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Enantioselective Bromoaminocyclization Using Amino−Thiocarbamate Catalysts

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Supporting Information

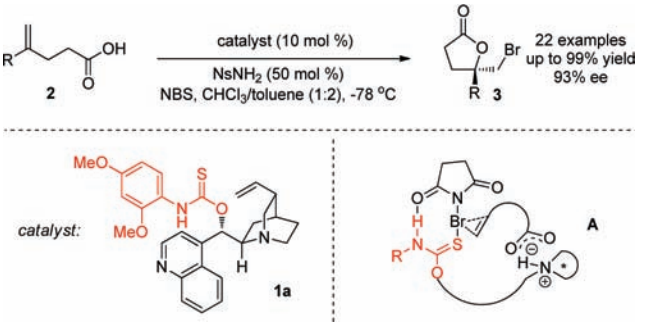
ABSTRACT: A facile and efficient enantioselective bromoaminocyclization of unsaturated sulfonamides has been developed using an amino−thiocarbamate catalyst. A range of enantioenriched pyrrolidines were prepared with up to 99% yield and 99% ee. The corresponding lactams could be obtained through oxidation of the pyrrolidines.

Intramolecular halocyclizations of olefins are important organic transformations.[1] Reactions involving halo-O-cyclizations (e.g., lactonization, etherification) and halo-N-cyclizations (e.g., lactamization, aminocyclization) have been well-documented.[1a,b] Among these reactions, haloaminocyclizations are of particular interest to many chemists, as the corresponding products (e.g., pyrrolidines) are essential units of many natural products and pharmaceuticals.[2] The development of the catalytic enantioselective versions of O-type halocyclization using achiral olefinic substrates and achiral halogen sources with substoichiometric amounts of catalysts has only emerged very recently.[3] For the electrophilic halo-N-cyclization, the catalytic asymmetric variant is still unknown to date.[4−6] Herein we describe an efficient, enantioselective, and organocatalytic bromoaminocyclization using an amino−thiocarbamate catalyst.

We recently reported the use of amino−thiocarbamate **1a** as a catalyst for the asymmetric bromolactonization of unsaturated carboxylic acids **2**, resulting in the formation of a number of lactones **3** with excellent ees (Scheme 1).[3i] A mechanism involving thiocarbamate−*N*-bromosuccinimide (NBS) and quinuclidine−carboxylic acid activation was proposed (Scheme 1, complex **A**). We reasoned that instead of the carboxylic acid moiety in **2**, a substrate with an acidic NH group could also interact with the quinuclidine in catalyst **1** to effect enantioselective haloaminocyclization.

To test this hypothesis, sulfonamide **4a** [R^1 = 4-$NO_2C_6H_4SO_2$ (4-Ns)], which contains an acidic NH group, was examined. The bromoaminocyclization of **4a** with NBS was carried out in CH_2Cl_2 at −78 °C, and various amino−thiocarbamate catalysts were screened (Table 1, entries 1−4). To our delight, the quinine-derived thiocarbamate **1d** was able to catalyze the reaction, affording pyrrolidine **5a** in excellent yield with appreciable enantioselectivity (Table 1, entry 4). The position of the nitro substituent in the aromatic system of **4a** was found to be important, as the reaction rate and enantioselectivity were reduced when substrates **4b** (R^1 = 3-Ns) and **4c** (R^1 = 2-Ns) were used (Table 1, entries 5 and 6). Other R^1 groups on substrate **4** were also examined. The Boc-amino

Scheme 1. Asymmetric Bromolactonization of 2



substrate **4d** did not offer any ee, although an excellent yield was obtained (Table 1, entry 7). Substrates **4e** (R^1 = *p*-Ts), **4f** (R^1 = $PhSO_2$), and **4g** (R^1 = 3,5-$F_2C_6H_3SO_2$) with relatively acidic N−H groups still did not offer good ees comparable to **4a** (Table 1, entries 8−10). The above-mentioned results illuminated the mechanistic picture to a certain extent: (1) the acidity of the N−H group may be important to the enantioselectivity, which can be attributed to the strength of the NH−quinuclidine interaction; (2) the bulkiness of the N substituent seems to be important to the substrate−catalyst interaction, as **4c** (R^1 = 2-Ns) returned almost no enantioselectivity while **4a** (R^1 = 4-Ns) offered up to 55% ee.

