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Enantioselective Bromocyclization of Olefins Catalyzed by Chiral Phosphoric Acid

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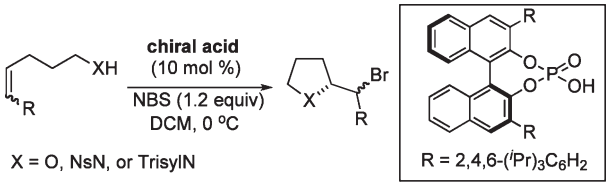
ABSTRACT



A chiral phosphoric acid catalyzed enantioselective bromocyclization of olefins is described. Various *cis*-, *trans*-, or trisubstituted γ-hydroxy-alkenes and γ-amino-alkenes can cyclize under the reaction conditions to give optically active 2-substituted tetrahydrofurans and tetrahydropyrroles in up to 91% ee.

Halogenation of olefins provides an effective approach to introduce two heteroatoms onto C−C double bonds.[1] In recent years, asymmetric halogenations have received considerable attention from chemists and significant progress has been made in this area.[2] A number of reagent-controlled enantioselective halogenations of olefins have been developed using chiral Lewis acids,[3,4] chiral amines,[5−7] or chiral sulfides.[8] A variety of catalytic systems have also been established with chiral Lewis acids,[9−12] chiral amines,[13−17] or chiral Pd(II) complexes[18] as the catalyst. As part of our general interest in functionalization of

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(1) For leading reviews on halogenation of olefins, see: (a) Dowle, M. D.; Davies, D. I. *Chem. Soc. Rev.* **1979**, *8*, 171. (b) Rodriguez, J.; Dulcère, J.-P. *Synthesis* **1993**, 1177. (c) Kitagawa, O.; Taguchi, T. *Synlett* **1999**, 1191. (d) Ranganathan, S.; Muraleedharan, K. M.; Vaish, N. K.; Jayaraman, N. *Tetrahedron* **2004**, *60*, 5273. (e) Li, G.; Kotti, S. R. S. S.; Timmons, C. *Eur. J. Org. Chem.* **2007**, 2745. (f) Rodríguez, F.; Fañanás, F. J. In *Handbook of Cyclization Reactions*; Ma, S., Ed.; Wiley-VCH: New York, 2010; Vol. 4, pp 951−990.

(2) For leading reviews on asymmetric halogenation of olefins, see: (a) French, A. N.; Bissmire, S.; Wirth, T. *Chem. Soc. Rev.* **2004**, *33*, 354. (b) Chen, G. F.; Ma, S. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2. (c) Castellanos, A.; Fletcher, S. P. *Chem.—Eur. J.* **2011**, *17*, 5766. (d) Tan, C. K.; Zhou, L.; Yeung, Y.-Y. *Synlett* **2011**, 1335.

(3) For leading references on reagent-controlled enantioselective halocyclization using chiral Lewis acids, see: (a) Kitagawa, O.; Hanano, T.; Tanabe, K.; Shiro, M.; Taguchi, T. *J. Chem. Soc., Chem. Commun.* **1992**, 1005. (b) Inoue, T.; Kitagawa, O.; Kurumizawa, S.; Ochiai, O.; Taguchi, T. *Tetrahedron Lett.* **1995**, *36*, 1479.

(4) For a leading reference on reagent-controlled intermolecular enantioselective halogenation of olefins using chiral Lewis acids, see: Snyder, S. A.; Tang, Z. Y.; Gupta, R. *J. Am. Chem. Soc.* **2009**, *131*, 5744.

(5) For leading references on reagent-controlled enantioselective halolactonization of olefins using chiral amines, see: (a) Grossman, R. B.; Trupp, R. J. *Can. J. Chem.* **1998**, *76*, 1233. (b) Haas, J.; Piguel, S.; Wirth, T. *Org. Lett.* **2002**, *4*, 297. (c) Wang, M.; Gao, L. X.; Yue, W.; Mai, W. P. *Synth. Commun.* **2004**, *34*, 1023. (d) Haas, J.; Bissmire, S.; Wirth, T. *Chem.—Eur. J.* **2005**, *11*, 5777. (e) Garnier, J. M.; Robin, S.; Rousseau, G. *Eur. J. Org. Chem.* **2007**, 3281.

