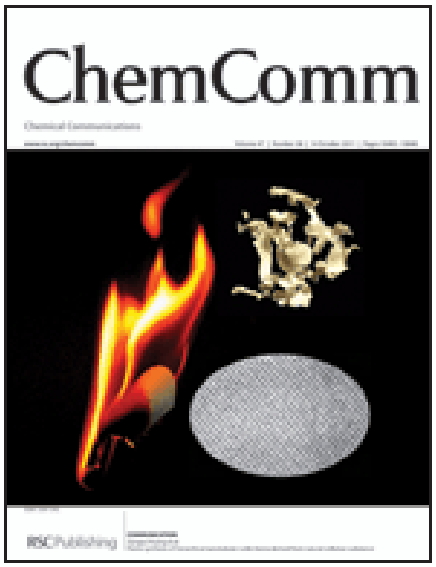

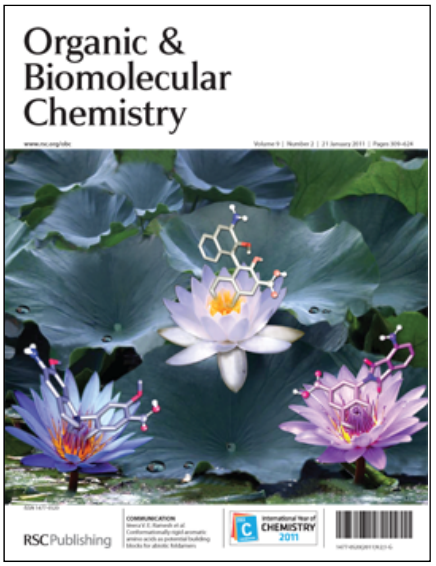

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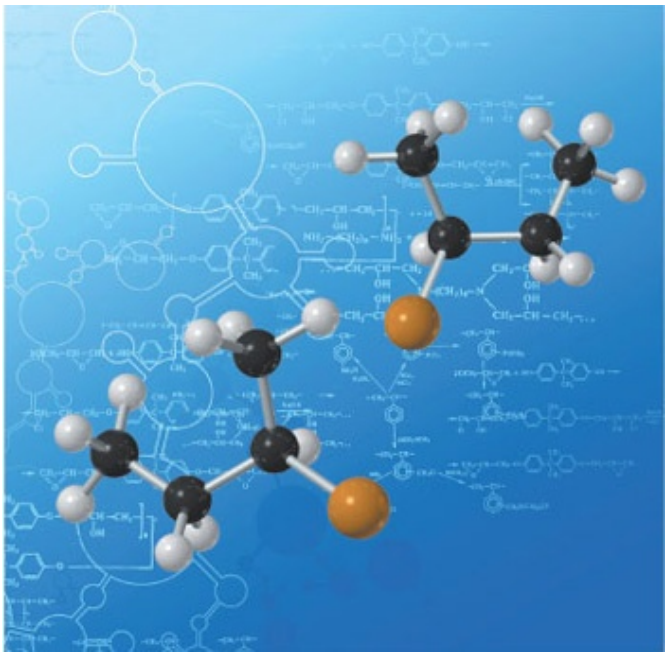

