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

Chong Kiat Tan, Jun Cheng Er, Ying-Yeung Yeung *

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

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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

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

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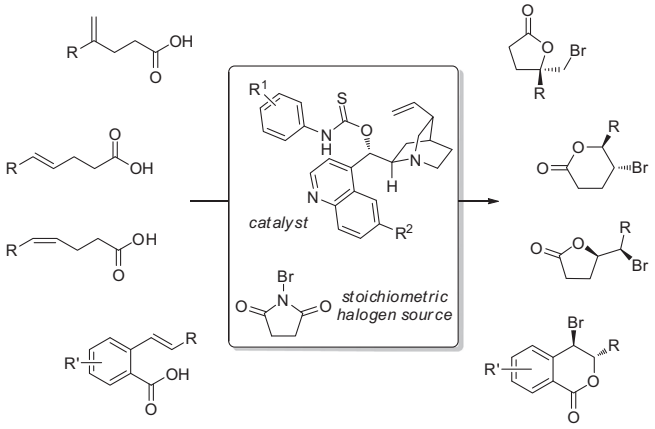
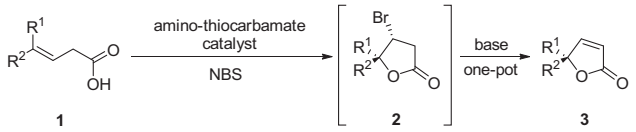


Scheme 1. Amino-thiocarbamate-catalyzed asymmetric bromolactonization.



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

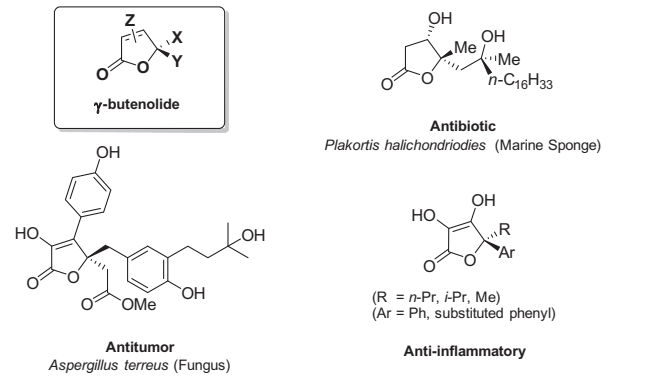
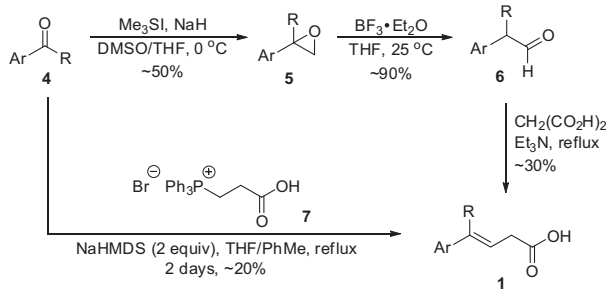
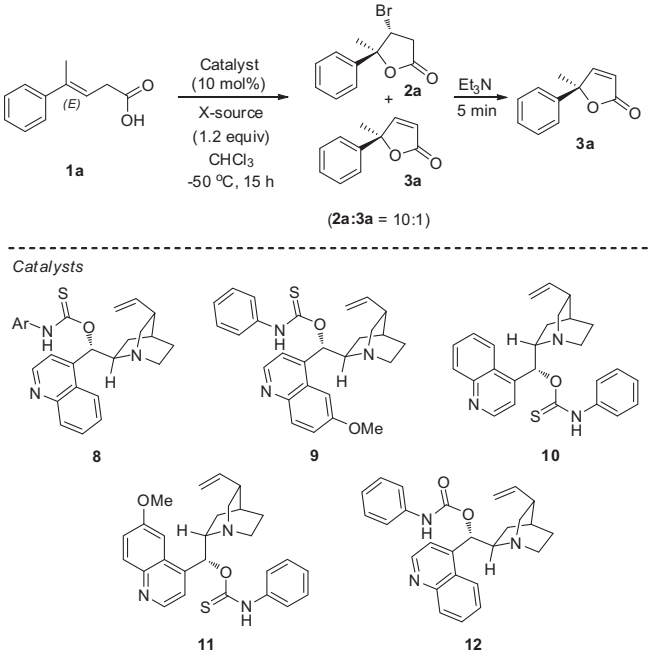


Figure 1. Selected examples of natural products and potential drug molecules containing the γ-butano- or γ-butenolide moiety.



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

Table 1
Evaluation of amino-thiocarbamates as asymmetric catalysts



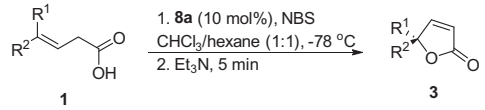
Entry[a]	Cat.	Ar	X-source	Yield (%)	ee (%)
1	**8a**	C_6H_5	NBS	98	46
2	**9**	—	NBS	99	38
3	**10**	—	NBS	99	−33
4	**11**	—	NBS	99	−29
5	**12**	—	NBS	95	12
6	**8b**	4-MeO-C_6H_4	NBS	99	45
7	**8c**	4-EtO-C_6H_4	NBS	99	46
8	**8d**	4-(*t*-BuO)-C_6H_4	NBS	99	44
9	**8e**	3-MeO-C_6H_4	NBS	99	40
10	**8f**	2-MeO-C_6H_4	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).

