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Kinetic Resolution of β-Substituted Olefinic Carboxylic Acids by Asymmetric Bromolactonization

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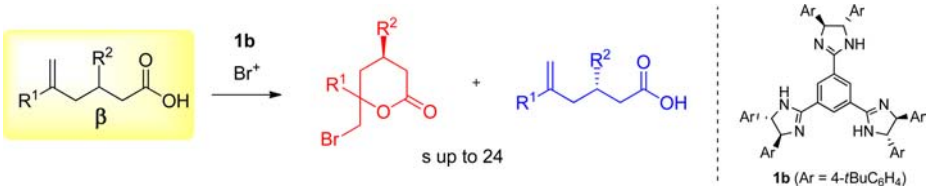
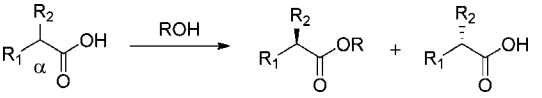
ABSTRACT



A strategically novel kinetic resolution of β-substituted olefinic carboxylic acids is developed by asymmetric bromolactonization using an organocatalyst, 4-*t*BuPh-tris 1b. The cyclization stage, which provides δ-lactone, is proposed to be operative for discrimination of each enantiomer of carboxylic acids.

Kinetic resolution of racemic carboxylic acids is one of the useful ways to obtain both enantiomers of chiral carboxylic acids.[1] Consequently, a significant effort has been devoted to the development of efficient chemical methods by artificial molecules, as well as enzymatic methods. Recently, a direct kinetic resolution of racemic carboxylic acids, which is based on asymmetric esterification reactions utilizing chiral acyl transfer catalysts, such as L-histidine derivatized sulfonamide or benzotetramisole (BTM) type catalysts, has been developed.[2] In these methods, various α-substituted carboxylic acids are effectively resolved (Scheme 1). In contrast, chemical methods for a kinetic resolution of β-substituted carboxylic acids have been less explored to date.[3] Although alternative strategies for β-chiral carboxylic acid derivatives as represented by asymmetric conjugate addition or the asymmetric hydrogenation exist,[4] it is important to develop a novel kinetic resolution method. Herein, we wish to report a strategically novel approach for kinetic resolution of β-substituted carboxylic acids, which features the utilization of an organocatalytic asymmetric bromolactonization reaction.

Scheme 1. Previous Reports: Kinetic Resolution of α-Substituted Carboxylic Acids by Esterification



In the case of β-substituted carboxylic acids, a stereocenter to be discriminated is located far from the carbonyl moiety. Therefore, we think that it would be difficult to resolve β-substituted carboxylic acids by an asymmetric esterification based approach. In fact, attempts at the

(1) Pellissier, H. *Adv. Synth. Catal.* **2011**, *353*, 1613.

(2) (a) Ishihara, K.; Kosugi, Y.; Umemura, S.; Sakakura, A. *Org. Lett.* **2008**, *10*, 3191. (b) Sakakura, A.; Umemura, S.; Ishihara, K. *Synlett* **2009**, *10*, 1647. (c) Shiina, I.; Nakata, K.; Onda, Y. *Eur. J. Org. Chem.* **2008**, 5887. (d) Nakata, K.; Onda, Y.; Ono, K.; Shiina, I. *Tetrahedron Lett.* **2010**, *51*, 5666. (e) Shiina, I.; Nakata, K.; Ono, K.; Onda, Y.; Itagaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 11629. (f) Shiina, I.; Ono, K.; Nakata, K. *Catal. Sci. Technol.* **2012**, *2*, 2200. (g) Yang, X.; Birman, V. B. *Chem.—Eur. J.* **2011**, *17*, 11296. (h) Yang, X.; Birman, V. B. *Angew. Chem., Int. Ed.* **2011**, *50*, 5553. (i) Yang, X.; Liu, P.; Houk, K. N.; Birman, V. B. *Angew. Chem., Int. Ed.* **2012**, *51*, 9638.

