of **1** at −20 °C, racemic lactone **3a** was obtained in 8% yield (entry 8). *These results indicated that the use of Brønsted base **1** controlled not only the stereoselectivity but also the reactivity.*

Table 1. Kinetic Resolution of (±)-**2a** Catalyzed by Chiral **1**·HX



entry	HX	temp (°C)	ee of **3a** (%)[a]	ee of **4a** (%)[a]	conv (%)[b]	S[c]
1[d]	TfOH	−40	95	33	26	54
2[d]	TfOH	−30	76	98	56	29
3	TfOH	−30	95	20	17	47
4	FSO_3H	−30	95	13	12	44
5	$ClSO_3H$	−30	92	65	41	46
6	$ClSO_3H$	−40	94	63	40	62
7	$ClSO_3H$	−20	82	95	54	40
8[e]	$ClSO_3H$	−20	—	—	8[f]	—

[a] Determined by chiral HPLC analysis. [b] Conversion was calculated as C = ee(**4a**)/(ee(**3a**) + ee(**4a**)). [c] The selectivity factor was calculated as $S = \ln[1 - C(1 + \text{ee}(\mathbf{3a}))]/\ln[1 - C(1 - \text{ee}(\mathbf{3a}))]$. [d] Reaction was conducted in the presence of **1** (40 mol %) and TfOH (10 mol %). [e] Reaction was conducted in the absence of **1**. [f] Isolated yield.

With the optimized reaction conditions in hand, we next examined the kinetic resolution of racemic carboxylic acids (±)-**2** bearing various α-substituents (Table 2). The reaction of (±)-**2** was conducted in the presence of **1** (20 mol %) and $ClSO_3H$ (5 mol %) in $CHCl_3$ at −40 to −20 °C for 1 day. The introduction of several aromatic rings at the α-position of carboxylic acids gave good to excellent selectivities (S = 26−62, entries 1−4). The absolute configuration of lactone **3b** was assigned to be (*S*) based on the results of an X-ray single crystallographic analysis.[7,8]

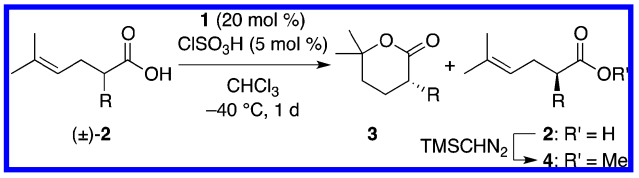
(3) (a) Anscll, M. F.; Palmer, M. H. *Quart. Rev.(London)* **1964**, *18*, 211. (b) Tiecco, M.; Testaferri, L.; Tingoli, M. *Tetrahedron* **1993**, *49*, 5351. (c) Mali, R. S.; Babu, K. N. *Helv. Chim. Acta* **2002**, *85*, 3525. (e) Miura, K.; Hayashida, J.; Takahashi, T.; Nishikori, H.; Hosomi, A. *J. Organomet. Chem.* **2003**, *686*, 242. (f) Zhou, Y.; Woo, L. K.; Angelici, R. J. *Appl. Catal. A: General* **2007**, *333*, 238.

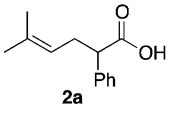
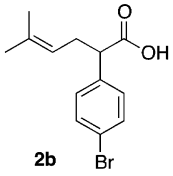
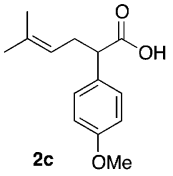
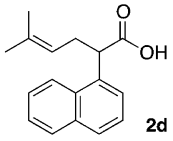
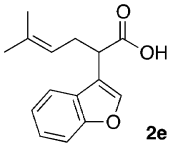
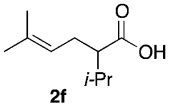
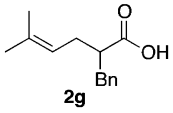
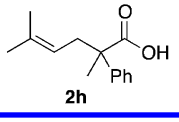
(4) Coulombel, L.; Duñach, E. *Synth. Commun.* **2005**, *35*, 153.

(5) For a report on the chiral LBA-induced polyene cyclization of unsaturated carboxylic acids, see: Upar, K. B.; Mishra, S. J.; Nalawade, S. P.; Singh, S. A.; Khandare, R. P.; Bhat, S. V. *Tetrahedron: Asymmetry* **2009**, *20*, 1637.

(6) Sakakura, A.; Sakuma, M.; Ishihara, K. *Org. Lett.* **2011**, *13*, 3130.

