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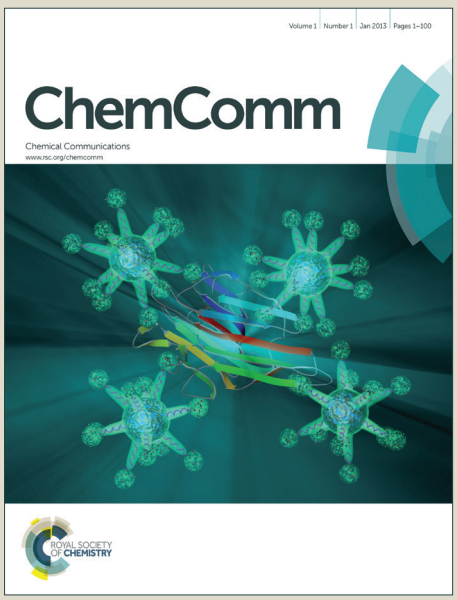

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Enantioselective Iodolactonization of Allenoic Acids

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An enantioselective iodolactonization reaction of allenoic acids has been developed using trisimidazoline catalyst and I_2. Our mechanistic study suggests the involvement of a π-allyl cation intermediate in this reaction system.

Halocyclization reactions between substrates bearing C–C multiple bonds and nucleophilic functionalities are powerful transformations in organic synthesis. Recently, extensive efforts have been devoted to the development of enantioselective halocyclization reactions and significant progress has been made in this field.[1–3] We have also developed asymmetric bromolactonization of 5-hexenoic acid derivatives to produce δ-lactones with trisimidazoline **1a** (Figure 1).[2i,4] In these transformations, alkene moieties are typically used in enantioselective halocyclization reactions. In addition to alkenes, several examples of asymmetric halolactonization using alkynes are reported. [2f, 5] On the other hand, substrates with allenes as multiple C–C bond systems have been less well explored.

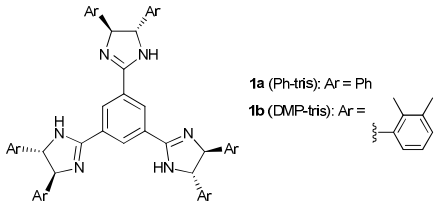


Figure 1 Structure of trisimidazoline **1a** and **1b**

In the case of halocyclization of alkenes, the reactions of one C–C double and one intermediate, such as bridged 3-membered ring halonium ion, should be considered. (Figure 2, i). On the other hand, the unique reactivity of allenes[6] presents different challenges for using these compounds in enantioselective halocyclization. (1) Allenes have two C–C double bonds, therefore regioselective halogen addition would be important. (2) It would also be a matter that the reaction of allenes with electrophilic halogen source could generate two different species, such as bridged 3-membered ring halonium ion intermediates and π-allyl cation intermediates[7] (Figure 2, ii). These factors could make it difficult to control enantioselectivity.[8]

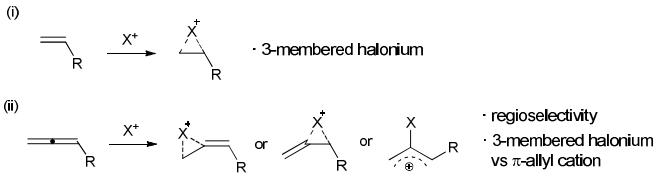


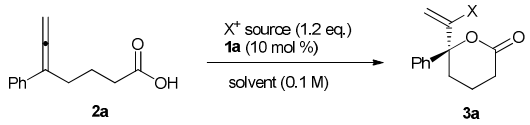
Figure 2 Electrophilic halogenation of alkene and allene and possible issues for enantioselective halocyclization.

The first enantioselective bromocyclization of allenes has recently been reported by Toste.[9] This demonstration used a chiral dinuclear gold complex and/or chiral phosphate anions with *N*-bromolactams to give a heterocyclic vinyl bromide having an allylic stereocenter, with high enantioselectivity. The reaction was proposed to proceed through a vinyl gold intermediate followed by bromodeauration with an electrophilic bromine source, namely stepwise halogenation process. On the other hand, enantioselective halocyclization via direct halogenation of unsaturated allene bonds had not been reported through the use of either organo- or metal catalysts, when we started this study. During preparing this manuscript, the first organocatalytic enantioselective bromolactonization of allenoic acids was appeared.[10,11] In this communication, we report the first enantioselective iodolactonization of allenoic acids using the organocatalyst, trisimidazoline **1b** (DMP-tris, Ar = 2,3-dimethyl-C_6H_3) and I_2, which proceeds via direct iodination of the allene. In this reaction, we propose the involvement of a π-allyl cation intermediate in the enantio-determining step, based on a mechanistic investigation using trisubstituted allenoic acid.

