Organocatalysis

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Asymmetric Bromolactonization Catalyzed by a C_3-Symmetric Chiral Trisimidazoline**

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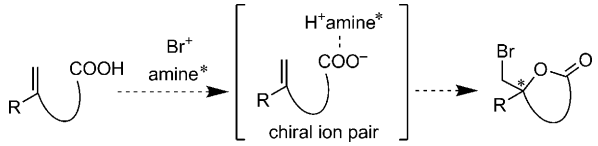
Halolactonization is one of the fundamental transformations in synthetic organic chemistry.[1] This reaction provides synthetically useful products, which can be employed as synthetic intermediates for divergent transformations. A catalytic asymmetric version of this transformation would be very attractive. 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.

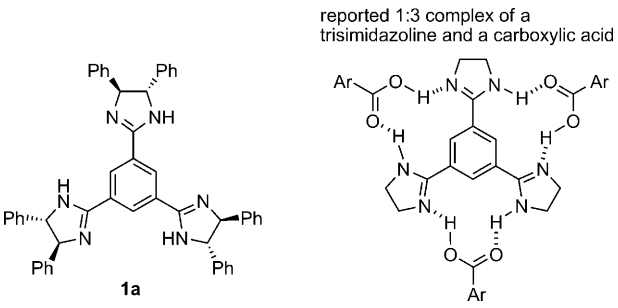
Our working hypothesis for the development of the enantioselective bromolactonization is shown in Scheme 1. We assumed that if the alkenyl carboxylic acid and an appropriate chiral amine could form an ion pair, a chiral environment would be created. At the same time, the carboxylic acid should be activated.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



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

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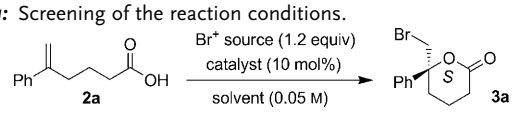
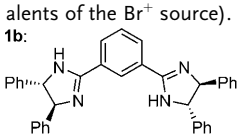
Table 1: Screening of the reaction conditions.



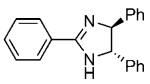
Entry	Catalyst	Solvent	Br^+ source	*T* [°C]	Yield [%]	*ee* [%][a]
1	**1a**	$CHCl_3$	NBS	RT	95	69
2	quinidine	$CHCl_3$	NBS	RT	86	−5
3	$(DHQD)_2PHAL$	$CHCl_3$	NBS	RT	89	47
4	**1b**	$CHCl_3$	NBS	RT	99	28
5	**1c**	$CHCl_3$	NBS	RT	92	6
6	**1a**	CH_2Cl_2	NBS	RT	86	69
7	**1a**	CH_3CN	NBS	RT	91	32
8	**1a**	toluene	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).

1b:



1c:

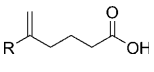
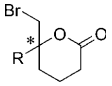
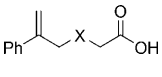
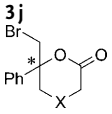


monoimidazoline catalysts **1b** and **1c** showed that the C_3-symmetric structure of the catalyst was crucial for good selectivity (Table 1, entries 4 and 5).[10] This interesting trend was similar to that observed in our previous study on the conjugate addition of β-ketoesters to nitroolefins in the 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 CH_3CN 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).

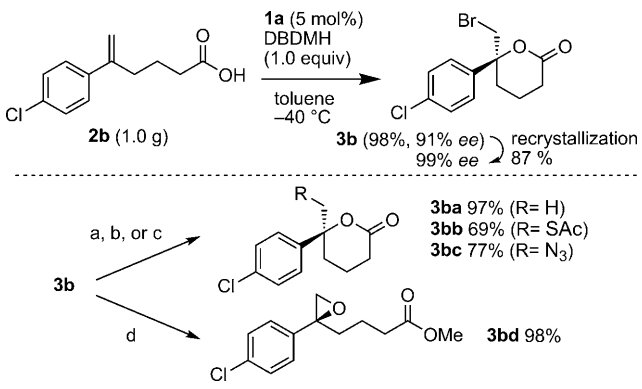
We investigated the scope of the reaction under the optimized reaction conditions. Generally, good results were observed with aryl-substituted substrates (Table 2, entries 1–9, 11).[12] Even with a catalyst loading of 2.5 mol%, **2a** was converted efficiently into **3a** with good enantioselectivity (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*-methoxyphenyl-substituted **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 **2j** was transformed into the corresponding lactone with moderate selectivity (Table 2, entry 10).[13] Substrates **2l** and **2m** were also tolerated and converted into dioxanone **3l** and morpholinone **3m** (Table 2, entries 12 and 13), although the selectivity was only moderate. In the study by Tang and coworkers, bromolactonization of **2l** produced a nearly racemic product.[4b]

Table 2: Generality of the asymmetric bromolactonization with **1a**.[a,b]