After the identification of an appropriate N substituent, the reaction was further optimized by varying the thiocarbamate moiety of catalyst **1d**. Similar to our previous observations in the bromolactonization, the electronic character of the aromatic substituent in the thiocarbamate moiety plays a crucial role in the enantioselectivity. A catalyst analogue of **1d** without the methoxy groups (**1e**, R = Ph) afforded a lower ee (Table 2, entry 1 vs Table 1, entry 4), and the highly electron-deficient pentafluorophenyl catalyst **1f** offered an even lower enantioselectivity (Table 2, entry 2). Replacing the two methoxy groups in **1d** with two methyl groups (**1g**) allowed us to obtain a comparable ee (Table 2, entry 3).

The significance of the 2-OMe and 4-OMe groups in catalyst **1d** was also examined through the use of catalysts **1h** and **1i** (Table 2, entries 4 and 5). It appears that the 2-OMe substitution plays a more dominant role in the enantioselectivity, which led us to investigate various ortho-substituted catalysts.

Catalyst **1j** containing a bulkier 2-*i*PrO group returned a measurable decrease in ee (Table 2, entry 5 vs 6). Interestingly, a dramatic increase in enantioselectivity was detected when 2,6-dimethoxy-substituted catalyst **1k** was used (Table 2, entry 7).

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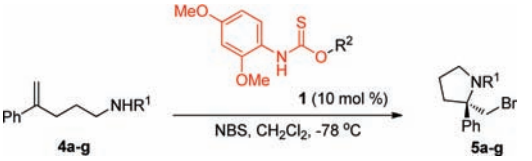
Table 1. Bromoaminocyclization of Unsaturated Amides 4a−g



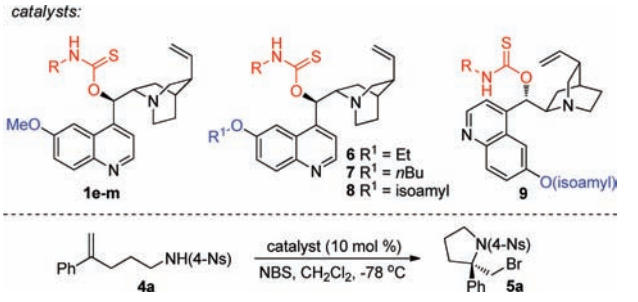
entry[a]	amide	R^1	catalyst	R^2	time (h)	yield (%),[b] ee (%)
1	**4a**	4-$NO_2C_6H_4SO_2$ (4-Ns)	**1a**	cinchonine	21	93, −45
2	**4a**	4-Ns	**1b**	cinchonidine	21	86, 41
3	**4a**	4-Ns	**1c**	quinidine	12	87, −48
4	**4a**	4-Ns	**1d**	quinine	12	98, 55
5	**4b**	3-$NO_2C_6H_4SO_2$ (3-Ns)	**1d**	quinine	72	78, 45
6	**4c**	2-$NO_2C_6H_4SO_2$ (2-Ns)	**1d**	quinine	72	78, 1
7	**4d**	Boc	**1d**	quinine	8	91, 0
8	**4e**	*p*-Ts	**1d**	quinine	17	87, 0
9	**4f**	$PhSO_2$	**1d**	quinine	17	63, 0
10	**4g**	3,5-$F_2C_6H_3SO_2$	**1d**	quinine	17	59, 10

[a] Reactions were carried out with amide **4** (0.1 mmol), catalyst **1** (0.01 mmol), and NBS (0.12 mmol) in CH_2Cl_2 (3 mL) in the absence of light. [b] Isolated yields.

When the 2,6-diethoxy-substituted catalyst **1m** was used, the ee increased to 79%, but the reaction rate was much lower (Table 2, entry 9). For the catalyst with a 2,4,6-trimethoxyphenyl group (**1l**), no significant ee change was observed (Table 2, entry 8 vs 7), which further suggests the importance of the ortho substituent in this catalyst system. To our surprise, searching for a better skeleton led us to discover that the 6-alkoxy group of the quinoline in catalyst **1** was a tunable handle, and the bulkier 6-*O*-isoamylquinoline system (catalyst **8**) allowed us to obtain a greater improvement in enantioselectivity (Table 2, entries 10−12). For the 2,6-dimethoxy-substituted catalyst **8a**, 85% yield and 80% ee were achieved, while better results (94% yield, 84% ee) were obtained when the 2,6-diethoxy-substituted catalyst **8b** was used. During these studies, the reaction yields ranged from moderate to excellent, while the enantioselectivities were significantly affected by different substituents in the catalysts. Overall, we noticed several important phenomena that may help us to gain further mechanistic insight into this kind of reaction: (1) Having a relatively more electron-rich aromatic system attached to the thiocarbamate appears to be important (Table 2, entry 1 vs 2). A possible consequence is the reduction in the NH acidity, which may be somewhat beneficial to the high enantioselectivity. (2) The bulkiness of the ortho substituent seems to be responsible for the high enantioselectivity. An explanation is that the ortho substituent may serve as a steric screening group. However, the reaction rate decreases with increasing bulkiness of the ortho substituent (cf. Scheme 2). (3) the 6-O substituent of the quinoline may also act as a steric screening group that affects the enantioselectivity.

