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Aminothiocarbamate-Catalyzed Asymmetric Bromolactonization of 1,2-Disubstituted Olefinic Acids

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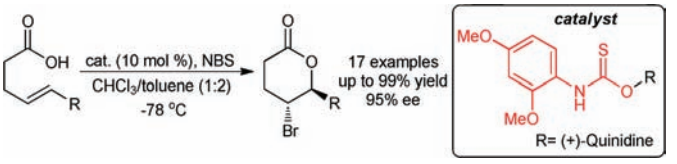
ABSTRACT



An efficient and enantioselective bromolactonization of 1,2-disubstituted olefinic acids using an amino-thiocarbamate catalyst has been developed, resulting in the formation of δ-lactones containing two chiral centers with up to 99% yield, 95% ee.

Halolactonization is an important class of organic transformation under the umbrella of halonium-induced cyclization. The resulting halolactones are of particular interest to synthetic chemists because of the importance of the lactone moieties that pervades a wide spectrum of molecular structures (e.g., the fundamental unit of many natural products). In addition, the halogen substituents can be readily modified to other useful functional groups (e.g., by nucleophilic substitution). The importance of halolactonization is underscored by the large number of applications to the synthesis of useful building blocks and biologically active molecules.[1,2] Although halolactonizations have been studied for decades, their modifications to the enantioselective versions have been problematic.[3,4] Recently, several elegant reports appeared that provided access to a number of valuable halolactones with a practical level of enantioselectivities.[5] However, the olefinic moieties in the substrates are limited to 1,1-disubstituted alkenes that result in γ- and δ-lactones containing quaternary centers. Halolactonizations that involve substrates with 1,2-disubstituted olefinic moieties[6] are attractive targets since the resulting lactones contain two stereogenic centers with a well-defined ester−halogen antirelationship; asymmetric halolactonization of this class of substrates remains uncommon, and until now only a substoichiometric catalytic and two stoichiometric chiral auxiliary-controlled

(1) (a) Rodríguez, F.; Fañanás, F. J. In *Handbook of Cyclization Reactions*; Ma, S., Ed.; Wiley-VCH: New York, 2010; Vol. 4, pp 10−20. (b) Ranganathan, S.; Muraleedharan, K. M.; Vaish, N. K.; Jayaraman, N. *Tetrahedron* **2004**, *60*, 5273–5308. (c) Lava, M. S.; Banerjee, A. K.; Cabrera, E. V. *Curr. Org. Chem.* **2009**, *13*, 720–730.

(2) Examples of related halonium-induced cyclizations: (a) Kang, S. H.; Lee, S. B.; Park, C. M. *J. Am. Chem. Soc.* **2003**, *125*, 15748–15749. (b) Sakakura, A.; Ukai, A.; Ishihara, K. *Nature* **2007**, *445*, 900–903. (c) Snyder, S. A.; Treitler, D. *Angew. Chem., Int. Ed.* **2009**, *48*, 7899–7903. (d) Snyder, S. A.; Treitler, D. S.; Brucks, A. P. *J. Am. Chem. Soc.* **2010**, *132*, 14303–14314. (e) Hennecke, U.; Müller, C. H.; Fröhlich, R. *Org. Lett.* **2011**, *13*, 860–863.

(3) Early examples of asymmetric halolactonization reactions: (a) Haas, J.; Piguel, S.; Wirth, T. *Org. Lett.* **2002**, *4*, 297–300. (b) Haas, J.; Bissmire, S.; Wirth, T. *Chem.—Eur. J.* **2005**, *11*, 5777–5785.

(4) For a mechanistic discussion on the problems of enantioselective halocyclization, see:(a) Brown, R. S. *Acc. Chem. Res.* **1997**, *30*, 131–137. (b) Cui, X.-L.; Brown, R. S. *J. Org. Chem.* **2000**, *65*, 5653–5658. (c) Denmark, S. E.; Burk, M. T.; Hoover, A. J. *J. Am. Chem. Soc.* **2010**, *132*, 1232–1233.

(5) (a) Whitehead, D. C.; Yousefi, R.; Jaganathan, A.; Borhan, B. *J. Am. Chem. Soc.* **2010**, *132*, 3298–3300. (b) Zhang, W.; Zheng, S.; Liu, N.; Werness, J. B.; Guzei, I. A.; Tang, W. *J. Am. Chem. Soc.* **2010**, *132*, 3664–3665. (c) Zhou, L.; Tan, C. K.; Jiang, X.; Chen, F.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 15474–15476. (d) Veitch, G. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2010**, *49*, 7332–7335. (e) Murai, K.; Matsushita, T.; Nakamura, A.; Fukushima, S.; Shimura, M.; Fujioka, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 9174–9177. (f) Ning, Z.; Jin, R.; Ding, J.; Gao, L. *Synlett* **2009**, 2291–2294. (g) Chen, G.; Ma, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 8306–8308.

