Asymmetric Catalysis

DOI: 10.1002/anie.201202079

Enantioselective Bromolactonization Using an *S*-Alkyl Thiocarbamate Catalyst**

*Xiaojian Jiang, Chong Kiat Tan, Ling Zhou, and Ying-Yeung Yeung**

Asymmetric halofunctionalization and related electrophile-promoted functionalization of unactivated olefins are powerful reactions in organic synthesis.[1] Despite the formidable challenges associated with these reactions, recently, there has been significant advancements using various organocatalysts; enantioselective variants of reactions such as halolactonization,[2] haloetherification,[3] haloaminocyclization,[4] haloamidation,[5] halocyclization of polyenes,[6] and others[7] have been reported.

In these reactions, several strategies were used to activate the electrophile. The use of promoters that contain Lewis basic sulfur or selenium atoms is especially interesting,[8] and Denmark et al. have reported an example of such a promoter, a phosphoramide derived from 1,1′-binaphthyl-2,2′-diamine (BINAM), which was used to catalyze thiofunctionalization.[9] In addition, Snyder et al. reported the use of bromodiethylsulfonium bromopentachloroantimonate (BDSB), a unique sulfur-containing bromination reagent that shows promising activity in mediating polyene cyclizations.[10]

Recently, we reported the use of cinchona alkaloid derived *O*-alkyl thiocarbamate catalysts in enantioselective bromocyclization reactions.[11] A dual-activation mechanism, which involves the activation of the bromine atom on the reagent through interaction with the Lewis basic sulfur atom on the catalyst, was proposed. Although the use of this class of catalyst gave products with excellent *ee* values and yields, a limitation was encountered during our research: although the pseudo-enantiomeric pair of cinchona alkaloids are available,[12] the corresponding enantiomeric products were not formed with equally high *ee* value.[11]

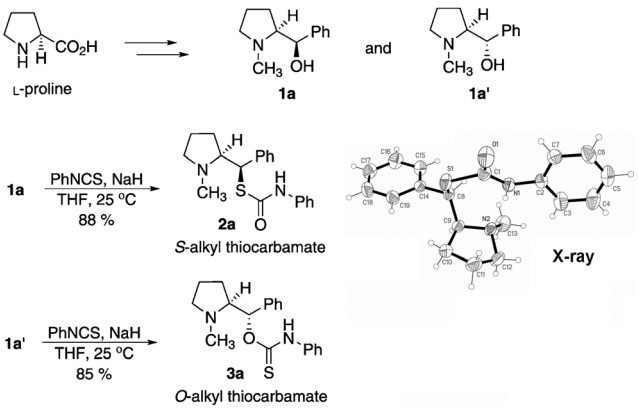
To solve this problem, we initiated a program to search for a new class of catalyst that satisfies two criteria: (1) the enantiomeric catalysts should be inexpensive and readily available; (2) the catalyst should contain readily modifiable handles to facilitate adaption to different substrates. Herein we report a synthetic route to an amino *S*-alkyl thiocarbamate catalyst and its application to asymmetric bromolactonization.

[*] X. Jiang, C. K. Tan, Dr. L. Zhou, Prof. Dr. Y.-Y. Yeung
Department of Chemistry, National University of Singapore
3 Science Drive 3, Singapore 117543 (Singapore)
E-mail: chmyyy@nus.edu.sg
Homepage: http://www.chemistry.nus.edu.sg/people/academic_staff/yeungyy.htm

[**] We thank the National University of Singapore (Grant No. 143-000-509-112) for financial support. We acknowledge the receipt of both an NUS Research Scholarship (to X.J.) and a President's Graduate Fellowship (to C.K.T.).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201202079.

