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Enantioselective Bromocyclization of Allylic Amides Catalyzed by BINAP Derivatives

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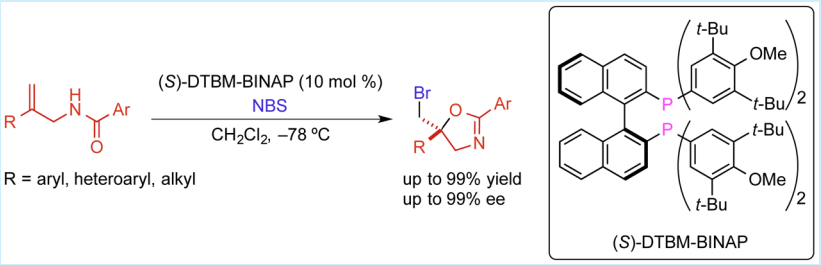
Supporting Information

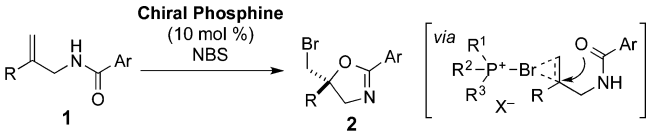


ABSTRACT: A highly enantioselective bromocyclization of allylic amides with *N*-bromosuccinimide (NBS) was developed with DTBM-BINAP as a catalyst, affording chiral oxazolines with a tetrasubstituted carbon center in high yield with up to 99% ee. By utilizing the bromo substituent as a handle, the obtained compounds were converted to synthetically useful chiral building blocks.

Electrophilic halofunctionalization of alkenes is a synthetically useful transformation, allowing for simultaneous incorporation of two heteroatom functionalities across nonactivated C−C double bonds. Further, stereodefined halogenated compounds are widely found among naturally occurring compounds and can serve as versatile chiral building blocks. Therefore, development of an asymmetric version of this reaction is of great interest,[1] and in recent years, there has been remarkable progress in catalytic asymmetric halogenation reactions using so-called intelligent chiral catalysts.[2−8] Among them, Lewis base catalysis is a straightforward approach for the generation of chiral halogenating agents, but is relatively underdeveloped, probably because racemization of halonium ion intermediates via olefin−olefin exchange reaction is considered to be rapid.[1d,9] In addition, soft Lewis bases (P, S, Se, etc.) are generally unstable under halogenation conditions. The application of Lewis base activation of a halogen to asymmetric reactions has been thought to be difficult, and such failures led to the development of bifunctional catalysts with a secondary interaction. Nonetheless, Yeung and co-workers recently developed optically active dialkyl sulfide and selenide as single-site Lewis base catalysts for asymmetric bromination of olefins with an alcohol or tosyl amide as a pendant nucleophile.[10] Also, Ishihara and co-workers used a chiral phosphoramidite as a stoichiometric promoter in a highly enantioselective iodocyclization of polyprenoids.[11] While phosphines (PR_3) and related compounds are potential promoters of electrophilic halogenation reactions,[11,12] their use in asymmetric catalysis has been less well studied. During our investigations on halogenation reactions,[13] we found that chiral phosphine compounds can catalyze the enantioselective delivery of halogen atoms. In this letter, we report a successful example of asymmetric halofunctionalization of olefins catalyzed by chiral phosphine compounds.

Bearing in mind that a chiral bromophosphonium ion is an active species, we aimed to develop an asymmetric bromocyclization of allylic amides **1** (Scheme 1). This reaction would

Scheme 1. Catalytic Asymmetric Bromocyclization of Allylic Amides



furnish chiral oxazoline compounds **2** with a tetrasubstituted stereogenic carbon center and was expected to be useful for synthesizing bioactive compounds. Also, these compounds would be useful as precursors to chiral 1,2-amino alcohols. Borhan and co-workers previously reported a chlorocyclization reaction with DCDPH (1,3-dichloro-5,5-diphenylhydantoin) catalyzed by $(DHQD)_2PHAL$, but their system was not applicable to the corresponding bromination reaction.[2c] Indeed, there is no precedent for such a bromination reaction in the literature, even though brominated products are amenable to various transformations. We initially designed quinine-triphenylphosphine conjugate **3**, since cinchona alkaloids were good catalysts for our asymmetric bromolactonization of prochiral cyclic dienes.[13] The chiral phosphine **3** promoted the reaction smoothly to give the product **2a** with appreciable enantioselectivity (Table 1, entry 1). This contrasted with the negligible

