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# Studies toward Lewis basic thiocarbamate and thiourea mediated bromolactonization: the effect of a trace amount of water on the reactivity and enantioselectivity

Chong Kiat Tan, Feng Chen, Ying-Yeung Yeung\*

Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543, Singapore

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## ABSTRACT

The effects of trace amounts of water on thiocarbamate- and thiourea-catalyzed bromolactonization reactions are studied. It was found that the thiourea- and the N–Me thiocarbamate-catalyzed bromolact-onization reactions were sensitive to trace amounts of moisture. In contrast, the N–H thiocarbamate-catalyzed bromolactonization proceeded equally smoothly in both anhydrous and non-anhydrous solvents.

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Halolactonization is an important reaction in organic synthesis as the corresponding halolactones are very useful building blocks for many natural products and drug molecules.<sup>1</sup> Recently, the study of catalytic halolactonization has undergone a renaissance. In particular, bromolactonization has been studied extensively using N-bromosuccinimide (NBS) as the halogen source. Various NBS activators, such as Lewis acids,<sup>2</sup> Lewis bases,<sup>3</sup> hydrogenbonding type catalysts,<sup>4</sup> amides,<sup>5</sup> and aryl iodides<sup>6</sup> have been reported. Highly reactive brominating sources (e.g., Et<sub>2</sub>SBr·SbCl<sub>5</sub>Br) were also studied as stoichiometric reagents, which are potentially useful for bromolactonization.<sup>7</sup> Despite these significant advances, the catalytic and enantioselective versions of halolactonizations, especially bromolactonization, are still lacking because a suitable catalytic system remains elusive.<sup>8–10</sup>

Recently, we described an efficient amino-thiocarbamate catalyzed enantioselective bromolactonization.<sup>11</sup> A number of  $\gamma$ -lactones **3** and  $\delta$ -lactones **6** were prepared with high ee values. Mechanistic studies show that both the S and the N–H of the thiocarbamate are responsible for the high enantioselectivity (Scheme 1). The exquisite need for the thiocarbamate is intriguing as it is not a common functional group in organocatalysis. Amino-thiocarbamates **1** and **4** were developed after an extensive study of the readily available thiocarbamates and thioureas **7–10** (Table 1). In this report, we describe the groundwork, in particular the water

effect, which led us to our eventual selection of the thiocarbamate motif over that of other structurally similar compounds.

At the outset of this work, we were aware of the various attempts to activate NBS as described above. Since a suitable catalytic asymmetric system had yet to emerge from these studies, we decided to begin our search by examining the feasibility of utilizing an underexplored Lewis basic sulfur activated electrophilic brominating source for enantioselective bromolactonization.<sup>12</sup> Indeed,



Scheme 1. Asymmetric bromolactonization of alkenoic acids 2 and 5.



<sup>\*</sup> Corresponding author. Tel.: +65 65167760; fax: +65 67791691. *E-mail address:* chmyyy@nus.edu.sg (Y.-Y. Yeung).

# Table 1Lewis basic sulfur promoted bromolactonization





 $^{a}$  Reactions were carried out with alkenoic acid (0.20 mmol), NBS (0.22 mmol), and catalyst (0.01 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) at -78 °C.  $^{b}$  Isolated yield.

#### Table 2

Effect of the water content on the reaction rate



Entry <sup>a</sup>	Catalyst	Water content <sup>b</sup> (ppm)	Temp (°C)	Time (min)	Yield <sup>c</sup> ( <b>6a + 6b</b> , %)
1	11	230	0	5	95 + 4
2	11	5	0	5	40 + 2
3	11	230	-15	10	95 + 2
4	11	5	-15	10	29 + 1
5	12	230	-15	10	91 + 4
6	12	5	-15	10	91 + 4
7	13	230	-15	10	93 + 4
8	13	5	-15	10	81 + 7
9	None	230	0	30	<1

<sup>a</sup> Reactions were carried out with alkenoic acid **5a** (0.20 mmol), NBS (0.22 mmol), and catalyst (0.01 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL).

<sup>b</sup> Water content was determined using a Metrohm 831 KF coulometer.

<sup>c</sup> The conversion yields were the average of two experiments and determined based on <sup>1</sup>H NMR spectroscopy.

such a sulfur–bromine interaction has already been elucidated using an X-ray crystallographic study.  $^{13}$ 

Thus, a number of C=S containing molecules (**7–10**, Table 1) were screened for their potential as bromolactonization catalysts.

The catalytic ability of the molecules was investigated with the unsaturated carboxylic acids **2a** and **5a** and NBS as the stoichiometric brominating agent. In general, the thioureas and thiocarbamates were found to be competent bromolactonization catalysts and were able to furnish moderate ees in some cases (Table 1, entries 4 and 7).

However, in the course of our research, the efficiency and the enantioselectivity obtained with the N–Me thiocarbamate **10** and thioureas **7** and **9** catalyzed bromolactonization reactions were hard to be reproduced unless strict control of the moisture content was applied. In stark contrast, the yields and ees of the N–H thiocarbamate **1**, **4**, and **8** catalyzed reactions were stable despite applying less rigor in our reaction set-up. The yields and enantiose-lectivities of the amino-thiocarbamate **1** and **4** catalyzed bromolactonizations (Scheme 1) were reproducible even when non-anhydrous NBS was used.<sup>11,14</sup>

To obtain a better understanding of this phenomenon, a careful study of the relationship between the water content and the bromolactonization reaction rate was performed using the simplified thiourea **11**, and thiocarbamates **12**, and **13** as the catalysts (Table 2) with alkenoic acid **5a** as the test substrate.<sup>15</sup>