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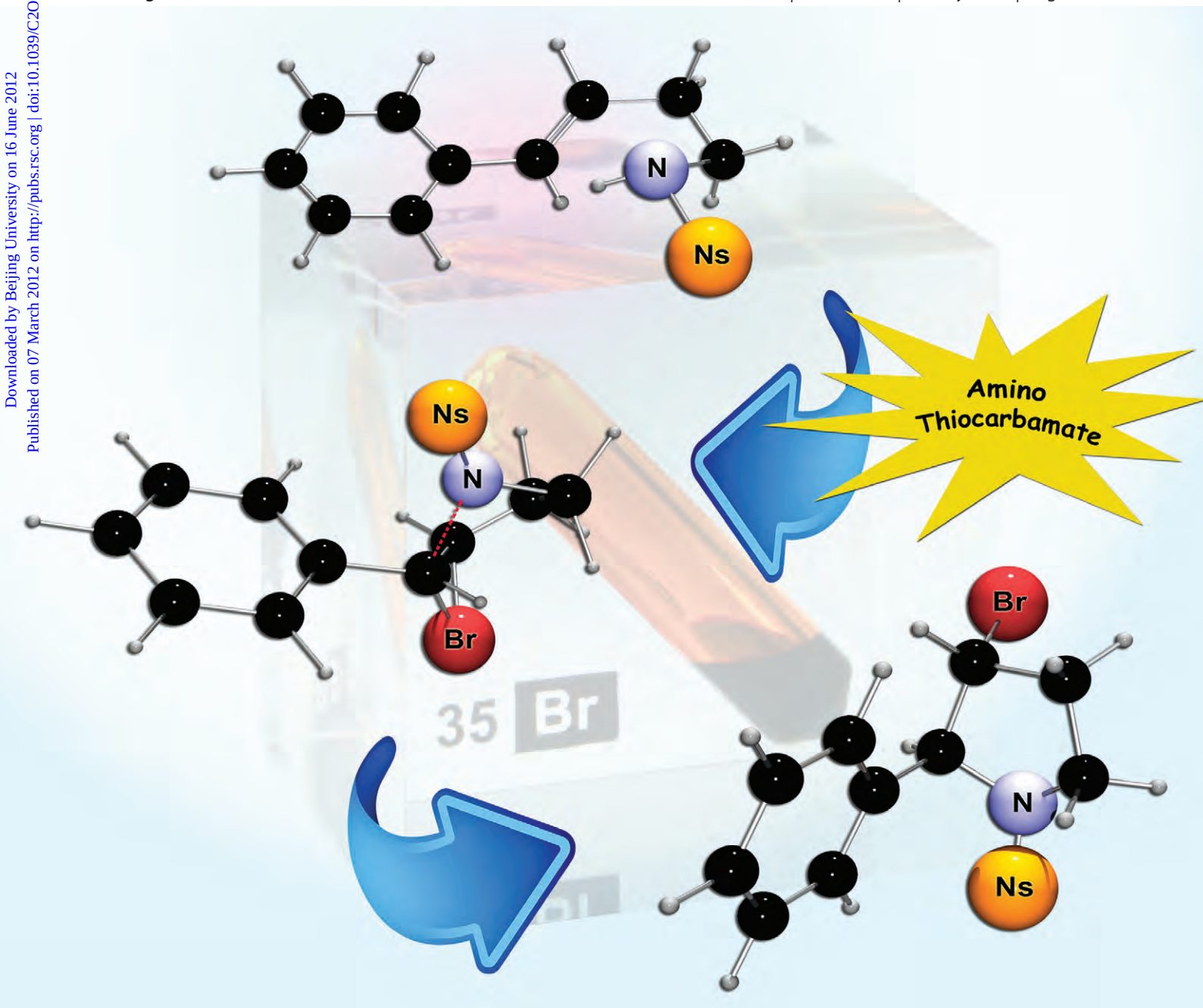

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A highly enantioselective approach towards 2-substituted 3-bromopyrrolidines

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COMMUNICATION

A highly enantioselective approach towards 2-substituted 3-bromopyrrolidines†‡

Jie Chen, Ling Zhou and Ying-Yeung Yeung*

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A facile and highly enantioselective approach towards 2-substituted 3-bromopyrrolidines has been developed. The process involves an amino-thiocarbamate catalyzed bromoaminocyclization of 1,2-disubstituted olefinic amides. The pyrrolidine products could readily be converted into other useful building blocks including a dihydropyrrole and a 2-substituted pyrrolidine.

Substituted pyrrolidine is the fundamental unit of many pharmaceutically relevant molecules.[1] For example, the synthesis of polyhydroxylated pyrrolidines has attracted considerable attention since these compounds possess interesting biological properties.[2]

Towards the synthesis of optically active substituted pyrrolidines, including polyhydroxylated pyrrolidines, 2-substituted 3-halopyrrolidine **1** and 2-substituted dihydropyrrolidine **2** (Fig. 1) appear to be attractive advanced intermediates. As a result, a number of catalytic protocols such as olefin metathesis of chiral allylic amines,[3] Heck reaction of 2-pyrrolidines,[4] and rhodium-catalyzed arylation of *N*-tosylalkylaldimines,[5] were reported on the construction of enantioenriched pyrrolidines.[6]

Halocyclization is an effective method for the construction of heterocyclic skeletons. For instance, cyclic amines can be synthesized through the halocyclization of olefinic amides.[7] As the beneficiaries of the recent breakthrough of the catalytic enantioselective co-halogenation reactions, several enantioenriched halo-heterocycles were prepared.[8]

