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# Asymmetric Chlorocyclization of Indole-3-yl-benzamides for the Construction of Fused Indolines

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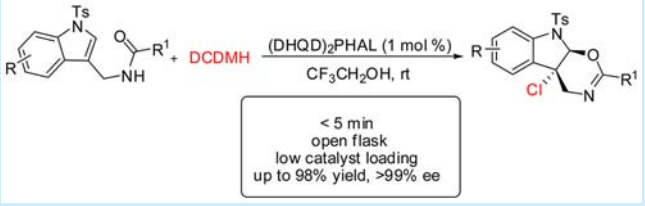
Supporting Information

**ABSTRACT:** $(DHQD)_2PHAL$ catalyzed enantioselective chlorocyclization of indole-3-yl-benzamides was realized. Fused indolines containing a continuous quaternary carbon center and tertiary carbon center were obtained in good yields with excellent enantioselectivity (up to 98% yield and >99% ee).




Asymmetric functionalization of indoles has attracted broad interest, as the resulting chiral indole or indoline scaffolds are important components of numerous biologically active alkaloids.[1] Asymmetric dearomatization of indole derivatives with an embedded nucleophile at either the C2 or C3 position provides a facile and efficient route to construct spiro or fused indoline motifs.[2] However, highly enantioselective synthesis of these privileged structures containing continuous chiral centers remains a formidable challenge and is therefore highly desirable.[3] On the other hand, asymmetric halofunctionalization of alkenes has become a research focus during the past several years.[4] The highly enantioselective halolactonization,[5] haloetherification,[6] haloaminocyclization,[7] halogenation/semipinacol rearrangement,[8] and other halofunctionalization reactions[9] of alkenes have been realized. Enantioselective halocyclization reactions of indoles are synthetically attractive as they could quickly construct enantioenriched spiro or fused indoline motifs with the simultaneous formation of a stereodefined C−X (Br, Cl, F) bond. However, highly enantioselective examples concerning asymmetric halocyclization of indole derivatives are rare.[10] This predicament could be ascribed to the very unstable chirality of the halonium ion intermediate, as a rapid olefin-to-olefin transfer process exists between the enantiomerically enriched halonium ion and electron-rich indole substrate.[11] We envisaged that regulation of the electronic property of the 2,3-double bond of indole might provide a benefit for the stereocontrol. This design has been applied in the enantioselective chloro- and bromocyclization of substituted indoles.[12] Herein we report the reaction between indole-derived benzamides with 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) under the catalysis of $(DHQD)_2PHAL$, providing an efficient synthesis of fused indolines with continuous stereogenic centers including a C−Cl bond containing a quaternary carbon center (Scheme 1).[13]

We began our studies by testing the reactions of indole-derived benzamide **1** with DCDMH under the catalysis of commercially available $(DHQD)_2PHAL$ (Table 1). To our delight, the reaction could proceed smoothly via a 6-endo-trig cyclization to generate a fused dihydrooxazine when a tosyl-protected indole substrate was utilized. The corresponding product could be obtained in a moderate yield with good enantioselectivity (65% yield, 86% ee, entry 1, Table 1). In contrast, indole-derived benzamides with a weaker electron-withdrawing group such as Ac or Boc gave much complicated reaction mixtures with only a trace of the desired product (entries 2−3, Table 1). These experimental results suggested that the electronic property of the 2,3-double bond of indole was critical for the reactivity and enantioselectivity. Screening of the solvents displayed that $CHCl_3$ and DCE could remarkably enhance the yield to 80% or 90%, respectively, without erosion of the enantioselectivity (87% ee, entries 4−5, Table 1). However, a dramatic decrease of the yield was observed when $CCl_4$ was utilized (entry 6, Table 1). The desired product was obtained in 23% yield in a racemic form when toluene was used, while no conversion was observed in THF (entries 7−8, Table 1). Further screening disclosed that polar solvents such as acetonitrile and alcohols gave better results in terms of yield and enantioselectivity (entries 9−12, Table 1). Excellent yields and enantioselectivity were obtained when MeOH or EtOH was utilized in an open flask (87−90% yields, 95−97% ee, entries 10−11, Table 1). Gratifyingly, an enantiopure product was obtained in 93% yield within 5 min when trifluoroethanol was employed as the solvent (entry 12, Table 1). The absolute configuration of the product was determined as (4*aS*, 9*aS*) by a

