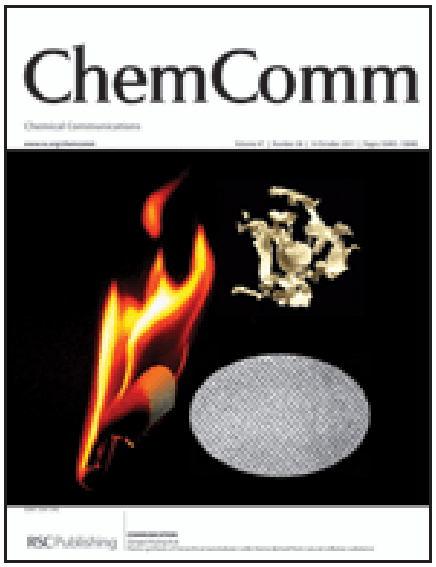

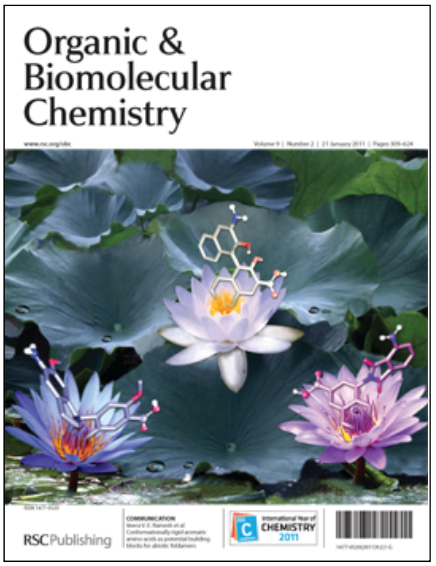

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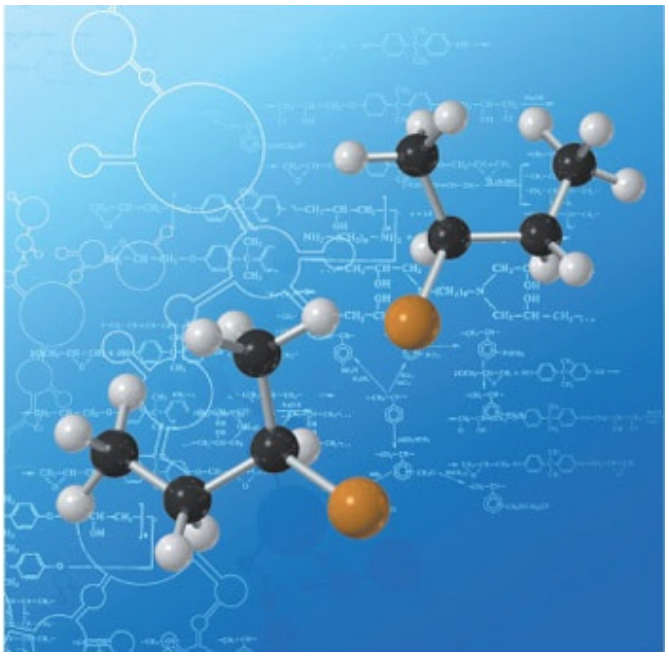

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COMMUNICATION

Enantioselective bromolactonization of *cis*-1,2-disubstituted olefinic acids using an amino-thiocarbamate catalyst†‡

Chong Kiat Tan, Chencheng Le and Ying-Yeung Yeung*

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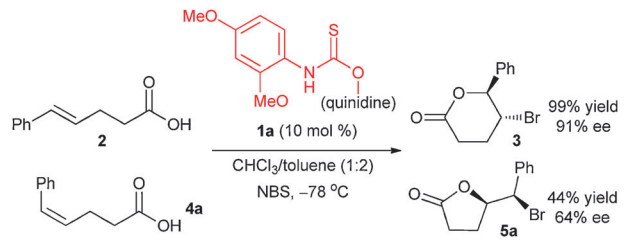
A facile, highly regio- and enantioselective amino-thiocarbamate-catalyzed bromolactonization of *cis*-1,2-disubstituted olefinic acids has been developed. The use of the enantio-enriched lactones in the synthesis of chiral synthetic intermediates is also demonstrated.

The asymmetric halocyclization of olefins is a class of reactions that remains under-investigated despite the usefulness of the products[1] and the promising breakthroughs in the recent years.[2,3] Most of the catalytic systems reported till date[4,5] are only applicable to a narrow spectrum of olefins. And this severely limits the application of enantioselective halocyclization to the synthesis of enantio-enriched biologically active molecules or natural products.