However, the asymmetric synthesis of cyclic amines through catalytic halocyclization processes remains challenging. Very recently, we reported the use of amino-thiocarbamate as the catalyst in the asymmetric haloaminocyclization, resulting in the 1,1-disubstituted pyrrolidines **4** (Scheme 1, eqn (1)).[9] Shi and co-workers also reported the use of BINOL-derived phosphoric acid catalyst in the enantioselective synthesis of pyrrolidines **6**

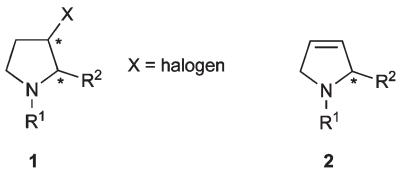
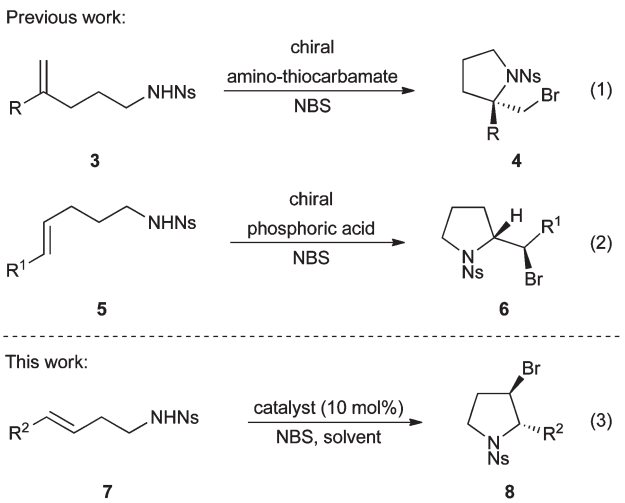


Fig. 1 2-Substituted pyrrolidines **1** and **2**.



Scheme 1 Enantioselective approaches toward pyrrolidines.

(Scheme 1, eqn (2)).[10] Although these pyrrolidines were achieved in high enantiopurity, further introduction of functionalities into the pyrrolidine ring system may not be straightforward since the halogen handles sit at the exocyclic positions.

We reasoned that the synthesis of pyrrolidine that contains a halogen in the pyrrolidine ring system should allow us to access many useful substituted pyrrolidines such as dihydropyrrole **2**. Herein we report the first case of bromoaminocyclization of *trans*-1,2-disubstituted olefinic amide **7**, resulting in the synthesis of 2-substituted 3-bromopyrrolidine **8**.

Initially, the cyclization of **7a** was investigated using various amino-thiocarbamate catalysts **9** (Table 1). After searching a number of 2,4-dimethoxyphenyl thiocarbamate catalysts, cinchonine-derived thiocarbamate **9a** gave the best ee of the desired product **8a** (Table 1, entries 1–4). Hence, the cinchonine core

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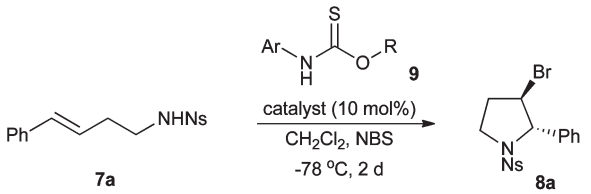
‡ Electronic supplementary information (ESI) available: NMR spectra, physical data, and crystallographic data. CCDC 859894 and 859895. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25327e

Table 1 Bromoaminocyclization of **7a** using various catalysts

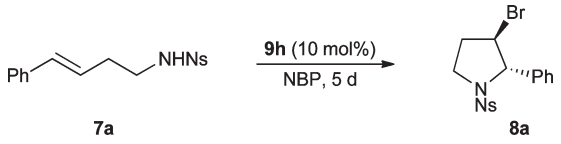


7a **8a**

Entry[a]	Catalyst	Ar	R	ee (%)[c]
1	**9a**	2,4-$(MeO)_2$-C_6H_3	Cinchonine	37
2	**9b**	2,4-$(MeO)_2$-C_6H_3	Cinchonidine	−30
3	**9c**	2,4-$(MeO)_2$-C_6H_3	Quinidine	17
4	**9d**	2,4-$(MeO)_2$-C_6H_3	Quinine	−18
5	**9e**	C_6H_5	Cinchonine	35
6	**9f**	4-MeO-C_6H_4	Cinchonine	50
7	**9g**	2,4,6-$(MeO)_3$-C_6H_2	Cinchonine	74
8	**9h**	2,6-$(EtO)_2$-C_6H_3	Cinchonine	81
9[b]	***9h***	*2,6-(EtO)$_2$-C$_6$H$_3$*	*Cinchonine*	*84*
10	**9i**	2,6-(nPrO)$_2$-C_6H_3	Cinchonine	70

