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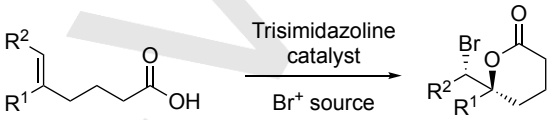
Enantioselective Bromolactonization of Trisubstituted Olefinic Acids Catalyzed by Chiral Pyridyl Phosphoramides

Yasuhiro Nishikawa*, Yuhta Hamamoto, Rika Satoh, Naho Akada, Shuhei Kajita, Marina Nomoto, Megumi Miyata, Madoka Nakamura, Chinatsu Matsubara, and Osamu Hara*

Abstract: Enantioselective bromolactonization of trisubstituted olefinic acids producing synthetically useful chiral lactones with two contiguous asymmetric centers has remained mainly unexplored except for the 6-exo cyclization mode. In this work, the 5-exo- and 6-endo modes of bromocyclization of trisubstituted olefinic acids were enabled for the first time using *N*-bromosuccinimide and pyridyl phosphoramide catalyst. The utility of the resulting bromolactones was demonstrated by transformations harnessing reactive alkyl bromide moieties without losing stereochemical information. Optimization studies and control experiments revealed that the basicity of pyridine moieties and presence of *N*-H protons in phosphoramide species strongly affected both the reactivity and enantioselectivity parameters.

Enantioselective halocyclization of olefins is an important organic transformation utilized for the construction of chiral heterocyclic compounds containing carbon-halogen bonds.[1] In 2010, the first successful application of organocatalysis in the asymmetric halolactonization of disubstituted olefins was reported by several groups.[2] These pioneering works triggered the development of various types of halocyclization reactions involving amides,[3] carbamates,[4] alcohols,[5] and tosylamides[6]. Among various heterocyclic products synthesized by these methods, chiral halolactones have attracted much attention because lactone derivatives include biologically active compounds and synthetically useful intermediates.[7] Numerous attempts to enlarge the scope of enantioselective halolactonization have been dedicated to achieving the 5-exo, 6-endo, and 6-exo modes of cyclization using 1,1-disubstituted or 1,2-disubstituted derivatives of olefinic acid.[2,8-11] On the other hand, the halolactonization process conducted using trisubstituted olefinic acids remains underdeveloped despite its ability to produce various types of lactones containing two contiguous stereocenters with tetrasubstituted carbons. The sole example of a highly enantioselective halolactonization reaction was reported by Fujioka and co-workers, in which 6-exo-cyclization was performed using chiral trisimidazoline catalysts (Scheme 1, Eq. (1)).[12,13] In contrast, a general method for the 5-exo- and 6-endo-cyclization of trisubstituted olefins via a highly enantioselective bromolactonization reaction has not been developed yet, although a few examples of 5-exo-cyclization with moderate stereoselectivity were reported (Scheme 1, Eq. (2) and (3)).[14] In this study, enantioselective bromolactonization reactions with two distinct modes of cyclization enabled using pyridyl phosphoramide as a single catalyst are described.

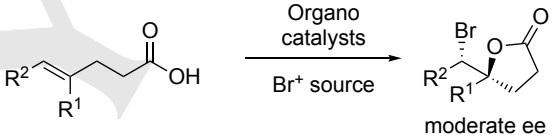
6-exo-cyclization: H. Fujioka *et al.* (2012)[11]



(eq 1)

up to 90% ee

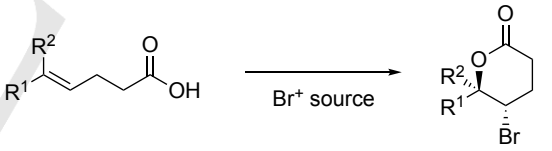
5-exo-cyclization: Several entries in Ref.[13] ***This work***



(eq 2)

moderate ee

6-endo-cyclization: unexplored, ***This work***



(eq 3)

Scheme 1. Several modes of the cyclization reaction enabled via the bromolactonization of trisubstituted olefinic acids.