(6) For leading references on reagent-controlled enantioselective fluorination of olefins using chiral amines, see: (a) Greedy, B.; Paris, J. M.; Vidal, T.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 3291. (b) Wang, M.; Wang, B. M.; Shi, L.; Tu, Y. Q.; Fan, C. A.; Wang, S. H.; Hu, X. D.; Zhang, S. Y. *Chem. Commun.* **2005**, 5580. (c) Wilkinson, S. C.; Lozano, O.; Schuler, M.; Pacheco, M. C.; Salmon, R.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2009**, *48*, 7083.

(7) For a leading reference on reagent-controlled enantioselective halocyclization of polyprenoids using chiral phosphoramidites, see: Sakakura, A.; Ukai, A.; Ishihara, K. *Nature* **2007**, *445*, 900.

(8) For a leading reference on reagent-controlled enantioselective intermolecular halogenation of olefins using chiral sulfides, see: Snyder, S. A.; Treitler, D. S.; Brucks, A. P. *J. Am. Chem. Soc.* **2010**, *132*, 14303.

(9) For leading references on Lewis acid catalyzed enantioselective iodocarbocyclization, see: (a) Inoue, T.; Kitagawa, O.; Ochiai, O.; Shiro, M.; Taguchi, T. *Tetrahedron Lett.* **1995**, *36*, 9333. (b) Inoue, T.; Kitagawa, O.; Saito, A.; Taguchi, T. *J. Org. Chem.* **1997**, *62*, 7384.

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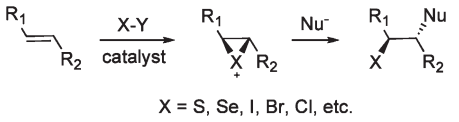
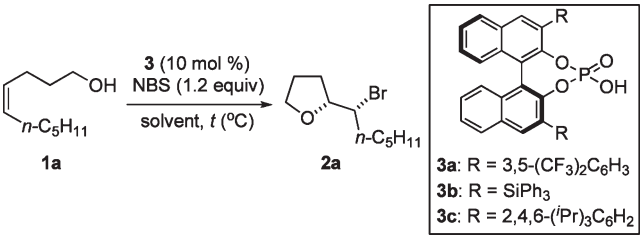
olefins,[19] recently we have been exploring various catalytic electrophilic addition reactions with olefins (Scheme 1).[20] Herein we wish to report our preliminary studies on chiral phosphoric acid catalyzed bromocyclization of γ-hydroxy-alkenes and γ-amino-alkenes.[21−23]

Scheme 1



Initial studies were carried out with *cis*-dec-4-en-1-ol (**1a**) as the substrate, NBS as the bromine source, and BINOL-derived chiral phosphoric acid as the catalyst. Among the catalysts examined, (*S*)-3,3′-bis(2,4,6-triisopropylphenyl)-BINOL phosphoric acid (**3c**)[24] was found to be the most effective catalyst for both conversion and ee (Table 1, entries 1, 2, 3). Among the solvents screened, DCM was found to be the solvent of choice

Table 1. Studies on Reaction Conditions[a]



entry	3	solvent	t (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	**3a**	DCM	−60	48	83	10
2	**3b**	DCM	−60	48	22	−68[d]
3	**3c**	DCM	−60	48	77	70
4	**3c**	$CHCl_3$	−60	48	74	57
5	**3c**	PhMe	−60	48	45	50
6	**3c**	DCM	−30	48	97	75
7	**3c**	**DCM**	**0**	**18**	**97**	**75**
8	**3c**	DCM	rt	6	93	71

[a] The reaction was carried out with **1a** (0.20 mmol), NBS (0.24 mmol), and **3** (0.02 mmol) in solvent (2.0 mL) unless otherwise stated. [b] Isolated yield. [c] Determined by chiral GC analysis. [d] The opposite enantiomer of product **2a** was obtained.

(Table 1, entries 3, 4, 5). For the current substrate (**1a**) and catalyst (**3c**), the reaction temperature did not have a large impact on the enantioselectivity (Table 1, entries 3, 6, 7, and 8). However, at higher temperature, the reaction gave a higher yield for the product and required a shorter

(10) For leading references on Lewis acid catalyzed enantioselective iodoetherification, see: (a) Kang, S. H.; Lee, S. B.; Park, C. M. *J. Am. Chem. Soc.* **2003**, *125*, 15748. (b) Kang, S. H.; Park, C. M.; Lee, S. B.; Kang, M. K. *Synlett* **2004**, 1279. (c) Kang, S. H.; Kang, S. Y.; Park, C. M.; Kwon, H. Y.; Kim, M. *Pure Appl. Chem.* **2005**, *77*, 1269. (d) Kwon, H. Y.; Park, C. M.; Lee, S. B.; Youn, J.-H.; Kang, S. H. *Chem.—Eur. J.* **2008**, *14*, 1023.