[a] Reactions were carried out with olefinic amide **7a** (0.1 mmol), catalyst **9** (0.01 mmol), and NBS (0.12 mmol) in CH_2Cl_2 (3 mL) in the absence of light. The reactions showed complete consumption of starting materials. [b] NBP was used instead of NBS. [c] The ee was determined by chiral HPLC analysis with a UV detector. A isopropanol–hexane mixture was used as the mobile phase and the UV wavelength was 254 nm or 230 nm.

Table 2 Solvent screening of the bromoaminocyclization of **7a**

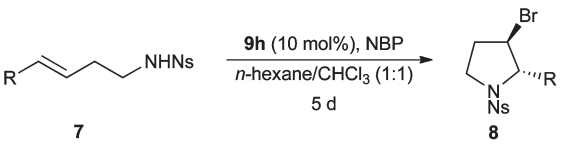


7a **8a**

Entry[a]	Solvent (ratio)	Temp (°C)	ee (%)
1	$PhCH_3$	−62	30
2	$PhCH_3$–$CHCl_3$ (3 : 1)	−78	48
3	$PhCH_3$–$CHCl_3$ (2 : 1)	−78	68
4	$PhCH_3$–$CHCl_3$ (1.5 : 1)	−78	74
5	$PhCH_3$–$CHCl_3$ (1 : 1)	−78	86
6	$PhCH_3$–$CHCl_3$ (1 : 1.5)	−78	88
7	*n-hexane–CHCl$_3$ (1 : 1)*	*−78*	*90*

[a] Reactions were carried out with olefinic amide **7a** (0.1 mmol), catalyst **9h** (0.01 mmol), and NBP (0.12 mmol) in solvent (3 mL) in the absence of light. The reactions showed complete consumption of starting materials.

Table 3 Substrate scope of the bromoaminocyclization of **7**



7 **8**

Entry[a]	Substrate	R	Temp (°C)	Yield[b] (%)	ee (%)
1	**7a**	C_6H_5	−78	91	90
2	**7b**	4-F-C_6H_4	−50	89	91
3	**7c**	4-Cl-C_6H_4	−60	93	91
4	**7d**	4-Br-C_6H_4	−50	90	86
5	**7e**	4-Me-C_6H_4	−78	95	85
6	**7f**	4-MeO-C_6H_4	−78	98	47
7	**7g**	3-Cl-C_6H_4	−50	56	77
8	**7h**	3-Me-C_6H_4	−78	96	87
9	**7i**	3-MeO-C_6H_4	−60	87	86
10	**7j**	2-Me-C_6H_4	−78	94	62
11	**7k**	2-Naphthyl	−50	97	88
12	**7l**	2-Thienyl	−50	96	70
13	**7m**	3-Thienyl	−50	84	84
14	**7n**	Et	−78	85	86

[a] Reactions were carried out with olefinic amide **7** (0.1 mmol), catalyst **9h** (0.01 mmol), and NBP (0.12 mmol) in n-hexane–$CHCl_3$ (1 : 1) (3 mL) in the absence of light. [b] Isolated yield.

was used for further optimization. Phenyl catalyst **9e** gave a 35% ee which was comparable to the 2,4-dimethoxyphenyl catalyst **9a** (Table 1, entry 5). Unexpectedly, the 4-methoxyphenyl catalyst **9f** offered a higher ee value than **9a** (Table 1, entry 6). A dramatic increase in ee was observed when the bulkier phenyl substituents were used. The use of catalyst **9h**, which contains a 2,6-diethoxyphenyl group, afforded **8a** in 81% ee (Table 1, entry 8). A slight improvement was observed when using *N*-bromophthalimide (NBP) instead of NBS (Table 1, entry 9). The use of a even bulkier 2,6-di-n-propoxyphenyl catalyst **9i**, however, gave a lower enantioselectivity (Table 1, entry 10).

