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Enantioselective, Desymmetrizing, Bromolactonization Reactions of Symmetric Olefinic Dicarboxylic Acids

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Abstract: The results of studies leading to the development of enantioselective desymmetrizing, bromolactonization reactions of symmetric olefinic dicarboxylic acids, which are promoted by a C_3-symmetric trisimidazoline catalyst, are described. These processes generated carboxylic-acid-containing bromolactones in moderately high enantiomeric excesses. The results of optimization studies showed that reactions in a mixed solvent system of toluene and acetone proceeded with the highest levels of enantioselectivity. NMR studies probing the interactions between the catalyst and dicarboxylic acid substrates, as well as the effect of acetone on the stereochemistry of the process, are also described.

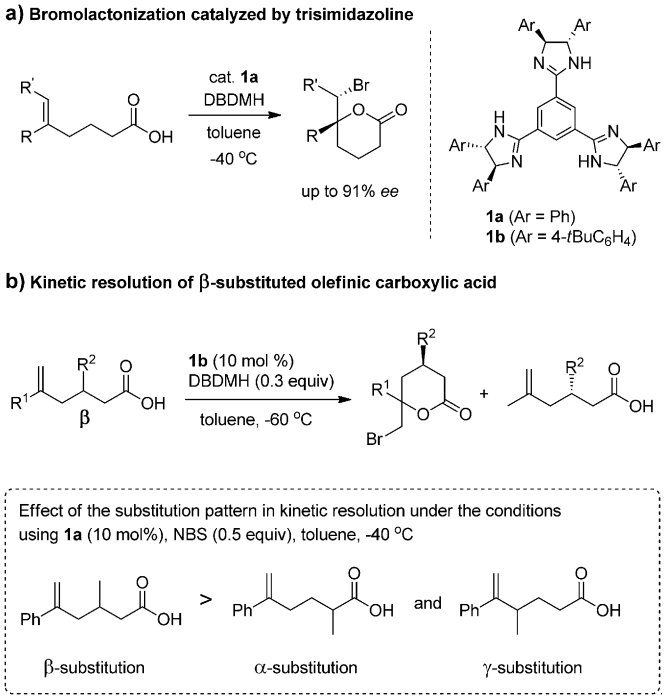
Keywords: asymmetric synthesis · bromolactonization · carboxylic acids · desymmetrization · organocatalysis

Introduction

The development of enantioselective halocyclization reactions has been an area of intensive recent study in organic synthesis. Over the past few years, new catalyst/reagent combinations have been devised for carrying out reactions of this type—including halolactonization, haloetherification, and haloamination reactions—in a highly enantioselective manner.[1–3] In addition to establishing optimal conditions for these processes, research concerning the application of these transformations is also important.

Previously, we reported a method for performing enantioselective bromolactonization reactions that utilized the structurally unique, C_3-symmetric trisimidazoline **1a**.[2j,4] This process generated chiral δ-lactones from 5-hexenoic acid derivatives that contained both terminal and internal olefin moieties (Scheme 1a).[5] In addition, we recently demonstrated that this method could be applied to the kinetic resolution of olefinic carboxylic acids. In the latter study, we observed that the kinetic resolution of β-substituted olefinic carboxylic acids was more effective than that of its α- or γ-substituted counterparts (Scheme 1b).[6]

As a part of our continuing interest in the development of stereoselective synthetic methods that use the halocyclization of symmetrical molecules,[7] we recently investigated the application of bromocyclization to the desymmetrization of symmetrical substrates. Based on a kinetic resolution study, we thought that the asymmetric desymmetrization of two types of β-branched symmetric compounds, such as diene **2** and dicarboxylic acid **3**, should be possible. Diene **2**



Scheme 1. Summary of our previous studies on enantioselective bromolactonization reactions.

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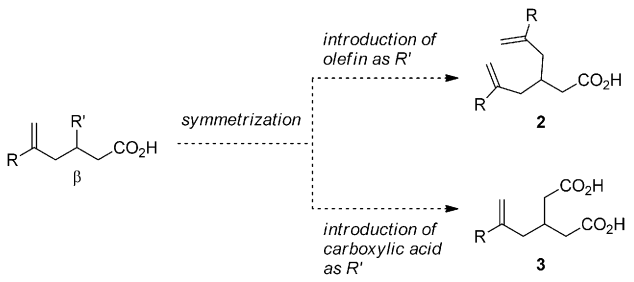


Scheme 2. Two types of β-branched symmetrical compounds.