Proline was chosen as a starting material for the preparation of catalysts in the study, because both the *R* and *S* enantiomers are commercially available, and in our previous study, the use of a proline-derived catalyst gave enantioenriched product.[11a] The diastereomeric prolinols **1a** and **1a′** were synthesized from L-proline according to literature procedures.[13] **1a** was then treated with phenyl isothiocyanate to give, exclusively and unexpectedly, *S*-alkyl thiocarbamate **2a** in excellent yield upon isolation; the corresponding *O*-alkyl thiocarbamate was not detected (Scheme 1). On the other hand, when **1a′** was treated with phenyl isothiocyanate, the expected *O*-alkyl thiocarbamate



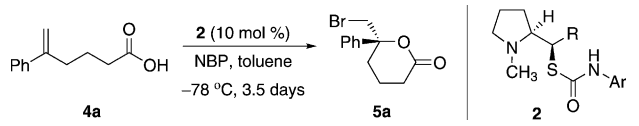
Scheme 1. Synthesis of thiocarbamate catalysts **2** and **3**. For the crystal structure of **2a**, thermal ellipsoids are shown at 50% probability.

3a was obtained as the sole product in 85% yield. It is plausible that *S*-alkyl thiocarbamate **2a** forms through a Newman–Kwart type rearrangement.[14] The structure of catalyst **2a** was confirmed by X-ray crystallographic analysis.[15,16]

We then tested **2a** for its ability to catalyze the bromolactonization of substrate **4a**. *N*-Bromophthalimide (NBP) was used as the stoichiometric halogen source and the reaction was conducted in toluene at −78 °C. Interestingly, amino *S*-alkyl thiocarbamate **2a** was able to catalyze the reaction to give the product in 90% yield and 26% *ee* (Table 1, entry 1). Notably, in a number of studies, catalysts that contain Lewis-basic oxygen in the form of C=O and P=O moieties were not suitable for activating the halogen atom, particularly the bromine atom, in electrophilic halofunctionalization.[17]

We then optimized the reaction by modifying the catalyst structure. When the R group was changed from phenyl to 2-naphthyl, a significant drop in enantioselectivity was

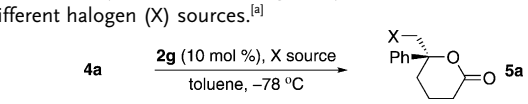
Table 1: Optimization of the *S*-alkyl thiocarbamate catalyst **2** for the enantioselective bromolactonization of **4a**.[a]



Entry	Catalyst	R	Ar	Yield [%][b]	*ee* [%]
1	**2a**	C_6H_5	C_6H_5	90	26
2	**2b**	2-naphthyl	C_6H_5	87	6
3	**2c**	1-naphthyl	C_6H_5	84	33
4	**2d**	1-naphthyl	2-$MeOC_6H_4$	86	40
5	**2e**	1-naphthyl	3-$MeOC_6H_4$	89	29
6	**2f**	1-naphthyl	4-$MeOC_6H_4$	90	87
7	**2g**	1-naphthyl	4-$EtOC_6H_4$	97	88
8	**2h**	1-naphthyl	4-*i*$PrOC_6H_4$	91	77

[a] Reactions were carried out with acid **4a** (0.05 mmol), catalyst **2** (0.005 mmol), and NBP (0.06 mmol) in toluene (1.5 mL) in the absence of light. [b] Yield upon isolation.

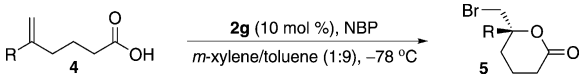
Table 2: *S*-Alkyl thiocarbamate **2g** catalyzed halolactonization using different halogen (X) sources.[a]

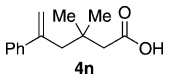
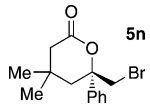


Entry	X source	X	*t* [days]	Yield [%][b]	*ee* [%]
1	NBA	Br	3.5	96	68
2	NBS	Br	3.5	94	87
3	DBH	Br	3.5	93	86
4	NCS	Cl	8	0	0
5	NIS	I	8	63	75

[a] Reactions were carried out with acid **4a** (0.05 mmol), catalyst **2g** (0.005 mmol), and X source (0.06 mmol) in toluene (1.5 mL) in the absence of light. [b] Yield upon isolation.