Solvent screening was performed using the optimum catalyst **9h** (Table 2). A sharp decrease in ee was observed when changing the solvent from chloroform to toluene (Table 2, entry 1). In contrast, a toluene–chloroform solvent blend allowed us to further improve the enantioselectivity, and an 88% ee was obtained when using a toluene–chloroform (1 : 1.5) mixture (Table 2, entry 6). A slight enhancement of ee was achieved when using a n-hexane–chloroform co-solvent system (Table 2, entry 7).

After identifying the optimized conditions, other substrates were examined and the scope is indicated in Table 3. In general, the desired 2-substituted 3-bromopyrrolidines **8** were obtained in high reaction yields. Good to excellent ees were observed for most of the 4-substituted and 3-substituted phenyl substrates **7** (Table 3, entries 2–5, 7–9). The deteriorating effect of the electron-rich 4-methoxyphenyl group on the enantioselectivity, which has been observed in some studies, is also apparent for this class of substrate (Table 3, entry 6).[11] The sterically strained 2-methylphenyl substrate **7j** gave a moderate ee (Table 3, entry 10). Good ees were achieved for other systems including 2-naphthyl, 2-thienyl, and 3-thienyl substrates (Table 3, entries 11–13). Finally, alkyl substrate also worked well in this reaction (Table 3, entry 14).

The absolute configuration of the products **8** were assigned based on the X-ray crystallographic studies on pyrrolidines **8a** and **8m** (Fig. 2 and 3). Based on our previous proposed working model, a plausible transition state was showed in Fig. 4. The mechanistic picture may involve a charge pair between the quinuclidine and the sulfonamide, and a Lewis basic sulfur-activated bromonium system (Fig. 4).[12] The generally high enantioselectivity can potentially be explained by less steric repulsion that exists between the 2,6-diethoxyphenyl group and the R substituent of the substrate in **TS-1** over **TS-2**.

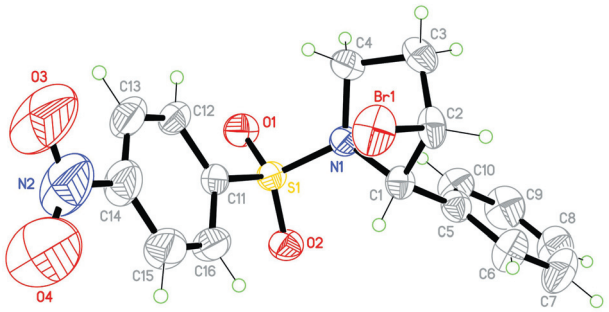


Fig. 2 X-ray structure of **8a**.

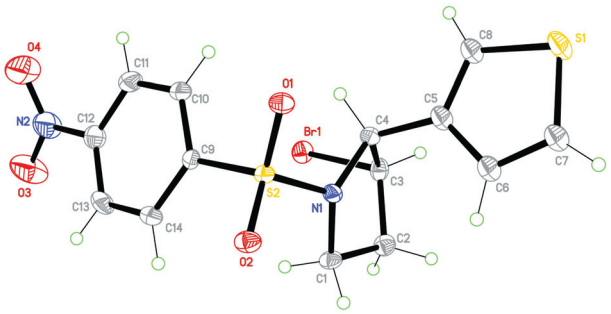


Fig. 3 X-ray structure of **8m**.

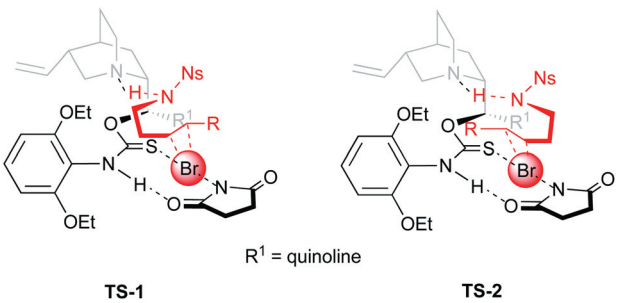
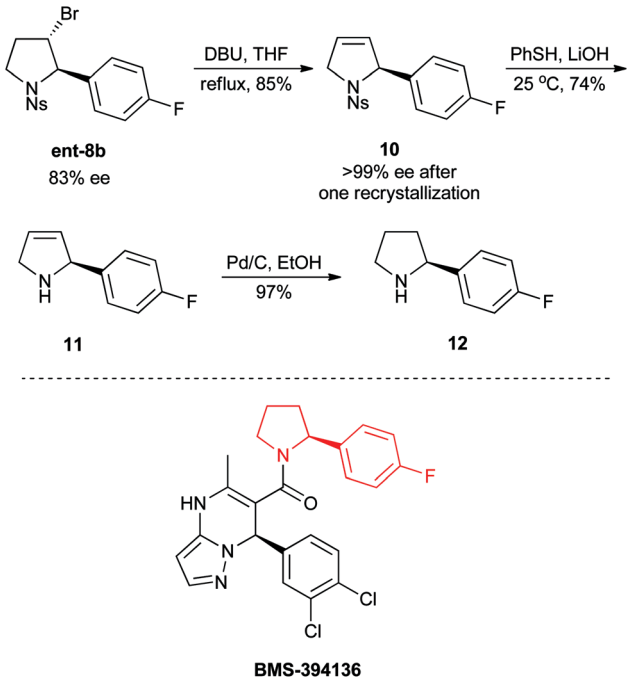


