Organocatalysis

Asymmetric Bromolactonization Catalyzed by a C₃-Symmetric Chiral Trisimidazoline**

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Halolactonization is one of the fundamental transformations in synthetic organic chemistry.^[1] This reaction provides synthetically useful products, which can be employed as synthetic intermediates for divergent transformations. A catalytic asymmetric version of this transformation would be very attractive. However, though a number of attempts to develop catalytic asymmetric halolactonization reactions have been made,^[2] and several related enantioselective halocyclizations have been developed,^[3] these reactions are still under development. Recently, highly enantioselective halolactonization reactions with organocatalysts were reported.^[4] Borhan and co-workers reported an enantioselective chlorolactonization of 4-substituted 4-pentenoic acids in the presence of hydroquinidine 1,4-phthalazinediyl diether ((DHQD)₂PHAL),^[4a] and Tang and co-workers reported an enantioselective bromolactonization of conjugated Z enynes with a bifunctional cinchona-alkaloid catalyst bearing a urea moiety.^[4b] However, the former reaction was limited to chlorolactonization; bromo- and iodolactonization were not successful, although Br and I are generally more readily transformed into various functional groups than Cl. The latter reaction is limited to particular substrates, such as conjugated Z enynes. Therefore, the development of a novel efficient method for catalytic asymmetric halolactonization is still important. During the preparation of this manuscript, Veitch and Jacobsen reported a tertiary-amine-catalyzed enantioselective iodolactonization.^[5] Herein, we present our study on organocatalytic asymmetric halolactonization. By using the structurally unique C_3 -symmetric trisimidazoline **1a**, we developed a novel asymmetric bromolactonization of 5-substituted 5-hexenoic acids.

Our working hypothesis for the development of the enantioselective bromolactonization is shown in Scheme 1. We assumed that if the alkenyl carboxylic acid and an appropriate chiral amine could form an ion pair, a chiral environment would be created. At the same time, the carboxylic acid should be activated. Bromolactonization would then proceed enantioselectively, because the olefin

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Scheme 1. Our working hypothesis for the development of an asymmetric bromolactonization.

and the two possible bromonium intermediates would be in equilibrium in the presence of the brominating reagent, and the activated carboxylic acid, which would be in a chiral environment, should react preferentially with one of the two bromonium ions.^[6] This approach is different from recent successful approaches, which mainly involved the creation of chiral environments around the halo cations.^[4,5] The key to this hypothesis was the appropriate choice of a chiral amine that would have a good interaction with carboxylic acids.^[7]

We envisioned that the C_3 -symmetric trisimidazoline **1a** (Scheme 2), which we developed recently as a new organocatalyst entry,^[8] could be suitable for our working hypothesis, because an interesting interaction of the trisimidazoline derived from ethylenediamine with carboxylic acids led to the formation of 1:3 complexes in the field of material sciences (Scheme 2).^[9]



Scheme 2. Structure of the C_3 -symmetric trisimidazoline **1a** and the reported 1:3 complex of a trisimidazoline with a carboxylic acid.

To test this idea, we examined the bromolactonization of 5-phenylhex-5-enoic acid (2a) with *N*-bromosuccinimide (NBS). As expected, the reaction with catalyst **1a** afforded the lactone **3a** with 69% *ee*, even at room temperature (Table 1, entry 1). The reaction of **2a** in the presence of other chiral amines, such as quinidine or $(DHQD)_2PHAL$, proceeded less selectively, although **3a** was formed with moderate enantioselectivity with $(DHQD)_2PHAL$ (Table 1, entries 2 and 3). Reactions with the bisimidazoline and

Table 1:	Screening	of the	reaction	conditions.
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	Ph 2a OH	Br ⁺ source (1.2 equiv) catalyst (10 mol%) solvent (0.05 M)		Ph S 3a		
Entry	Catalyst	Solvent	Br ⁺ source	т [°С]	Yield [%]	ee [%] ^[a]
1	la	CHCl₃	NBS	RT	95	69
2	quinidine	CHCl ₃	NBS	RT	86	-5
3	(DHQD) ₂ PHAL	CHCl₃	NBS	RT	89	47
4	1b	CHCl₃	NBS	RT	99	28
5	1c	CHCl₃	NBS	RT	92	6
6	1a	CH_2Cl_2	NBS	RT	86	69
7	1a	CH₃CN	NBS	RT	91	32
8	1a	toluene	NBS	RT	91	73
9	1a	toluene	NBS	-25	99	85
10	1a	toluene	NBS	-40	97	87
11	1a	toluene	DBDMH	-40	69	91
12 ^[b]	1a	toluene	DBDMH	-40	99	91