Table 2. Substrate Scope for the Kinetic Resolution of (±)-**2**



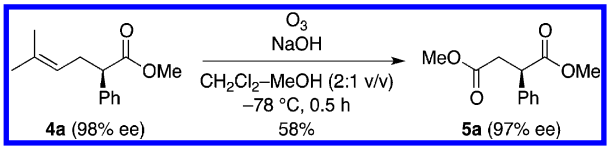
entry	2	temp (°C)	ee (%)[a] [yield (%)][b] 3	4	conv (%)[c]	S[d]
1	 **2a**	–40	94 [40]	63 [52]	40	62
2	 **2b**	–30	84 (98)[e] [36]	75 [45]	47	26
3	 **2c**	–40	90 [35]	56 [56]	38	33
4	 **2d**	–40	91 [37]	66 [51]	42	42
5[f]	 **2e**	–30	75 [52]	94 [43]	56	26
6	 **2f**	–20	88 [37]	78 [50]	47	37
7[g]	 **2g**	–30	49 [nd]	42 [57]	46	4
8	 **2h**	–20	62 [nd]	33 [50]	35	6

[a] Determined by chiral HPLC or GC analysis. [b] Isolated yield. [c] Conversion was calculated as C = ee(**4**)/(ee(**3**) + ee(**4**)). [d] The selectivity factor was calculated as $S = \ln[1 - C(1 + \text{ee}(\mathbf{3}))]/\ln[1 - C(1 - \text{ee}(\mathbf{3}))]$. [e] After recrystallization. [f] Reaction was conducted in the presence of **1** (20 mol %) and $ClSO_3H$ (10 mol %). [g] Reaction was conducted in the presence of **1** (40 mol %) and $ClSO_3H$ (10 mol %).

Furthermore, substrate **2e** bearing a 3-benzofuranyl group was also tolerated, and the use of $ClSO_3H$ (10 mol %) at −40 °C gave the recovered carboxylic acid in 43% yield with 94% ee (S = 26, entry 5). Substrate **2f** bearing an isopropyl group also gave good selectivity (S = 37, entry 6). On the other hand, this method was not effective for benzyl-substituted substrate **2g** due to the lower steric hindrance of the primary alkyl substituent (S = 4, entry 7). The kinetic resolution of racemic tertiary carboxylic acid **2h** did not give a satisfactory level of enantioselectivity (S = 6, entry 8).

Oxidative cleavage of the isoprenyl group of recovered chiral ester **4a** gave 2-phenylsuccinate **5a**[9] without a significant loss of optical purity (Scheme 2).[10] Chiral 2-substituted succinates **5** are important chiral building blocks for the synthesis of various bioactive compounds and natural products.[11] Since (*R*)-**5a** was obtained from recovered **4a**, the absolute configuration of **4a** was determined to be (*R*), which was consistent with the fact that the absolute configuration of lactone **3b** was (*S*).

Scheme 2. Synthesis of Chiral 2-Substituted Succinate **5a**



To explore the substrate scope of the reaction, we examined the kinetic resolution of racemic 4-methyl-4-pentenoic acids **6** bearing an α-substituent (Table 3). Since the protonation of 1,1-disubstituted alkenes **6** would generate carbocation intermediates similar to those in the reaction of **2**, a high level of enantioselectivity is expected to be induced. The asymmetric protolactonization of (±)-**6a** in the presence of **1** (20 mol %) and $ClSO_3H$ (10 mol %) at −40 °C showed good selectivity (S = 21, entry 1). This reaction proceeded through 5-*exo*-cyclization to give the corresponding five-membered lactone **7a** with 83% ee. The absolute configuration of recovered ester **8a** was assigned to be (*R*).[7] The introduction of 2-bromophenyl and 1-naphthyl groups at the α-position of 4-methyl-4-pentenoic acids also gave the corresponding lactones **7** with good S values (entries 2 and 3).

Based on the kinetic resolution of racemic α-substituted carboxylic acids, we envisioned that the chiral **1**·$ClSO_3H$-catalyzed system could be applied to the desymmetrization of achiral unsaturated carboxylic acids **9** and **11** (Scheme 3). It could also be a useful approach to the synthesis of optically active lactones. When the reaction of **9** was conducted in the presence of **1** (40 mol %) and $ClSO_3H$ (10 mol %) at −30 °C, the desired lactone **10** was obtained in 82% yield with 79% ee. For substrate **11** bearing 1,1-disubstituted alkenes,

(7) See Supporting Information for details.

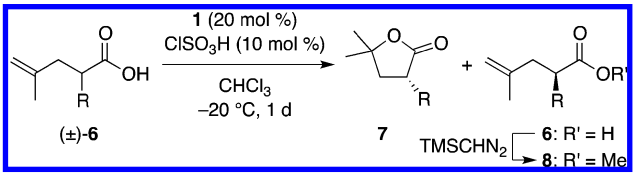
(8) The supplementary crystallographic data for this paper can be found as CCDC 934314 (**3b**) and CCDC 934315 (**1**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(9) Chung, Y.-C.; Janmanchi, D.; Wu, H.-L. *Org. Lett.* **2012**, *14*, 2766.

(10) LaLonde, R. L.; Wang, Z. J.; Mba, M.; Lackner, A. D.; Toste, F. D. *Angew. Chem., Int. Ed.* **2010**, *49*, 598.

(11) (a) Schöttner, M.; Spiteller, G.; Gansser, D. *J. Nat. Prod.* **1998**, *61*, 119. (b) Ayres, D. C.; Loike, J. D. In *Lignans, Chemical, Biological, and Clinical Properties*; Cambridge University: Cambridge, 1990; Chapters 3 and 4 and references therein. (c) Ward, R. S. *Chem. Soc. Rev.* **1982**, *11*, 75. (d) Ward, R. S. *Tetrahedron* **1990**, *46*, 5029.

