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Asymmetric Bromolactonization Using Amino-thiocarbamate Catalyst

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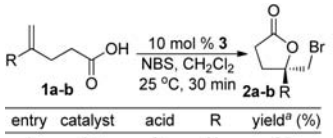
Abstract: A novel amino-thiocarbamate-catalyzed bromolactonization of unsaturated carboxylic acids has been developed. The scope of the reaction is evidenced by 22 examples of γ-lactones with up to 99% yield and 93% ee. The protocol was applied in the enantioselective synthesis of the key intermediates of VLA-4 antagonists.

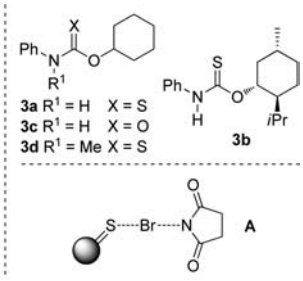
Halocyclization of olefins is an important class of organic transformations. Reactions involving halolactonization, haloetherification, and polyene cyclization are well documented. Among these reactions, halolactonization has been studied extensively and applied in the synthesis of many bioactive molecules.[1] However, the catalytic and enantioselective version of halolactonization, especially bromolactonization, is still lacking because a suitable catalytic system is elusive.[2,3] Herein we describe an efficient, enantioselective, and organocatalytic bromolactonization using an amino-thiocarbamate as the catalyst.

Inexpensive and commercially available *N*-bromosuccinimide (NBS) is a halogen source commonly used in bromolactonization reactions. Various NBS activators such as Lewis acids,[4] hydrogen-bonding-type catalysts,[5] amides,[6] and aryl iodides[7] have been reported. Recently, Denmark and co-workers reported the use of a sulfur Lewis basic catalyst in the activation of a phenylselenium group for the electrophilic lactonization.[8] We rationalized that the sulfur Lewis base should also be able to activate a halogen for the bromolactonization (Table 1, complex **A**). Thus, we screened some sulfur Lewis bases and found that thiocarbamates were exceptionally active in catalyzing the bromolactonization reactions (Table 1). In addition, modification of the thiocarbamate through the replacement of S with O (Table 1, entry 6) or N−H with N−Me (Table 1, entry 7) resulted in a decrease in efficiency, which indicated that both the S and the N−H were responsible for the reactivity. Keeping this in mind, we attempted to incorporate the thiocarbamate into a chiral scaffold, for instance into (−)-menthol, to form a chiral catalyst for the enantioselective bromolactonization. Initially, the bromolactonization of alkenoic acid **1b** (Table 1, R = Ph) was carried out using a stoichiometric amount of NBS and 10 mol % of thiocarbamate **3b** in CH_2Cl_2 at −78 °C. Bromolactone **2b** was isolated in 95% yield; however, no enantioselectivity was observed, and the reaction was sluggish (Table 1, entry 4). Subsequent attempts to accelerate the reaction by increasing the nucleophilicity of the carboxylate group were unsuccessful (Table 1, entry 5).[9] The failure to achieve any enantioselectivity might be attributed to the following reasons: (1) the chiral moiety linked to the thiocarbamate may be too remote from the olefin to effect stereocontrol;[10] (2) the enantiomerically enriched bromonium−olefin intermediate may racemize through a rapid olefin−olefin halogen exchange.[11] Toward these problems, we reasoned that encapsulating the electrophilic bromonium ion and the olefinic substrate into a pocket might provide a solution. We therefore decided to incorporate a Br activator (a thiocarbamate) and a carboxylate activator (an amine) into a rigid skeleton, and the resulting amino-thiocarbamate bifunctional catalyst was investigated. A simple experiment was conducted using a prolinol-derived amino-thiocarbamate, **4a** (10 mol %), to catalyze the bromolactonization of **1b**, which allowed us to achieve a −14% ee of **2b** (Table 2).

Table 1. Thiocarbamate-Catalyzed Bromolactonization



entry	catalyst	acid	R	yield[a] (%)
1	**3a**	**1a**	H	84
2	**3a**	**1b**	Ph	91
3	**3b**	**1b**	Ph	92
4[b]	**3b**	**1b**	Ph	95
5[b,c]	**3b**	**1b**	Ph	84
6	**3c**	**1a**	H	18
7	**3d**	**1a**	H	73



[a] Isolated yield. [b] Reactions were conducted at −78 °C for 5 h. [c] 10 mol % of Et_3N was added.