[a] The ee value was determined by HPLC. [b] The reaction was carried out with 1.0 equivalent of DBDMH (which corresponds to 2.0 equivalents of the Br⁺ source).



monoimidazoline catalysts 1b and 1c showed that the C_3 -symmetric structure of the catalyst was crucial for good selectivity (Table 1, entries 4 and 5).^[10] This interesting trend was similar to that observed in our previous study on the conjugate addition of β -ketoesters to nitroolefins in the presence of 1a.^[8]

Next, we optimized the reaction with 1a. The polarity of the solvent was found to be important (Table 1, entries 1 and 6-8): the use of polar CH₃CN resulted in poor selectivity, whereas nonpolar toluene increased the selectivity to 73 % ee. When the reaction temperature was lowered to -40 °C, 3a was produced with high selectively (87% ee; Table 1, entry 10). Furthermore, the use of 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) instead of NBS as the bromine source increased the selectivity, although the conversion was moderate when 0.6 equivalents were used (Table 1, entry 11). With 1.0 equivalent of DBDMH, the reaction proceed in high yield with good selectivity (99% yield, 91% ee; Table 1, entry 12). Under the optimized conditions, when no catalyst was used, the conversion of the reaction was only 10% in the same reaction time (11 h), as judged by ¹H NMR spectroscopy of the crude product. This result indicates that 1a effectively accelerates the reaction. Other halogen sources, such as N-chlorosuccinimide (NCS) and N-iodosuccinimide (NIS), were ineffective; NCS did not give the corresponding lactone,^[11] and NIS did not give a good result (43% yield and 62% ee). The absolute configuration of **3a** was determined by comparison of the specific optical rotation of its debromo derivative with literature data (see the Supporting Information).

We investigated the scope of the reaction under the optimized reaction conditions. Generally, good results were observed with aryl-substituted substrates (Table 2, entries 1-

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Entry	Substrate	Product	Yield [%]	ee [%] ^[c]			
	R	Br R O C					
1	2a : R=Ph	3 a	99 (96) ^[d]	91 (90) ^[d]			
2	2b : R=4-ClC ₆ H ₄	3 b	93	87			
3	2c : R=4-BrC ₆ H ₄	3 c	93	89			
4	2d : $R = 4-FC_6H_4$	3 d	94	87			
5	2e: R=4-CF ₃ C ₆ H ₄	3 e	96	89			
6	2 f : R = 4-MeC ₆ H ₄	3 f	96	90			
7 ^[e]	2g : R=4-MeOC ₆ H ₄	3 g	74	80			
8	2h : R=2,4-diMeC ₆ H ₃	3 h	91	75			
9	2i: R = 2-naphthyl	3 i	82	89			
10 ^[f]	2 j: R=cyclohexyl	3j ^{Br}	95	72			
	Ph X OH	Ph X 0					
11	2k : X = CMe ₂	3 k	96	81			
12 ^[f]	21: X=0	31	74	71			
13 ^[f]	2 m: X = NTs	3 m	89	75			

[a] Unless otherwise noted, the reaction was carried out with la (10 mol%) and DBDMH (1.0 equiv) in toluene at -40 °C. [b] Reaction time: 4-46 h (see the Supporting Information for details). [c] The ee value was determined by HPLC. [d] The reaction was carried out with 2.5 mol% of 1a. [e] The reaction was carried out with DBDMH (2.0 equiv) at -78 °C. [f] The reaction was carried out at -60 °C.

9, 11).^[12] Even with a catalyst loading of 2.5 mol%, **2a** was converted efficiently into 3a with good enantioselectivity (Table 2, entry 1). The aromatic ring could have both electron-withdrawing and electron-donating substituents; however, the presence of a bulky aromatic group, such as 2,4-dimethylphenyl, decreased the selectivity (Table 2, entry 8). The good result observed with p-methoxyphenylsubstituted 2g stands in contrast to reported halolactonization reactions, in which good selectivity was not observed with substrates bearing a p-methoxyphenyl group.^[4a,5] Not only aryl-substituted substrates were suitable for the bromolactonization: the cyclohexyl-substituted alkenyl carboxylic acid 2i was transformed into the corresponding lactone with moderate selectivity (Table 2, entry 10).^[13] Substrates 21 and 2m were also tolerated and converted into dioxanone 31 and morpholinone 3m (Table 2, entries 12 and 13), although the selectivity was only moderate. In the study by Tang and coworkers, bromolactonization of 21 produced a nearly racemic product.[4b]