**Scheme 1. Chlorocyclization of Indoles Bearing an Embedded Nucleophile**

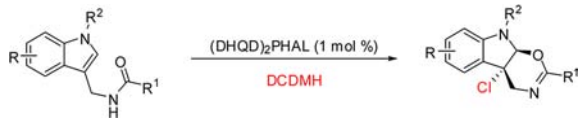



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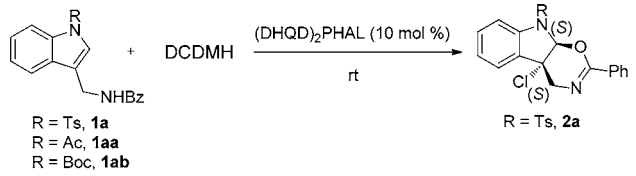
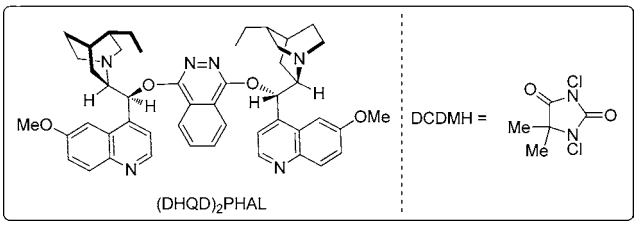
**Table 1. Optimization of the Reaction Conditions**[a]



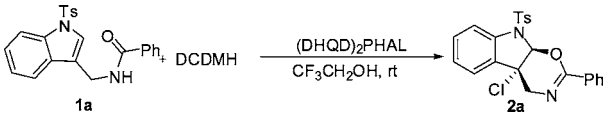

| entry | R | solvent | time | yield (%)[b] | *ee* (%)[c] |
|---|---|---|---|---|---|
| 1 | R = Ts, **1a** | DCM | 4 h | 65 | 86 |
| 2 | R = Ac, **1aa** | DCM | 4 h | trace | – |
| 3 | R = Boc, **1ab** | DCM | 4 h | trace | – |
| 4 | R = Ts, **1a** | $CHCl_3$ | 12 h | 80 | 87 |
| 5 | R = Ts, **1a** | DCE | 12 h | 90 | 87 |
| 6 | R = Ts, **1a** | $CCl_4$ | 24 h | 18 | 55 |
| 7 | R = Ts, **1a** | toluene | 24 h | 23 | 0 |
| 8 | R = Ts, **1a** | THF | 24 h | – | – |
| 9 | R = Ts, **1a** | $CH_3CN$ | 2 h | 82 | 80 |
| 10 | R = Ts, **1a** | MeOH | 5 min | 87 | 95 |
| 11 | R = Ts, **1a** | EtOH | 5 min | 90 | 97 |
| 12 | R = Ts, **1a** | $CF_3CH_2OH$ | <5 min | 93 | >99 |

[a]Reactions were performed with **1a** (0.1 mmol), DCDMH (0.15 mmol) and 10 mol % of $(DHQD)_2PHAL$ at rt in open flask. [b]Isolated yield. [c]Determined by HPLC.

single crystal X-ray analysis of enantiopure **2a** (see the Supporting Information).

Encouraged by the high efficiency of this chlorocyclization reaction, we further screened the loading of $(DHQD)_2PHAL$. As depicted in Table 2, when the catalyst loading was decreased

**Table 2. Evaluation of the Catalyst Loading**[a]



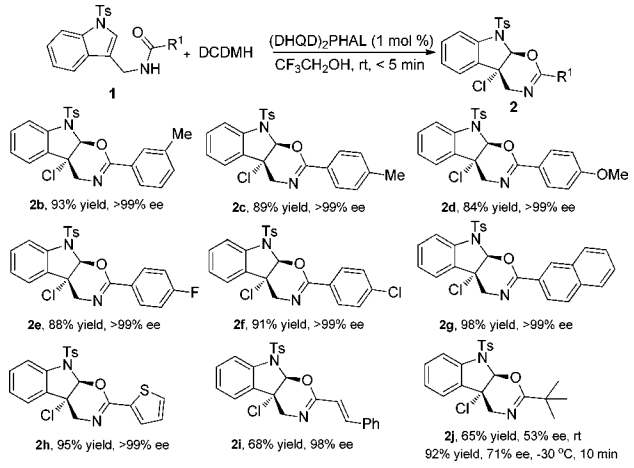

| entry | catalyst loading | time | yield (%)[b] | *ee* (%)[c] |
|---|---|---|---|---|
| 1 | 5 mol % | <5 min | 92 | >99 |
| 2 | 1 mol % | <5 min | 93 | >99 |
| 3 | 0.5 mol % | 5 min | 92 | 99 |
| 4 | 0.1 mol % | 10 min | 73 | 94 |
| 5 | 0.01 mol % | 1 h | 37 | 90 |

[a]Reactions were performed with **1a** (0.1 mmol), DCDMH (0.15 mmol) in $CF_3CH_2OH$ at rt in open flask. [b]Isolated yield. [c]Determined by HPLC.

from 10 to 0.5 mol %, comparable results were achieved. However, a further decrease of the catalyst loading led to a decline in terms of both yield and enantioselectivity. Finally, a 1 mol % catalyst loading was chosen for examination of the substrate scope.