(11) For a leading reference on Lewis acid catalyzed enantioselective iodolactonization, see: Ning, Z. L.; Jin, R. Z.; Ding, J. Y.; Gao, L. X. *Synlett* **2009**, 2291.

(12) For leading references on Lewis acid catalyzed intermolecular enantioselective halogenation of olefins, see: (a) Sakurada, I.; Yamasaki, S.; Gottlich, R.; Iida, T.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 1245. (b) Cai, Y. F.; Liu, X. H.; Hui, Y. H.; Jiang, J.; Wang, W. T.; Chen, W. L.; Lin, L. L.; Feng, X. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 6160. (c) Cai, Y. F.; Liu, X. H.; Jiang, J.; Chen, W. L.; Lin, L. L.; Feng, X. M. *J. Am. Chem. Soc.* **2011**, *133*, 5636.

(13) For leading references on chiral amines catalyzed enantioselective halolactonization, see: (a) Wang, M.; Gao, L. X.; Mai, W. P.; Xia, A. X.; Wang, F.; Zhang, S. B. *J. Org. Chem.* **2004**, *69*, 2874. (b) Whitehead, D. C.; Yousefi, R.; Jaganathan, A.; Borhan, B. *J. Am. Chem. Soc.* **2010**, *132*, 3298. (c) Zhou, L.; Tan, C. K.; Jiang, X.; Chen, F.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 15474. (d) Veitch, G. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2010**, *49*, 7332. (e) Murai, K.; Matsushita, T.; Nakamura, A.; Fukushima, S.; Shimura, M.; Fujioka, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 9174. (f) Zhang, W.; Zheng, S.; Liu, N.; Werness, J. B.; Guzei, I. A.; Tang, W. P. *J. Am. Chem. Soc.* **2010**, *132*, 3664. (g) Yousefi, R.; Whitehead, D. C.; Mueller, J. M.; Staples, R. J.; Borhan, B. *Org. Lett.* **2011**, *13*, 608. (h) Tan, C. K.; Zhou, L.; Yeung, Y.-Y. *Org. Lett.* **2011**, *13*, 2738.

(14) For leading references on chiral amine catalyzed enantioselective halocyclization using amides or sulfonamides as nucleophiles, see: (a) Jaganathan, A.; Garzan, A.; Whitehead, D. C.; Staples, R. J.; Borhan, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 2593. (b) Zhou, L.; Chen., J.; Tan, C. K.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2011**, *133*, 9164.

(15) For leading references on chiral amine catalyzed enantioselective fluorination of olefins, see: (a) Fukuzumi, T.; Shibata, N.; Sugiura, M.; Nakamura, S.; Toru, T. *J. Fluorine Chem.* **2006**, *127*, 548. (b) Ishimaru, T.; Shibata, N.; Horikawa, T.; Yasuda, N.; Nakamura, S.; Toru, T.; Shiro, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4157. (c) Lozano, O.; Blessley, G.; Martinez del Campo, T.; Thompson, A. L.; Giuffredi, G. T.; Bettati, M.; Walker, M.; Borman, R.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2011**, *50*, 8105.

(16) For a leading reference on chiral amine catalyzed intermolecular enantioselective halogenation of olefins, see: Nicolaou, K. C.; Simmons, N. L.; Ying, Y.; Heretsch, P. M.; Chen, J. S. *J. Am. Chem. Soc.* **2011**, *133*, 8134.

(17) For leading references on chiral amine catalyzed enantioselective halogenation−rearrangement, see: (a) 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. (b) Li, H.; Zhang, F. M.; Tu, Y. Q.; Zhang, Q. W.; Chen, Z. M.; Chen, Z. H.; Li, J. *Chem. Sci.* **2011**, *2*, 1839. (c) Müller, C. H.; Wilking, M.; Rühlmann, A.; Wibbeling, B.; Hennecke, U. *Synlett* **2011**, 2043.