From the results of our previous study on pyridinium phosphoramide, we predicted that Brønsted acid catalysts could be utilized for the enantioselective bromolactonization of olefinic acids.[15] Contrary to our expectations, pyridyl phosphoramide **1** exhibited much higher reactivity in the preliminary bromolactonization of 1,1-disubstituted alkenoic acid than that of pyridinium phosphoramide **1•TfOH**; hence, several pyridyl phosphoramides were screened in this work (Table 1).[16] As a result, **1a** demonstrated the best catalytic performance in the bromolactonization of (*Z*)-trisubstituted olefinic acid **2a** with *N*-bromosuccinimide (NBS) characterized by good yield and excellent enantioselectivity (entry 1). The *E*/*Z* ratio of the starting compound **2a** reflected the diastereomeric ratio of the resulting bromolactone **3a**, indicating that the reaction proceeded in a highly diastereoselective manner. The effect of the Lewis basicity of the catalyst was evaluated using catalyst **1a–c** with a substituted pyridine ring. The obtained results suggest that the

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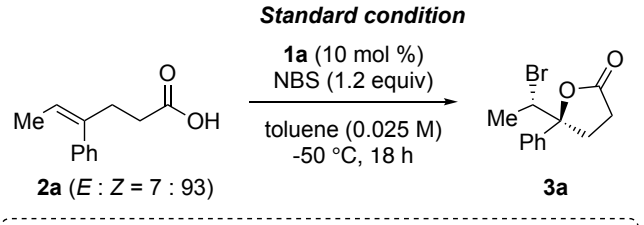
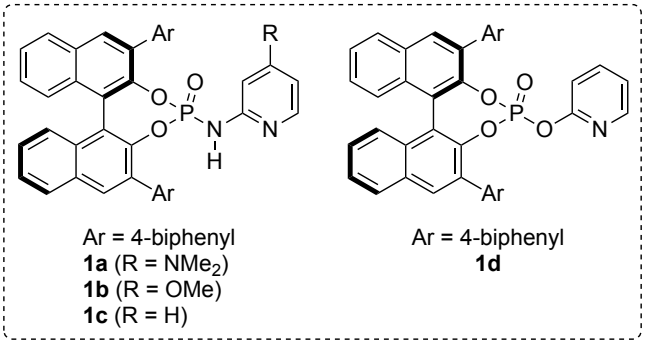
Table 1. Optimization of the reaction conditions.[a]

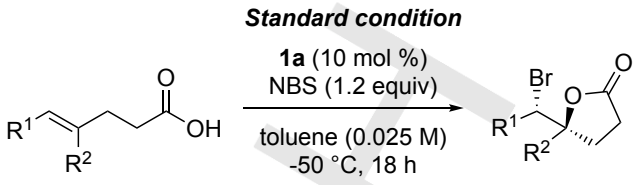


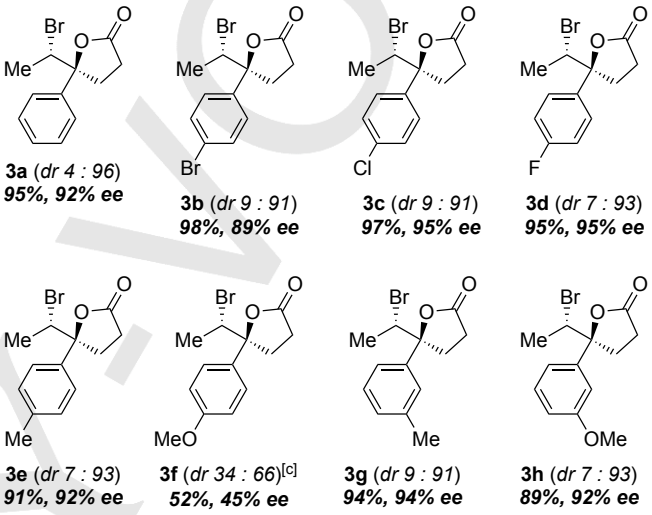


Entry	Varietion from standard conditions	**3a**: Yield [%][b]	ee [%][c]
1	Standard[a]	95	92
2	**1b** (R = OMe) instead of **1a**	94	87
3	**1c** (R = H) instead of **1a**	6	85
4	**1d** instead of **1a**	13	5
5	CH_2Cl_2 instead of toluene	73	69
6	THF instead of toluene	8	–
7	Toluene (0.05 M)	95	90
8	Toluene (0.1 M)	98	86
9	DBDMH instead of NBS	86	88
10	–30 °C	84	87
11	–70 °C	4	94
12	5 mol% of **1a**	87	88

[a] Reactions were performed by dissolving 0.1 mmol of **2a**, 0.01 mmol of **1a**, and 0.12 mmol of NBS in toluene (4 mL) at –50 °C. See Supporting Information for details. [b] Isolated yields of diastereomer mixtures (*dr* = 96 : 4). [c] Determined by chiral HPLC.