Fig. 4 Proposed mechanism.

We then attempted to modify the 2-substituted 3-bromopyrrolidines and synthesize some useful functional molecules. Thus, treatment of **ent-8b** with DBU gave dihydropyrrole **10** (Scheme 2). **ent-8b** was prepared using the pseudoenantiomeric catalyst of **9h**, *i.e.* using cinchonidine instead of cinchonine core. After one recrystallization, **10** was obtained in high enantiomeric excess (>99% ee). **10** is an advanced intermediate in the synthesis of some polyhydroxylated pyrrolidines such as a natural amino acid (−)-2,3-*trans*-3,4-*cis*-dihydroxyproline[13] and an azasugar (+)-2-(hydroxymethyl)pyrrolidine-3,4-diol.[14] Subsequent deprotection and hydrogenation of **10** afforded pyrrolidine **12** in good yield in which **12** is an essential unit of a selective Kv1.5 blocker BMS-394136.[15]

In summary, we reported the first case of enantioselective synthesis of 2-substituted 3-bromopyrrolidines **8** through a facile amino-thiocarbamate catalyzed bromoaminocyclization reaction. Pyrrolidines **8** are useful building blocks and can readily be converted into biologically relevant molecules.



Scheme 2 Enantioselective synthesis of **12**.

Acknowledgements

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Notes and references

1 (*a*) *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, vol. 7; (*b*) *Comprehensive Heterocyclic Chemistry II*, ed. A. Padwa, Pergamon Press, Oxford, UK, 1996, vol. 1A; (*c*) *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky and E. F. V. Scriven, Pergamon, Oxford, 1996, vol. 3; (*d*) N. Toyooka and H. Nemoto, in *New Methods for the Asymmetric Synthesis of Nitrogen Heterocycles*, ed. J. L. Vicario, D. Badia and L. Carrillo, 2005, p. 149; (*e*) D. Mal, B. Shome and B. K. Dinda, in *Heterocycles in Natural Product Synthesis*, ed. K. C. Majumdar and S. K. Chattopadhyay, 2011, p. 187; (*f*) A. D. Borthwick, *Med. Res. Rev.*, 2005, **25**, 427; (*g*) F.-X. Felpin and J. Lebreton, *Eur. J. Org. Chem.*, 2003, 3693.

2 (*a*) C.-H. Wong, L. Provencher, J. A. Porco, Jr., S.-H. Jung, Y.-F. Wang, L. Chen, R. Wang and D. H. Steensma, *J. Org. Chem.*, 1995, **60**, 1492; (*b*) G. Mikkelsen, T. V. Christensen, M. Bols, I. Lundt and M. R. Sierks, *Tetrahedron Lett.*, 1995, **36**, 6541; (*c*) M.-J. Blanco and F. J. Sardina, *J. Org. Chem.*, 1996, **61**, 4748; (*d*) Y. J. Kim, M. Kido, M. Bando and T. Kitahara, *Tetrahedron*, 1997, **53**, 7501; (*e*) M.-J. Blanco and F. J. Sardina, *J. Org. Chem.*, 1998, **63**, 3411; (*f*) A. Dondoni and D. Perrone, *Tetrahedron Lett.*, 1999, **40**, 9375; (*g*) B. W. Lee, I.-Y. Jeong, M. S. Yang, S. U. Choi and K. H. Park, *Synthesis*, 2000, 1305; (*h*) T. Sifferlen, A. Defoin, J. Streith, D. Le Nouen, C. Tarnus, I. Dosbaa and M.-J. Foglietti, *Tetrahedron*, 2000, **56**, 971; (*i*) M. Lombardo, S. Fabbroni and C. Trombini, *J. Org. Chem.*, 2001, **66**, 1264.