Table 3: *S*-Alkyl thiocarbamate **2g** catalyzed enantioselective bromolactonization of **4**.[a]



Entry	Substrate	R	Product	*t* [days]	Yield [%][b]	*ee* [%]
1	**4a**	C_6H_5	**5a**	3.5	97	92
2[c]	**4a**	C_6H_5	**5a**	3.5	96	92
3	**4b**	2-naphthyl	**5b**	3.5	97	92
4	**4c**	4-MeC_6H_4	**5c**	3.5	95	90
5	**4d**	2,4-$Me_2C_6H_3$	**5d**	3.5	97	81
6	**4e**	4-$MeOC_6H_4$	**5e**	2.5	95	19
7	**4f**	4-FC_6H_4	**5f**	5.5	99	91
8	**4g**	4-ClC_6H_4	**5g**	4.5	99	88
9	**4h**	4-BrC_6H_4	**5h**	4.5	95	91
10	**4i**	4-$CF_3C_6H_4$	**5i**	8	96	70
11	**4j**	Me	**5j**	2	97	78
12	**4k**	Et	**5k**	2.5	96	85
13	**4l**	isopropyl	**5l**	3.5	99	82
14	**4m**	cyclohexyl	**5m**	3.5	98	88
15				3.5	95	86

[a] Reactions were carried out with acid **4** (0.05 mmol), catalyst **2g** (0.005 mmol), and NBP (0.06 mmol) in *m*-xylene/toluene (1:9) (1.5 mL) in the absence of light. [b] Yield upon isolation. [c] The reaction was conducted on a 1.0 mmol scale.

observed (Table 1, entry 2). In contrast, when the R group was 1-naphthyl, that is, catalyst **2c**, the desired product **5a** was obtained in 33% *ee* (Table 1, entry 3).

The effect of the nature of the *N*-aryl group in the *S*-alkyl thiocarbamate catalyst on the bromolactonization was also investigated. Unlike a previous investigation of *O*-alkyl thiocarbamate catalysts, a study, wherein it was found that the 2-MeO substituent on the aryl moiety was crucial for obtaining a halocyclization product with high *ee* value,[11b] in the study herein, the use of catalyst **2d**, which contains the *N*-2-methoxyphenyl moiety, resulted in only a slight increase in enantioselectivity (Table 1, entry 4).

When the *N*-phenyl group was changed from *N*-2-methoxyphenyl to *N*-3-methoxyphenyl, a slight drop in enantioselectivity was observed (Table 1, entry 5). In sharp contrast, changing the *N*-phenyl group to an *N*-4-methoxyphenyl group, that is, catalyst **2f**, a dramatic increase in enantioselectivity was observed (Table 1, entry 6). The steric demand of the 4-alkoxy unit was found to affect the enantioselectivity of the reaction. Although the use of catalyst **2g**, which contains an *N*-4-ethoxyphenyl moiety, resulted in enantioselectivity that was similar to that obtained when using **2f** (Table 1, entry 7), the use of catalyst **2h**, which contains an *N*-4-isopropoxyphenyl moiety, resulted in a sharp decrease in enantioselectivity (Table 1, entry 8).

With the optimized catalyst **2g** in hand, we investigated the scope of the halogen source. The use of *N*-bromoamides other than NBP, including *N*-bromoacetamide (NBA), *N*-bromosuccinimide (NBS), and 1,3-dibromo-5,5-dimethylhydantoin (DBH) resulted in moderate to high enantioselectivity (Table 2, entries 1–3). The use of *N*-iodosuccinimide (NIS) gave the corresponding iodolactone with 75% *ee* (Table 2, entry 5). However, no reaction was observed when *N*-chlorosuccinimide (NCS) was used as a chlorine source (Table 2, entry 4). An extensive survey of solvent was also conducted and it was found that *m*-xylene/toluene (1:9) was optimal (see the Supporting Information, Table S1).[16]

Next, the substrate scope was investigated (Table 3). In general, most of the substrates gave the corresponding products with high yields and *ee* values. When the R group on the alkene moiety is phenyl or 2-naphthyl, the corresponding products were obtained in 92% *ee* (Table 3, entries 1 and 3). For substrates in which the R group is an electron-rich phenyl group, the corresponding products were obtained in good yield with high *ee* value, an exception being the substrate **4e**, which contains a 4-methoxyphenyl substituent (Table 3, entries 4–6).[11]