(6) During the preparation of this paper, an elegant report appeared in the literature that is related to the asymmetric co-chlorination of 1, 2-disubstituted olefins: Jaganathan, A.; Garzan, A.; Whitehead, D. C.; Staples, R. J.; Borhan, B. *Angew Chem., Int. Ed.* **2011**, *50*, 2593–2596.

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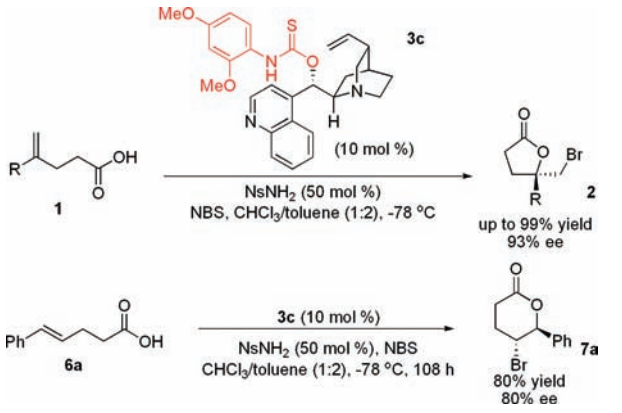
approaches were disclosed that offered low to moderate enantiomeric purities.[7]

Recently, the use of aminothiocarbamate catalyst **3c** in the asymmetric bromolactonization of **1** to **2** was described by our research group.[5c] In the same report, we also disclosed that aminothiocarbamate **3c** was not only applicable to 1,1-disubstituted olefinic acids but also to **6a**, a 1,2-disubstituted alkene substrate (Scheme 1). In this

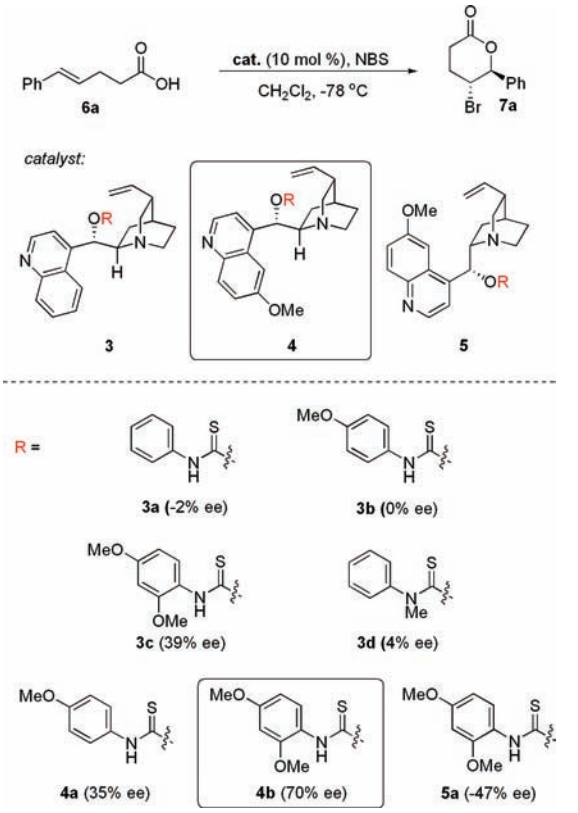
Scheme 1. Enantioselective Synthesis of γ-Lactones **2** and δ-Lactone **7a**



paper, we disclose our success at attaining practical enantioselectivities of δ-lactones (up to 95% ee). With it, we aim to demonstrate that the catalyst is tunable to match a different alkenoic acid substrate and that the stereochemistry of the δ-lactone is consistent with our previously proposed model.

Motivated by the promising results with catalyst **3c** (Scheme 1), we embarked on a round of catalyst screening in hope of boosting the enantioselectivity. As shown in Table 1, the best catalyst **3c** for the enantioselective synthesis of γ-lactones **1** (R = Ph, 50% ee in CH_2Cl_2)[5c] was only able to afford the δ-lactone **7a** with 39% ee (Scheme 2). In fact, both **3a** and **3b** were unable to provide any enantioenriched δ-lactone **7a** in CH_2Cl_2 despite **3b** being able to furnish the γ-lactone **1** (R = Ph) with 40% ee.[5c] Additionally, **3d** was only able to afford 4% ee. Surprisingly, a switch to a quinidine core results in a dramatic change in the enantioselectivity (Scheme 2, **3b** vs **4a**, **3c** vs **4b**), and **4b** catalyzed bromolactonization of **6a** afforded **7a** with 70% ee. On the other hand, catalyst **5a** could only afford **7a** with −47% ee. Since catalysts **3c** and **4b** differ in only a methoxy group on the quinoline unit, the dramatic increase in ee suggests yet another site for potential tuning. This implies that the tuning of steric and electronic properties of the alkoxy substituent on the quinoline and *N*-aryl of the thiocarbamate may allow the accommodation of other substrates to the asymmetric bromolactonization protocol.