The developed bromolactonization could be performed on a gram scale. Thus, the reaction of carboxylic acid 2b (1.0 g) with catalyst **1a** (5 mol%) afforded the lactone **3b** in 98% yield with 91% ee (Scheme 3). Recrystallization of this product gave 3b with 99% ee. The absolute configuration of 3b was assumed from the absolute configuration of 3a. The synthetic utility of the products obtained by bromolactonization was also shown by the derivatization of 3b. The bromine atom could be substituted not only for a hydrogen atom by a radical reduction with nBu₃SnH/AIBN but also for azide and thioacetate functionalities by nucleophilic substitution with sodium azide or potassium thioacetate. Furthermore, ring

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Scheme 3. Gram-scale preparation (top) and derivatization of **3 b** (bottom). a) Reaction conditions for the synthesis of **3 ba**: nBu_3SnH , AIBN, benzene, reflux, 30 min; b) for **3 bb**: AcSK, DMF, 60–75 °C, 6.5 h; c) for **3 bc**: NaN₃, DMF, 130 °C, 6 h; d) for **3 bd**: Cs₂CO₃, MeOH, room temperature, 45 min. AIBN = azobisisobutyronitrile, DMF = N,N-dimethylformamide.

opening of the δ -lactone in MeOH with Cs₂CO₃ directly produced the epoxyester **3bd**. In these transformations, no decrease in the *ee* value was observed: products **3ba–3bd** were obtained with 99% *ee* from lactone **3b** with 99% *ee*.

Finally, we performed several preliminary experiments to gain mechanistic insight. An ¹H NMR spectroscopic experiment was carried out to confirm the interaction of trisimidazoline **1a** with the carboxylic acid. In the ¹H NMR spectrum of a 1:3 mixture of **1a** and **2a** in CDCl₃ (Figure 1b), an unusual singlet peak was observed at $\delta = 10.38$ ppm. In the reports which documented the 1:3 complexes of trisimidazoline and carboxylic acids (as shown in Scheme 2), a similar singlet peak was described as the H peak of the core benzene



Figure 1. ¹H NMR spectroscopic study: a) **2a**; b) 1:3 mixture of **1a** and **2a**; c) **1a**.

ring.^[9a,d] Therefore, this characteristic peak at $\delta = 10.38$ ppm was also assigned as the H peak of the core benzene ring and implied the association of **1a** and **2a**. Thus, the chiral trisimidazoline **1a** derived from 1,2-diphenylethylenediamine, as well as that derived from ethylenediamine, can form a 1:3 complex with carboxylic acids.

Aside from our working hypothesis that an ion pair could create a chiral environment, we considered that it might be possible that a chiral bromonium species could be generated to promote the asymmetric bromolactonization. Therefore, as a control experiment, we subjected 5-phenyl-5-hexen-1-ol (4) instead of a carboxylic acid of type 2 to the bromocyclization with 1a (Scheme 4). If the trisimidazoline 1a also interacted



Scheme 4. Control experiment with the alcohol **4.** Reaction conditions: I) **1a** (10 mol%), NBS (1.2 equiv); II) **1a** (10 mol%), Ph(CH₂)₃CO₂H (30 mol%), NBS (1.2 equiv).

with NBS or DBDMH, and a complex formed by such an interaction mainly engaged in the reaction, bromocyclization of the alcohol **4** should give one of the enantiomers of product **5** preferentially. However, the tetrahydropyran **5** was produced in almost racemic form $(4 \% \ ee)$. It was also possible that the imidazolium salt generated from **1a** and a carboxylic acid might function as a proton donor^[14] to activate NBS or DBDMH and thus create a chiral environment. However, the bromocyclization of **4** in the presence of 4-phenylbutyric acid also gave **5** in almost racemic form.^[15]

Therefore, we now think that the interaction of **1a** with the carboxylic acid moiety of substrates is crucial in our reaction system to create a chiral environment by the formation of an ion pair. However, more detailed investigation of the reaction mechanism is necessary, because the possibility that **1a** could function as a bifunctional catalyst (one imidazoline moiety could activate the carboxylic acid, and another could activate NBS or DBDMH) cannot be ruled out at this stage.

In summary, we have developed an enantioselective bromolactonization of 5-substituted 5-hexenoic acids catalyzed by the trisimidazoline **1a** on the basis of the interesting molecular-recognition properties of this catalyst. Further studies to uncover the details of the mechanism and investigate applications for related reactions are now under way.

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