Table 2. Substrates for the 5-exo mode of bromolactonization.[a]

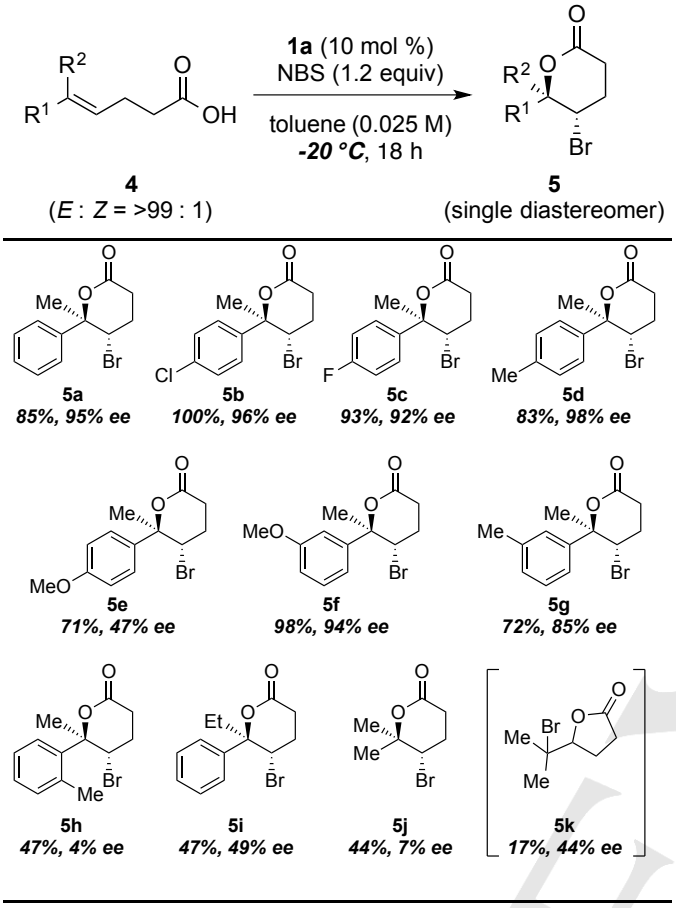




[a] Reactions were performed by dissolving 0.1 mmol of **2**, 0.01 mmol of **1a**, and 0.12 mmol of NBS in toluene (4 mL) at –50 °C. See Supporting Information for details. The isolated yields of the diastereomer mixtures are listed. [b] ^{1}H-NMR yield. [c] The *E*/*Z* ratio of **2f** was 7/93. [d] The *E*/*Z* ratio of **2k** was 8/92.

strong Lewis basicity of the pyridine catalyst is essential for achieving high reactivity (entries 1–3). Notably, pyridyl phosphoric ester **1d** without phosphoramide *N*-H groups showed almost no enantioselectivity (entry 4). These results clearly suggest that the presence of *N*-H protons in phosphoramide **1a–c** was a critical factor affecting the enantioselectivity of the reaction. The screening of the reaction solvents revealed that toluene produced higher yield and enantioselectivity as compared to those of relatively polar solvents (entries 5 and 6). In addition, more diluted toluene solutions exhibited higher reaction enantioselectivity values (entries 7 and 8). The use of 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) as a brominating

Table 3. Substrates for the 6-endo mode of bromolactonization.[a]