From this study it emerged that the rate of the thiourea 11 catalyzed bromolactonization was highly dependent on the water content. For an anhydrous system (water content was 5 ppm), 42% (0 °C, 5 min) and 30% yields (-15 °C, 10 min) of lactone 6 were achieved (Table 2, entries 2 and 4). On the other hand, the same reaction proceeded smoothly in the relatively high water content (230 ppm) system and high conversions (99% at 0 °C and 5 min; 97% at -15 °C and 10 min) were observed (Table 2, entries 1 and 3). The effect of water on the bromolactonization using thiocarbamate catalyst 12 was less apparent. The results showed that thiocarbamate **12** was able to catalyze the reaction equally smoothly using both anhydrous and non-anhydrous systems (Table 2, entries 5 and 6). In contrast, the effect of the water content on the reaction rate was quite significant when the N-methylated thiocarbamate 13 was used (Table 2, entries 7 and 8). In the absence of any catalyst, the reaction was sluggish (Table 2, entry 9), thus proving that water alone did not catalyze the bromolactonization.<sup>16</sup>

The effect of water on the enantioselectivity of the asymmetric bromolactonization was also investigated. A set of parallel bromolactonization reactions under anhydrous (water content = 46 ppm) and non-anhydrous (water content = 672 ppm) conditions were performed using catalysts **1** and **10** (Table 3). As shown, the enantioselectivity conferred by **10** suffered a drop under non-anhydrous conditions (Table 3, entries 3 and 4). In comparison, catalyst **1** was only affected slightly by moisture (Table 3, entries 1 and 2).

The effect of water on the bromolactionization was rather intriguing as it had led to an increased reaction rate, but a decreased enantioselectivity when the N–Me thiocarbamate **10** was used. Since water was proven not to catalyze the bromolactonization (Table 2, entry 9), the promotion of reaction rate under high moisture content appears to proceed via another pathway.

Since the complex formed between the Lewis basic sulfur and NBS (e.g., **14**) is believed to be the active intermediate, one possibility is that water might collapse the complex to afford a new species which is: (1) a better bromination mediator than the N–Me thiocarbamate and the thiourea; (2) catalyzing the reaction through a non-asymmetric pathway. Although the nature of the possible alternative pathway due to the moisture remains unclear<sup>17</sup> and requires further investigation, the small interference of water on the N–H thiocarbamate catalyzed reaction was the deciding factor for our eventual selection of the thiocarbamate motif for further development. The stability of the N–H thiocarbamate may also suggest that the N–H thiocarbamate–NBS complex (e.g., **15**, a proposed intermediate in the previous study)<sup>11</sup> could be more resistant to moisture-promoted decomposition (Fig. 1).

#### Table 3

Effect of the water content on the enantioselectivity



Entry <sup>a</sup>	Catalyst	Water content <sup>b</sup> (ppm)	Yield <sup>c</sup> (%)	ee (%)
1	1	46	96	76
2	1	672	98	74
3	10	46	80	17
4	10	672	94	10
5	None	672	20	0

<sup>a</sup> Reactions were carried out with alkenoic acid **5a** (0.15 mmol), NBS (0.18 mmol) and catalyst (0.015 mmol) in CHCl<sub>3</sub>/toluene (4.5 mL, 1:2 v/v).

<sup>b</sup> Water content was determined using a Metrohm 831 KF coulometer.

<sup>c</sup> Isolated yield.



Figure 1. Catalyst-NBS complexes 14 and 15.

In summary, we have demonstrated the stability of N–H thiocarbamates over thiourea and N–Me thiocarbamate in bromolactonization reactions under high moisture content. The purpose of our study was not to rule out the possibility of developing asymmetric bromination or other halogenation reactions using tetrasubstituted thiourea or N–Me thiocarbamate as the catalyst. Instead, we wanted to show that the observation of high tolerance to moisture led us to select the N–H thiocarbamate for further development as a chiral catalyst for asymmetric bromolactonization. The less moisture sensitive thiocarbamate is operationally more convenient to use in which no rigorous moisture control is necessary.

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- 14. Commercially available NBS was used as received without any additional treatment.
- 15. Anhydrous solvents used in these experiments were obtained from an Innovative Technology solvent purification system. The non-anhydrous solvents were obtained directly from the commercial bottle (Merck LiChrosolv, solvent was taken under ambient conditions with air humidity of 60%). N-Bromosuccinimide was recrystallized from deionized water and dried over P<sub>2</sub>O<sub>5</sub> under vacuum for three days.
- 16. Representative procedure for the anhydrous reaction: The alkenoic acid (0.20 mmol, 1.0 equiv) and catalyst (0.01 mmol, 0.05 equiv) were charged into a flame-dried two-necked round-bottomed-flask and evacuated under vacuum for 4 h. The flask was shielded from light by wrapping in aluminum foil. Thereafter, the contents were subjected to 3 cycles of vacuum evacuation and nitrogen flushing. A continuous flow of nitrogen was maintained throughout the reaction. Anhydrous (5 ppm H<sub>2</sub>O content) CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was then injected into the flask and the mixture was stirred at -15 °C (dry ice in an ethylene glycol bath). N-Bromosuccinimide (42.7 mg, 0.24 mmol, 1.2 equiv) was added and the reaction was monitored by TLC. The reaction mixture was quenched with sat. Na<sub>2</sub>SO<sub>3</sub> (2.0 mL) at -15 °C and then warmed to 25 °C. The solution was acidified with aqueous HCl (10%) dropwise until pH 2.0. The crude product and unreacted starting material were then extracted with CH2Cl2  $(3 \times 5 \text{ mL})$ . The combined extracts were concentrated in vacuo. The conversion yield was determined via integration of the corresponding peaks in the <sup>1</sup>H NMR spectra. The physical data of the lactone products were in full accordance with literature values.
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