Table 2. Amino-thiocarbamate-Catalyzed Bromolactonization

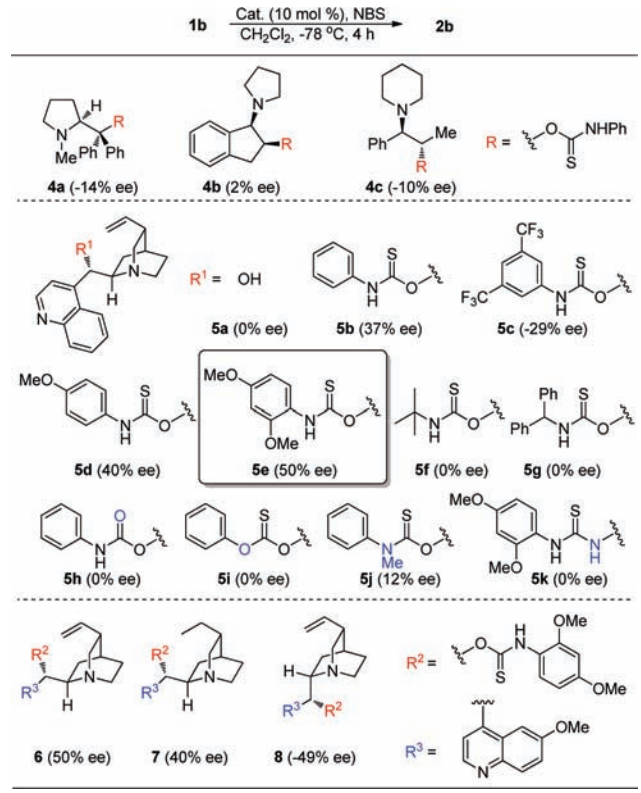


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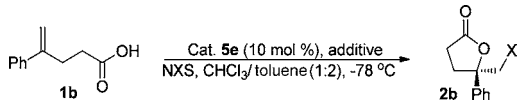
Table 3. Optimization of The Asymmetric Bromolactonization



entry[a]	halogen source	X	additive (mol %)	time (h)	yield,[b] ee (%)
1	NBS	Br	−	17	96, 87
2	NCS	Cl	−	48	0
3	NIS	I	−	80	80, 20
4	NBP	Br	−	16	99, 82
5	DBDMH	Br	−	12	71, 53
6	NBS	Br	BzOH (100)	14	55, 82
7	NBS	Br	TFA (100)	17	28, 0
8	NBS	Br	$CF_3SO_2NH_2$ (100)	21	86, 73
9	NBS	Br	$NsNH_2$ (100)	84	80, 89
10	**NBS**	**Br**	**$NsNH_2$ (50)**	**40**	**98, 90**
11[c]	**NBS**	**Br**	**$NsNH_2$ (50)**	**40**	**99, 90**
12[d]	**NBS**	**Br**	**$NsNH_2$ (50)**	**45**	**99, 90**
13	NBS	Br	$NsNH_2$ (20)	19	96, 86

[a] Reactions were carried out with acid **1b** (0.1 mmol), catalyst **5e** (0.01 mmol), additive, and halogen source (0.12 mmol) in $CHCl_3$/toluene (1:2) (3 mL). [b] Isolated yield. [c] 1 mmol of acid **1b** was used. [d] 2 mmol of acid **1b** was used.

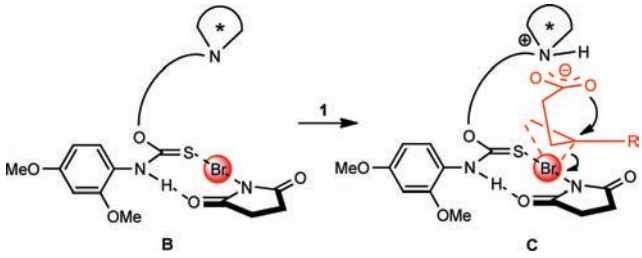
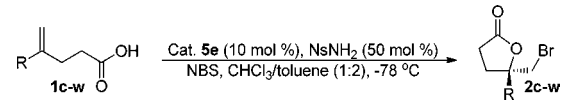


Figure 1. Proposed mechanism of the bromolactonization.

Further screening for efficient amino-thiocarbamate frameworks led us to identify the cinchonine skeleton **5**, and a 37% ee of **2b** was observed when catalyst **5b** was used. Attempts to increase the acidity of the thiocarbamate proton by replacing the phenyl ring with an electron-deficient 3,5-bis(trifluoromethyl)phenyl group, however, resulted in a negative effect on the enantioselectivity (**5c**, −29% ee). Surprisingly, an increase in the electron density of the phenyl group has an enhancing effect on the enantioselectivity. 4-Methoxyphenyl catalyst **5d** gave 40% ee, and the more electron-rich 2,4-dimethoxyphenyl catalyst **5e** afforded 50% ee. Changing the skeleton to quinidine furnished the same ee (**6**, 50% ee), while saturation of the olefin in **6** resulted in a lower ee (**7**, 40% ee). Replacing the phenyl group with other units such as *t*Bu (Table 2, **5f**) or Ph_2CH (Table 2, **5g**) resulted in a total loss of enantioselectivity. Finally, an exactly opposite ee was achieved when **8** (−49% ee) was used (compared to **5e**).[12]