Substrates **4f—i**, which contain electron-deficient aromatic substituents on the alkene moiety, gave the corresponding products with high *ee* value, although relatively long reaction times were required to obtain high yields of product (Table 3, entries 7–10). Remarkably, substrates containing aliphatic substituents on the alkene moiety also gave the corresponding products with high *ee* value (Table 3,

entries 11–14). The product derived from 3,3-dimethyl olefinic acid **4n** was also obtained in good yield and with high *ee* value (Table 3, entry 15). The absolute configuration of the lactones **5** were assigned based on the X-ray crystal structure of **5f**.[15,16]

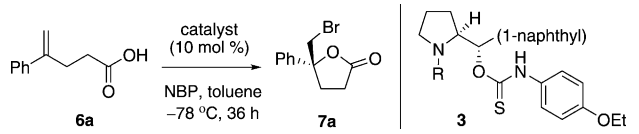
Next, we examined the cyclization of the homologous substrate **6** in the presence of the *S*-alkyl thiocarbamate catalyst **2g**. Unexpectedly, the cyclization of **6a** in toluene, a reaction catalyzed by **2g**, gave the corresponding product with a low *ee* value of 15% (Table 4, entry 1).[18] Further experiments led to the discovery that the use of catalyst **2e** gave product **7a** with 41% *ee*, favoring the same enantiomer that was observed when using catalyst **2g** (Table 4, entry 3; see the Supporting Information, Table S2).[16] We ultimately identified the *O*-alkyl thiocarbamate catalyst **3** as being suitable for mediating the cyclization of olefinic acid **6** (see the Supporting Information, Table S3).[19] An investigation of the effect of catalyst structure on reaction outcome led to the conclusion that an *O*-alkyl thiocarbamate catalyst containing a 1-naphthyl substituent at the carbinol carbon atom and a *N*-4-ethoxyphenyl substituent at the carbamyl moiety is optimal for the bromolactonization of **6**. These structural features were previously found to be optimal for the *S*-alkyl thiocarbamate catalyst **2**.[16] In addition, the identity of the substituent on the nitrogen atom of the pyrrolidine moiety was found to affect the enantioselectivity of the reaction; an *N*-allyl substitutent was found to be suitable (Table 4, entry 8). After systematic variation of the solvent, a toluene/chlorobenzene (9:1) solvent mixture together with NBP was found to be optimal (see the Supporting Information, Table S5).[16] By using these reaction conditions in the bromolactonization of **6a**, lactone **7a** could be obtained with high yield and high enantiopurity (Table 4, entry 10). Notably, when using the family of catalysts **3**, the sense of asymmetric induction is opposite that observed with the family of catalysts **2**; the absolute configuration of lactones **7** were determined based on the literature data.[11a] The reaction was readily scalable without loss of enantioselectivity (Table 4, entry 11).

Other derivatives of **6a** were investigated as substrates (Table 5). The catalytic protocol was suitable for the bromolactonization of a range of sterically-hindered and electronic-deficient olefins **6** (Table 5, entries 1–8). The enantioselectivity was relatively low for the reactions of electronic-rich substrates, a result that was also found in previous studies (Table 5, entry 9).[11] For substrates containing alkyl substituents on the alkene moiety, the *ee* values of the resulting products were moderate, although that of the product obtained from **6l**, which contains a methyl substituent, was poor (Table 5, entries 11–14).

The selection of proline-derived catalysts allowed lactones of either configuration to be obtained, a characteristic, which is important for applications. For example, treatment of **7k** with nBu$_3$SnH and AIBN gave (*R*)-(+)-boivinianin A (**8**) in 90% yield (Scheme 2). One could use the *ent*-**3f** catalyst if one wanted to synthesize (*S*)-(−)-boivinianin A.[20]

After achieving a number of successes with the *O*-alkyl thiocarbamates, the ability of the *S*-alkyl thiocarbamates to catalyze asymmetric bromolactonization came as a surprise.