3 (*a*) F. A. Davis, T. Ramachandar, J. Chai and E. Skucas, *Tetrahedron Lett.*, 2006, **47**, 2743; (*b*) R. Martín, M. Alcón, M. A. Pericàs and A. Riera, *J. Org. Chem.*, 2002, **67**, 6896; (*c*) P. A. Evans and J. E. Robinson, *Org. Lett.*, 1999, **1**, 1929.

4 (*a*) J. Mazuela, O. Pàmies and M. Diéguez, *Eur. J. Org. Chem.*, 2010, 3434; (*b*) W.-Q. Wu, Q. Peng, D.-X. Dong, X.-L. Hou and Y.-D. Wu, *J. Am. Chem. Soc.*, 2008, **130**, 9717; (*c*) F. Ozawa and T. Hayashi, *J. Organomet. Chem.*, 1992, **428**, 267; (*d*) T. Tu, X.-L. Hou and L.-X. Dai, *Org. Lett.*, 2003, **5**, 3651.

5 Z. Cui, H.-J. Yu, R.-F. Yang, W.-Y. Gao, C.-G. Feng and G.-Q. Lin, *J. Am. Chem. Soc.*, 2011, **133**, 12394.

6 (*a*) A. Tsuhako, D. Oikawa, K. Sakai and S. Okamoto, *Tetrahedron Lett.*, 2008, **49**, 6529; (*b*) C. Jonasson, A. Horvath and J.-E. Backvall, *J. Am. Chem. Soc.*, 2000, **122**, 9600; (*c*) B. M. Trost, A. B. Pinkerton and D. Kremzow, *J. Am. Chem. Soc.*, 2000, **122**, 12007; (*d*) L. L. Anderson, J. Arnold and R. G. Bergman, *Org. Lett.*, 2004, **6**, 2519; (*e*) M. D'hooghe, W. Aelterman and N. De Kimpe, *Org. Biomol. Chem.*, 2009, **7**, 135; (*f*) M. Brichacek, M. N. Villalobos, A. Plichta and J. T. Njardarson, *Org. Lett.*, 2011, **13**, 1110; (*g*) J. L. Vicario, D. Badia, L. Carrillo, N. Ruiz and E. Reyes, *Targets Heterocycl. Syst.*, 2008, **12**, 302.

7 (*a*) M. Amjad and D. W. Knight, *Tetrahedron Lett.*, 2006, **47**, 2825; (*b*) A. D. Jones, D. W. Knight and D. E. Hibbs, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1182; (*c*) A. N. French, S. Bissmire and T. Wirth, *Chem. Soc. Rev.*, 2004, **33**, 354; (*d*) D. W. Knight, *Prog. Heterocycl. Chem.*, 2002, **14**, 19; (*e*) F. Rodríguez and F. J. Fañanás, in *Handbook of Cyclization Reactions*, ed. S. Ma, WILEY-VCH, New York, 2010, vol. 4, p. 10; (*f*) S. Ranganathan, K. M. Muraleedharan, N. K. Vaish and N. Jayaraman, *Tetrahedron*, 2004, **60**, 5273; (*g*) M. S. Lava, A. K. Banerjee and E. V. Cabrera, *Curr. Org. Chem.*, 2009, **13**, 720.