With the optimized reaction conditions in hand, the scope of the dearomative chlorocyclization reaction was explored. The results are summarized in Scheme 2. Either an electron-

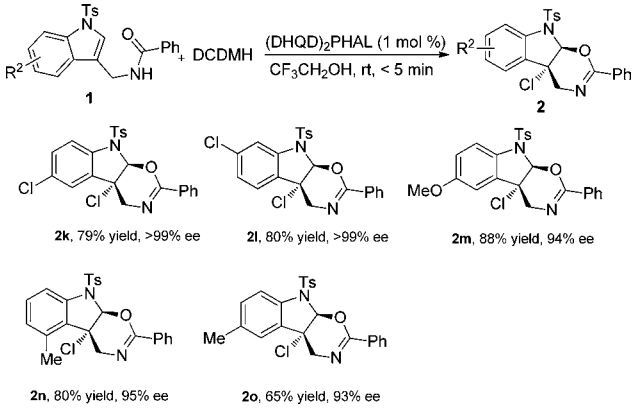
**Scheme 2. Substrate Scope for Chlorocyclization of 1**




donating group (**2b**–**2d**, 84–93% yields, >99% ee) or an electron-withdrawing group (**2e**–**2f**, 85–91% yields, >99% ee) at the *meta* or *para* position of the benzamide ($R^1$) was well tolerated. In addition, 2-naphthamide **1g** and **1h** containing heteroarylamide were also suitable substrates (**2g**–**2h**, 95–98% yields, >99% ee). In all cases, the corresponding products were obtained in enantiomerically pure forms. To be noted, cinnamamide **1i** was also well tolerated, leading to product **2i** in 68% yield and 98% ee. A decreased ee, however, was obtained when benzamide was replaced with pivalamide (**2j**, 65% yield, 53% ee). A decrease in the reaction temperature could slightly enhance the enantioselectivity to 71% ee.

To further broaden the substrate scope, substrates with various substituents on the indole core were also tested. As displayed in Scheme 3, substrates with a chlorine atom at either

**Scheme 3. Further Expansion of Substrate Scope**




the C5 or C6 position of indole were well tolerated, and the corresponding products could be obtained in good yields and excellent ee (**2k**–**2l**, 79–80% yields, >99% ee). When substrates with electron-donating groups on the indole core were tested, the enantioselectivity of the corresponding products remained at excellent levels (**2m**–**2o**, 65–88% yields, 93–95% ee).

To evaluate the practicality of this catalytic process, a gram-scale reaction was carried out. As shown in Scheme 4, product **2a** could be obtained in 81% yield and 99% ee.

In summary, we have developed a highly efficient method for the construction of fused indoline skeletons by enantioselective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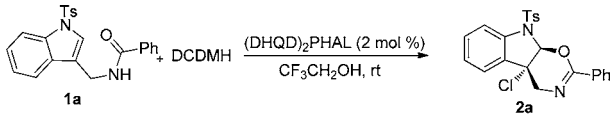
**Scheme 4. Gram-Scale Experiment**




1a
2.5 mmol, 1.01 g

2a
81% yield, 99% ee

chlorocyclization of indole derived benzamides. With 1 mol % $(DHQD)_2PHAL$, enantiopure products were obtained in excellent yields. The reaction features high efficiency, a low catalyst loading, and operationally simple procedures. Further synthetic application and mechanistic studies of this transformation are currently under investigation.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures and analysis data for all new compounds. 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) (a) Takano, S.; Ogasawara, K. *Alkaloids* **1989**, *36*, 225. (b) Dewick, P. M. *Medicinal Natural Products: A Biosynthetic Approach*, 2nd ed.; Wiley: New York, 2002; pp 1−507. (c) *Modern Alkaloids: structure, isolation, synthesis and biology*; Fattorusso, E., Taglialatela-Scafati, O., Eds; WILEY-VCH: Weinheim, 2008.