After identifying the suitable catalyst **5e**, we attempted to optimize the reaction by varying different parameters systematically. Initially, various solvents including CH_2Cl_2, $CHCl_3$, toluene, ethanol, and ethyl acetate were screened,[12] and we eventually discovered that a $CHCl_3$/toluene (1:2) system dramatically enhanced the enantioselectivity to 87% ee (Table 3, entry 1). The enhanced ee in nonpolar solvents could be a result of reduced noncatalyzed reaction and/or strengthened polar interaction among substrate, NBS, and catalyst (cf. Figure 1). We have also investigated other halogen sources including *N*-chlorosuccinimide (NCS), *N*-iodosuccinimide (NIS), *N*-bromophthalimide (NBP), and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH), none of which was found to be as effective as NBS in terms of ee and reaction yield (Table 3, entries 2−5). Further attempts to improve the reaction led us to explore

Table 4. Asymmetric Bromolactonization of **1**



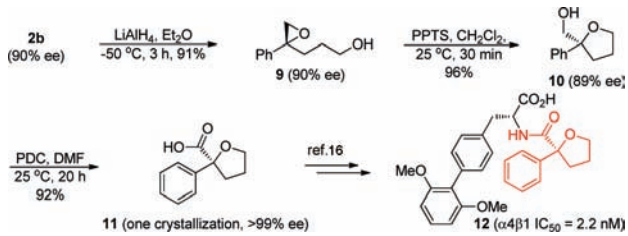
entry[a]	acid	R	time (h)	yield,[b] ee (%)
1	**1c**	4-Cl-C_6H_4	40	88, 91
2	**1d**	4-F-C_6H_4	26	93, 91
3	**1e**	4-CF_3-C_6H_4	56	71, 85
4	**1f**	4-NO_2-C_6H_4	96	85, 83
5	**1g**	4-EtOCO-C_6H_4	60	98, 87
6	**1h**	4-CF_3O-C_6H_4	24	85, 90
7	**1i**	4-Me-C_6H_4	36	87, 84
8	**1j**	4-MeO-C_6H_4	36	67, 28
9	**1k**	4-Ph-C_6H_4	30	71, 70
10	**1l**	3-F-C_6H_4	44	99, 90
11	**1m**	3-CF_3-C_6H_4	36	89, 86
12	**1n**	3,5-F_2-C_6H_3	48	98, 87
13	**1o**	3,5-$(CF_3)_2$-C_6H_3	96	88, 90
14	**1p**	3-MeO-C_6H_4	46	92, 82
15	**1q**	2-Me-C_6H_4	36	95, 52
16	**1r**	2-naphthyl	20	98, 90
17	**1s**	3-thienyl	67	91, 80
18	**1t**	3-furanyl	66	93, 84
19	**1u**	methyl	126	81, 41
20	**1v**	cyclohexyl	60	99, 82
21	**1w**	*tert*-butyl	36	97, 93

[a] Reactions were carried out with acid **1** (0.1 mmol), catalyst **5e** (0.01 mmol), $NsNH_2$ (0.05 mmol), and NBS (0.12 mmol) in $CHCl_3$/toluene (1:2) (3 mL). [b] Isolated yield.

the use of additive. On the basis of complex **A**, we reasoned that a weak hydrogen-bonding donor could coordinate to the carbonyl group of succinimide and further enhance the electrophilicity of Br. Thus, some weak acids were screened, and the results are listed in Table 3. Relatively acidic additives were found to have a detrimental effect on the yield and the enantioselectivity of the reaction (Table 3, entries 6−8). In the case of strongly acidic TFA, the enantioselectivity plunged to 0%. This result is a likely indication of a disruption to the ion-pairing of alkenoic acid **1** and catalyst **5e**. To our surprise, the addition of 1.0 equiv of $NsNH_2$ was found to increase the enantioselectivity to 89% ee, but with retardation of the reaction rate (Table 3, entry 9). Reducing the amount of $NsNH_2$ to 0.5 equiv could regain some of the reaction efficiency with similar enantioselectivity (Table 3, entry 10). Further reducing the amount of $NsNH_2$ resulted in no effect on the yield and the ee (Table 3, entry 13). Apparently, the effect of $NsNH_2$ on the reaction time implied that the role of $NsNH_2$ might not be as a hydrogen-bonding donor. Alternatively, we suspect that NsNHBr, a compound generated through the Br exchange between NBS and $NsNH_2$, could contribute to the increase in ee.[13,14] In fact, the existence of NsNHBr was described in the literature[15] and was confirmed by our ^{1}H NMR study on a mixture of NBS and $NsNH_2$.[12] Finally, the reaction was readily scalable without losing any efficiency and enantioselectivity (Table 3, entries 11 and 12).