(18) For leading references on Pd(II) catalyzed intermolecular enantioselective halogenation of olefins, see: (a) El-Qisairi, A.; Hamed, O.; Henry, P. M. *J. Org. Chem.* **1998**, *63*, 2790. (b) Hamed, O.; Henry, P. M. *Organometallics* **1998**, *17*, 5184. (c) El-Qisairi, A.; Henry, P. M. *J. Organomet. Chem.* **2000**, *603*, 50. (d) El-Qisairi, A. K.; Qaseer, H. A.; Katsigras, G.; Lorenzi, P.; Trivedi, U.; Tracz, S.; Hartman, A.; Miller, J. A.; Henry, P. M. *Org. Lett.* **2003**, *5*, 439.

(19) (a) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488. (b) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 762.

(20) (a) Wang, H. N.; Huang, D. S.; Cheng, D. H.; Li, L. J.; Shi, Y. *Org. Lett.* **2011**, *13*, 1650. (b) Huang, D. S.; Wang, H. N.; Guan, H.; Huang, H.; Shi, Y. *Org. Lett.* **2011**, *13*, 1548.

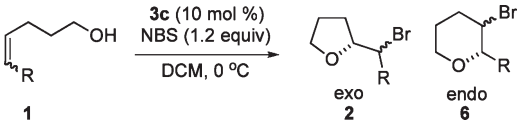
(21) For a leading reference on desymmetrization of *meso*-halonium ions using chiral sodium phosphate, see: Hennecke, U.; Müller, C. H.; Fröhlich, R. *Org. Lett.* **2011**, *13*, 860.

(22) For leading references on Lewis acid catalyzed halogenation of olefins, see: (a) Hajra., S.; Maji, B.; Karmakar, A. *Tetrahedron Lett.* **2005**, *46*, 8599. (b) Yeung, Y.-Y.; Gao, X.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 9644. (c) Hajra., S.; Bar, S.; Sinha, D.; Maji, B. *J. Org. Chem.* **2008**, *73*, 4320. (d) Yadav, J. S.; Subba Reddy, B. V.; Narasimha Chary, D.; Chandrakanth, D. *Tetrahedron Lett.* **2009**, *50*, 1136.

(23) For a leading reference on studies of stability of halonium ions, see: Denmark, S. E.; Burk, M. T.; Hoover, A. J. *J. Am. Chem. Soc.* **2010**, *132*, 1232.

(24) For leading reviews on chiral phosphoric acid catalyzed reactions, see: (a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (b) Terada, M. *Synthesis* **2010**, 1929. (c) Kampen, D.; Reisinger, C. M.; List, B. *Top. Curr. Chem.* **2010**, *291*, 395. (d) Zamfir, A.; Schenker, S.; Freund, M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2010**, *8*, 5262. (e) Yu, J.; Shi, F.; Gong, L.-Z. *Acc. Chem. Res.* **2011**, *44*, 1156.

Table 2. Enantioselective Bromoetherification of γ-Hydroxy-alkenes[a]



1 2 6

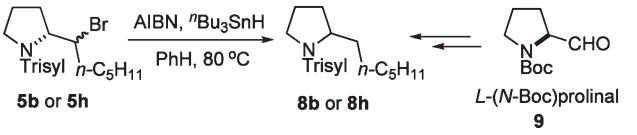
entry	substrates	products[b]	yield %[c]	ee %[d]
1	R = n-C_5H_{11}, **1a**	**2a**	95	75
2	R = Me, **1b**	**2b**	81	76
3	R = Et, **1c**	**2c**	96	81
4	R = n-C_9H_{19}, **1d**	**2d**	93	70
5	R = t-Bu, **1e**	**2e**	86	75
6	R = CH_2CH_2Ph, **1f**	**2f**	84	61
7[f]	**1g**	**2g**:**6g** = 11:1	63	71(**2g**) 71(**6g**)
8	R = n-C_5H_{11}, **1h**	**2h**:**6h** = 12:1	87	61(**2h**) 38(**6h**)
9	R = CH_2CH_2Ph, **1i**	**2i**:**6i** = 15:1	90	58(**2i**)[e] 55(**6i**)[e]
10	R = Cy, **1j**	**2j**:**6j** = 33:1	91	79(**2j**) 46(**6j**)
11	R = t-Bu, **1k**	**2k**	81	75
12	**1l**	**2l**	93	21
13[g]	**1m**	**6m**:**2m** = 5:1	45	2(**6m**) 78(**2m**)

[a] The reactions were carried out with **1** (0.50 mmol), NBS (0.60 mmol), and **3c** (0.05 mmol) in DCM (5.0 mL) at 0 °C for 18 h unless otherwise stated. [b] The ratio of isomers was by determined the ^{1}H NMR of the isolated products. The stereochemistry indicated represents the relative stereochemistry. [c] Isolated yield. [d] Determined by chiral GC analysis unless otherwise stated. [e] Determined by chiral HPLC analysis. [f] Reacted for 48 h. [g] Reacted for 72 h.

reaction time. Running the reaction in DCM at 0 °C appeared to be optimal for both yield and ee.