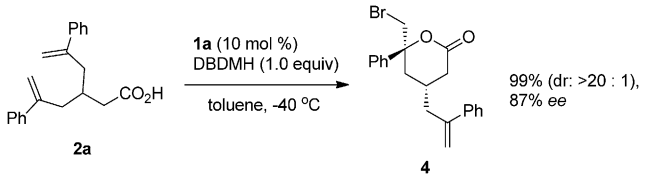
contained an olefin moiety as the R′ group, whereas dicarboxylic acid **3** contained a carboxylic acid moiety as the R′ group (Scheme 2).

Several reports describing the asymmetric desymmetrization of diene- and dialkyne-carboxylic acids that utilized halolactonization methods have been reported.[8] For example, Hamashima, Kan, and co-workers demonstrated that asymmetric bromolactonization reactions of 1,4-cyclohexadienyl carboxylic acids produced synthetically useful β- and γ-lactones in a highly enantioselective manner with bis-cinchona alkaloid catalysts, such as $(DHQD)_2PHAL$.[9] In addition, asymmetric bromolactonization reactions of dialkyne-carboxylic acids that utilize the same catalyst have very recently been described by Hennecke and co-workers.[10] Several successful examples of the desymmetrizing haloetherification of ene-diol substrates have also been reported. The first desymmetrizing iodolactonization reaction of diols, such as alk-4-ene-1,8-diols, was reported by Hennecke and co-workers, which proceeded through the desymmetrization of in-situ-generated *meso*-halonium ions.[3u,11] Very recently, Yeung and co-workers reported the bromoetherification of olefinic or diolefinic 1,3-diols.[12] On the other hand, the desymmetrization of dicarboxylic acid substrates has been less explored. For example, an attempt using Hennecke's *meso*-halonium-ion strategy for dicarboxylic acid substrates was reported to result in poor enantioselectivities, which contrasted with the high levels of stereocontrol for related idoetherification reactions of ene-diols.[3u]

In the design of conditions/catalysts that could promote the bromolactonization of substrates that contained two carboxylic acids, we envisaged that the interactions between the carboxylic acid groups and an organocatalyst with an amino functionality—which are often used for asymmetric halolactonization reactions—could be complicated, which might lead to poor efficiencies and low enantioselectivities. Herein, we report our investigations into asymmetric desymmetrization through a bromolactonization reaction with a trisimidazoline catalyst. In particular, our study on the reactions with dicarboxylic acids was mainly performed owing to our interest in the properties of the trisimidazoline catalyst, which could form ion pairs with carboxylic acids, and the fact that their reactivity has been less well-explored.

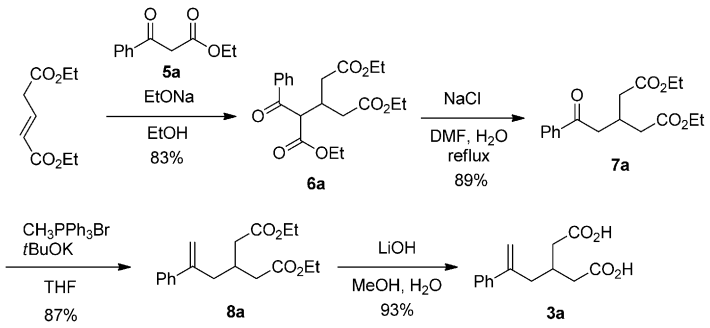
Results and Discussion

As part of a study designed to develop a method for asymmetric bromolactonization reactions of β-branched symmetric compounds of type **2** and **3** (Scheme 2), we initially explored the reaction of diene-carboxylic acid **2a**. As expected, treatment of compound **2a** under standard asymmetric bromolactonization conditions developed in our earlier efforts (i.e. Ph-tris **1a** (10 mol%), 1,3-dibromo-5,5-dimethylhydantoin (DBDMH, 1.0 equiv), toluene, −40 °C) led to the generation of bromolactone **4** in 99% yield and 87% *ee* (Scheme 3).[13,14]



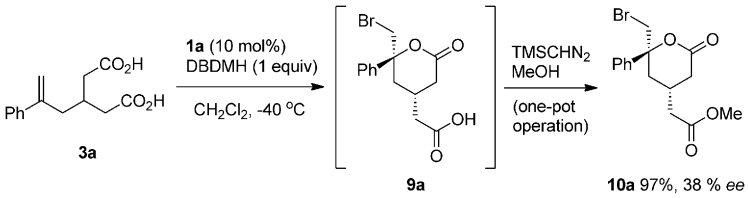
Scheme 3. Asymmetric bromolactonization of diene-carboxylic acid **2a**.