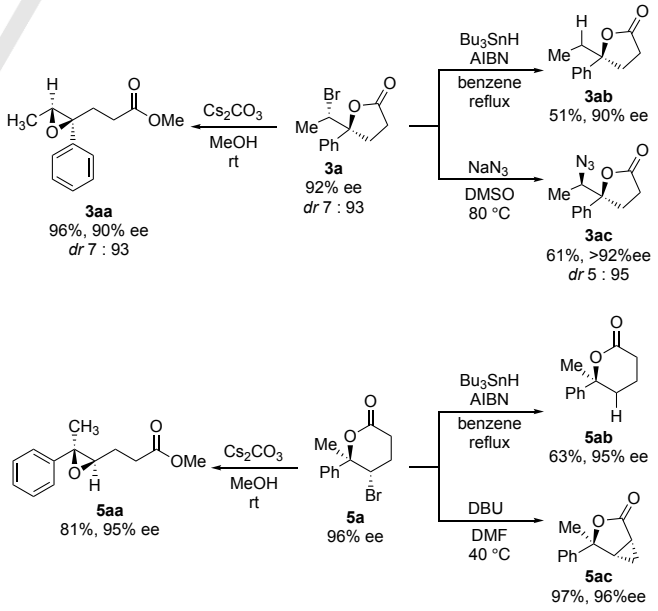


[a] Reactions were performed by dissolving 0.1 mmol of **2a**, 0.01 mmol of **1a**, and 0.12 mmol of NBS in toluene (4 mL) at −20 °C. See Supporting Information for details. The isolated yields of the obtained products are listed.

reagent instead of NBS produced a comparable yield with lower selectivity (entry 9). The optimal reaction temperature was equal to −50 °C (for comparison, the reactions conducted at −30 °C and 70 °C demonstrated high enantioselectivities and lower yields; see entries 10 and 11). Finally, the catalyst loading could be reduced to 5 mol.% without significant decreases in the yield and selectivity (entry 12).

After performing the stereoselective 5-exo-*dig* bromolactonization of **2a**, we tested the applicability of our method to various trisubstituted alkenoic acids **2b–n** (Table 2). The bromolactonization of (*Z*)-4-aryl-4-hexenoic acids containing various electron withdrawing halogen moieties on their phenyl groups proceeded smoothly with relatively high yields and excellent enantioselectivities (products **3b–d**). The presence of electron donating groups (such as methyl ones) was also tolerated (product **3e**). However, electron-rich groups including the methoxy species of *p*-methoxyphenyl groups had a deleterious effect on both the yield and stereoselectivity, probably because the Lewis basic olefins activated by these groups were prone to producing racemic bromonium ion intermediates with NBS prior to the interactions with the chiral catalyst **1a** (product **3f**).[17] On the other hand, the meta-substituted phenyl groups containing both methyl and methoxy moieties resulted in good yields and excellent enantioselectivities (products **3g** and **3h**). The bulky environment of the olefin-containing reaction sites inhibited the bromolactonization reaction, as was shown for the case of *ortho*-substituted derivative **2i** (product **3i**). Subsequently, the substrates having 2-naphthyl, 3-thienyl, or 3-indenyl groups (in addition to phenyl groups) were investigated as well; the resulting bromolactones demonstrated moderate and good enantioselectivities (products **3j–l**). Unfortunately, **2m** containing a cyclohexyl group reacted smoothly, but with low enantioselectivity. For **2i**, the 4-heptenoic acid derivative **2n** having a bulky functional group near the olefin structure produced a low value of ee (product **3n**).

After achieving these results, the 6-endo mode of the enantioselective bromolactonization of (*E*)-trisubstituted olefinic acids was realized. To our delight, the standard conditions for 5-exo-cyclization could be applied for the reaction of 5-phenyl-4-heptenoic acid **4a** by changing the reaction temperature to −20 °C, producing **5a** as a single diastereomer with good yield and excellent enantioselectivity. Both electron withdrawing and donating moieties attached to the para positions of phenyl groups (such as halogens and methyl groups) produced no negative effects, leading to the formation of the cyclized products **5b–d** with high ee values. Moderate enantioselectivity was observed when the substrate **5e** with a *p*-methoxy group was used, probably for the reason suggested for the reaction of **2f**. In contrast, *m*-methoxy derivative **4f** was a good substrate for this system (product **5f**). While the use of *m*-tolyl derivative **4g**



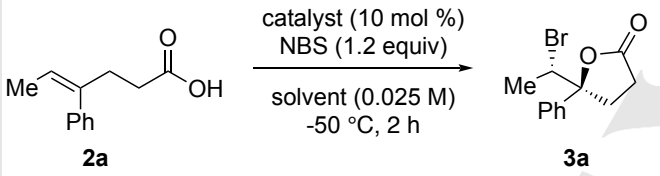
Scheme 2. Derivatization of bromolactones **3a** and **5a**.

resulted in a slightly lower enantioselectivity, *o*-tolyl derivative **4h** produced almost racemic compound **5h** with a moderate yield. Likewise, the substrate **5i** containing a bulky ethyl group with a double bond exhibited inferior reactivity and selectivity as compared to those of the methyl derivative **5a**. When R^1 substituent consisted of a methyl, not aromatic group, no control of cyclization regioselectivity was observed, producing a mixture of the 6-membered lactone **5j** and 5-membered lactone **5k** with low to moderate yields and enantioselectivities.