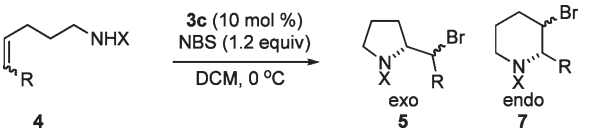
With the optimized reaction conditions in hand, various *cis*-, *trans*-, and trisubstituted γ-hydroxy-alkenes were subsequently investigated for the bromocyclization (Table 2, entries 1−12). In general, the reaction proceeded cleanly in all cases examined (63−96% yield). Only in a few cases (especially *trans*-olefins), there were small amounts of isomers (possibly 6-*endo* products) formed as judged by the ^{1}H NMR (Table 2, entries 7−10). Up to 81% ee was obtained for *cis*- and *trans*-γ-hydroxy-alkenes (**1a**−**k**) (Table 2, entries 1−11). In the case of the trisubstituted olefin examined, a much lower enantioselectivity (21% ee) was obtained (Table 2, entry 12). For phenyl substituted olefin **1m**, the 6-*endo* product was formed predominately with little enantioselectivity (Table 2, entry 13).

Scheme 2



5b or **5h** **8b** or **8h** *L*-(*N*-Boc)prolinal **9**

Table 3. Enantioselective Bromoaminocyclization of γ-Amino-alkenes[a]



4 5 7

entry	substrates	products[b]	yield %[c]	ee %[d]
1	X = Ns, **4a**	**5a**	90	90
2	X = Trisyl, **4b**	**5b**	76	89
3	X = Ns, **4c**	**5c**	81	87
4	X = Trisyl, **4d**	**5d**	85	91
5	R = Me, **4e**	**5e**	76	81
6[e]	R = t-Bu, **4f**	**5f**	36	90
7	R = CH_2CH_2Ph, **4g**	**5g**	62	85
8	R = n-C_5H_{11}, **4h**	**5h**	81	70
9	R = Me, **4i**	**5i**:**7i** = 14:1	72	58
10	R = CH_2CH_2Ph, **4j**	**5j**	65	56
11	R = Cy, **4k**	**5k**	70	63
12	**4l**	**5l**	59	74

[a] The reactions were carried out with **4** (0.30 mmol), NBS (0.36 mmol), and **3c** (0.03 mmol) in DCM (3.0 mL) at 0 °C for 72 h unless otherwise stated. [b] The ratio of isomers was determined by ^{1}H NMR of the isolated products. For entries 2 and 8, the absolute configurations were determined by comparing the optical rotations with L-proline derivatives after reductive debromination. For entries 1, 3−7, and 9−11, the absolute configurations were tentatively proposed by analogy. For entry 12, the stereochemistry indicated represents the relative stereochemistry. [c] Isolated yield. [d] Determined by chiral HPLC analysis. [e] Reacted for 120 h. Ns = 4-Nitrobenzenesulfonyl; Trisyl = 2,4,6-Triisopropylbenzenesulfonyl.

Further studies showed that various sulfonyl-protected γ-amino-alkenes were effective substrates. Generally higher enantioselectivities (81−91% ee) were obtained with *cis*-γ-amino-alkenes (Table 3, entries 1−7) as compared to *trans*-γ-amino-alkenes (56−70% ee) (Table 3, entries 8−11).

Good enantioselectivity (74% ee) was also obtained in the case of the trisubstituted olefin investigated (Table 3, entry 12). The effect of a sulfonyl protecting group on the enantioselectivity was found to be highly dependent on the substrate. For example, in some cases, similar ee's were obtained with 4-Ns and Trisyl protected substrates (Table 3, entry 1 vs 2, entry 3 vs 4). However, in other cases, much lower yields and ee's were obtained with the 4-Ns group as compared to the Trisyl group. The stereochemistry of **5d**, **5k**, and **5l** were determined by the X-ray structures (Figure 1 and Supporting Information). The absolute configurations of **5b** and **5h** were determined by comparing the optical rotations with L-proline derivatives after reductive debromination (Scheme 2).