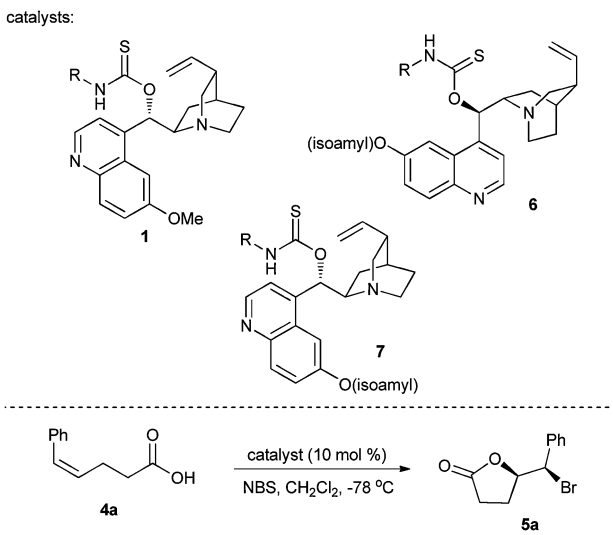
A case in point is our recent report on the enantioselective bromolactonization of the olefinic acid **2** to 6-*endo* lactone **3** using catalyst **1a** (Scheme 1).[5b] While lactone **3** was formed with 91% ee, the bromolactonization of the isomeric *cis*-olefinic acid **4a** resulted in the formation of the 5-*exo* lactone **5a** with only 64% ee. It is important to note that both lactones **3** and **5**, which are not readily interchangeable, are valuable synthetic building blocks (*vide infra*). Although **2** and **4a** have a similar structure, a catalytic and highly enantioselective cyclization of **4a** remains absent. In addition, controlling the regioselectivity, *i.e.* the 5-*exo*/6-*endo* ratio, seems not a trivial task as shown by Denmark and Burk.[6] In this report we will describe the structural modifications of the catalyst needed to resolve the problem. In addition, the applications of both lactones **3** and **5a** in the synthesis of highly useful chiral building blocks are shown.



Scheme 1 Asymmetric bromolactonization of acids **2** and **4a**.

To tackle the lack of enantioselectivity of **5a**, acid **4a** was subjected to optimization using various catalysts (Table 1). After a round of screening of the quinidine-derived catalysts **1**, it was found that **1a** was still superior (Table 1, entry 1).

Table 1 Catalyst screening of the bromolactonization of **4a**



Entry[a]	Cat.	R	Time/h	Yield[b], ee(%)
1	**1a**	2,4-$(MeO)_2$-C_6H_3	43	76, 60
2	**1b**	C_6H_5	19	94, 11
3	**1c**	4-MeO-C_6H_4	21	83, 38
4	**1d**	2,5-$(MeO)_2$-C_6H_3	21	62, 38
5	**1e**	4-(NMe_2)-C_6H_4	23	88, 0
6	**1f**	4-Br-C_6H_4	19	98, 17
7	**1g**	2,4-$(CF_3)_2$-C_6H_3	18	52, 19
8	**6a**	2,4-$(MeO)_2$-C_6H_3	24	82, −33
9	**6b**	2,6-$(EtO)_2$-C_6H_3	18	51, −71
10	**7**	2,6-$(EtO)_2$-C_6H_3	18	50, 83
11[c]	**6b**	2,6-$(EtO)_2$-C_6H_3	30	80, −82
12[c]	*7*	*2,6-(EtO)$_2$-C_6H_3*	*21*	*77, 93*
13[c,d]	**7**	2,6-$(EtO)_2$-C_6H_3	48	84, 93

[a] Reactions were conducted with acid **4a** (0.05 mmol) and NBS (0.06 mmol) in CH_2Cl_2 (1.5 ml). [b] Isolated yield. [c] Reactions were conducted in a blend of $CHCl_3$ (0.5 ml) and *n*-hexane (1.0 ml). [d] Reaction was conducted on a 1 mmol scale.

Department of Chemistry, NUS, 3 Science Drive 3, Singapore, 11754, Singapore. E-mail: chmyyy@nus.edu.sg; Fax: +65-6779-1691; Tel: +65-6516-7760

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‡ Electronic supplementary information (ESI) available. CCDC 864876. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc31148h

Next, we drew lessons from our previous studies which confirmed the 6-alkoxy position as another tunable site. Thus, catalyst **6a**, which contains a 2,4-dimethoxyphenyl thiocarbamate and a 6-*O*-isoamylquinoline unit, was used. However, only −33% ee of the desired product was obtained (Table 1, entry 8). Next, substituting 2,4-dimethoxyphenyl with 2,6-diethoxyphenyl (catalyst **6b**) gave a much improved −71% ee (Table 1, entry 9). A switch to the pseudo-enantiomeric core (catalyst **7**) returned with 83% ee in CH_2Cl_2 (Table 1, entry 10). With further solvent screening, we determined the blend of $CHCl_3$/*n*-hexane (1 : 2) to be the optimal system (Table 1, entries 11 and 12). Lastly, the reaction was also scalable to at least 1 mmol (Table 1, entry 13).