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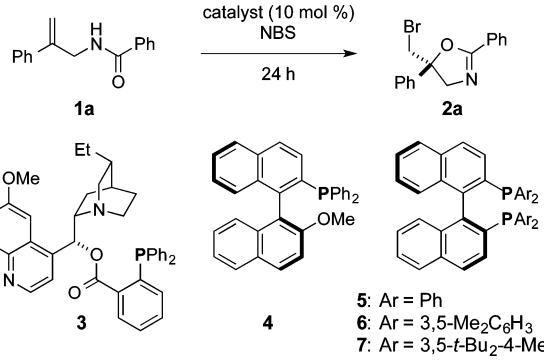
Table 1. Optimization of the Reaction Conditions



entry	cat.	solvent	temp (°C)	yield (%)[a]	ee (%)[b,c]
1	**3**	toluene	0	99	19
2	**4**	toluene	0	99	5
3	**5**	toluene	0	99	39
4	**6**	toluene	0	92	38
5	**7**	toluene	0	99	66
6	**7**	toluene	−60	95	73
7	**7**	CH_2Cl_2	−60	99	95
8	**7**	CH_2Cl_2	−78	99	99
9[d]	**7**	CH_2Cl_2	−78	99	99

[a]Isolated yield. [b]The ee was determined by chiral HPLC analysis. [c]The absolute configuration of **2a** was determined to be *R* after conversion (*vide infra*). [d]12 h. NBS = *N*-bromosuccinimide.

asymmetric induction observed with commercially available cinchona alkaloids as catalysts under identical conditions,[14] suggesting that the phosphine moiety has an important role in this reaction. Among various chiral phosphine compounds examined, only BINAPs showed promising asymmetric induction.[14] Since MOP (**4**) was totally ineffective for chirality control, the bisphosphine structure with axial chirality is likely essential for achieving high enantioselectivity. As shown in entries 3−5, DTBM-BINAP (**7**)[15] was found to be the best catalyst. While lowering the reaction temperature had little influence on the reaction efficiency, a change in solvent caused marked improvement of the ee without reducing the reaction rate (entries 6, 7). When the reaction was conducted in CH_2Cl_2 at −78 °C, the reaction was complete within 12 h, affording **2a** quantitatively with 99% ee (entry 9). As described later, the absolute stereochemistry of **2a** was determined to be *R* after the conversion.

It should be noted that other brominating reagents gave comparable enantioselectivity, regardless of their different structural and electronic properties (Scheme 2). This is distinct from other reported reactions, as the choice of halogenating reagent is generally crucial for high enantioselectivity. These results are suggestive of the generation of a similar chiral brominating species in all cases.

Having established the optimum reaction conditions, we next examined the scope of the reaction (Table 2). Our reaction displayed broad generality with respect to the R group, and various oxazoline compounds were accessible in high yield with excellent enantioselectivity.[16] Though the reaction of **1b** was less enantioselective, the ee was improved to 95% when the amino group was protected with a 4-bromobenzoyl group (entries 1, 2).[17] In line with previous reports, the reaction of an electron-rich 4-methoxyphenyl-substituted substrate gave an almost racemic mixture, probably because a carbocation intermediate would be generated (entry 3). In contrast, **1e**

Scheme 2. Effect of Brominating Reagents on Enantioselectivity

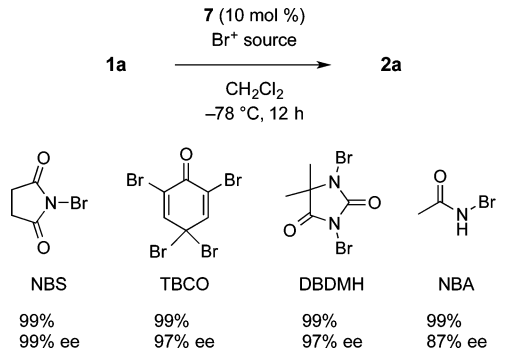
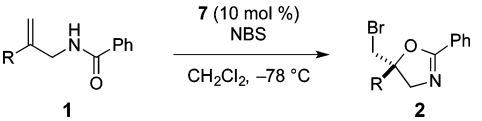