(3) Enzymatic kinetic resolution of β-substituted carboxylic esters were reported. For examples, see: (a) Reis, J. S.; Andrade, L. H. *Tetrahedron: Asymmetry* **2012**, *23*, 1294. (b) Brem, J.; Naghi, M.; Tosa, M.-I.; Boros, Z.; Poppe, L.; Irimie, F.-D.; Paizs, C. *Tetrahedron: Asymmetry* **2011**, *22*, 1672. (c) Felluga, F.; Pitacco, G.; Valentin, E.; Venneri, C. D. *Tetrahedron: Asymmetry* **2008**, *19*, 945.

(4) For examples, see: (a) Khumsubdee, S.; Burgess, K. *ACS Catal.* **2013**, *3*, 237. (b) Chauhan, P.; Chimni, S. S. *RSC Adv.* **2012**, *2*, 6117.

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kinetic resolution of β-substituted carboxylic acids by using chiral acyl transfer catalysts have not yet been described. Instead, we envisioned that a process-including cyclization reaction should be suitable for this purpose. In particular, δ-lactone forming process should be promising because the steric repulsion associated with 1,3-diaxial interactions in 6-membered transition states could expected to work for distinction of stereoisomers.

Asymmetric halolactonization reactions are one of the recent intensively developed areas of asymmetric reactions.[5] We have recently developed the asymmetric bromolactonization reaction catalyzed by trisimidazoline **1a** (Figure 1).[6] This reaction efficiently produces δ-lactones from 5-hexenoic acid derivatives. Accordingly, we hypothesized that this bromolactonization reaction would be applicable to a kinetic resolution of β-substituted olefinic carboxylic acids. In the course of our studies probing this proposal, Hamashima and Kan and Martin described kinetic resolutions based on halolactonization reactions of specific substrates, including 1,4-dihydronaphthalene-1-carboxylic acids and 2-cyclopentene-1-acetic acid, as one aspect of their work.[7] These reports prompted us to describe the results of our investigation of this methodology.

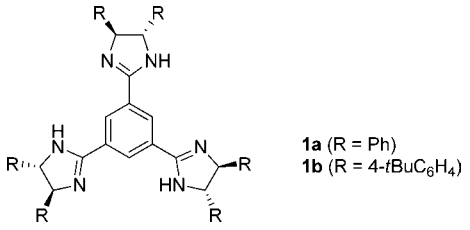
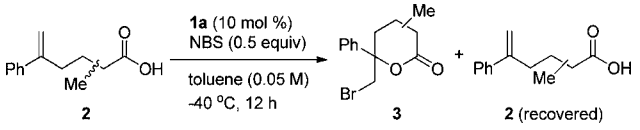


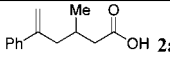
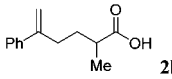
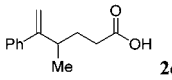
Figure 1. Trisimidazoline catalysts.

In order to probe the feasibility of the use of halolactonization reactions for the kinetic resolution of β-substituted carboxylic acids, we initially examined the reaction of the olefinic carboxylic acid **2a**, which contains a methyl group at the β-position. To our delight, we observed that, under the bromolactonization conditions using trisimidazoline **1a** (10 mol %) and *N*-bromosuccinimide (NBS) (0.5 equiv), **2a** is transformed to the corresponding bromolactone with a moderate s factor (Table 1, entry 1, $s = 7.4$, calculated using the reported equation[8]). To obtain insight into the reaction, we further tested the two regioisomeric olefinic carboxylic acids, α-isomer **2b** and γ-isomer **2c**, under the same conditions. Interestingly, these isomer showed poor selectivity compared to β-isomer **2a**: *s* factors of **2b** and **2c** are 2.1 and 5.3, respectively. These observations suggest that the substrate having substituent at the remote position both from the carboxylic acid and the olefin (i.e., β-position) is more efficient to be resolved by this bromolactonization reaction.