Table 3. Kinetic Resolution of (±)-**6** through Asymmetric **5**-*exo*-Protolactonization



entry	**6** (R)	ee (%)[a] [yield (%)][b] **7**	**8**	conv (%)[c]	S[d]
1	**6a** (Ph)	83 [nd]	64 [50]	44	21
2	**6b** (2-BrC_6H_4)	78 [nd]	30 [57]	28	11
3	**6c** (1-naphthyl)	82 [nd]	53 [54]	39	17

[a] Determined by chiral HPLC analysis. [b] Isolated yield. [c] Conversion was calculated as C = ee(**8**)/(ee(**7**) + ee(**8**)). [d] The selectivity factor was calculated as S = ln[1 − C(1 + ee(**7**))]/ln[1 − C(1 − ee(**7**))].

the five-membered lactone **12** was obtained with 76% ee. These reactions gave the corresponding lactones **10** and **12** with good enantioselectivities, although the selectivity of the kinetic resolution of racemic carboxylic acid **2g** bearing a primary alkyl substituent at the α-position was low.

Scheme 3. Desymmetrization of Achiral α-Substituted Carboxylic Acids **9** and **11**

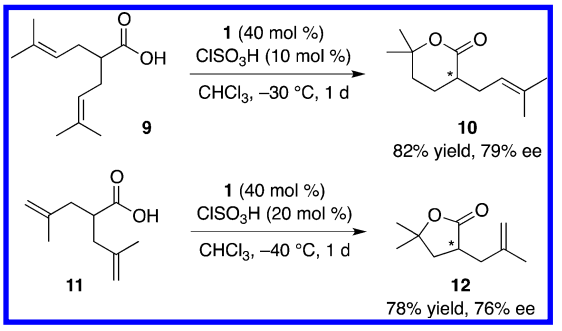


Figure 1 shows a proposed explanation for the absolute stereopreference we observed. Structure **A** is the Newman projection of the chiral phosphonium salt **1**·$ClSO_3H$ viewed along the H−P bond. Based on our previous study[6] and the X-ray single crystallographic structure of **1**,[7,8] **1**·$ClSO_3H$ selectively reacts with the *Re*-face of the terminal isoprenyl group of **2**, the dimethyl group of which is placed at the least-hindered side in the transition-state assembly. (*S*)-Carboxylic acid **2** immediately undergoes protolactonization through transition state **B** to give the corresponding (*S*)-lactone **3**. On the other hand, the reaction of (*R*)-carboxylic acid **2** through transition state **C** is much slower than that of **B** due to the steric repulsion

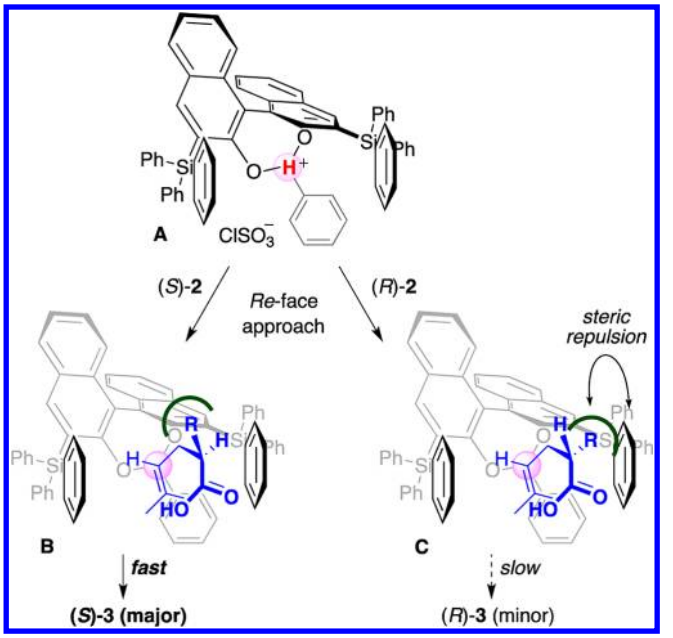


Figure 1. Proposed explanation for the absolute stereopreference observed in **1**·$ClSO_3H$-catalyzed kinetic resolution.

of α-substituent R with a triphenylsilyl group. Thus, (*R*)-carboxylic acid **2** is selectively recovered after the reaction.

In conclusion, we have achieved the kinetic resolution of racemic α-substituted carboxylic acids **2** and **6** through asymmetric protolactonization catalyzed by a chiral Brønsted acid, **1**·$ClSO_3H$. This reaction system may represent a novel and straightforward approach for obtaining optically active carboxylic acids and lactones. In addition, the desymmetrization reactions of achiral carboxylic acids **9** and **11** were also accomplished via the chiral **1**·$ClSO_3H$-catalyzed protolactonization. To the best of our knowledge, these are the first successful examples of reactions that give δ-lactones with high enantioselectivities through the chiral Brønsted acid catalyzed asymmetric protolactonization of unsaturated carboxylic acids.

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Supporting Information Available. Experimental procedure and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.