Scheme 2. Enantioselectivities Obtained with Various Aminothiocarbamates



After the identification of the best aminothiocarbamate catalyst **4b**, the reaction solvent was varied to further boost the enantioselectivity. Gratifyingly, the $CHCl_3$/toluene (1:2) solvent blend reported previously was found to boost the enantioselectivity to 91% ee (Table 1, entry 1).

A series of alkenoic acids **6** was then subjected to this optimal reaction condition.[8−10] For the olefinic acids with electron-rich aryl substituents, generally excellent yields and ees were obtained (Table 1, entries 1−12). It is noteworthy that the electron-rich system (e.g., 4-methoxyphenyl in **6h**) typically has a negative effect on the enantioselectivity in some reports.[5] Nonetheless, this

(7) (a) Wang, M.; Gao, L. X.; Mai, W. P.; Xia, A. X.; Wang, F.; Zhang, S. B. *J. Org. Chem.* **2004**, *69*, 2874–2876. (b) Garnier, J. M.; Robin, S.; Rousseau, G. *Eur. J. Org. Chem.* **2007**, 3281–3291. (c) Grossman, R. B.; Trupp, R. J. *Can. J. Chem.* **1998**, *76*, 1233–1237.

(8) For details see the Supporting Information.

(9) Representative procedure: to a solution of alkenoic acid **6** (0.05 mmol, 1.0 equiv), catalyst (2.8 mg, 0.005 mmol, 0.1 equiv) in $CHCl_3$ (0.5 mL), and toluene (1.0 mL) at −78 °C in the dark under N_2 was added *N*-bromosuccinimide (10.6 mg, 0.06 mmol, 1.2 equiv). The resulting mixture was stirred at the corresponding temperature and monitored by TLC. The reaction mixture was quenched with satd Na_2SO_3 (2.0 mL) at −78 °C and then was warmed to rt. The solution was diluted with water (3.0 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were washed with brine (5.0 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography to yield the corresponding product **7**.

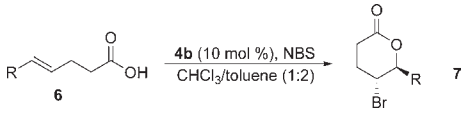
(10) Under the optimized conditions, there was no improvement in ee when $NsNH_2$ was added as an additive.

effect was not apparent in the present studies (Table 1, entries 3−5, 9, and 10). On the other hand, the 2-substituted aryl systems returned with lower enantioselectivities, which may be ascribed to the steric interaction with the olefinic moiety (Table 1, entries 6 and 8). In some cases, especially for the electron-deficient substrates, the reactions were sluggish at −78 °C. Nevertheless, these reactions could be brought to completion by simply raising the temperature and high yields, and enantioselectivities were still achieved (Table 1, entries 4, 8, and 13−17). Heteroaromatic substrates are also amendable to our protocol (Table 1, entries 11 and 12). The highest enantioselectivity (95% ee) was obtained with the 2-thiophene-substituted **7j**. The scalability of the protocol was tested at 2 mmol with success (Table 1, entry 2). The absolute stereoconfigurations of **7** were assigned on the basis of the X-ray crystallographic structure of **7a**.[8]

All of the substrates were found to be selective toward the generation of the 6-*endo* lactone **7** as the only products.[11] Such selectivity should not be taken for granted as demonstrated by a recent study reported by Denmark and co-workers.[12] In the series of Lewis bases in their study, some of the catalytic systems suffer from poor 6-*endo* to 5-*exo* selectivity. This result further demonstrates an additional selectivity (besides enantioselectivity) that our catalyst confers toward the bromolactonization of (*E*)-5-substituted pent-4-enoic acids.