Table 2. Scope of the Bromocyclization of Allylic Amides



entry	R	2	time (h)	yield (%)[a]	ee (%)[b]
1	4-MeC_6H_4	**2b**	12	92	80
2[c]	4-MeC_6H_4	**2c**	24	91	95
3	4-MeOC_6H_4	**2d**	12	99	7
4	3-MeOC_6H_4	**2e**	12	85	93
5	2-naphthyl	**2f**	12	99	90
6	2-ClC_6H_4	**2g**	12	81	86
7	3-ClC_6H_4	**2h**	12	90	99
8	4-ClC_6H_4	**2i**	12	73	95
9	4-FC_6H_4	**2j**	12	99	97
10	4-BrC_6H_4	**2k**	12	99	98
11	3-F_3CC_6H_4	**2l**	12	94	99
12	3-NCC_6H_4	**2m**	24	89	97
13	4-NCC_6H_4	**2n**	24	95	98
14	3-pyridyl	**2o**	24	84	90
15[c]	3-thienyl	**2p**	24	97	91
16[c]	*c*-hexyl	**2q**	12	91	86
17[c]	*n*-octyl	**2r**	12	85	60
18[c]	H	**2s**	24	90	39
19[d]	Ph	**2a**	12	92	99
20[e]	Ph	**2a**	24	99	96

[a]Isolated yield. [b]The ee was determined by chiral HPLC analysis. [c]The Ph group of **1** was replaced with 4-BrC_6H_4 group. [d]1 mmol of **1a** was used. [e]5 mol % of **7** was used.

with a MeO group at the meta position underwent the desired reaction in a highly enantioselective manner (entry 4). A bulkier naphthyl-substituted amide was also a good substrate (entry 5). As for electron-withdrawing groups, any halogen group was tolerated, affording products with up to 99% ee (entries 6−11). Regardless of possible steric repulsion, a 2-chlorophenyl-substituted amide reacted without difficulty to give **2g** in good yield with 86% ee. Additionally, 3- and 4-cyano-substituted substrates were converted to the desired oxazoline compounds with 97 and 98% ee, respectively (entries 12, 13). Notably, our reaction was compatible with medicinally important heteroaromatic substructures such as a pyridine ring and a thiophene ring, and high enantioselectivity was observed in both cases (entries 14, 15). Alkyl-substituted amides **1q** and **1r** were also available for this reaction, affording the corresponding products with reasonably high enantiose-

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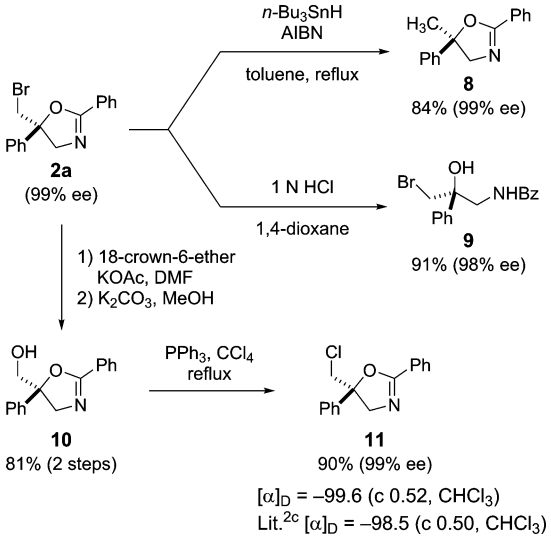
lectivity (entries 16, 17). However, terminal olefin **1s** was a difficult substrate, giving lower enantioselectivity (entry 18). Our reaction was easy to scale up, and **2a** was obtained in 92% yield with 99% ee on a 1 mmol scale (entry 19). Finally, the amount of the catalyst could be reduced to 5 mol % (entry 20). Although a longer reaction time was required, comparable results were obtained (24 h, 99%, 96% ee).

To confirm the synthetic utility of the reaction, we next examined the conversion of **2a** (Scheme 3). First, radical

Scheme 3. Conversion of 2a



debromination was successfully carried out to give **8** in 84% yield. Hydrolysis under acidic conditions gave chiral tertiary alcohol **9** without racemization. Additionally, the substitution reaction with an acetate anion, followed by solvolysis, delivered primary alcohol **10** in good yield. The obtained **10** was readily converted to **11** under conventional chlorination conditions, which enabled determination of the absolute configuration of **2a** by comparing the optical rotation with the reported value.[2c]