(2) For recent reviews, see: (a) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608. (b) Bartoli, G.; Bencivenni, G.; Dalpozzo, R. *Chem. Soc. Rev.* **2010**, *39*, 4449. (c) Zhuo, C.-X.; Zhang, W.; You, S.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 12662. For a recent highlight, see: (d) Loh, C. C. J.; Enders, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 46.

(3) For selected recent organocatalytic asymmetric reactions, see: (a) Zheng, C.; Lu, Y.; Zhang, J.; Chen, X.; Chai, Z.; Ma, W.; Zhao, G. *Chem.—Eur. J.* **2010**, *16*, 5853. (b) Xiao, Y.-C.; Wang, C.; Yao, Y.; Sun, J.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2011**, *50*, 10661. (c) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183. (d) Zhang, Z.; Antilla, J. C. *Angew. Chem., Int. Ed.* **2012**, *51*, 11778. For selected recent metal-catalyzed asymmetric reactions, see: (e) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314. (f) Barluenga, J.; Tudela, E.; Ballesteros, A.; Tomás, M. *J. Am. Chem. Soc.* **2009**, *131*, 2096. (g) Benkovics, T.; Guzei, I. A.; Yoon, T. P. *Angew. Chem., Int. Ed.* **2010**, *49*, 9153. (h) Repka, L. M.; Ni, J.; Reisman, S. E. *J. Am. Chem. Soc.* **2010**, *132*, 14418. (i) Zhu, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2012**, *134*, 10815. (j) Spangler, J. E.; Davies, H. M. L. *J. Am. Chem. Soc.* **2013**, *135*, 6802. (k) Xiong, H.; Xu, H.; Liao, S.; Xie, Z.; Tang, Y. *J. Am. Chem. Soc.* **2013**, *135*, 7851.

(4) For recent reviews on asymmetric halogenation of olefins, 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) Hennecke, U. *Chem.—Asian J.* **2012**, *7*, 456. (e) Denmark, S. E.; Kuester, W. E.; Burk, M. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 10938. (f) Murai, K.; Fujioka, H. *Heterocycles* **2013**, *87*, 763. (g) Tan, C. K.; Yeung, Y.-Y. *Chem. Commun.* **2013**, *49*, 7985. (h) Cheng, Y. A.; Yu, W. Z.; Yeung, Y.-Y. *Org. Biomol. Chem.* **2014**, *12*, 2333.

(5) For selected recent examples, see: (a) Whitehead, D. C.; Yousefi, R.; Jaganathan, A.; Borhan, B. *J. Am. Chem. Soc.* **2010**, *132*, 3298. (b) Zhou, L.; Tan, C. K.; Jiang, X.; Chen, F.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 15474. (c) Veitch, G. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2010**, *49*, 7332. (d) Murai, K.; Matsushita, T.; Nakamura, A.; Fukushima, S.; Shimura, M.; Fujioka, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 9174. (e) Zhang, W.; Zheng, S.; Liu, N.; Werness, J. B.; Guzei, I. A.; Tang, W. *J. Am. Chem. Soc.* **2010**, *132*, 3664. (f) Yousefi, R.; Whitehead, D. C.; Mueller, J. M.; Staples, R. J.; Borhan, B. *Org. Lett.* **2011**, *13*, 608. (g) Dobish, M. C.; Johnston, J. N. *J. Am. Chem. Soc.* **2012**, *134*, 6068. (h) Zhang, W.; Liu, N.; Schienebeck, C. M.; Decloux, K.; Zheng, S.; Werness, J. B.; Tang, W. *Chem.—Eur. J.* **2012**, *18*, 7296. (i) Jiang, X.; Tan, C. K.; Zhou, L.; Yeung, Y.-Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 7771. (j) Paull, D. H.; Fang, C.; Donald, J. R.; Pansick, A. D.; Martin, S. F. *J. Am. Chem. Soc.* **2012**, *134*, 11128. (k) Tungen, J. E.; Nolsøe, J. M. J.; Hansen, T. V. *Org. Lett.* **2012**, *14*, 5884. (l) Ikeuchi, K.; Ido, S.; Yoshimura, S.; Asakawa, T.; Inai, M.; Hamashima, Y.; Kan, T. *Org. Lett.* **2012**, *14*, 6016. (m) Murai, K.; Matsushita, T.; Nakamura, A.; Hyogo, N.; Nakajima, J.; Fujioka, H. *Org. Lett.* **2013**, *15*, 2526. (n) Wilking, M.; Mück-Lichtenfeld, C.; Daniliuc, C. G.; Hennecke, U. *J. Am. Chem. Soc.* **2013**, *135*, 8133.