We began by screening halogenating agents for the reaction of allenoic acid **2a** in the presence of trisimidazoline catalyst **1a** in $CHCl_3$ (Table 1). We found that iodine rather than bromine was the preferred halogen source to give the desired lactone **3a**. Reactions with bromine sources, such as DBDMH and NBS produced complex mixtures, while NIS gave **3a** in moderate yield (62%, entry 2) with an enantiomeric ratio (er) of 64:36 indicating a definite but low enantioselectivity. Changing the reaction media to toluene or CH_3CN, and lowering the reaction temperature to −40°C did not improve the selectivity (entries 3-5). The use of $I(collidine)_2PF_6$[12] or ICl also did not give any improvements (entries 6 and 7). However,

I_2 was found to give the best results (73:27 er, entry 8). Although the reaction with I_2 was slow in $CHCl_3$, the reaction could be accelerated using toluene while maintaining similar yield and selectivity (entry 9). In these conditions, 8-membered lactone, a possible regioisomeric adduct, was not obtained. Based on these preliminary studies, we tested further optimizations using I_2 and toluene as a solvent. It should be noteworthy that the difference in selectivity between NIS and I_2 gives some indication about the mechanism of the reaction as will be discussed later in more detail.

Table 1 Initial screening of halolactonization of allenoci acid **2a**[a,b]



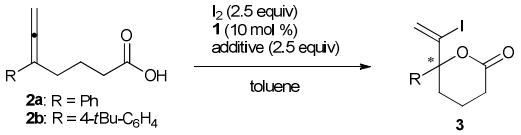
2a **3a**

Entry	Solvent, temp.	X^+ source	Time (h)	Yield (%)	er[c]
1	$CHCl_3$, rt	DBDMH or NBS		complex mixtures	
2	$CHCl_3$, rt	NIS	0.5	62	64:36
3	toluene, 0 °C	NIS	8	44	60:40
4	CH_3CN, 0 °C	NIS	15	67	51:49
5	$CHCl_3$, -40 °C	NIS	24	37	60:40
6	$CHCl_3$, rt	$I(collidine)_2PF_6$	1.3	34	51:49
7	$CHCl_3$, -40 °C	ICl	23	25	61:39
8	$CHCl_3$, rt	I_2	67	65	73:27
9	toluene, rt	I_2	26	68	75:25

[a] DBDMH: 1,3-dibromo-5,5-dimethyl hydantoin, NBS: *N*-bromo succineimide, NIS: *N*-iodo succineimide, [b] 0.05-0.1 mmol of **2a** was used. [c] Er was determined by HPLC.

Further optimization studies initially focused on the use of additives to increase the product yield (Table 2). We believed that the moderate yield of the reaction under the above conditions could be caused by deactivation of the catalyst by hydrogen iodide generated from I_2 during the lactonization reaction. We therefore examined the effect of several basic additives for trapping hydrogen iodide. With inorganic bases, such as K_2CO_3 and Li_2CO_3, the yield of **3a** increased but enantioselectivity decreased (entries 1 and 2). Conversely, the use of bulky organic bases, such as 2,6-di-*tert*-butylpyridine (DTBP) increased the yield while maintaining enantioselectivity (entry 3). The reaction with 2,4,6-collidine, gave lower selectivity and yields (entry 4), illustrating the importance of bulkiness of pyridine base. Because further screening of additives and molecular ratios of I_2 and DTBP gave no further improvements in enantioselectivity, we investigated the effect of the phenyl group substituents of the trisimidazoline catalyst. After screening (see Electronic Supplementary Information), we found that introduction of substituents on the 2-position of the phenyl group of Ph-tris (**1a**) improved the enantioselectivity and a trisimidazoline **1b** (DMP-tris, Figure 1) gave better results (entry 5, 81:19 er). Further improvement in enantioselectivity was achieved by conducting the reaction at 0 °C, although this improvement was small (entry 6, 83:17 er), likely because of the low solubility of **2a** under these conditions. We then tested the iodolactonization reaction of a more lipophilic substrate **2b** (R = 4-*t*BuC_6H_4) under the same conditions. We found that **2b** dissolved at 0 °C and provided good enantioselectivity as expected (entry 7, 91:9 er). The selectivity was decreased by conducting the reaction at lower temperatures (−20 °C, entry 8), and so the reaction conditions described in entry 7 were taken as the optimal conditions.