Further variation of the solvent and temperature systematically allowed us to discover the optimal conditions: a 98% yield of **5a** with 95% ee was obtained when the reaction was conducted in $CHCl_3$ at −62 °C (Table 2, entry 14).[7,8] Enantioenriched *ent*-**5a** was furnished under the same conditions using catalyst **9** (Table 2, entry 15). Finally, the reaction was readily scalable without loss of efficiency and enantioselectivity (Table 2, entry 16).

Table 2. Amino−Thiocarbamate-Catalyzed Bromoaminocyclization



entry[a]	catalyst	R	time (h)	yield (%),[b] ee (%)
1	**1e**	Ph	14	62, 48
2	**1f**	C_6F_5	14	60, 33
3	**1g**	2,4-$Me_2C_6H_3$	14	96, 58
4	**1h**	4-$MeOC_6H_4$	16	66, 44
5	**1i**	2-$MeOC_6H_4$	16	78, 50
6	**1j**	2-*i*$PrOC_6H_4$	16	78, 46
7	**1k**	2,6-$(MeO)_2C_6H_3$	16	79, 71
8	**1l**	2,4,6-$(MeO)_3C_6H_2$	14	78, 70
9	**1m**	2,6-$(EtO)_2C_6H_3$	70	90, 79
10	**6**	2,6-$(MeO)_2C_6H_3$	16	90, 75
11	**7**	2,6-$(MeO)_2C_6H_3$	16	87, 78
12	**8a**	2,6-$(MeO)_2C_6H_3$	38	85, 80
13	**8b**	2,6-$(EtO)_2C_6H_3$	70	94, 84
14[c]	**8b**	**2,6-$(EtO)_2C_6H_3$**	**60**	**98, 95**
15	**9**	2,6-$(EtO)_2$-C_6H_3	36	98, −93
16[c,d]	**8b**	**2,6-$(EtO)_2C_6H_3$**	**72**	**97, 94**

[a] Reactions were carried out with sulfonamide **4a** (0.1 mmol), catalyst (0.01 mmol), and NBS (0.12 mmol) in CH_2Cl_2 (3 mL) in the absence of light. [b] Isolated yields. [c] Reaction was conducted in $CHCl_3$ (0.025 M) at −62 °C. [d] 2 mmol of **4a** was used.

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Scheme 2. Proposed Mechanism of the Bromoaminocyclization

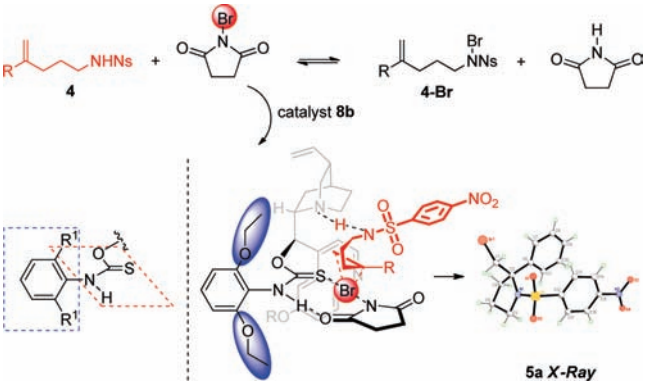
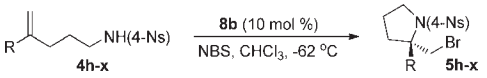