Entry	Substrate	Product	Yield [%]	*ee* [%][c]
				
1	**2a**: R = Ph	**3a**	99 (96)[d]	91 (90)[d]
2	**2b**: R = 4-ClC_6H_4	**3b**	93	87
3	**2c**: R = 4-BrC_6H_4	**3c**	93	89
4	**2d**: R = 4-FC_6H_4	**3d**	94	87
5	**2e**: R = 4-$CF_3C_6H_4$	**3e**	96	89
6	**2f**: R = 4-MeC_6H_4	**3f**	96	90
7[e]	**2g**: R = 4-$MeOC_6H_4$	**3g**	74	80
8	**2h**: R = 2,4-diMeC_6H_3	**3h**	91	75
9	**2i**: R = 2-naphthyl	**3i**	82	89
10[f]	**2j**: R = cyclohexyl	**3j**	95	72
				
11	**2k**: X = CMe_2	**3k**	96	81
12[f]	**2l**: X = O	**3l**	74	71
13[f]	**2m**: X = NTs	**3m**	89	75

[a] Unless otherwise noted, the reaction was carried out with **1a** (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.

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 nBu_3SnH/AIBN but also for azide and thioacetate functionalities by nucleophilic substitution with sodium azide or potassium thioacetate. Furthermore, ring



Scheme 3. Gram-scale preparation (top) and derivatization of **3b** (bottom). a) Reaction conditions for the synthesis of **3ba**: nBu$_3$SnH, AIBN, benzene, reflux, 30 min; b) for **3bb**: AcSK, DMF, 60–75 °C, 6.5 h; c) for **3bc**: NaN_3, DMF, 130 °C, 6 h; d) for **3bd**: Cs_2CO_3, MeOH, room temperature, 45 min. AIBN = azobisisobutyronitrile, DMF = *N*,*N*-dimethylformamide.

opening of the δ-lactone in MeOH with Cs_2CO_3 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 ^{1}H NMR spectroscopic experiment was carried out to confirm the interaction of trisimidazoline **1a** with the carboxylic acid. In the ^{1}H NMR spectrum of a 1:3 mixture of **1a** and **2a** in $CDCl_3$ (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 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.

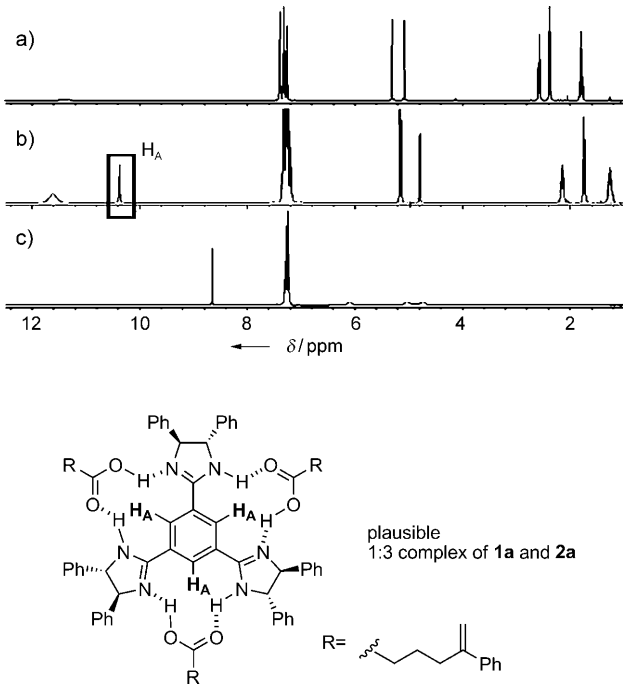
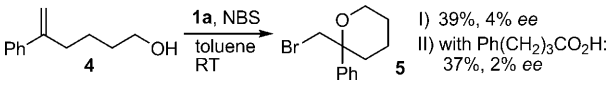


Figure 1. ^{1}H NMR spectroscopic study: a) **2a**; b) 1:3 mixture of **1a** and **2a**; c) **1a**.

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%), $Ph(CH_2)_3CO_2H$ (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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[11] The reaction was also examined with DCDMH, but almost no reaction occurred in 48 h.

[12] Unfortunately, the reaction of 4-phenylpent-4-enoic acid gave the corresponding γ-lactone with just 33% *ee* under these conditions.

[13] A primary alkyl substituent decreased the selectivity. When R was $Ph(CH_2)_2$, the lactone was obtained in 83% yield with 52% *ee*.

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[15] We also investigated the effect of a carboxylic acid as an additive in our reaction system and found that the additional acid had a slight influence. The reaction of **2a** with **1a** (10 mol%) and DBDMH (1.0 equiv) in the presence of 4-phenylbutyric acid (30 mol%) in toluene at −40°C gave **3a** in 97% yield with 87% *ee*.