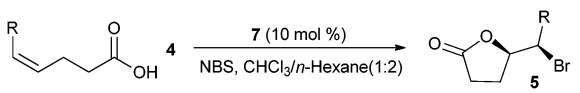
Having determined the optimal conditions, the substrate scope of the catalytic protocol was probed. As shown in Table 2, good yields and excellent ees (up to 98% ee) were generally obtained. The highest enantioselectivity obtained in our study is for lactone **5b** (98% ee) which carries a 4-methylphenyl substituent (Table 2, entry 2).

Surprisingly, acid **4e** bearing the 4-methoxyphenyl substituent reacted sluggishly even at −30 °C (Table 2, entry 5). In addition the corresponding 6-*endo* lactone **8e** was isolated exclusively with only 30% ee. This lack of enantioselectivity is consistent with the observations from various reports on the halolactonization of substrates bearing the 4-methoxyphenyl substituent.[7]

Another interesting observation is the surprisingly good 86% ee obtained for lactone **5d** bearing a 2-methylphenyl substituent (Table 2, entry 4). While previous observations have found *ortho*-substituents to be detrimental to the enantioselectivity, this example appears to be an exception.[5] The bromolactonization of substrates bearing alkyl substituents resulted in moderate ees (Table 2, entries 14 and 15). The absolute configuration of lactones **5** was assigned unambiguously by an X-ray crystallographic study on **5a**.[8]

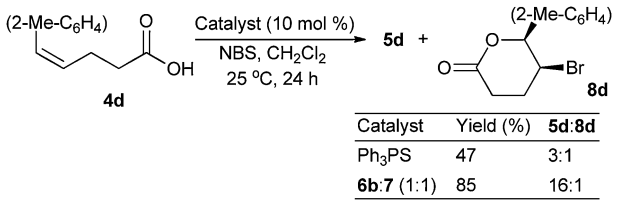
It is noteworthy that the regioselectivity of the bromolactonization favoured the 5-*exo* lactones **5** almost exclusively. However, during the preparation of racemic samples for the HPLC analysis,

Table 2 Substrate scope of the bromolactonization of **4**



Entry[a]	Acid	R	Temp/°C	Time/h	Yield[b], ee (%)
1	**4a**	C_6H_5	−78	21	77, 93
2	**4b**	4-Me-C_6H_4	−78	43	94, 98
3	**4c**	3-Me-C_6H_4	−78	42	95, 97
4[c]	**4d**	2-Me-C_6H_4	−78	48	90, 86
5[d]	**4e**	4-MeO-C_6H_4	−30	72	49, 30
6	**4f**	3-MeO-C_6H_4	−78	42	65, 95
7[c]	**4g**	4-F-C_6H_4	−78	95	83, 93
8	**4h**	3-F-C_6H_4	−78	96	80, 92
9	**4i**	4-Cl-C_6H_4	−78	96	78, 93
10[c]	**4j**	4-Br-C_6H_4	−60	70	75, 94
11	**4k**	4-CF_3-C_6H_4	−78	108	70, 91
12	**4l**	4-CF_3O-C_6H_4	−60	94	85, 87
13	**4m**	2-Napthyl	−78	108	83, 95
14	**4n**	Isopropyl	−78	60	89, 53
15	**4o**	Cyclohexyl	−78	60	80, 75

[a] Reactions were conducted with acid **4a** (0.05 mmol) and NBS (0.06 mmol) in a blend of $CHCl_3$ (0.5 ml) and *n*-hexane (1.0 ml). [b] Isolated yield. [c] Trace amount of 6-*endo* lactone was obtained. [d] The 6-*endo* δ-lactone was isolated exclusively.



Catalyst	Yield (%)	**5d**:**8d**
Ph_3PS	47	3:1
6b:**7** (1:1)	85	16:1

Scheme 2 Regioselectivity of the bromolactonization of **4d**.