Table 3. Asymmetric Bromoaminocyclization of 4

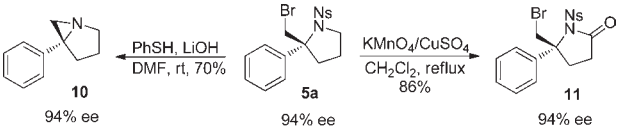


entry[a]	substrate	R	time (days)	yield (%),[b] ee (%)
1	**4h**	4-ClC_6H_4	3	98, 98
2	**4i**	4-FC_6H_4	3	99, 95
3	**4j**	4-$CF_3C_6H_4$	3	91, 99
4	**4k**	4-MeC_6H_4	3	62, 66
5	**4l**	4-$MeOC_6H_4$	3	61, 19
6	**4m**	3-ClC_6H_4	4	87, 97
7	**4n**	3-FC_6H_4	3	90, 96
8	**4o**	3-$CF_3C_6H_4$	4	95, 96
9	**4p**	3-MeC_6H_4	3	98, 86
10	**4q**	3-$MeOC_6H_4$	4	85, 95
11	**4r**	2-MeC_6H_4	4	82, 94
12	**4s**	3,5-$F_2C_6H_3$	6	66, 93
13	**4t**	2-naphthyl	4	93, 96
14	**4u**	H	3	99, 46
15	**4v**	methyl	4	96, 40
16	**4w**	cyclohexyl	3	96, 10
17	**4x**	*tert*-butyl	4	NR, –

[a] Reactions were carried out with sulfonamide **4** (0.1 mmol), **8b** (0.01 mmol), and NBS (0.12 mmol) in $CHCl_3$ (4 mL) in the absence of light. [b] Isolated yields.

Having identified the optimized conditions, we examined other substrates, and the scope of the bromoaminocyclization is indicated by the examples listed in Table 3. Generally, excellent enantioselectivities (95−99% ee) were obtained for electron-deficient 3-aryl- and 4-aryl-substituted substrates (Table 3, entries 1−3 and 6−8). The electron-deficient 3,5-difluorophenyl-substituted substrate **4s** also returned an excellent ee but required a longer reaction time to achieve a moderate yield (Table 3, entry 12). Substrates with electron-rich 4-aryl substituents, which were known to racemize the halonium intermediate, returned moderate to low ees (Table 3, entries 4 and 5).[8,9] However, the negative effects of the electron-rich aryl systems on the enantioselectivities were not apparent when the electron-donating group was at the meta or ortho position (Table 3, entries 9−11 and 13). Surprisingly, substrates with small-sized substituents (**4u**, R = H; **4v**, R = Me) offered moderate ees (Table 3, entries 14 and 15), while bulkier alkyl substituents led to slow and poorly selective reactions (Table 3, entries 16 and 17). In fact, only a trace amount of racemic **5x** was detected when the nonasymmetric bromoamination of **4x** was conducted at room temperature for 72 h; this could be attributed to the steric hindrance of the substrate. The absolute configurations were assigned on the basis of the structure of **5a**, which was confirmed unambiguously by an X-ray crystallographic study.[8]

Scheme 3. Asymmetric Syntheses of Aziridine 10 and Lactam 11



The reaction mechanism may follow our previous proposal that involves quinuclidine−amine and thiocarbamate−NBS pairs and allows the asymmetric delivery of Br (Scheme 2).[3i] The quinine-derived amino−thiocarbamate catalyst **1d** offered better ee for sulfonamide substrates, while the cinchonine-derived catalyst **1a** worked better for carboxylic acid substrates **2**; this could be ascribed to the fact that carboxylate (planar) and sulfonate (tetrahedral) adopt different coordination geometries.[8] In addition, we believe that the 2,6-disubstituted phenyl ring should rotate out of the conjugation with the thiocarbamate planar, and hence, the diethoxy groups can offer a better steric screening effect.[10] Since the existence of the aromatic units in the substrates and the catalysts seemed to contribute to the enantioselectivity, the aromatic interaction (potentially π-stacking) may exist in the transition state; investigations to obtain a clearer mechanistic picture are still in progress.

During the optimization studies, an interesting mechanistic clue came to light. When we attempted to optimize the reaction through the addition of $NsNH_2$, an additive that enhanced the ee but reduced the rate of the bromolactonization in our previous report, no measurable changes in reaction rate, yield, or ee were detected. We speculate that instead of $NsNH_2$, the NsNH moiety in substrate **4** could undergo Br exchange with NBS, and the resulting NsNBr moiety could serve as a "Br" sink.[3i,11] The generally slow reaction may be also ascribed to the existence of **4-Br** ,which could "trap" substrate **4**.[8,12]