The utility of chiral bromolactones was demonstrated as shown in Scheme 2. Upon the methanolysis of the lactone moieties of **3a** and **5a** by the treatment with Cs_2CO_3 in methanol, the corresponding methyl esters with tertiary alcohols were generated and simultaneously cyclized to produce epoxide **3aa** and **5aa** while retaining the stereochemical information.[17] In turn, the carbon-halogen bonds of **3a** and **5a** can be reduced selectively under a radical condition, forming the products **3ab** and **5ab** with intact lactone moieties.[18] Furthermore, the substitution reaction of the neopentyl bromide group in **3a** with sodium azide at the bulky position can be performed to produce the corresponding azide **3ac** in the diastereomerically pure form. Interestingly, the same reaction condition for **5a** resulted in the formation of cyclopropane **5ac** with a relatively low yield; therefore, we deliberately synthesized **5ac** with a good yield by the treatment of DBU in DMF.

To gain mechanistic insights into the bromolactonization reaction catalyzed by the chiral pyridyl phosphoramide **1a**, several control experiments were performed (Table 4). To evaluate the possibility of the Lewis basic activation of NBS with **1a**, the reactivity of **1a** was compared with that of PPh_3 Lewis base during a short reaction time.[19] While PPh_3 reacted better in THF than in toluene, **1a** produced lactone **2a** with higher yield in toluene, indicating that the reaction pathway catalyzed by **1a** was different from that catalyzed by PPh_3. In addition, an important structural element in **1a** was elucidated by conducting control experiments involving 4-dimethylaminopyridine (DMAP). To our surprise, the reactions with DMAP in toluene and THF were very slow, suggesting that the simultaneous presence of DMAP and *N*-H species in phosphoramide moieties was also essential for good reactivity (entries 1, 2, 5, and 6). Furthermore, ^{1}H-NMR analysis of **2a** with or without one equivalent of **1a** was performed. While the methylene protons in **2a** were observed to be magnetically equivalent as two triplet signals (Figure 1, above), the same protons appeared upfield and magnetically non-equivalent in the presence of **1a** (Figure 1, below). These results indicate that the methylene protons of **2a** become diastereotopic in the chiral environment caused by the complexation of **2a** and chiral pyridylphosphoramide **1a**.

Table 4. Description of the control experiments.



Entry[a]	Catalyst	Solvent	Yield [%][b]	ee [%][c]
1	**1a**	Toluene	94	90
2	**1a**	THF	8	-
3	PPh_3	Toluene	33	-
4	PPh_3	THF	90	-
5	DMAP	Toluene	15	-
6	DMAP	THF	15	-

[a] Reactions were performed by dissolving 0.1 mmol of **2a** (*E*/*Z* = 4/96), 0.01 mmol of **1a**, and 0.12 mmol of NBS in toluene (4 mL) at –50 °C. See Supporting Information for details. [b] ^{1}H-NMR yields as diastereomer mixtures. [c] Determined by chiral HPLC.