Table 2 Optimization study of iodolactonization of allenoic acid with **2a** and **2b**[a,b]

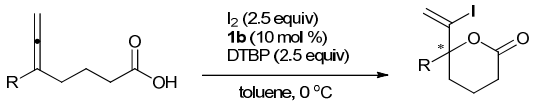


Entry	1	2	Additive, temp.	Time (h)	Yield (%)	er[c]
1	**1a**	**2a**	K_2CO_3, rt	5	86	61:39
2	**1a**	**2a**	Li_2CO_3, rt	24	76	61:39
3	**1a**	**2a**	DTBP, rt	7	85	74:26
4	**1a**	**2a**	2,4,6-collidine, rt	1	69	67:33
5	**1b**	**2a**	DTBP, rt	9	77	81:19
6	**1b**	**2a**	DTBP, 0 °C	48	83	83:17
7	**1b**	**2b**	DTBP, 0 °C	18	89	91:9
8	**1b**	**2b**	DTBP, -20 °C	48	18	76:24

[a] DTBP: 2,6-di-*tert*-butylpyridine [b] 0.05-0.1 mmol of **2a** and **2b** was used. [c] Er was determined by HPLC.

The generality of iodolactonization reaction using trisimidazoline **1b** and I_2 with the series of lipophilic allenoic acids **2c**–**k** was investigated (Table 3). For reference the results of **2a** and **2b** are shown as entries 1 and 2. When the reactions were conducted with the substrate **2c** (R= 4-TBSOC$H_2C_6H_4$) and **2d** (R= 4-TMSC_6H_4), similarly good selectivities were obtained (entries 3 and 4). Changing the electron density of the aromatic ring revealed the sensitivity of the reaction to electronic effects. The efficiency was poor for allenoic acids having an electron rich aromatic ring such as **2e** (R= 4-*t*BuOC_6H_4), leading to racemic products (entry 5). Conversely, the allenoic acid **2f** (R= 4-FC_6H_4) showed similar selectivity to **2a** (entry 6). The substrate **2g** (R= 4-$CF_3C_6H_4$) also gave comparable selectivity, although with decreased yield (entry 7). Several allenoic acids **2h**–**j** with *meta* or *ortho* substituents were also used in the reaction (entries 8–10). These conditions were found to work even with aliphatic substituents, however a much lower selectivity was achieved. These results suggest the importance of the aromatic substituent on the allene.[13] The absolute stereochemistry

Table 3 Generality of iodolactonization of allenoic acid[a]

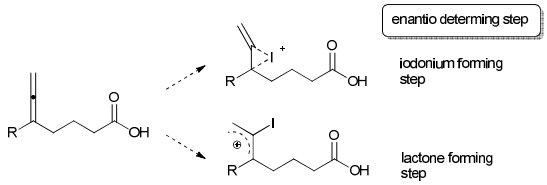


Entry	2	R	Time (h)	3	Yield (%)	er[b]
1	**2a**	C_6H_5	48	**3a**	83	83:17
2	**2b**	4-*t*Bu-C_6H_4	18	**3b**	89	91:9
3	**2c**	4-TBSOCH_2-C_6H_4	24	**3c**	88	90:10
4	**2d**	4-TMS-C_6H_4	24	**3d**	78	90:10
5	**2e**	4-*t*BuO-C_6H_4	24	**3e**	85	51:49
6	**2f**	4-F-C_6H_4	42	**3f**	78	84:16
7	**2g**	4-CF_3-C_6H_4	48	**3g**	53	81:19
8	**2h**	3,5-diMe-C_6H_3	24	**3h**	85	82:18
9	**2i**	3-TBSOCH_2-C_6H_4	48	**3i**	82	83:17
10	**2j**	2-Me-C_6H_4	72	**3j**	35	87:13
11	**2k**	$PhCH_2CH_2$	24	**3k**	74	67:33

[a] The reaction was carried out with **2** (0.1-0.04 mmol), I_2 (2.5 equiv), **1b** (10 mol %) and DTBP (2.5 equiv) in toluene (0.05 M) at 0 °C. [b] Er was determined by HPLC.

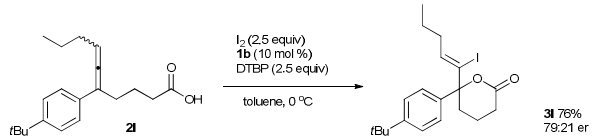
of major enantiomer of **3a** was determined to be (*S*), which is the same configuration with previously reported bromolactone produced by the bromolactonization reaction using trisimidazoline catalyst.[2i,4]

It is interesting how the enantioselectivity was induced with allenoic acid substrates in this reaction. We think the intermediates generated from the allenes with the iodine source should be particularly important. As described above, one possibile intermediate is a 3-membered ring iodonium ion (Scheme 1). Alternatively, π-allyl cation can also be formed. For asymmetric induction to occur, a key step should be different by the respective intermediates: In the case of a mechanism via an iodonium ion, the stereochemistry should be determined when the iodine adds to C–C double bond of the allene because the following nucleophilic attack may be expected to occur in an *anti*-fashion. Alternatively, for a mechanism proceeding via a π-allyl cation, the lactone forming step would be the crucial for determining the stereochemistry because of the planarity of the π-allyl cation. Ma's group has reported that the formation of either of these intermediates depends on the iodine source.[7] In their study on diastereoselective iodolactonization of allenoic acids, reactions using NIS were reported to proceed via iodonium ion, while reactions with I_2 proceed via π-allyl cation. Therefore, we infer that our reaction system using I_2 may also proceed via a π-allyl cation intermediate.