It should be noted that the ee value of the product was determined as the olefinic carboxylic acid (or corresponding methyl ester). The olefinic carboxylic acids are regenerated by using reductive cleavage conditions with zinc in the presence of NH_4Cl in good yield (Scheme 2).[9] This transformation of bromolactone which can readily regenerate the starting carboxylic acids is an important component of this resolution method.

Table 1. Effect of the Methyl Group Position on the Kinetic Resolution of Olefinic Carboxylic Acid



entry	substrate	yield of **3** [ee(p)]	yield of **2** [ee(s)]	s
1[a]	 **2a**	51% [57% ee]	40% [70% ee]	7.4
2[b]	 **2b**	51 % [26% ee]	49% [25% ee]	2.1
3[a]	 **2c**	25% [63% ee]	68% [19% ee]	5.3

[a] Ee was determined using HPLC analysis of the corresponding methyl esters (see the Supporting Information). [b] Ee was determined using HPLC analysis of the olefinic carboxylic acids (see the Supporting Information).

Encouraged by the promising results obtained by the preliminary study shown in Table 1, we carried out an optimization study of the kinetic resolution of β-substituted olefinic carboxylic acid (Scheme 3). The β-phenyl-substituted

(5) (a) Whitehead, D. C.; Yousefi, R.; Jaganathan, A.; Borhan, B. *J. Am. Chem. Soc.* **2010**, *132*, 3298. (b) Yousefi, R.; Whitehead, D. C.; Mueller, J. M.; Staples, R. J.; Borhan, B. *Org. Lett.* **2011**, *13*, 608. (c) Zhang, W.; Zheng, S.; Liu, N.; Werness, J. B.; Guzei, I. A.; Tang, W. *J. Am. Chem. Soc.* **2010**, *132*, 3664. (d) Zhang, W.; Liu, N.; Schienebeck, C. M.; Decloux, K.; Zheng, S.; Werness, J. B.; Tang, W. *Chem.—Eur. J.* **2012**, *18*, 7296. (e) Veitch, G. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2010**, *49*, 7332. (f) Zhou, L.; Tan, C. K.; Jiang, X.; Chen, F.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 15474. (g) Tan, C. K.; Zhou, L.; Yeung, Y.-Y. *Org. Lett.* **2011**, *13*, 2738. (h) Chen, J.; Zhou, L.; Tan, C. K.; Yeung, Y.-Y. *J. Org. Chem.* **2012**, *77*, 999. (i) Tan, C. K.; Le, C.; Yeung, Y.-Y. *Chem. Commun.* **2012**, *48*, 5793. (j) Jiang, X.; Tan, C. K.; Zhou, L.; Yeung, Y.-Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 7771. (k) Dobish, M. C.; Johnston, J. N. *J. Am. Chem. Soc.* **2012**, *134*, 6068. (l) Paull, D. H.; Fang, C.; Donald, J. R.; Pansick, A. D.; Martin, S. F. *J. Am. Chem. Soc.* **2012**, *134*, 11128. (m) Tungen, J. E.; Nolsøe, J. M. J.; Hansen, T. V. *Org. Lett.* **2012**, *14*, 5884.

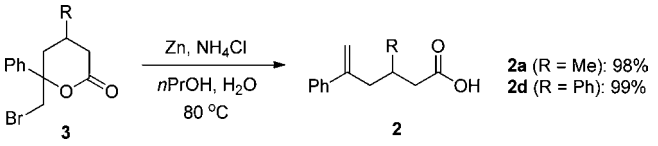
(6) (a) Murai, K.; Matsushita, T.; Nakamura, A.; Fukushima, S.; Shimura, M.; Fujioka, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 9174. (b) Murai, K.; Nakamura, A.; Matsushita, T.; Shimura, M.; Fujioka, H. *Chem.—Eur. J.* **2012**, *18*, 8448.