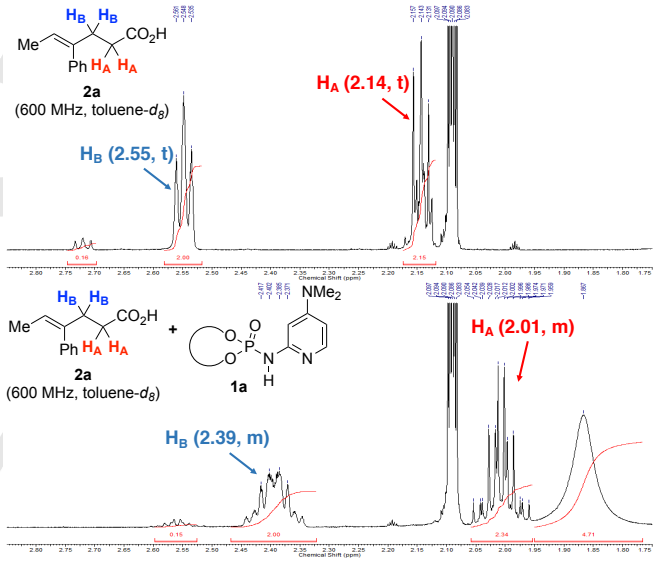
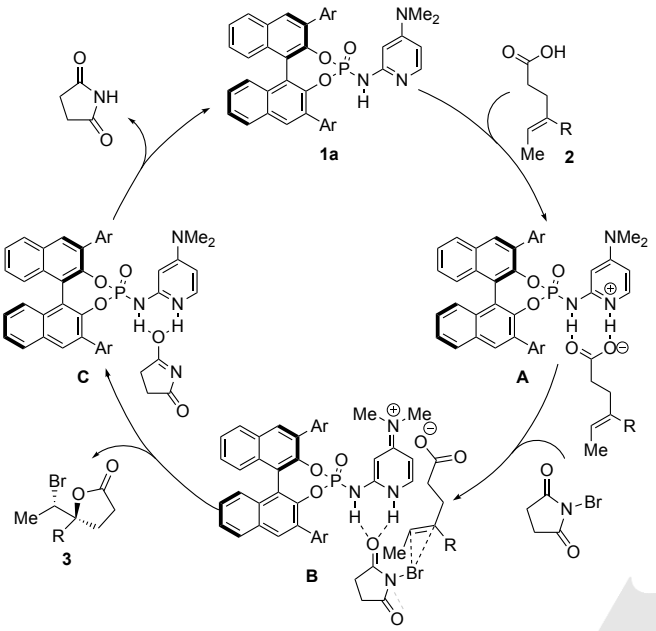


Figure 1. ^{1}H-NMR analysis of the complex of carboxylic acid **2a** and catalyst **1a**.

Based on these data, we proposed a plausible mechanism for the bromolactonization reaction (Scheme 3). We predicted that **1a** might first react with carboxylic acid **2** as a Brønsted base catalyst to form the pyridinium salt **A** through double hydrogen bonding interactions.[8c,20] The initial pyridinium cation in **A** is transformed to the dimethylammonium cation first and then interact ionically with the carboxylate anion.[21] The resulting two acidic *N*-H moieties activate the carbonyl group of NBS in a bidentate manner, arranging **2** and NBS in a proximal position (intermediate **B**). It should be noted that the phosphoramide *N*-H group strongly affected not only the reactivity, but also the enantiodiscriminating step as intermediate **B** (Table 1, entry 4 and Table 4, entry 5). Polar solvents (such as THF) can disturb the ionic and hydrogen bonding interactions in **B** (Table 4, entry

2). Furthermore, the different enantioselectivities obtained using NBS and DBDMH suggest that the brominating reagents are parts of the transition state. Intermediate **B** undergoes bromocyclization to produce **3** and **C**, which release succinimide and catalyst **1a**, thus completing the catalytic cycle.



Scheme 3. A plausible mechanism of the bromolactonization reaction.

In conclusion, the catalytic enantioselective bromocyclization of trisubstituted olefinic acids in both the 5-exo and 6-endo cyclization modes was performed for the first time. In this system, pyridyl phosphoramide **1a** promotes two different modes of cyclization, producing a variety of bromolactones, which can be further transformed to useful derivatives. The results of optimization and mechanistic studies revealed that **1a** might potentially serve as a dual catalyst activating both carboxylic acid and the brominating reagent simultaneously through ionic and hydrogen bonding interactions. The findings of this study may help to develop a new strategy of catalyst design for promoting asymmetric transformations.

Acknowledgements

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Keywords: asymmetric catalysis • cyclization • halogenation • lactones • organocatalysis

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Layout 2:

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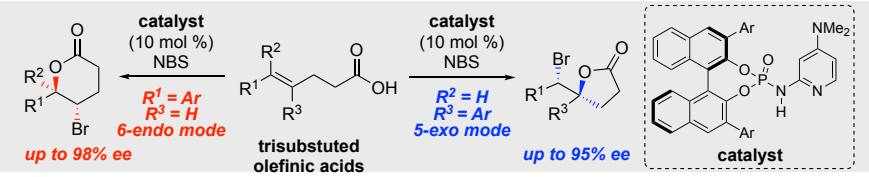

Enantioselevtive bromolactonization of trisubstituted olefinic acids producing synthetically useful chiral lactones with two contiguous asymmetric centers was performed. The use of pyridyl phosphoramide as a Brønsted base catalyst enabled the 5-exo and 6-endo modes of bromolactonization leading to the formation of a variety of chiral lactones, which can be transformed to synthetically useful compounds.

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