Guided by the positive results arising from our brief study with compound **2a**, our attention turned the desymmetrization reaction of ene-dicarboxylic acid **3a**. Our synthetic route to this substrate is shown in Scheme 4. Thus, the 1,4-addition of β-ketoester **5a** to the known 1,5-diethyl 2-pentenedioate[15] afforded triester **6a**. Then, compound **6a** was subjected to Krapcho decarboxylation with NaCl in DMF and water,[16] followed by Wittig olefination with the ylide of CH_3PPh_3Br to produce olefinic diester **8a**. Hydrolysis of the diester groups in compound **8a** with LiOH gave dicarboxylic acid **3a**. A series of ene-dicarboxylic acids (**3b**–**3j**, Table 3) was also prepared in a similar manner.



Scheme 4. Preparation of ene-dicarboxylic acid **3a**.

Next, dicarboxylic acid **3a** was subjected to the bromolactonization conditions. To our delight, it underwent the enantioselective desymmetrizing bromolactonization reaction with moderate enantioselectivity (38% *ee*, Scheme 5). In this study, the reaction product was isolated as its corresponding methyl ester (**10a**), owing to the ease of purification with column chromatography on silica gel, and to the ease of determination of enantioselectivity by HPLC analysis compared to carboxylic acid **9a**.[14,17] Methyl ester **10a**

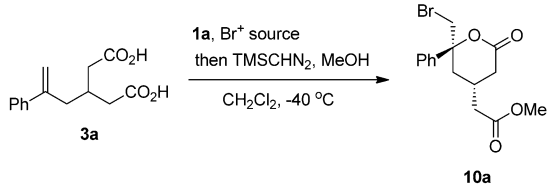


Scheme 5. Bromolactonization of dicarboxylic acid **3a**.

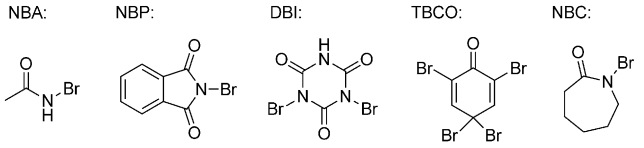
was readily prepared in a one-pot operation by treatment of the reaction mixture with trimethylsilyl diazomethane directly after the bromolactonization reaction was completed.

Our optimization of the reaction of compound **3a** began by screening various bromine sources, including *N*-bromosuccinimide (NBS), *N*-bromoacetamide (NBA), *N*-bromophthalimide (NBP), 1,3-dibromoisocyanuricacid (DBI), 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCO), and *N*-bromocaprolactam (NBC; Table 1). However, no significant improvement in enantioselectivity took place and the maximum *ee* value was about 40%. In addition, the use of more-bulky trisimidazoline catalyst **1b**, as well as several other trisimidazoline derivatives (Ar = 4-MeOC$_6$H$_4$, 4-FC$_6$H$_4$, 2-MeOC$_6$H$_4$, 3,5-dimethylC$_6$H$_3$, 2-naphthyl), did not lead to improved enantioselectivity.

Table 1. Screen of bromine sources in the reaction of compound **3a**[a]



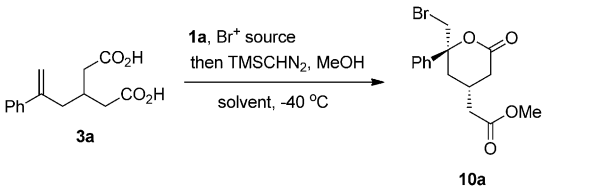
Entry	Br^+ source	Yield [%]	*ee* [%][b]
1[c]	DBDMH	97	38
2	NBS	98	37
3	NBA	91	33
4	NBP	85	21
5[c]	DBI	68	18
6	TBCO	91	26
7	NBC	87	41



[a] Unless otherwise noted, the reactions were performed with compound **3a** (0.060 mmol), a Br^+ source (0.060 mmol), compound **1a** (0.006 mmol), $TMSCHN_2$ (0.2 mmol), and MeOH (0.6 mL) in CH_2Cl_2 (3 mL) at −40 °C. [b] The *ee* value was determined by HPLC and the *ee* value of the major diastereomer is shown. [c] 1.2 equiv of the Br^+ source was used.