(7) (a) Ikeuchi, K.; Ido, S.; Yoshimura, S.; Asakawa, T.; Inai, M.; Hamashima, Y.; Kan, T. *Org. Lett.* **2012**, *14*, 6016. (b) Fang, C.; Paull, D. H.; Hethcox, J. C.; Shugrue, C. R.; Martin, S. F. *Org. Lett.* **2012**, *14*, 6290.

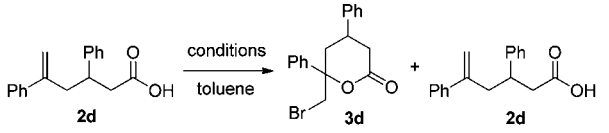
(8) $S = \ln[(1-c)\{1-\text{ee(s)}\}]/\ln[(1-c)\{1+\text{ee(s)}\}]$, $c = \text{ee(s)}/\{\text{ee(s)} + \text{ee(p)}\}$ (ee(s) = ee of recovered carboxylic acid; ee(p) = ee of regenerated carboxylic acid); see: Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.

(9) Examples for the zinc-mediated reductive cleavage of bromolactones: (a) Yoshino, T.; Nagata, Y.; Itoh, E.; Hashimoto, M.; Katoh, T.; Terashima, S. *Tetrahedron* **1997**, *53*, 10239. (b) Doi, T.; Yanagisawa, A.; Yamamoto, K.; Takahashi, T. *Chem. Lett.* **1996**, *25*, 1085.

Scheme 2. Regeneration of the Olefinic Carboxylic Acids



Scheme 3. Optimization Study



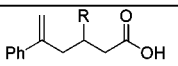
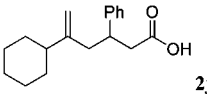
conditions		result[a]
NBS (0.5 equiv), -40 °C **1a** (10 mol %), 0.05 M	S = 6.0	**3d**: 49% [56% ee] **2d**: 49% [55% ee]
DBDMH (0.3 equiv), -60 °C **1a** (5 mol %), 0.1 M	S = 14.3	**3d**: 30% [82% ee] **2d**: 69% [36% ee]
DBDMH (0.3 equiv), -60 °C **1b** (5 mol %), 0.1 M	S = 20.8	**3d**: 43% [84% ee] **2d**: 50% [62% ee]

[a] Ee of **3d** was determined as the regenerated carboxylic acid **2d**.

carboxylic acid **2d** was employed in this effort in place of **2a** because analysis of its optical purity by HPLC is more easily carried out.[10] Under the same conditions used for the reaction of **2a** (Table 1), **2d** was also resolved with a moderate *s* factor (s = 6.0). The results of studies in which the reaction conditions were varied showed that a good s factor (s = 14.3) was obtained under the reaction conditions using 1,3-dibromodimethylhydantoin (DBDMH, 0.3 equiv) as bromine source with 5 mol % of catalyst **1a** in toluene (0.1 M) at −60 °C. Furthermore, more bulky catalyst **1b** containing a 4-*tert*-butylphenyl group (4-*t*BuPh-tris) was found to be an effective catalyst to give sufficient selectivity (s = 20.8).[11]

Having established optimized reaction conditions and the ideal catalyst **1b**, the scope of the kinetic resolution reaction was investigated (Table 2). β-Aryl-substituted olefinic carboxylic acids were observed to serve as good substrates for this process, as reflected in the finding that the 4-chloro-, 4-bromo-, 4-methoxyphenyl-substituted carboxylic acids **2e**, **2f**, and **2g** all are resolved with moderate to good levels of selectivity (entries 2−4). In particular, bromolactonization reaction of **2e** takes place with the highest level of selectivity in the series (entry 2, s = 24.7), while 4-bromobenzene substituted carboxylic acid **2f** reacts with a lower selectivity (entry 3, s = 6.4), a finding that might be associated with lower solubility of **2f** under the reaction conditions. β-Alkyl-substituted olefinic carboxylic acids also serve as good substrates for this kinetic

