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Synthesis of chiral butenolides using amino-thiocarbamate-catalyzed asymmetric bromolactonization

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ABSTRACT

The asymmetric cyclization of 4,4-disubstituted 3-butenoic acids is studied. Amino-thiocarbamates are used as the catalysts and *N*-bromosuccinimide is used as the stoichiometric halogen source. The resulting γ-butanolide products are readily converted into the corresponding γ-butenolides (up to 58% ee) derivatives in one-pot.

The area of enantioselective synthesis of halolactones from prochiral olefins has witnessed a recent flurry of reports to tackle this long-standing problem.[1] In our laboratory, we discovered that the cinchona alkaloid derived amino-thiocarbamates offer a framework for catalyst modification to accommodate a number of olefinic acids of various substitution patterns (Scheme 1).[2]

While the advances have enabled the synthesis of various useful chiral halolactone motifs, reports on asymmetric halolactonizations of alkenoic acids with a tri-substituted olefin remain scarce.[3,4] Herein we describe our recent progress on the asymmetric bromocyclization of 4,4-disubstituted 3-butenoic acids **1**. Amino-thiocarbamate and *N*-bromosuccinimide (NBS) were used as the catalyst and the stoichiometric halogen source, respectively. The result is a stereochemically defined γ-butanolide **2** which can readily be converted into a γ-butenolide **3** by a simple base-mediated elimination (vide infra) (Scheme 2).

The synthesis of γ-butano- and γ-butenolides would be particularly useful as such motifs rank among the most prevalent subunits found in natural isolates and pharmaceutically useful organic molecules.[5] Many of these compounds exhibit diverse biological properties such as anti-inflammatory, antibacterial, antifungal, or phytotoxic activities, with several having been described as potential antitumor and anticancer agents, or antimalarial, antituberculosis, anti-aldosteronic and anti-asthmatic drug candidates (Fig. 1).

The olefinic acid substrates **1** were synthesized via Knoevenagel condensation of aldehyde **6**, as reported by Rousseau and co-workers.[3c] Aldehyde **6** could readily be prepared from ketone **4** through a **4**→**5**→**6** sequence (Scheme 3). Alternatively, olefinic acid **1** could be furnished in one-step from ketone **4** by reacting with Wittig salt **7** using sodium bis(trimethylsilyl)amide as the base, although the yield was not promising.[6]

In the initial phase, amino-thiocarbamates derived from four cinchona alkaloid cores were evaluated for their potential to catalyze asymmetrically the bromolactonization. Alkenoic acid **1a** was used as the model substrate and the reaction was conducted in chloroform at −50 °C (Table 1). The work-up of the reaction revealed not only the formation of the bromolactone **2a**, but also the elimination product **3a** (**2a**:**3a** = 10:1). The product mixture containing **2a** and **3a** was duly converted into **3a** by adding triethylamine during the work-up process. Consequently, evaluation of the enantioselectivity of the reaction was based on that of butenolide **3a**.

The result of the catalyst screening showed that the cinchonine derived catalyst **8a** was the best with 46% ee (Table 1, entry 1). The amino-thiocarbamates with the pseudo enantiomeric cinchonidine and quinine cores afforded **3a** of opposite stereo-configuration (entry 3). Contrary to our previous reports, the presence of a 6-alkoxy substituent on the catalyst framework did not lead to positive enhancement of the ee of the reaction (Table 1, entry 1 vs 2, entry 3 vs 4). We also found that carbamate catalyst **12** returned a much lower ee, which verifies the importance of the Lewis basic sulfur atom.

The *N*-aryl substituent on **8** was then varied in an attempt to improve the ee. It was found that 4- and 3-alkoxyphenyl substituents had only a small effect on the enantioselectivity (Table 1, entries 6–9), whereas 2-alkoxyphenyl substitution significantly

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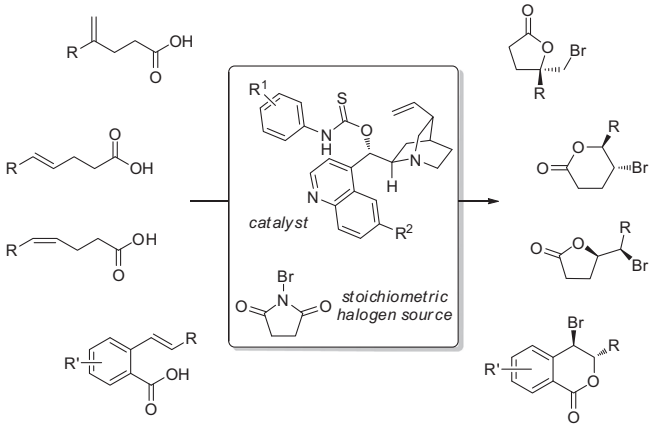
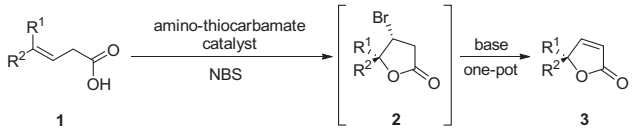


Scheme 1. Amino-thiocarbamate-catalyzed asymmetric bromolactonization.



Scheme 2. Amino-thiocarbamate catalyzed asymmetric bromolactonization of 4,4-disubstituted 3-butenoic acid **1**.