A screen of various solvents led to the observation that the use of a mixed solvent system that was comprised of toluene and acetone caused the bromolactonization reaction of compound **3a** to occur with a higher level of enantioselectivity (Table 2, entries 4–6) compared to other solvent systems

Table 2. Effect of the solvent.[a]



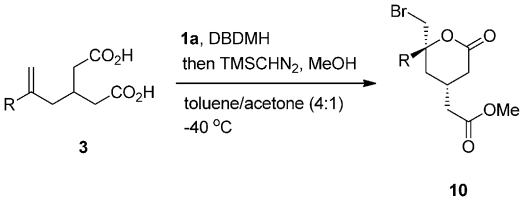
Entry	Solvent system	Br^+ source	Yield [%]	*ee* [%][b]
1	CH_2Cl_2	NBC	97	38
2	toluene	NBC	99	45
3	toluene/CH_2Cl_2 (1:1)	NBC	99	47
4	toluene/acetone (1:1)	NBC	57	78
5	toluene/acetone (1:2)	NBC	76	70
6	toluene/acetone (4:1)	NBC	80	81
7[c]	toluene/acetone (4:1)	DBDMH	98	82
8[c]	acetone	DBDMH	74	21

[a] Unless otherwise noted, the reactions were performed with compound **3a** (0.060 mmol), Br^+ source (0.072 mmol), compound **1a** (0.006 mmol), $TMSCHN_2$ (0.2 mmol), and MeOH (0.6 mL) in solvent (3 mL) at −40 °C. [b] The *ee* value was determined by HPLC and the *ee* value of the major diastereomer is shown. [c] 1.0 equiv of the Br^+ source was used.

that were comprised of toluene and CH_2Cl_2 (Table 2, entries 1–3). In particular, the reaction in toluene/acetone (4:1 v/v) generated compound **9a** with 81% *ee* (Table 2, entry 6). When this mixed solvent system was combined with changing the bromine source to DBDMH, the reaction of compound **3a** took place in high yield and with a slightly higher enantioselectivity (98% yield and 82% *ee*; Table 2, entry 7). Interestingly, performing this reaction in neat acetone proceeded with a low level of enantioselectivity (21% *ee*; Table 2, entry 8). Because further optimization did not improve the enantioselectivity, the reaction conditions of 10 mol% of compound **1a**, 1 equivalent of DBDMH in toluene/acetone (4:1) at −40 °C were determined to be optimal for these desymmetrization reactions of ene-dicarboxylic acids.[18]

Under the optimized reaction conditions, the reactions of dicarboxylic acids that contained different aryl groups were investigated. As shown in Table 3, substrates with 2-napthyl, 3-MeOC$_6$H$_4$, 3-BrC$_6$H$_4$, and 3,5-dimethyl-C$_6$H$_3$ groups reacted with high levels of enantioselectivity (Table 3, entries 2–5, 82–76% *ee*). On the other hand, we found that the degree of desymmetrization was lessened by changing the electron density on the aromatic ring. Thus, substrates with 4-halo (71–66% *ee*; Table 3, entries 6–8) and 4-methoxy substituents (13% *ee*; Table 3, entry 9) afforded their corresponding products with lower levels of enantioselectivity. In the latter case, a lower diastereoselectivity (2:1) was also observed. In addition, substrate **3j**, which contained a 2-MeC$_6$H$_4$ group, did not give high selectivity, thus suggesting that substitution at the *ortho* position of the benzene ring also had a negative effect on the enantioselectivity of this transformation (55% *ee*; Table 3, entry 10). Although they took place with only modest levels of enantioselectivity, these reactions represent the first examples of enantioselective bromolactonizations of ene-dicarboxylic acids.