Table 2
Substrate scope of the asymmetric bromolactonization of **1**



Entry[a]	Acid	R^1	R^2	Time (h)	Yield (%)	ee (%)
1	**1a**	Me	Ph	38	98	52
2	**1b**	H	Ph	13	93	7
3	**1c**	Me	2-Naphthyl	15	99	58
4	**1d**	Me	4-F-C_6H_4	40	99	54
5	**1e**	Me	4-Br-C_6H_4	60	98	56
6	**1f**	Me	4-MeO-C_6H_4	36	97	19
7	**1g**	Me	3-MeO-C_6H_4	36	97	51
8	**1h**	Me	2-Benzofuranyl	36	99	58

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

Prior to the examination of the substrate scope with catalyst **8a**, extensive solvent screening was performed. The reaction using $CHCl_3$/hexane (1:1) was found to offer an improved ee of 52% for the bromolactonization of **1a** (Table 2, entry 1). Using the optimized conditions, other derivatives of olefinic acid **1** were examined.[7]

The replacement of methyl with a hydrogen atom in the R^1 position (substrate **1b**) resulted in a drastic decrease in ee to 7% (Table 2, entry 2). Introduction of bulkier substituents at the R^2 position proved to be favorable; butenolides **3c** and **3h** bearing 2-naphthyl and 2-benzofuranyl substituents were both obtained with 58% ee (Table 2, entries 3 and 8). Variation of the electronic demand of the phenyl ring system at R^2 was found not to affect the ee adversely (Table 2, entries 4, 5, and 7). However, olefinic acid **1f** bearing a 4-methoxyphenyl substituent was found to offer only 19% ee (Table 2, entry 6). This observation is also consistent with our findings in previous reports.[1,2] The absolute configurations of products **3** were established based on the X-ray crystallographic study of **2h** (Fig. 2).[8]

In summary, we have reported that tri-substituted olefinic acids **1** are amenable to amino-thiocarbamate catalyzed asymmetric bromolactonization offering moderate ees of the products. This protocol allows for the facile synthesis of enantioenriched γ-butenolides which are fundamental units of many pharmaceutically important molecules.

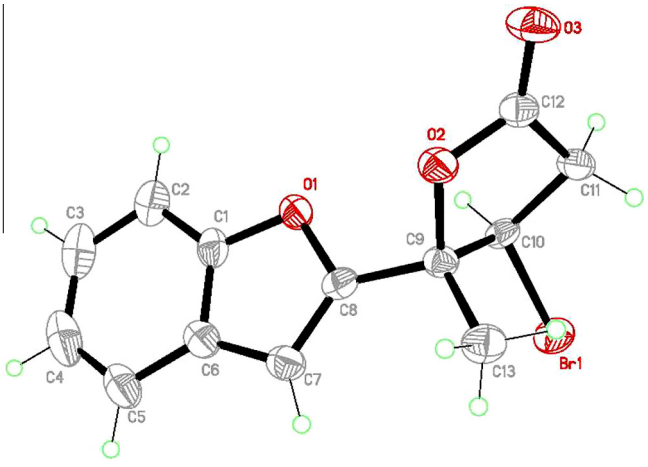


Figure 2. X-ray crystal structure of **2h** (CCDC: 818046).

Acknowledgments

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7. General procedure: to an oven-dried 10 mL Schlenk flask were added alkenoic acid **1** (0.05 mmol, 1.0 equiv) and amino-thiocarbamate catalyst **8a** (0.005, 0.1 equiv) in $CHCl_3$/hexane (1:1, 1.5 mL) under N_2. The solution was cooled to −78 °C and recrystallized NBS (10.8 mg, 0.06 mmol, 1.2 equiv) was added. The resulting mixture was stirred at the same temperature for 15 h. Upon completion, the reaction was quenched with saturated Na_2SO_3 (2 mL) and warmed to 25 °C. Et_3N (1 mL) was added and the solution was stirred for 5 min. The resultant mixture was diluted with H_2O (3 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with aqueous HCl (1 M, 3 × 5 mL) and brine (15 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 3:1) to afford the corresponding γ-butenolide **3**.
*Selected data: 5-(benzofuran-2-yl)-4-bromo-5-methyldihydrofuran-2(3H)-one (**2h**):* white solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.33 (t, J = 8.0 Hz, 1H), 7.28 (t, J = 8.0 Hz, 1H), 6.80 (s, 1H), 4.96 (dd, J = 7.0, 3.8 Hz, 1H), 3.44 (dd, J = 18.3, 7.0 Hz, 1H), 3.00 (dd, J = 18.3, 3.8 Hz, 1H), 2.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.0, 154.1, 127.3, 125.3, 123.4, 121.5, 111.4, 104.6, 84.3, 53.4, 48.7, 40.3, 24.2; MS (EI): m/z $[M]^+$ = 295.0.
*5-(Benzofuran-2-yl)-5-methylfuran-2(5H)-one (**3h**):* yellow solid; ^{1}H NMR

(300 MHz, $CDCl_3$): δ = 7.60 (d, J = 5.6 Hz, 1H), 7.56 (ddd, J = 8.1, 1.3, 1.0 Hz, 1H), 7.46 (ddd, J = 8.0, 1.1 Hz, 1H), 7.31 (ddd, J = 8.1, 8.0, 1.3 Hz, 1H), 7.24 (ddd, J = 8.1, 8.0, 1.1 Hz, 1H), 6.74 (d, J = 1.0 Hz, 1H), 6.21 (d, J = 5.6 Hz, 1H), 1.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.3, 157.3, 154.9, 154.1, 127.3, 125.1, 123.2, 121.4, 121.1, 111.4, 104.1, 84.5, 23.0; MS (EI): m/z $[M]^+$ = 214.2. Determination of ee by chiral HPLC (CHIRALPAK® IB Column, *i*-PrOH/hexane = 15:85, 0.6 mL/min, 214 nm): t_1 = 14.5 min (major), t_2 = 15.3 min (minor).

8. CCDC 818046 (**2h**) contains 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.