8 For some examples of catalytic enantioselective halo-cyclization reactions, see: Halo-*O*-cyclization: (*a*) S. H. Kang, S. B. Lee and C. M. Park, *J. Am. Chem. Soc.*, 2003, **125**, 900; (*b*) Z. Ning, R. Jin, J. Ding and L. Gao, *Synlett*, 2009, 2291; (*c*) D. C. Whitehead, R. Yousefi, A. Jaganathan and B. Borhan, *J. Am. Chem. Soc.*, 2010, **132**, 3298; (*d*) W. Zhang, S. Zheng, N. Liu, J. B. Werness, I. A. Guzei and W. Tang, *J. Am. Chem. Soc.*, 2010, **132**, 3664; (*e*) L. Zhou, C. K. Tan, X. Jiang, F. Chen and Y.-Y. Yeung, *J. Am. Chem. Soc.*, 2010, **132**, 15474; (*f*) G. E. Veitch and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2010, **49**, 7332; (*g*) K. Murai, T. Matsushita, A. Nakamura, S. Fukushima, M. Shimura and H. Fujioka, *Angew. Chem., Int. Ed.*, 2010, **49**, 9174; (*h*) G. Chen and S. Ma, *Angew. Chem., Int. Ed.*, 2010, **49**, 8306; (*i*) C. K. Tan, L. Zhou and Y.-Y. Yeung, *Org. Lett.*, 2011, **13**, 2738; (*j*) C. K. Tan, F. Chen and Y.-Y. Yeung, *Tetrahedron Lett.*, 2011, **52**, 4892; (*k*) C. K. Tan, L. Zhou and Y.-Y. Yeung, *Synlett*, 2011, 1335; (*l*) A. Castellanos and S. P. Fletcher, *Chem.–Eur. J.*, 2011, **17**, 5766; (*m*) S. A. Synder, D. S. Treitler and A. P. Brucks, *Aldrichimica Acta*, 2011, **44**, 27; (*n*) O. Lozano, G. Blessley, T. Martinez del Campo, A. L. Thompson, G. T. Giuffredi, M. Bettati, M. Walker, R. Borman and V. Gouverneur, *Angew. Chem., Int. Ed.*, 2011, **50**, 8105; (*o*) U. Hennecke, C. H. Müller and R. Fröhlich, *Org. Lett.*, 2011, **13**, 860; (*p*) S. E. Denmark and M. T. Burk, *Org. Lett.*, 2012, **14**, 256; (*q*) J. Chen, L. Zhou, C. K. Tan and Y.-Y. Yeung, *J. Org. Chem.*, 2012, **77**, 999; for halo-*N*-cyclization, see: (*r*) A. Jaganathan, A. Garzan, D. C. Whitehead, R. J. Staples and B. Borhan, *Angew. Chem., Int. Ed.*, 2011, **50**, 2593; for related intermolecular enantioselective halogenation reaction, see: (*s*) Y. Cai, X. Liu, Y. Hui, J. Jiang, W. Wang, W. Chen, L. Lin and X. Feng, *Angew. Chem., Int. Ed.*, 2010, **49**, 6160; (*t*) H. Li, F.-M. Zhang, Y.-Q. Tu, Q.-W. Zhang, Z.-M. Chen, Z.-H. Chen and J. Li, *Chem. Sci.*, 2011, **2**, 1839; (*u*) Y. Cai, X. Liu, J. Jiang, W. Chen, L. Lin and X. Feng, *J. Am. Chem. Soc.*, 2011, **133**, 5636; (*v*) Z.-M. Chen, Q.-W. Zhang, Z.-H. Chen, H. Li, Y.-Q. Tu, F.-M. Zhang and J.-M. Tian, *J. Am. Chem. Soc.*, 2011, **133**, 8818.

9 L. Zhou, J. Chen, C. K. Tan and Y.-Y. Yeung, *J. Am. Chem. Soc.*, 2011, **133**, 9164.

10 D. Huang, H. Wang, F. Xue, H. Guan, L. Li, X. Peng and Y. Shi, *Org. Lett.*, 2011, **13**, 6350.

11 The deteriorating effect of the *p*-methoxyphenyl group on the enantioselectivity has been reported in some studies. For references, see ref. 8.

12 The mechanistic proposal is based on our previous studies on the halocyclization reactions. For references, see: ref. 8*e*,*i*,*j*,*p* and 9. However, we cannot rule out the possibility that an alternative activation mode, which involves an amine-halogen activation, exists in the enantioselection state. The sole origin of the mechanism is still under active investigation.

13 (*a*) S. W. Taylor, J. H. Waite, M. M. Ross, J. Shabanowitz and D. F. Hunt, *J. Am. Chem. Soc.*, 1994, **116**, 10803; (*b*) F. Zanardi, L. Battistini, M. Nespi, G. Rassu, P. Spanu, M. Cornia and G. Casiraghi, *Tetrahedron: Asymmetry*, 1996, **7**, 1167 and references cited therein.

14 R. Kumareswaran and A. Hassner, *Tetrahedron: Asymmetry*, 2001, **12**, 3409 and references cited therein.

15 J. Lloyd, H. J. Finlay, W. Vacarro, T. Hyunh, A. Kover, R. Bhandaru, L. Yan, K. Atwal, M. L. Conder, T. Jenkins-West, H. Shi, C. Huang, D. Li, H. Sun and P. Levesque, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 1436.