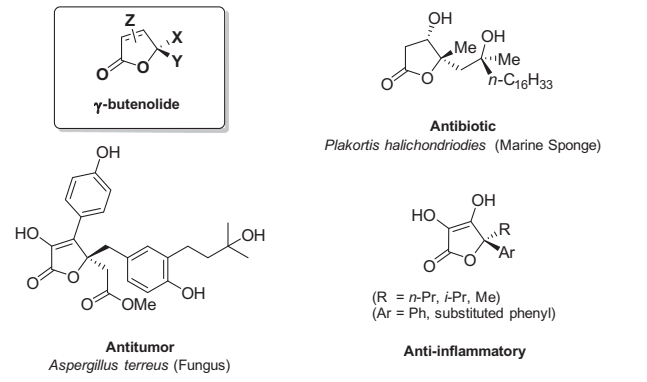
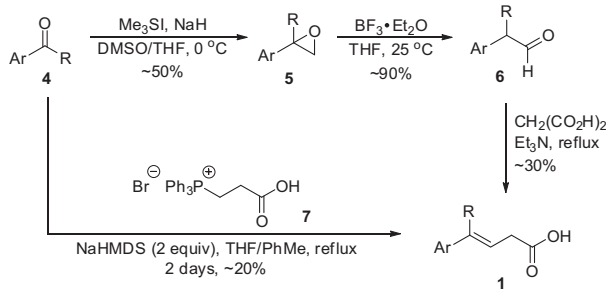
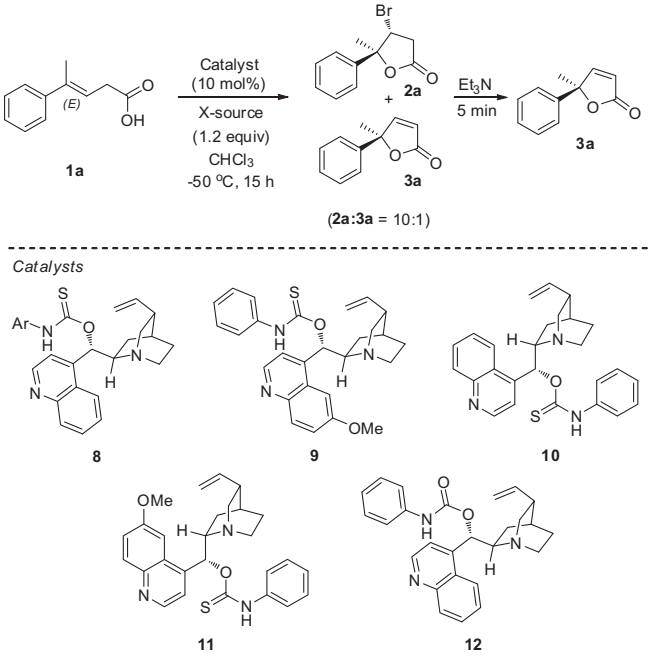


Figure 1. Selected examples of natural products and potential drug molecules containing the γ-butano- or γ-butenolide moiety.



Scheme 3. Synthesis of olefinic acid substrates **1**.

Table 1
Evaluation of amino-thiocarbamates as asymmetric catalysts



Entry[a]	Cat.	Ar	X-source	Yield (%)	ee (%)
1	**8a**	C_6H_5	NBS	98	46
2	**9**	—	NBS	99	38
3	**10**	—	NBS	99	−33
4	**11**	—	NBS	99	−29
5	**12**	—	NBS	95	12
6	**8b**	4-MeO-C_6H_4	NBS	99	45
7	**8c**	4-EtO-C_6H_4	NBS	99	46
8	**8d**	4-(*t*-BuO)-C_6H_4	NBS	99	44
9	**8e**	3-MeO-C_6H_4	NBS	99	40
10	**8f**	2-MeO-C_6H_4	NBS	99	16
11	**8g**	2,4-$(MeO)_2$-C_6H_3	NBS	99	14
12	**8h**	2,4,6-$(MeO)_2$-C_6H_3	NBS	84	7
13	**8i**	4-Me-C_6H_4	NBS	99	40
14	**8j**	3,5-$(CF_3)_2$-C_6H_3	NBS	96	20
15	**8k**	4-NO_2-C_6H_4	NBS	81	32
16	**8a**	C_6H_5	NBP	99	48
17	**8a**	C_6H_5	DBDMH	99	40
18	**8a**	C_6H_5	TABCO	93	6
19	**8a**	C_6H_5	NIS	99	15
20	**8a**	C_6H_5	NCS	NR	—
21	**8a**	C_6H_5	DBDMH	15	0

[a] Reactions were carried out with alkenoic acid **1** (0.1 mmol), NBS (0.12 mmol), catalyst **8a** (0.01 mmol) in $CHCl_3$/hexane (1:1) (3.0 mL).

diminished the ee (Table 1, entries 10–12). In addition, relatively less electron-donating or highly electron-deficient substituents returned lower ees (Table 1, entries 13–15). Thus, catalyst **8a** was selected for further development.

Examination of other halogenation sources was also conducted. *N*-Bromophthalimide (NBP) afforded a minor enhancement in the enantioselectivity, while the more reactive Br-sources, 1,3-dibromo-2,2-dimethylhydantoin (DBDMH) and 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TABCO) returned eroded ees (Table 1, entries 16–18). Similar to our previous observation,[2] the iodinating agent *N*-iodosuccinimide (NIS) gave a much lower ee, and the use of chlorinating agents gave sluggish reactions (Table 1, entries 19–21).