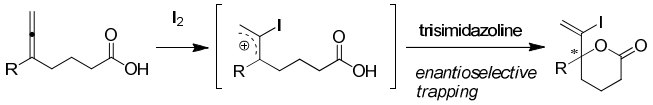
Scheme 1 Possible intermediates generated from allene

To obtain further insight into the mechanism, the reaction was carried out using the trisubstituted allenoic acid **2l**, which contained a 1:1 mixture of allene stereoisomers. Under the enantioselective iodolactonization conditions given in Table 3 the racemic allenoic acid **2l** gave the lactone **3l** in 76% yield with 79:21 er (Scheme 2) even though the conditions were optimized for trisubstituted allenoic acids. It was noted that the product was obtained as a *Z*-isomer in a highly selective manner (>20:1) determined by NOSEY.



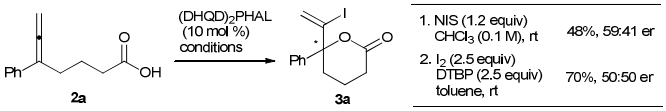
Scheme 2 Reaction with trisustituted allenoic acid **2l**

These observations suggest that a π-allyl cation intermediate is involved in this reaction system for the following reasons. If the reaction underwent a mechanism involved an iodonium ion intermediate predominantly, the yield of one enantiomer should be up to 50% given the observed selective formation of a *Z*-isomer and the expected *anti*-addition of carboxylic acid to the iodonium intermediate. However, based on the results (76% yield and 79:21 er), a major enantiomer was produced in 60% yield. In our previous report on the enantioselective bromolactonization reactions of the alkenoic acids with trisimidazoline, we proposed that a chiral carboxylate formed with trisimidazoline could introduce asymmetry into the racemic bromonium ion intermediates and allow discrimination between the enantiomers.[2i,4] Because the observations in this study agree with our previous reports, we consider that the enantioselective iodolactonization of allenoic acids in this reaction system proceeds mainly via a π-allyl cation intermediate and that the trisimidazoline may facilitate enantioselective trapping of the intermediates (Scheme 3). The selectivity trend that moderately electron rich aromatic rings gave better results (Table 3), though strongly electron donating 2e gave poor results, could be due to this proposed reaction pathway.



Scheme 3 Proposed reaction pathway

To obtain further insight into the iodolactonization of allenoic acids, the reaction with $(DHQD)_2PHAL$, which is a widely used organocatalyst for asymmetric halocyclizations,[1j] was also investigated (Scheme 4). Two conditions using NIS and I_2, which respectively correspond to the conditions of entry 2 in Table 1 and entry 4 in Table 2, were applied to allenoic acid **2a**. Interestingly, the contrasting selectivity trend to the reaction with trisimidazoline was observed: NIS gave low but significant enantioselectivity (59:41 er), while I_2 gave a racemic product. It was then implied that π-allyl cation intermediate could not appropriate to induce the enantioselectivity with $(DHQD)_2PHAL$.[14] These observations suggest the importance of appropriate combination of catalysts and halogen sources for enantioselective halocyclization with allenes, which afford **2** possible halo-intermediates.



Scheme 4 Reaction with $(DHQD)_2PHAL$

In conclusion, we report the first example of an enantioselective iodolactonization reaction of allenoic acids. The combination of a trisimidazoline catalyst and I_2 is found to be effective. The involvement of a π-allyl cation intermediate in this system is proposed, based on mechanistic studies using a trisubstituted allenoic acid. This work illustrates the importance of controlling the halo- intermediate for enantioselective halocyclization reaction with allenes. Further investigations toward understanding the details of this reaction mechanism are now underway.

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Notes and references

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13 The γ-lactones formation with 4-(4-(*tert*-butyl)- phenyl)hexa-4,5-dienoic acid (**2m**) resulted in 74% yield with 60:40 er.

14 The significance of interraction between $(DHQD)_2PHAL$ and halogen sources have been proposed, see: ref 2e. Also see, (a) W. Zhang, N. Liu, C. M. Schienebeck, X. Zhou, I. I. Izhar, I. A. Guzei, and W. Tang, *Chem. Sci.* 2013, **4**, 2652. (b) K. C. Nicolaou, N. L. Simmons, Y. Ying, P. M. Heretsch, and J. S. Chen, *J. Am. Chem. Soc.* 2011, **134**, 10389.