Bromopyrrolidines **5** appear to be useful building blocks and synthetic intermediates. Upon removal of the Ns group in **5a** by treatment with PhSH and LiOH, the corresponding free amine was obtained and simultaneously cyclized to afford bicyclic aziridine **10** in 70% yield. In addition, enantioenriched lactam[13] **11** could be prepared efficiently by the oxidation of **5a** using $KMnO_4/CuSO_4$ (Scheme 3).[14]

We also explored other skeletons in addition to substrate **4**. Preliminary studies showed that substrate **12** could be transformed into the corresponding isoindoline **13** (99% yield, 88% ee) under the above-mentioned optimized conditions. Further oxidation of **13** with $KMnO_4/CuSO_4$ allow us to access isoindolinone **14**, whose isoindolinone ring system is a well-known pharmacophore (Scheme 4).[15]

In summary, we have developed an enantioselective organocatalytic bromoaminocyclization using an amino−thiocarbamate catalyst. To the best of our knowledge, this methodology represents the first example of a catalytic, enantioselective halo-N-cyclization that proceeds with synthetically useful yields and enantioselectivities. In this study, we also discovered that the ortho position of the

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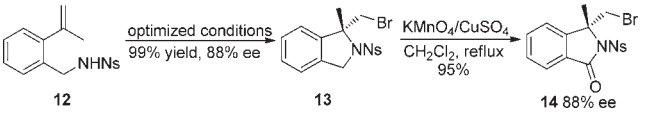
Scheme 4. Asymmetric Syntheses of Isoindoline 13 and Isoindolinone 14



aryl thiocarbamate and the 6-alkoxy group of the quinoline in the alkaloid skeleton are tunable, which allowed us to adopt different substrate skeletons. Further investigation of other applications, including piperidine formation, and studies of the mechanism are underway.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, spectroscopic data, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) (a) Rodríguez, F.; Fañanás, F. J. In *Handbook of Cyclization Reactions*; Ma, S., Ed; Wiley-VCH: New York, 2010; Vol. 4, pp 951−990. (b) Ranganathan, S.; Muraleedharan, K. M.; Vaish, N. K.; Jayaraman, N. *Tetrahedron* **2004**, *60*, 5273–5308. For selected examples of halocyclization reactions, see: (c) Snyder, S. A.; Treitler, D. S. *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) Cui, X.-L.; Brown, R. S. *J. Org. Chem.* **2000**, *65*, 5653–5658. (f) Hu, T.; Liu, K.; Shen, M.; Yuan, X.; Tang, Y.; Li, C. *J. Org. Chem.* **2007**, *72*, 8555–8558. (g) Denmark, S. E.; Burk, M. T. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20655–20660.

(2) (a) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435–446. (b) Felpin, F. X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693–3712. (c) Cheng, X. C.; Wang, Q.; Fang, H.; Xu, W. F. *Curr. Med. Chem.* **2008**, *15*, 374–385.

(3) For examples of catalytic enantioselective halo-O-cyclization reactions, see: (a) Kang, S. H.; Lee, S. B.; Park, C. M. *J. Am. Chem. Soc.* **2003**, *125*, 15748–15749. (b) Wang, M.; Gao, L. X.; Mai, W. P.; Xia, A. X.; Wang, F.; Zhang, S. B. *J. Org. Chem.* **2004**, *69*, 2874–2876. (c) Ning, Z.; Jin, R.; Ding, J.; Gao, L. *Synlett* **2009**, 2291–2294. (d) Chen, G.; Ma, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 8306–8308. (e) Denmark, S. E.; Burk, M. T.; Hoover, A. J. *J. Am. Chem. Soc.* **2010**, *132*, 1232–1233. (f) Whitehead, D. C.; Yousefi, R.; Jaganathan, A.; Borhan, B. *J. Am. Chem. Soc.* **2010**, *132*, 3298–3300. (g) Zhang, W.; Zheng, S.; Liu, N.; Werness, J. B.; Guzei, I. A.; Tang, W. *J. Am. Chem. Soc.* **2010**, *132*, 3664–3665. (h) Veitch, G. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2010**, *49*, 7332–7335. (i) Zhou, L.; Tan, C. K.; Jiang, X.; Chen, F.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 15474–15476. (j) Murai, K.; Matsushita, T.; Nakamura, A.; Fukushima, S.; Shimura, M.; Fujioka, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 9174–9177. (k) Hennecke, U.; Müller, C. H.; Fröhlich, R. *Org. Lett.* **2011**, *13*, 860–863. For closely related research on enantioselective halopolyene cyclization, see: (l) Sakakura, A.; Ukai, A.; Ishihara, K. *Nature* **2007**, *445*, 900–903.