Examination of the stereoconfiguration of **7a** from the X-ray study appears to indicate a chiral transition-state model that is consistent with our initial proposal for the enantioselective formation of γ-lactones, which involves a dual activation of NBS by the thiocarbamate.[5c] The key features of this proposed mechanism are the activation of the Br by a Lewis basic sulfur[13,14] and the activation of the carbonyl of succinimide by the N−H hydrogen-bonding interaction. A plausible mechanism is proposed in Scheme 3, in which alkenoic acid **6** may be captured and assembled into **A**,[15] where the ensuing nucleophilic attack by the carboxylate would lead to **7** with the designated stereoconfiguration. The significant enhancement in ee when using an *ortho*-OMe catalyst (e.g., Scheme 1, **4a** vs **4b**) further suggests that the methoxy substituent may serve as a steric screening group that can destabilize transition state **B** and hence minimize the formation of *ent*-**7**. A lower ee was obtained when the *cis*-olefinic acid **6q** was used (Table 1, entry 18), which could be ascribed to the less repulsion in transition state **B**.

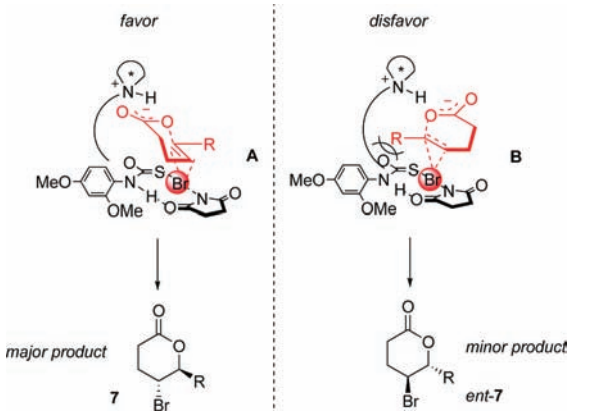
Table 1. Enantioselective Bromolactonization of **6**



entry[a]	acid	R	temp (°C)	time (h)	yield[b] (%), ee (%)
1	**6a**	Ph	−78	32	99, 91
2[c]	**6a**	Ph	−78	48	99, 91
3	**6b**	4-Me-C_6H_4	−78	21	99, 94
4	**6c**	4-*t*Bu-C_6H_4	−50	56	92, 80
5	**6d**	3-Me-C_6H_4	−78	80	99, 88
6	**6e**	2-Me-C_6H_4	−78	25	70, 64
7	**6f**	1-naphthyl	−78	40	95, 61
8	**6g**	2-naphthyl	−55	52	99, 86
9	**6h**	4-MeO-C_6H_4	−78	54	99, 81
10	**6i**	3-MeO-C_6H_4	−78	25	80, 94
11	**6j**	2-thienyl	−78	55	99, 95
12	**6k**	3-thienyl	−78	48	98, 86
13[d]	**6l**	4-CF_3O-C_6H_4	−40	48	90, 90
14	**6m**	4-Cl-C_6H_4	−50	42	99, 94
15	**6n**	3-Cl-C_6H_4	−50	54	64, 89
16[d]	**6o**	4-Br-C_6H_4	−40	48	85, 88
17	**6p**	4-F-C_6H_4	−30	14	99, 92
18[e]	**6q**	Ph	−78	48	44, 64

[a] Reactions were conducted with alkenoic acid **6** (0.05 mmol) with NBS (0.06 mmol). [b] Isolated yield. [c] Reaction was conducted on a 2 mmol scale. [d] A small amount of γ-lactone was detected. For details, see the Supporting Information. [e] **6q** is a *cis*-olefinic substrate and the corresponding 5-exo lactone was obtain as the only product.

Scheme 3. Plausible Mechanism of the Bromolactonization of **6**



In summary, we have developed an efficient and enantioselective bromolactonization of 1,2-disubstituted olefinic acids using a substoichiometric amount of aminothiocarbamate as the catalyst. This report represents the first asymmetric bromolactonization resulting in the formation of δ-lactones containing two stereogenic centers

(11) A small amount of 5-exolactone products was obtained when substrates **6n** and **6o** were used. For details, see the Supporting Information.

(12) Denmark, S. E.; Burk, M. T. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20655–20660.

(13) (a) Arduengo, A. J.; Burgess, E. M. *J. Am. Chem. Soc.* **1977**, *99*, 2376–2378. (b) Boyle, P. D.; Godfrey, S. M. *Coord. Chem. Rev.* **2001**, *223*, 265–299.

(14) An extensive review on Lewis base catalysis: Denmark, S. E.; Beuter, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560–1638.

(15) No ee was observed when the alcohol substrate corresponding to acid **6a** was used, which indicated that a substrate containing an acidic proton may be necessary.

with synthetically useful yields and enantioselectivities. The dramatic increase in ee with just the inclusion of a methoxy subsituent on the quinoline unit indicates a promising site for tuning the catalyst's reactivity profile. Further investigation to clarify the mechanistic picture, including the role to the MeO group on the quinoline, is underway.

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Supporting Information Available. Experimental procedures and additional information. This material is available free of charge via the Internet at http://pubs.acs.org.