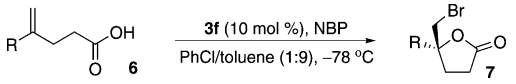
Table 4: Optimization of thiocarbamate catalysts **2** and **3** for the enantioselective bromolactonization of **6a**.[a]



Entry	Catalyst	R	Yield [%][b]	*ee* [%]
1	**2g**	–	93	15[c]
2[d]	**2g**	–	94	18[c]
3	**2e**	–	96	41[c]
4	**3b**	Me	95	31
5	**3c**	Et	94	31
6	**3d**	*n*Pr	93	32
7	**3e**	Bn	95	72
8	**3f**	allyl	93	83
9	**3g**	isopropenyl	92	18
10[d]	**3f**	allyl	95	90
11[d,e]	**3f**	allyl	98	90

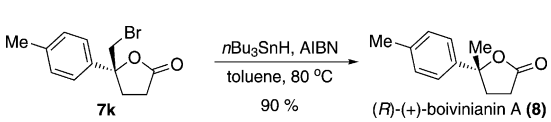
[a] Reactions were carried out with acid **6a** (0.05 mmol), catalyst (0.005 mmol), and NBP (0.06 mmol) in toluene (1.5 mL) in the absence of light. [b] Yield upon isolation. [c] *ent*-**7a** was obtained as the major enantiomer. [d] PhCl/toluene (1:9) (1.5 mL) was used as the solvent. [e] The reaction was conducted on a 1.0 mmol scale. The reaction time was 42 h.

Table 5: *O*-Alkyl thiocarbamate **3f** catalyzed enantioselective bromolactonization of **6**.[a]



Entry	Substrate	R	Product	*t* [h]	Yield [%][b]	*ee* [%]
1	**6b**	1-naphthyl	**7b**	42	99	91
2	**6c**	2-naphthyl	**7c**	40	98	90
3	**6d**	9-phenanthryl	**7d**	48	96	91
4	**6e**	1-pyrenyl	**7e**	56	97	91
5	**6f**	3-FC_6H_4	**7f**	40	95	78
6	**6g**	4-FC_6H_4	**7g**	40	96	84
7	**6h**	3,5-$F_2C_6H_3$	**7h**	48	94	76
8	**6i**	4-$CF_3OC_6H_4$	**7i**	36	96	74
9	**6j**	4-$MeOC_6H_4$	**7j**	30	97	48
10	**6k**	4-MeC_6H_4	**7k**	48	93	82
11	**6l**	Me	**7l**	32	96	13
12	**6m**	Et	**7m**	32	94	45
13	**6n**	isopropyl	**7n**	36	93	57
14	**6o**	cyclohexyl	**7o**	36	94	84

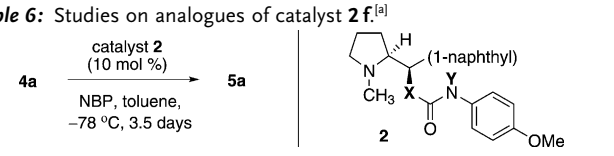
[a] Reactions were carried out with acid **6** (0.05 mmol), catalyst **3f** (0.005 mmol), and NBP (0.06 mmol) in PhCl/toluene (1:9) (1.5 mL) in the absence of light. [b] Yield upon isolation.



Scheme 2. Synthesis of (*R*)-(+)-boivinianin A (**8**). AIBN = 2,2′-azoisobutyronitrile.

Towards an understanding of the mechanism, we synthesized analogues of **2f**, namely, catalysts **2i** and **2j** (Table 6). When they were used for catalyzing the bromolactonization of **4a** under the same reaction conditions, it became clear that the presence of both the sulfur atom and NH moiety was necessary for attaining high enantioselectivity. However, the exact role played by the sulfur atom in the reaction mechanism remains uncertain.[21]

Table 6: Studies on analogues of catalyst **2f**.[a]



Entry	Catalyst	X	Y	Yield [%]	*ee* [%]
1	**2f**	S	H	90	87
2	**2i**	O	H	83	44
3	**2j**	S	Me	84	12

In summary, we have prepared a novel L-proline-derived *S*-alkyl thiocarbamate and used it for catalyzing bromolactonization reactions that lead to the formation of δ-lactones with high enantioselectivity. The corresponding *O*-alkyl thiocarbamate analogue was found to be a useful catalyst for the enantioselective synthesis of γ-lactones. The simplicity of the prolinol synthesis facilitates the synthesis of catalyst analogues with different steric and electronic environments. The tunable handles, which include: a) the amine substituent, b) the substituent on the oxygen- or sulfur-bearing methine carbon, c) the thiocarbamate, which can be S type or O type, and d) the *N*-aryl substituent of the thiocarbamate allow us to modify the catalyst to adapt to different substrates. Further investigation of the mechanism of the *S*-alkyl thiocarbamate catalyzed halolactonization, as well as further expansion of the substrate scope, are currently in progress.