In summary, we have developed a highly enantioselective bromocyclization of allylic amides. This reaction provides chiral brominated oxazoline compounds, which can be converted to synthetically useful chiral building blocks. As mentioned above, achieving high enantioselectivity with Lewis base activation has been thought to be difficult. Therefore, we believe that our work will be informative in the discovery of other halogenation reactions, since various chiral phosphine compounds are known and readily available. Further investigations of the substrate scope and reaction mechanism will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Typical experimental procedure and characterization for all new products are presented in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews, see: (a) Chen, G.; Ma, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 8306. (b) Tan, C. K.; Zhou, L.; Yeung, Y.-Y. *Synlett* **2011**, 1335. (c) Castellanos, A.; Fletcher, S. P. *Chem.—Eur. J.* **2011**, *17*, 5766. (d) Denmark, S. E.; Kuester, W. E.; Burk, M. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 10938. (e) Hennecke, U. *Chem.—Asian J.* **2012**, *7*, 456. (f) Tan, C. K.; Yeung, Y.-Y. *Chem. Commun.* **2013**, *49*, 7985. (g) Murai, K.; Fujioka, H. *Heterocycles* **2013**, *87*, 763. (h) Cheng, Y. A.; Yu, W. Z.; Yeung, Y.-Y. *Org. Biomol. Chem.* **2014**, *12*, 2333.

(2) For selected examples of amine catalysts, see: (a) Haas, J.; Piguel, S.; Wirth, T. *Org. Lett.* **2002**, *4*, 297. (b) Whitehead, D. C.; Yousefi, R.; Jaganathan, A.; Borhan, B. *J. Am. Chem. Soc.* **2010**, *132*, 3298. (c) Jaganathan, A.; Garzan, A.; Whitehead, D. C.; Staples, R. J.; Borhan, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 2593. (d) Nicolaou, K. C.; Simmons, N. L.; Ying, Y.; Heretsch, P. M.; Chen, J. S. *J. Am. Chem. Soc.* **2011**, *133*, 8134. (e) Chen, Z.-M.; Zhang, Q.-W.; Chen, Z.-H.; Li, H.; Tu, Y.-Q.; Zhang, F.-M.; Tian, J.-M. *J. Am. Chem. Soc.* **2011**, *133*, 8818. (f) Li, H.; Zhang, F.-M.; Tu, Y.-Q.; Zhang, Q.-W.; Chen, Z.-M.; Chen, Z.-H.; Li, J. *Chem. Sci.* **2011**, *2*, 1839. (g) Jaganathan, A.; Staples, R. J.; Borhan, B. *J. Am. Chem. Soc.* **2013**, *135*, 14806. (h) Wilking, M.; Mück-Lichtenfeld, C.; Daniliuc, C. G.; Hennecke, U. *J. Am. Chem. Soc.* **2013**, *135*, 8133. (i) Zhang, Y.; Xing, H.; Xie, W.; Wan, X.; Lai, Y.; Ma, D. *Adv. Synth. Catal.* **2013**, *355*, 68. (j) Zhang, W.; Liu, N.; Schienebeck, C. M.; Zhou, X.; Izhar, I. I.; Guzei, I. A.; Tang, W. *Chem. Sci.* **2013**, *4*, 2652. (k) Yin, Q.; You, S.-L. *Org. Lett.* **2014**, *16*, 2426. (l) Jaganathan, A.; Borhan, B. *Org. Lett.* **2014**, *16*, 3616. (m) Li, L.; Su, C.; Liu, X.; Tian, H.; Shi, Y. *Org. Lett.* **2014**, *16*, 3728.

(3) For selected examples of Brønsted acids, see: (a) Huang, D.; Wang, H.; Xue, F.; Guan, H.; Li, L.; Peng, X.; Shi, Y. *Org. Lett.* **2011**, *13*, 6350. (b) Denmark, S. E.; Burk, M. T. *Org. Lett.* **2012**, *14*, 256. (c) Dobish, M. C.; Johnston, J. N. *J. Am. Chem. Soc.* **2012**, *134*, 6068. (d) Toda, Y.; Pink, M.; Johnston, J. N. *J. Am. Chem. Soc.* **2014**, *136*, 14734.

(4) For selected examples of hydrogen bonding catalysts, see: (a) Brindle, C. S.; Yeung, C. S.; Jacobsen, E. N. *Chem. Sci.* **2013**, *4*, 2100. (b) Murai, K.; Matsushita, T.; Nakamura, A.; Fukushima, S.; Shimura, M.; Fujioka, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 9174. (c) Murai, K.; Shimizu, N.; Fujioka, H. *Chem. Commun.* **2014**, *50*, 12530.