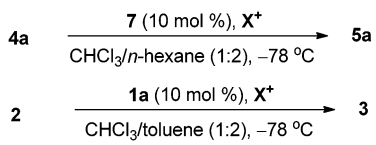
it was found that substantial amounts of 6-*endo* lactones were obtained for some substrates. As shown in Scheme 2, the preparation of racemic **5d** with triphenylphosphine sulfide came with a substantial amount of the 6-*endo* lactone **8d**. Alternatively, the use of a 1 : 1 blend of the pseudo-enantiomeric **6b** and **7** led to a highly regioselective bromolactonization favouring the formation of **5d**, indicating that the amino-thiocarbamate catalyst could somewhat control the regioselectivity.[9]

In addition, we rescreened the reaction with various bromine sources. It emerged from the study that there was virtually no difference in the enantioselectivity and regioselectivity when NBP was used (Table 3, entry 1 *vs.* 2). However, the ee deteriorated to 84% when DBH was used (Table 3, entry 3). Interestingly, 89% ee was obtained when TABCO[10] was used together with a negligible deterioration in the regioselectivity (Table 3, entry 4). In addition, the bromolactonization of **2** with TABCO resulted in a slightly diminished 85% ee (Table 3, entry 5 *vs.* Scheme 1).

The synthetic applications of both the 6-*endo* lactone **3** from the previous study as well as the 5-*exo* lactone **5a** are demonstrated by the various transformations shown in Scheme 3. Displacement of the bromide in **3** with sodium azide followed by hydrogenation led to the formation of γ-lactam **11** with preservation of the enantioselectivity (Scheme 3, eqn (1)). γ-Lactam **11** is an important building block of several biologically active molecules[11] as well as a chiral backbone as the oxazaborolidine catalyst.[12] In addition, treatment of **3** with DBU in refluxing THF affected the cyclopropanation that yielded the bicyclic system **12** (Scheme 3, eqn (2)); this represents a useful metal-free asymmetric cyclopropanation protocol.[13] Indeed, hydrolysis of **12** affords a cyclopropyl entity that is found in several peptidomimetics[14] and other natural products synthesis.[15]

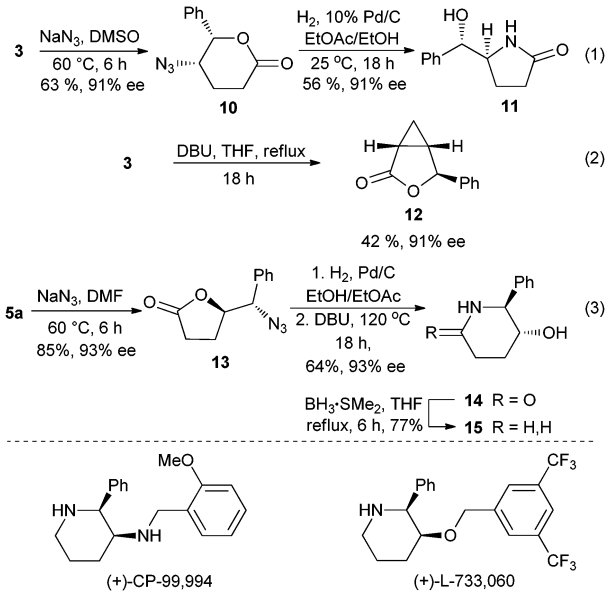
Next, in a similar scheme to eqn (1), **5a** → **13** → **14** transformation could be achieved. δ-Lactam **14** has been used as a

Table 3 Effect of various halogen sources on bromolactonization



Entry	Acid	Catalyst	X^+	Time/h	Yield[a] (%)	ee (%)
1	**4a**	**7**	NBS	21	77	93
2	**4a**	**7**	NBP	40	49	93
3	**4a**	**7**	DBH	40	60	84
4[b]	**4a**	**7**	TABCO	94	66	89
5	**2**	**1a**	TABCO	48	61	85

NBP = *N*-bromophthalimide, DBH = 1,3-dibromo-5,5-dimethylhydantoin, TABCO = 2,4,4,6-tetrabromo-2,5-cyclohexadienone. [a] Isolated yield. [b] Trace amount of the 6-*endo* product was obtained (5-*exo*/6-*endo* 17 : 1).



Scheme 3 Synthetic applications of bromolactones **3** and **5**.

synthetic precursor to several alkaloids (Scheme 3, eqn (3)).[16] For example, reduction of δ-lactam **14** with $BH_3{\cdot}SMe_2$ gave 3-hydroxypiperidine **15**, which is found in the skeleton of several biologically active molecules such as CP-99994 and L-733060.[17]

In summary, we disclosed a facile and highly enantioselective amino-thiocarbamate-catalyzed bromolactonization of *cis*-1,2-disubstituted olefinic acids. The reaction is also highly regioselective, forming 5-*exo* lactones in most cases. The lactones from both the *trans* and the *cis*-1,2-disubstituted olefinic acid could readily be modified into useful advanced intermediates.

We are grateful for the financial support from National University of Singapore (grant no. 143-000-428-112).

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8 CCDC no: 864876.

9 The sole origin of the regioselective bromolactonization with the amino-thiocarbamate catalyst is still under further investigation.

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