(4) For an elegant intermolecular bromoamination of chalcones, see: Cai, Y.; Liu, X.; Hui, Y.; Jiang, J.; Wang, W.; Chen, W.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2010**, *49*, 6160–6164.

(5) For substrate-controlled steroselective halo-N-cyclizations, see: (a) Tamaru, Y.; Kawamura, S.; Tanaka, K.; Yoshida, Z. *Tetrahedron Lett.* **1984**, *25*, 1063–1066. (b) Tamaru, Y.; Kawamura, S.; Bando, T.; Tanaka, K.; Hojo, M.; Yoshida, Z. *J. Org. Chem.* **1988**, *53*, 5491–5501. (c) Williams, D. R.; Osterhout, M. H.; McGill, J. M. *Tetrahedron Lett.* **1989**, *30*, 1327–1330. (d) Jones, A. D.; Knight, D. W.; Hibbs, D. E. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1182–1203. (e) Verhelst, S. H. L.; Paez Martinez, B.; Timmer, M. S. M.; Lodder, G.; van der Marel, G. A.; Overkleeft, H. S.; van Boom, J. H. *J. Org. Chem.* **2003**, *68*, 9598–9603. (f) Shen, M.; Li, C. *J. Org. Chem.* **2004**, *69*, 7906–7909. (g) Wang, Y.-N.; Kattuboina, A.; Ai, T.; Banerjee, D.; Li, G. *Tetrahedron Lett.* **2007**, *48*, 7894–7898. (h) Yeung, Y.-Y.; Corey, E. J. *Tetrahedron Lett.* **2007**, *48*, 7567–7570.

(6) For applications of halo-N-cyclization reactions, see: (a) Kim, Y. G.; Cha, J. K. *Tetrahedron Lett.* **1989**, *30*, 5721–5724. (b) Yeung, Y.-Y; Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 6310–6311. (c) Beshore, D. C.; Smith, A. B., III. *J. Am. Chem. Soc.* **2007**, *129*, 4148–4149. (d) Beshore, D. C.; Smith, A. B., III. *J. Am. Chem. Soc.* **2008**, *130*, 13778–13789.

(7) Catalyst analogues, including carbamate, thiourea, and *N*-methyl thiocarbamate, were also examined, and they did not offer any enantioselectivity.

(8) Details are given in the Supporting Information.

(9) This phenomenon has appeared in some reports. For details, see refs 3f, 3i, and 4. For a related study, see: Ruasse, M. F.; Argile, A.; Dubois, J. E. *J. Am. Chem. Soc.* **1978**, *100*, 7645–7652.

(10) Although we were unable to obtain an X-ray structure of catalyst **8**, the crystal structure of **1a** shows that the aryl ring and the thiocarbamate are not coplanar. For the data for **1a**, please see ref 3i.

(11) (a) Catino, A. J.; Nichols, J. M.; Forslund, R. E.; Doyle, M. P. *Org. Lett.* **2005**, *7*, 2787–2790. (b) Chen, Z. G.; Wei, J. F.; Wang, M. Z.; Zhou, L. Y.; Zhang, C. J.; Shi, X. Y. *Adv. Synth. Catal.* **2009**, *351*, 2358–2368.

(12) The existence of **4-Br** was proved by a ^{1}H NMR study. However, attempts to isolate **4-Br** were unsuccessful.

(13) (a) Wei, L.; Malhotra, S. V. *Curr. Med. Chem.* **2010**, *17*, 234–253. (b) Dolbeare, K.; Pontoriero, G. F.; Gupta, S. K.; Mishra, R. K.; Johnson, R. L. *J. Med. Chem.* **2003**, *46*, 727–733. (c) Elison, C.; Lien, E. J.; Zinger, A. P.; Hussain, M.; Tong, G. L.; Golden, M. *J. Pharm. Sci.* **1971**, *60*, 1058–1062.

(14) Noureldin, N. A.; Zhao, D.; Lee, D. G. *J. Org. Chem.* **1997**, *62*, 8767–8772.

(15) (a) Comins, D. L.; Hiebel, A.-C. *Tetrahedron Lett.* **2005**, *46*, 5639–5642 and references therein. (b) Mertz, E.; Mattei, S.; Zimmerman, S. C. *Bioorg. Med. Chem.* **2004**, *12*, 1517–1526. (c) Mertz, E.; Mattei, S.; Zimmerman, S. C. *Org. Lett.* **2000**, *2*, 2931–2934.