Table 2. Generality[a]

entry	substrate	results yield [ee]	s
1[b]	 **2d** (R = Ph)	**3d**: 43% [84% ee] **2d**: 50% [62% ee]	20.8
2[c]	**2e** (R = 4-ClC$_6$H$_4$)	**3e**: 43% [85% ee] **2e**: 49% [66% ee]	24.7
3[c]	**2f** (R = 4-BrC$_6$H$_4$)	**3f**: 43% [61% ee] **2f**: 49% [47% ee]	6.4
4[b]	**2g** (R = 4-MeOC$_6$H$_4$)	**3g**: 38% [85% ee] **2g**: 62% [53% ee]	20.5
5[c]	**2a** (R = Me)	**3a**: 56% [65% ee] **2a**: 34% [94% ee]	15.6
6[b]	**2h** (R = *i*Pr)	**3h**: 58% [69% ee] **2h**: 41% [89% ee]	15.7
7[b]	**2i** (R = *t*Bu)	**3i**: 58% [52% ee] **2i**: 41% [86% ee]	8.4
8[c]	 **2j**	**3j**: 58% [50% ee] **2j**: 41% [72% ee]	6.1

[a] Reaction was carried out using **1b** (5 mol %) and DBDMH (0.3 equiv) in toluene (0.1 M) at −60 °C. Reaction time: 24 h. [b] Ee was determined using HPLC analysis of the olefinic carboxylic acids (see the Supporting Information). [c] Ee was determined using HPLC analysis of the corresponding methyl esters (see the Supporting Information).

resolution process (entries 5−7). The β-methyl **2a** as well as isopropyl **2h** substituted acids react with good selectivity (s = 15.6 and 15.7). Surprisingly, carboxylic acids possessing a more bulky β-alkyl group, such as *tert*-butyl, do not serve as good substrates (entry 7, s = 8.4). In addition, alkyl substituents (e.g., cyclohexyl) rather than phenyl on the olefin moiety unfortunately promote decreased levels of selectivity (entry 8, s = 6.1). It should be noted that in previously studied asymmetric bromolactonization reactions using trisimidazoline **1a**, substrates containing aromatic groups on the olefin moiety react with higher levels enantioselectivity than those possessing alkyl groups.[5] Thus, it appears that the current kinetic resolution process follows trends that have been observed earlier for the related enantioselective bromolactonization reaction.

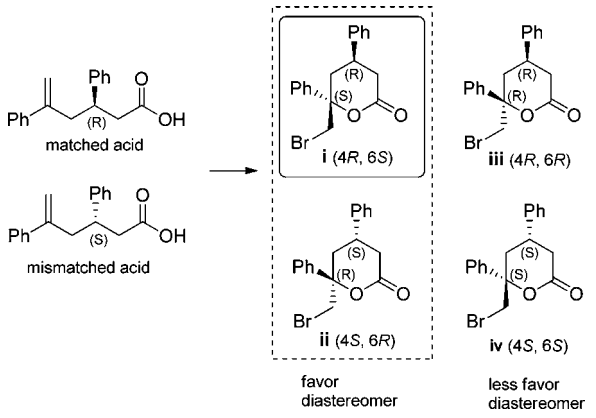
An analysis of the bromolactones **3d** obtained from kinetic resolution of the carboxylic acid **2d** provides interesting insight into the origin of stereoselectivity in the process. As depicted in Scheme 4, the four stereoisomers of bromolactone (**i** (4*R*,6*S*), **ii** (4*S*,6*R*), **iii** (4*S*,6*R*), and **iv** (4*S*,6*S*)) can possibly form by cyclization of **2d**. In the bromolactonization reaction (Table 2), four stereoisomers of lactone **3d i**: **ii**: **iii**: **iv** are actually produced in a respective **i**:**ii**:**iii**:**iv** ratio of approximately 90.7:6.8:0.1:2.4, as estimated by analysis of HPLC peak area %. Among the two diastereomers, the one having the *trans* relationship between the two phenyl groups (i.e., **i** and **ii**) is preferably produced according to the nature of substrate.[12] These observations

(10) Ee of **2a** was not determined as the carboxylic acid, and preparation of the methyl ester was necessary.