Received: March 15, 2012
Revised: June 4, 2012
Published online: ■■ ■■, ■■■■

Keywords: asymmetric catalysis · cyclization · lactones · Lewis bases · natural products

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[13] J. Bejjani, F. Chemla, M. Audouin, *J. Org. Chem.* **2003**, *68*, 9747 – 9752.
[14] Typically, elevated temperature is required to effect a Newman–Kwart rearrangement. For representative reviews of Newman–Kwart rearrangement, see: a) E. Schaumann, in *Sulfur-Mediated Rearrangement II*, Springer, New York, **2007**; b) G. C. Lloyd-Jones, J. D. Moseley, J. S. Renny, *Synthesis* **2008**, 661 – 689; the Newman – Kwart rearrangement, which presumably forms part of the conversion of **1** into **2**, proceeded smoothly at room temperature, a facility, which could be attributed to the neighboring-group effect. Products derived from a Newman – Kwart rearrangement were not observed in the synthesis of **3**, an observation, which could be due to geometrical restriction. For examples of the Newman – Kwart rearrangement that occur at relatively low temperature, see: c) R. E. Hackler, T. W. Balko, *J. Org. Chem.* **1973**, *38*, 2106 – 2109; d) M. Alajarin, M. Marin-Luna, M. Ortin, P. Sanchez-Andrada, A. Vidal, *Tetrahedron* **2009**, *65*, 2579 – 2590. For a proposed mechanism of the formation of catalyst **2**, see the Supporting Information, Scheme S1.
[15] CCDC 870474 (**2a**) and 870475 (**5f**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[16] For more details, see the Supporting Information.
[17] Reactivity and enantioselectivity were not satisfactory in these studies; see Refs. [8b] and [11].
[18] Despite the fact that **4** and **6** are homologs, it has been observed that their behaviour in asymmetric halocyclization can be very different; see Ref. [2j].
[19] We have examined the ability of **3** to catalyse the transformation of olefinic acid **4a**. Although the corresponding product was obtained in good yields, the *ee* value was low; for more details, see the Supporting Information, Table S4.
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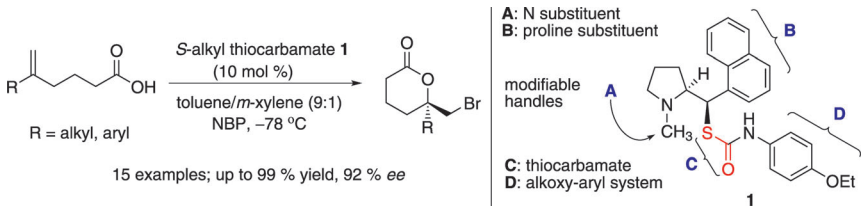
[21] We performed a series of NMR experiments with the carbamate analogues. Preliminary results indicated that both *S*- and *O*-alkyl thiocarbamates can interact with NBS but not with acetic acid. For details, see the Supporting Information, Figure S1.

Communications

Asymmetric Catalysis

X. Jiang, C. K. Tan, L. Zhou,
Y.-Y. Yeung* ——— ■■■■–■■■■

Enantioselective Bromolactonization Using an *S*-Alkyl Thiocarbamate Catalyst



The apple never falls far from the tree: *S*-alkyl thiocarbamate **1** (see scheme, NBP = *N*-bromophthalimide) was prepared in high yield through a synthetic sequence involving a Newman–Kwart rearrangement of the corresponding *O*-alkyl thiocarbamates. Compound **1** was used to catalyze bromolactonization, thus providing enantioenriched δ-lactones in excellent yield and enantioselectivity.