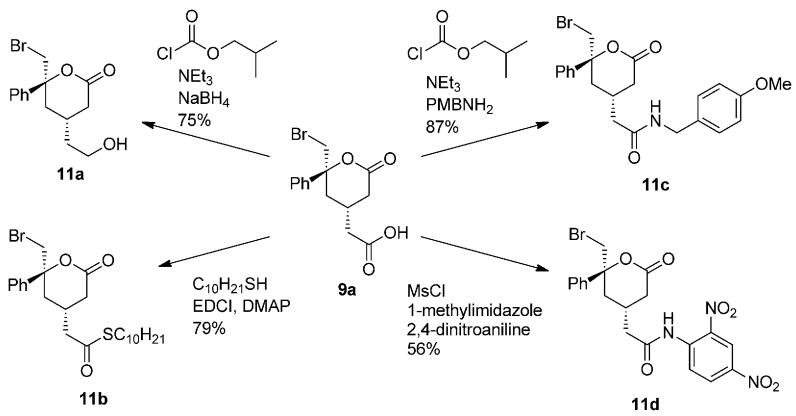
Table 3. Scope of the reaction.[a]



Entry	Substrate (R)	Yield [%] (dr)	*ee* [%][b]
1	**3a** (Ph)	98 (>20:1)	82
2	**3b** (2-naphtyl)	97 (>20:1)	82
3	**3c** (3-$MeOC_6H_4$)	98 (>20:1)	82
4	**3d** (3-BrC_6H_4)	97 (>20:1)	78
5	**3e** (3,5-dimethyl-C_6H_3)	98 (>20:1)	76
6	**3f** (4-ClC_6H_4)	93 (>20:1)	71
7	**3g** (4-BrC_6H_4)	100 (>20:1)	66
8	**3h** (4-FC_6H_4)	99 (>20:1)	67
9	**3i** (4-$MeOC_6H_4$)	91 (2:1)	13
10	**3j** (2-MeC_6H_4)	100 (5:1)	55

[a] Unless otherwise noted, the reactions were performed with compound **3** (0.10 mmol), a Br^+ source (0.10 mmol), compound **1a** (0.01 mmol), $TMSCHN_2$ (0.4 mmol), and MeOH (1 mL) in solvent (5 mL) at −40 °C. [b] The *ee* value was determined by HPLC and the *ee* value of the major diastereomer is shown.

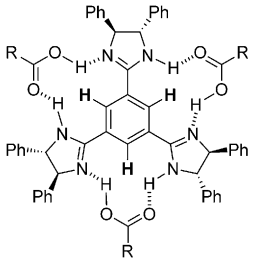
The bromolactones produced in the reactions described above are potentially useful intermediates in organic synthesis because they contain readily transformable functional groups, such as bromine, lactone, and carboxylic acid or ester moieties. Because several transformations of bromine and lactone groups in substances of this type were described in our previous report,[2j] only those of the carboxylic acid moiety were explored herein, by using compound **9a**, which was obtained by isolation of the bromolactonization reaction product of compound **3a**, as a model compound (Scheme 6). Selective reduction of the carboxylic acid moiety to form alcohol **11a** was achieved by mixed-anhydride formation and reduction with $NaBH_4$. Thioester **11b** was prepared in high yield by reaction with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) and 4-dimethylaminopyridine (DMAP). In addition, amide-forming reactions with aliphatic and aromatic amines produced their corresponding amides (**11c** and **11d**) without destruction of the lactone moiety. In these transformations, we confirmed that the *ee* values of the products did not decrease.



Scheme 6. Transformations of carboxylic acid **9a**.

Two intriguing questions arose when seeking an explanation for the enantioselective desymmetrizing bromolactonization reaction. The first question concerned how the C_3-symmetric trisimidazoline catalyst interacted with the dicarboxylic acids and the second was why a mixed solvent system containing acetone was more effective in governing the stereochemical control.

We have previously shown the formation a chiral ion pair between trisimidazoline **1a** and the carboxylic acids and this interaction was proposed to be responsible for the asymmetric induction in the bromolactonization reaction (Scheme 7). This association was implied by ^1H NMR measurements of a 1:3 mixture of compound **1a** and the carboxylic acids, which induced a characteristic downfield shift of the signal for the protons of the core benzene ring.[2i,19]



Scheme 7. 1:3 complex between compound **1a** and a carboxylic acid.