(6) For selected examples, see: (a) Kang, S. H.; Lee, S. B.; Park, C. M. *J. Am. Chem. Soc.* **2003**, *125*, 15748. (b) Hennecke, U.; Müller, C. H.; Fröhlich, R. *Org. Lett.* **2011**, *13*, 860. (c) Huang, D.; Wang, H.; Xue, F.; Guan, H.; Li, L.; Peng, X.; Shi, Y. *Org. Lett.* **2011**, *13*, 6350. (d) Denmark, S. E.; Burk, M. T. *Org. Lett.* **2012**, *14*, 256. (e) Zeng, X.; Miao, C.; Wang, S.; Xia, C.; Sun, W. *Chem. Commun.* **2013**, *49*, 2418. (f) Zhao, Y.; Jiang, X.; Yeung, Y.-Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 8597.

(7) For selected examples, see: (a) Zhou, L.; Chen, J.; Tan, C. K.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2011**, *133*, 9164. (b) Bovino, M. T.; Chemler, S. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 3923. (c) Chen, F.; Tan, C. K.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2013**, *135*, 1232. (d) Brindle, C. S.; Yeung, C. S.; Jacobsen, E. N. *Chem. Sci.* **2013**, *4*, 2100. (e) Huang, D.; Liu, X.; Li, L.; Cai, Y.; Liu, W.; Shi, Y. *J. Am. Chem. Soc.* **2013**, *135*, 8101.

(8) For selected examples, 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) Müller, C. H.; Wilking, M.; Rühlmann, A.; Wibbeling, B.; Hennecke, U. *Synlett* **2011**, 2043. (c) Li, H.; Zhang, F.-M.; Tu, Y.-Q.; Zhang, Q.-W.; Chen, Z.-M.; Chen, Z.-H.; Li, J. *Chem. Sci.* **2011**, *2*, 1839. (d) Romanov-Michailidis, F.; Guénée, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 9266. (e) Yin, Q.; You, S.-L. *Org. Lett.* **2014**, *16*, 1810.

(9) For selected examples, see: (a) Cai, Y.; Liu, X.; Hui, Y.; Jiang, J.; Wang, W.; Chen, W.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2010**, *49*, 6160. (b) Rauniyar, V.; Lackner, A. D.; Hamilton, G. L.; Toste, F. D. *Science* **2011**, *334*, 1681. (c) Cai, Y.; Liu, X.; Jiang, J.; Chen, W.; Lin, L.; Feng, X. *J. Am. Chem. Soc.* **2011**, *133*, 5636. (d) Nicolaou, K. C.; Simmons, N. L.; Ying, Y.; Heretsch, P. M.; Chen, J. S. *J. Am. Chem. Soc.* **2011**, *133*, 8134. (e) Alix, A.; Lalli, C.; Retailleau, P.; Masson, G. *J. Am. Chem. Soc.* **2012**, *134*, 10389. (f) Wang, Y.-M.; Wu, J.; Hoong, C.; Rauniyar, V.; Toste, F. D. *J. Am. Chem. Soc.* **2012**, *134*, 12928. (g) Tripathi, C. B.; Mukherjee, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 8450. (h) Zhang, W.; Liu, N.; Schienebeck, C. M.; Zhou, X.; Izhar, I. I.; Guzei, I. A.; Tang, W. *Chem. Sci.* **2013**, *4*, 2652.

(10) (a) 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. For an enantioselective fluorinative dearomatization of phenols, see: (b) Phipps, R. J.; Toste, F. D. *J. Am. Chem. Soc.* **2013**, *135*, 1268.

(11) (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) Denmark, S. E.; Burk, M. T.; Hoover, A. J. *J. Am. Chem. Soc.* **2010**, *132*, 1232.

(12) (a) Yin, Q.; You, S.-L. *Org. Lett.* **2013**, *15*, 4266. (b) Cai, Q.; Yin, Q.; You, S.-L. *Asian J. Org. Chem.* **2014**, *3*, DOI: 10.1002/ajoc.201300146. During the preparation of this manuscript, a bromocyclization of tryptamines by chiral anionic phase-transfer catalysis appeared; see: (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.

(13) For recent examples on enantioselective chlorocyclization of unsaturated amides, see: (a) Jaganathan, A.; Garzan, A.; Whitehead, D. C.; Staples, R. J.; Borhan, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 2593. (b) Jaganathan, A.; Staples, R. J.; Borhan, B. *J. Am. Chem. Soc.* **2013**, *135*, 14806.