While a precise understanding of the origin of the enantioselectivity awaits further study, a plausible transition state

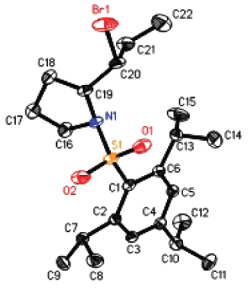


Figure 1. X-ray structure of compound **5d**.

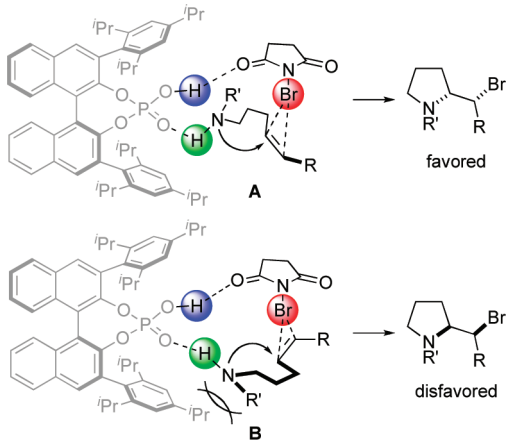


Figure 2. Proposed transition state model for bromoaminocyclization of *cis*-γ-amino-alkenes.

model is proposed in Figures 2 and 3. Phosphoric acid **3c** bearing both acidic and basic sites may act as a bifunctional catalyst to activate both NBS and the nucleophile via

(25) When NBS (1.0 equiv) was mixed with acid **3c** (1.0 equiv) in CD_2Cl_2, no obvious interaction between these two compounds was observed by ^1H NMR. Also little reaction was observed by ^1H NMR when the mixture was kept at 0 °C for 18 h.

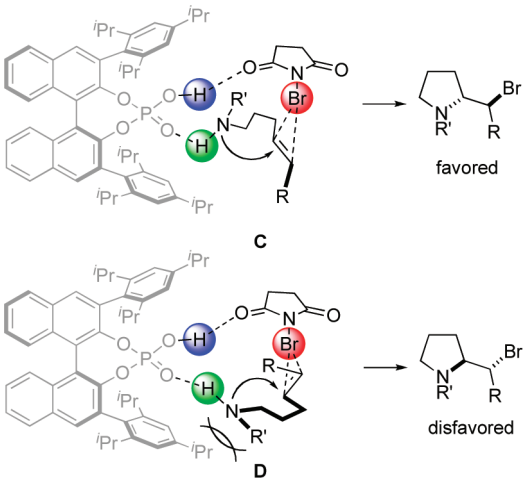


Figure 3. Proposed transition state model for bromoaminocyclization of *trans*-γ-amino-alkenes.

hydrogen bonding.[25] Based on the established configuration of **5b** (Table 3, entry 2), it appears that transition state **B** is disfavored for the *cis*-olefin probably due to the unfavorable interaction between the triisopropylphenyl group of the catalyst and the sulfonamide group of the substrate (Figure 2). For the *trans*-olefin, transition state **C** appears to be favored over **D** based on the determined configuration of **5h** (Table 3, entry 8) (Figure 3). Generally lower ee's obtained for *trans*-olefins than *cis*-olefins (Table 3) could be attributed to the unfavorable interaction between the triisopropylphenyl group of the catalyst and the R group of the substrate in transition state **C** as compared to **A**.

In summary, we have shown that various γ-hydroxy-alkenes and γ-amino-alkenes can undergo efficient bromocyclization using NBS as the bromine source and chiral phosphoric acid as the catalyst, giving 2-substituted tetrahydrofurans and tetrahydropyrroles with generally good yields and up to 91% ee. The current process illustrates the potential of chiral Brønsted acid catalyzed halogenation[21] as a viable approach to enantioselectively functionalize olefins. Further efforts will be devoted to better understanding the origin of enantioselectivity and developing more effective catalytic systems to improve the enantioselectivity and to expand the substrate scope as well as exploring other electrophilic addition reactions.

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Supporting Information Available. Experimental procedures, characterization data, X-ray structures (**5d**, **5k**, and **5l**), data for determination of enantiomeric excess, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.