Once the optimized conditions were identified (Table 3, entry 10), other substrates were examined, and the scope of the bromolactonization is indicated by the examples listed in Table 4.[12] The reactions were all performed smoothly with high yields and ee's. For aromatic-substituted acid substrates, the highest enantioselectivity of 91% ee was obtained with **1c** and **1d** (Table 4, entries 1 and 2), both bearing para-substituted halogens. In general, electron-rich aryl substituents gave lower enantioselectivities, which could be ascribed to the enhanced background reaction (Table 4, entries 1−6, 10−13 vs 7−9, 14). In some cases, the steric effect appeared to have negative effects on the ee values (Table 4, entries 3−5, 15). For 4-methyl and 4-cyclohexyl alkenoic acids, reactions gave good yields and moderate

Scheme 1. Asymmetric Synthesis of **11**

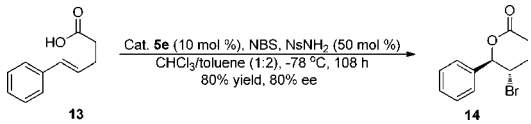


to good ee's (Table 4, entries 19 and 20). Notably, 93% ee was obtained when acid **1w** (R = *t*Bu) was used (Table 4, entry 21). Additionally, heteroaromatic substrates (Table 4, entries 17 and 18) were found to be amenable to our catalytic asymmetric protocol, with no observation of bromination on the heteroaromatic ring. The absolute configuration of lactones **2** was assigned on the basis of X-ray crystallographic structures of **2o** and **2w**.[12]

To probe the mechanism, several catalyst analogues of **5e** were examined. The catalyst with S replaced by O (**5h**), N−H replaced by O (**5i**), or N−H replaced by N−Me (**5j**) was found to be ineffective in offering appreciable ee in the bromolactonization of **1b** (Table 2). Replacing the thiocarbamate of **5e** with the well-known double-hydrogen-bonding catalyst thiourea (Table 2, **5k**) also showed no enantioselectivity in the **1b**→**2b** transformation. The above results led us to speculate that either a pure Lewis base[8] or a hydrogen-bonding activation[5] of NBS is unlikely to be the sole origin of enantioselectivity in this bromolactonization. We cannot rule out the possibility of quinuclidine as a NBS activator,[2b] but taking into account the importance of both N−H and S of the thiocarbamate toward enantioselectivity, an intermediate **B** with dual activation of NBS with the thiocarbamate is proposed (Figure 1). The quinuclidine can interact with the carboxylic acid, and the electron-rich 2,4-dimethoxyphenyl ring can act as a steric screening group and control the acidity of the thiocarbamate's N−H (Figure 1, **C**). The generally high ee results also support this rigid transition-state proposal, in which the olefin−olefin halogen exchange racemization could be suppressed.[11]

To demonstrate the synthetic utility of this methodology, we transformed bromolactone **2b** into a synthetically useful building block (Scheme 1). Thus, **11** was prepared from **2b** through a **2b**→**9**→**10**→**11** sequence, in which carboxylic acid **11** is a key intermediate for the synthesis of specific VLA-4 antagonists (e.g., **12**).[16]

We have also attempted to apply the optimized protocol in the formation of δ-lactones. Preliminary studies showed that lactone **14** could be prepared from **13** in good yield and ee.



In summary, we have developed a novel amino-thiocarbamate-catalyzed enantioselective bromolactonization for asymmetric synthesis of γ-lactones. Further investigations on other applications, including δ-lactone formation, and on mechanistic studies are underway.

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Supporting Information Available: Experimental procedures and spectral and X-ray data for reactions products (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) The details are in the Supporting information.
(13) A mixture of $NsNH_2$, NsNHBr, and $NsNBr_2$ was obtained when $NsNH_2$ was reacted with various kinds of brominating agents; attempts to isolate pure NsNHBr were unsuccessful. Pure $NsNBr_2$ was prepared by treating $NsNH_2$ with 2.2 equiv of Br_2. However, only 48% ee was observed when $NsNBr_2$ was used.
(14) Since a rapid Br exchange should exist between NBS and $NsNH_2$, we suspect that NsNHBr could serve as a "Br sink", in which NBS was regenerated slowly (as a virtual slow addition) for the bromolactonization reaction. Attempts to add NBS portionwise into the reaction in the absence of $NsNH_2$ resulted in a comparable improvement in ee; however, the process was operationally inconvenient. On the other hand, we also acknowledge the possibility of NsNHBr acting as a better Br source than NBS. The role of $NsNH_2$ is still under investigation.
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