(11) For optimization study and screening of catalysts, see the Supporting Information.

(12) This selectivity trend was confirmed by exploring the reaction of **2d** with NBS and $NaHCO_3$ in CH_3CN at rt which showed that the *trans* isomer is produced with a 6.2: 1 diastereoselectivity.

Scheme 4. Analysis of Produced Bromolactone



suggest the following reactivity of each enantiomer of olefinic carboxylic acids under the asymmetric bromolactonization conditions: (1) For the matched carboxylic acid (*R*-isomer), the diastereoselectivity (**i** vs **iii**) is very high. An interesting aspect of this finding is that double-asymmetric induction occurs in highly selective manner. (2) For the mismatched carboxylic acid (*S*-isomer), the bromolactone isomer **ii** is formed in preference to isomer **iv**. Since our previous results indicate reactions promoted by catalysts **1** prefer to form a new lactone stereo center with *S* configuration,[6] this observation suggested that the stereo chemical control by catalyst **1** was not over the substrate control.

Although a detailed transition-state analysis including interactions between the catalyst and substrate has not been clear at this stage, the source of stereochemical control in the kinetic resolution reactions of β-substituted olefinic carboxylic acids is presumed to be associated with the cyclization step in the process (Figure 2). On the basis of the analysis of the structures displayed in Scheme 4, the matched carboxylic acid (*R* isomer) would produce corresponding bromolactone through 6-membered ring TS1 predominantly. On the other hand, cyclization of the mismatched carboxylic acid (*S* isomer) could take place through TS2 (giving isomer **iv**) or TS3 (giving isomer **ii**). TS2 or TS3 probably have disadvantages owing to the 1,3-diaxial interaction between the two phenyl groups or the repulsive interaction with catalyst due to the mismatch stereochemistry of the generating tetrasubstituted

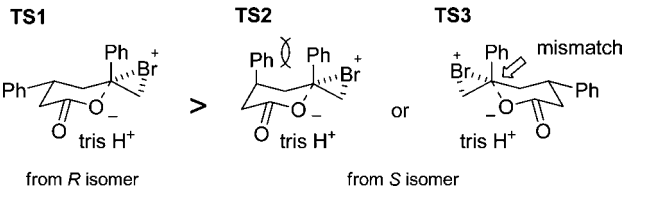


Figure 2. Proposed TS1−3.

carbon center. On the other hand, TS1 may have little such disadvantages. Therefore, the observation that the *R* isomers of β-substituted olefinic carboxylic acids react faster than the *S* isomers seems reasonable.

In conclusion, we have demonstrated a new approach for the kinetic resolution of β-substituted carboxylic acids that is based on asymmetric bromolactonization reactions. The cyclization stage is proposed to be important for the discrimination of stereoisomers. The reductive cleavage process is also shown to be useful for ready regeneration of the starting olefinic carboxylic acids from the bromolactones. Although the substrate scope of the bromolactonization reaction is limited to olefinic carboxylic acids, the olefin moiety is useful because it can be employed to various transformations. We believe that the present study provides a novel strategy for kinetic resolution of β-substituted carboxylic acids and it can be further applicable to other enantioselective halocyclization reactions of various olefinic substrates.[13]

Acknowledgment. This work was financially supported by a Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" from MEXT.

Supporting Information Available. Experimental details and detailed spectroscopic data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(13) Recently, asymmetric halocyclizations have been extensively developed as well as halolactonizations. For recent reviews, see: (a) Hennecke, U. *Chem. Asian. J.* **2012**, *7*, 456. (b) Denmark, S. E.; Kuester, W. E.; Burk, M. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 10938. (c) Murai, K.; Fujioka, H. *Heterocycles* **2013**, *4*, 763.

The authors declare no competing financial interest.