(5) For selected examples of bifunctional catalysts, see: (a) Zhang, W.; Zheng, S.; Liu, N.; Werness, J. B.; Guzei, I. A.; Tang, W. *J. Am. Chem. Soc.* **2010**, *132*, 3664. (b) Veitch, G. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2010**, *49*, 7332. (c) Paull, D. H.; Fang, C.; Donald, J. R.; Pansick, A. D.; Martin, S. F. *J. Am. Chem. Soc.* **2012**, *134*, 11128. (d) Tripathi, C. B.; Mukherjee, S. *Org. Lett.* **2014**, *16*, 3368. (e) Guo, B.; Fu, C.; Ma, S. *Chem. Commun.* **2014**, *50*, 4445. (f) Zhou, L.; Tan, C. K.; Jiang, X.; Chen, F.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 15474. (g) Zhou, L.; Chen, J.; Tan, C. K.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2011**, *133*, 9164. (h) Jiang, X.; Tan, C. K.; Zhou, L.; Yeung, Y.-Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 7771.

(6) For Lewis acid catalysts, see: (a) Inoue, T.; Kitagawa, O.; Saito, A.; Taguchi, T. *J. Org. Chem.* **1997**, *62*, 7384. (b) Kang, S. H.; Lee, S. B.; Park, C. M. *J. Am. Chem. Soc.* **2003**, *125*, 15748. (c) Ning, Z.; Jin, R.; Ding, J.; Gao, L. *Synlett* **2009**, 2291. (d) Huang, D.; Liu, X.; Li, L.; Cai, Y.; Liu, W.; Shi, Y. *J. Am. Chem. Soc.* **2013**, *135*, 8101. (e) Miles, D. H.; Veguillas, M.; Toste, F. D. *Chem. Sci.* **2013**, *4*, 3427. (f) Arai, T.; Sugiyama, N.; Masu, H.; Kado, S.; Yabe, S.; Yamanaka, M. *Chem. Commun.* **2014**, *50*, 8287.

(7) For phase transfer catalysts, see: (a) Rauniyar, V.; Lackner, A. D.; Hamilton, G. L.; Toste, F. D. *Science* **2011**, *334*, 1681. (b) Wang, Y.-

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Org. Lett. XXXX, XXX, XXX−XXX

M.; Wu, J.; Hoong, C.; Rauniyar, V.; Toste, F. D. *J. Am. Chem. Soc.* **2012**, *134*, 12928. (c) Xie, W.; Jiang, G.; Liu, H.; Hu, J.; Pan, X.; Zhang, H.; Wan, X.; Lai, Y.; Ma, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 12924.

(8) For a phosphate anion catalyst, see: Hennecke, U.; Müller, C. H.; Fröhlich, R. *Org. Lett.* **2011**, *13*, 860.

(9) (a) Brown, R. S.; Nagorski, R. W.; Bennet, A. J.; McClung, R. E. D.; Aarts, G. H. M.; Klobukowski, M.; McDonald, R.; Santarsiero, B. D. *J. Am. Chem. Soc.* **1994**, *116*, 2448. (b) Neverov, A. A.; Brown, R. S. *J. Org. Chem.* **1996**, *61*, 962. (c) Brown, R. S. *Acc. Chem. Res.* **1997**, *30*, 131.

(10) (a) Chen, F.; Tan, C. K.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2013**, *135*, 1232. (b) Ke, Z.; Tan, C. K.; Chen, F.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2014**, *136*, 5627.

(11) Sakakura, A.; Ukai, A.; Ishihara, K. *Nature* **2007**, *445*, 900.

(12) (a) Denmark, S. E.; Burk, M. T. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20655. (b) Sawamura, Y.; Nakatsuji, H.; Sakakura, A.; Ishihara, K. *Chem. Sci.* **2013**, *4*, 4181.

(13) (a) Ikeuchi, K.; Ido, S.; Yoshimura, S.; Asakawa, T.; Inai, M.; Hamashima, Y.; Kan, T. *Org. Lett.* **2012**, *14*, 6016. (b) Ikeuchi, K.; Hayashi, M.; Yamamoto, T.; Inai, M.; Asakawa, T.; Hamashima, Y.; Kan, T. *Eur. J. Org. Chem.* **2013**, 6789.

(14) See Supporting Information for details.

(15) DTBM-BINAP was purchased from WAKO Pure Chemical Industries Ltd. and used as received.

(16) The use of substrates with other substitution patterns such as *trans*-disubstituted olefins was found to be difficult in our present reaction system. See Supporting Information.

(17) In general, the ee was improved when electron-withdrawing groups were present at the para position of the benzamide group. Electron-donating groups reduced the ee. See Supporting Information.

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