To investigate how the dicarboxylic acids interacted with compound **1a**, we conducted ^1H NMR experiments with a 1:3 mixture of compound **1a** and dicarboxylic acid **3a**. Owing to the low solubility of both substances in toluene, $CDCl_3$ was used as the solvent. The ^1H NMR spectrum of the mixture is shown in Figure 1c and, as a reference, individual spectra of compounds **1a** and **3a** are shown in Figure 1b,a, respectively. Similar to our previous observations with a monocarboxylic acid, the signal of the aromatic protons of the core benzene ring shifted downfield to $\delta =$ 10.2 ppm. This observation suggested that an ion pair formed between the catalyst and the dicarboxylic acids, as was observed with the monocarboxylic acid. Furthermore, in the ^1H NMR spectrum, the α protons of the carbonyl groups were observed as separate peaks, whilst in the ^{13}C NMR spectrum of the mixture (Figure 2), the resonances of two carbonyl carbons, as well as of the two carbonyl α-carbon atoms, were resolved. These results demonstrated that trisimidazoline **1a** could distinguish between the two carboxylic acid moieties in ene-dicarboxylic acid **3a**.[20]

Next, we investigated the effect of acetone in a mixed solvent system on the stereochemical outcome of the bromolactonization reaction. First, we explored the bromolactonization of an ene-monocarboxylic acid, 5-phenylhex-5-enoic acid (**12**),

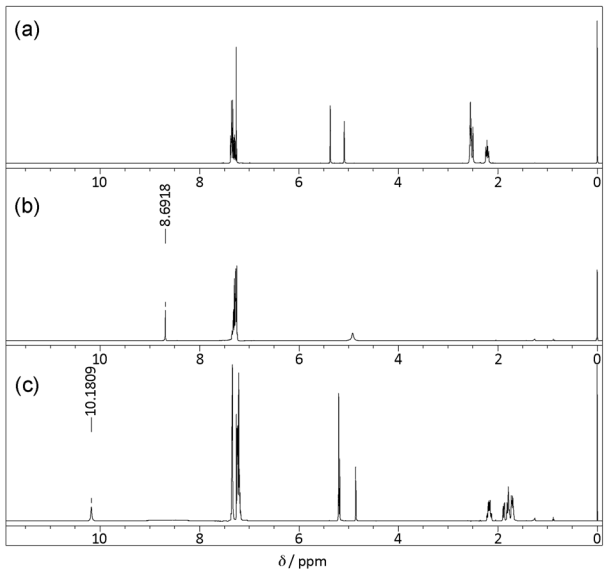


Figure 1. ^{1}H NMR spectra in $CDCl_3$: a) compound **3a**, b) compound **1a**, and c) compound **3a+1a**.

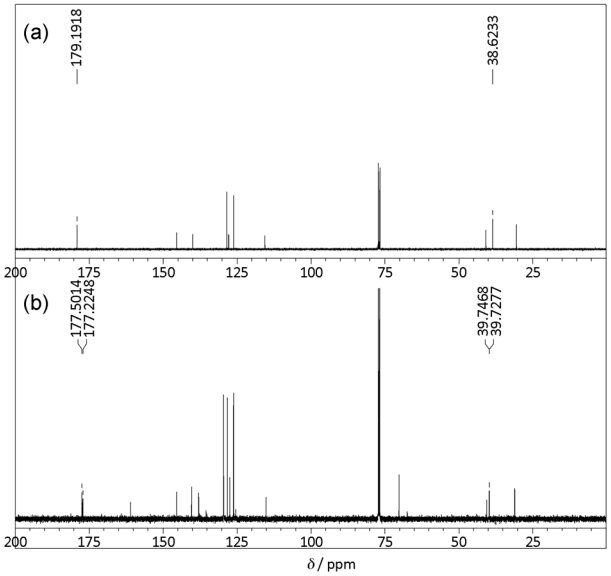
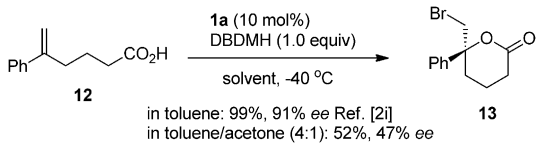


Figure 2. ^{13}C NMR spectra in $CDCl_3$: a) compound **3a** and b) compound **3a+1a**.



Scheme 8. Solvent effect on the reaction of compound **12**.

in the acetone-containing mixed solvent system (Scheme 8) with the aim of improving the selectivity of the reaction of the monocarboxylic acid. However, disappointingly, the reaction did not work effectively. Thus, compared to neat toluene, in which bromolactone **13** was produced in 91% *ee*, the reaction in a mixed, acetone-containing solvent took place with a significantly lower level of enantioselectivity (47% *ee*). Thus, it appeared that acetone did not have a positive effect on the enantioselectivity of the bromolactonization reaction of this ene-monocarboxylic acid.

Next, a ^{1}H NMR study was performed with a mixture of compounds **1a** and **3a** in [D_6]acetone as the solvent. In this case, unlike in $CDCl_3$ (Figure 3), the characteristic large

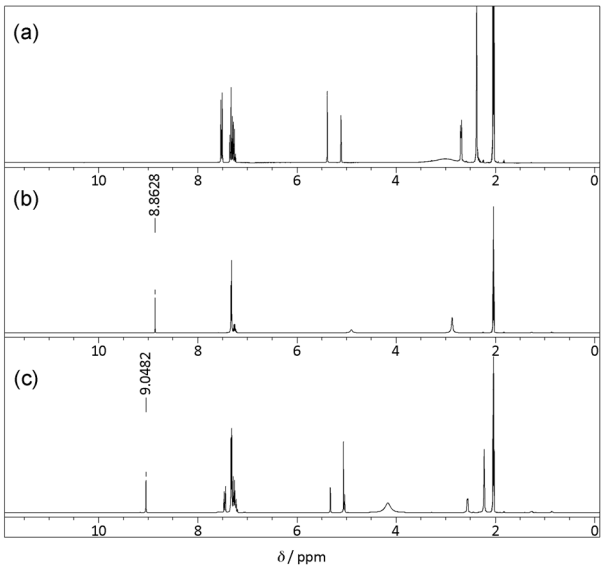
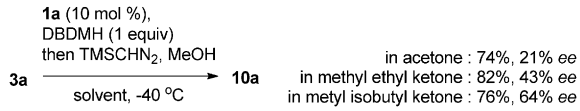


Figure 3. ^{1}H NMR spectra in [D_6]acetone: a) compound **3a**, b) compound **1a**, and c) compound **3a+1a**.

downfield shift of the core benzene ring protons of compound **1a** did not take place, but rather only a moderate downfield shift from $\delta = 8.86$ to 9.05 ppm was observed. This observation suggested that, owing to its higher polarity, acetone was unfavorable for tight ion-pair formation. To obtain further insight into the effect of solvent polarity, various reactions were also performed in a series of ketone-type solvents, such as acetone, methyl ethyl ketone, and methyl isobutyl ketone. As expected, less-polar ketone-type solvents provided higher enantioselectivities (Scheme 9).[21,22]



Scheme 9. Comparison of reactions of compound **3a** in various ketone solvents.

The reaction mixture of the desymmetrization reaction contains several kinds of carboxylic acids, such as two carboxylic acids in the substrates and a remaining acid in the produced bromolactone, which was composed of possible stereoisomers. Consequently, suitable interactions between

the catalyst and the carboxylic acid should be required for the catalyst to work efficiently. Thus, tuning the polarity with a mixed solvent system with acetone could then be considered to provide a proper equilibrium balance in this reaction system.[23]

Conclusion

We have developed an enantioselective desymmetrizing bromolactonization reaction of symmetric olefinic dicarboxylic acids that was promoted by a C_3-symmetric trisimidazoline organocatalyst. To the best of our knowledge, this result represents the first example of an enantioselective bromolactonization reaction of substrates that contain two carboxylic acids as intramolecular nucleophiles. The mixed solvent system of toluene and acetone was found to be the most efficient and was proposed to provide a proper balance of interactions between the catalyst and the carboxylic acid.

Experimental Section

A solution of olefinic dicarboxylic acid **3** and trisimidazoline **1a** (10 mol%) in toluene/acetone (4:1, 0.02 M) was stirred for 10 min at RT under an Ar atmosphere and the resulting solution was cooled to −40 °C. DBDMH (1 equiv) was added in one portion to the solution and the reaction mixture was stirred at −40 °C for a further 24 h. $TMSCHN_2$ (TMS = trimethylsilyl, 2.0 M solution in Et_2O, 4 equiv) and MeOH (20% of the volume of the toluene/acetone solution) were added to the reaction and the resulting mixture was stirred for 30 min at −40 °C. The reaction was quenched with AcOH and a saturated aqueous solution of $Na_2S_2O_3$ at −40 °C. A saturated aqueous solution of $NaHCO_3$ was added to the resulting solution at room temperature and the mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give bromolactone **10**.

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[23] Although the binding of the catalyst to the substrate was stronger in toluene than in acetone, the reaction was faster in acetone than in toluene (as judged by TLC).

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