DIGITAL ACCESS TO SCHOLARSHIP AT HARVARD
DASH.HARVARD.EDU

HARVARD LIBRARY

Thiourea-Catalyzed Enantioselective Addition of Indoles to Pyrones: Alkaloid Cores with Quaternary Carbons

Citation

Yeung, Charles S., Robert E. Ziegler, John A. Porco, and Eric N. Jacobsen. 2014. "Thiourea-Catalyzed Enantioselective Addition of Indoles to Pyrones: Alkaloid Cores with Quaternary Carbons." Journal of the American Chemical Society 136 (39): 13614-13617. doi:10.1021/ja508523g. http://dx.doi.org/10.1021/ja508523g.

Published version

https://doi.org/10.1021/ja508523g

Link

http://nrs.harvard.edu/urn-3:HUL.InstRepos:22856910

Terms of use

This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Other Posted Material (LAA), as set forth at
https://harvardwiki.atlassian.net/wiki/external/NGY5NDE4ZjgzNTc5NDQzMGIzZWZhMGFlOWI2M2EwYTg

Accessibility

https://accessibility.huit.harvard.edu/digital-accessibility-policy

Share Your Story

The Harvard community has made this article openly available.
Please share how this access benefits you. Submit a story

This is an open access article published under an ACS AuthorChoice License, which permits copying and redistribution of the article or any adaptations for non-commercial purposes.

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Thiourea-Catalyzed Enantioselective Addition of Indoles to Pyrones: Alkaloid Cores with Quaternary Carbons

Charles S. Yeung,[†,§] Robert E. Ziegler,[‡,§] John A. Porco, Jr.,*[,‡] and Eric N. Jacobsen*[,†]

[†]Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138, United States

[‡]Department of Chemistry and Center for Chemical Methodology and Library Development (CMLD-BU), Boston University, Boston, Massachusetts 02215, United States

Supporting Information

ABSTRACT: We report the development of a catalytic method for the enantioselective addition of indoles to pyrone-derived electrophiles. Arylpyrrolidino-derived thioureas catalyze the addition with high stereoselectivity in the presence of catalytic quantities of an achiral Brønsted acid. The indole−pyrone adducts feature a quaternary stereocenter and represent an unusual class of indolines bearing structural resemblance to the hybrid natural product pleiocarpamine.

Complex indole alkaloids are important compounds that possess a wide range of bioactivities. For instance, pleiomaltinine is a hybrid natural product that features both indoline and γ-pyrone functionalities and exhibits an impressive ability to reverse multidrug resistance in vincristine-resistant cells.[1] Recently, we described a synthetic approach to pleiomaltinine through a Brønsted acid-promoted indole−pyrone annulation (Figure 1) involving a putative quinone methide-like intermediate.[2] Inspired by both the structural and biological uniqueness of pleiomaltinine and the relative scarcity of enantioselective catalytic transformations involving quinone methide intermediates,[3] we sought to explore the development of a general asymmetric annulation of indoles and pyrones. The established ability of neutral hydrogen-bond donors to catalyze enantioselective transformations of cationic intermediates through anion-binding mechanisms[4] led us to consider whether the cooperative action of a chiral thiourea and an achiral Brønsted acid[5] could promote stereoselective additions of nucleophilic indoles to cationic pyrone-derived quinone methide-like intermediates. In such a transformation, the formation of a chiral ion pair could render the formal nucleophilic addition step enantioselective to afford a chiral indoline bearing a quaternary carbon stereocenter at C3

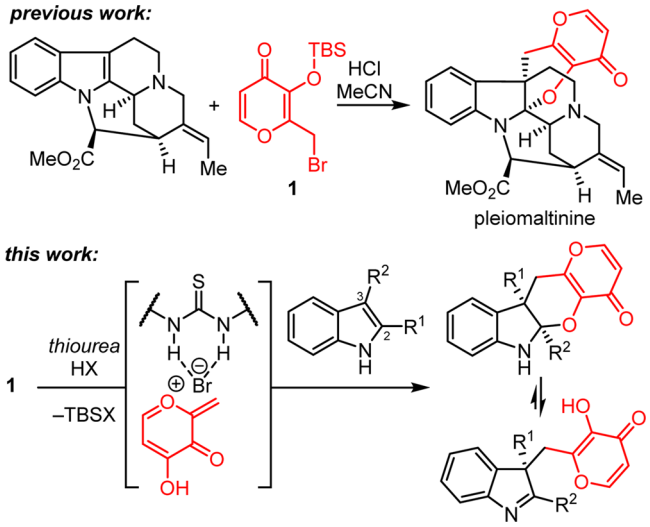
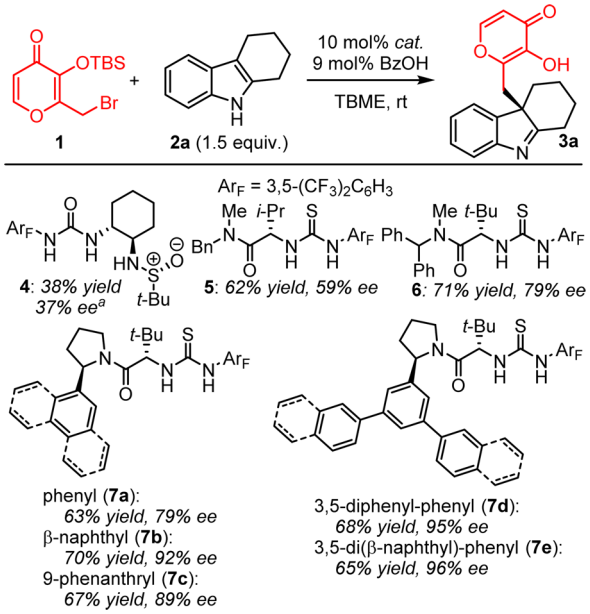


Figure 1. An indole−pyrone annulation approach to pleiomaltinine and a proposed enantioselective variant.

Table 1. Catalyst Structure Optimization Studies

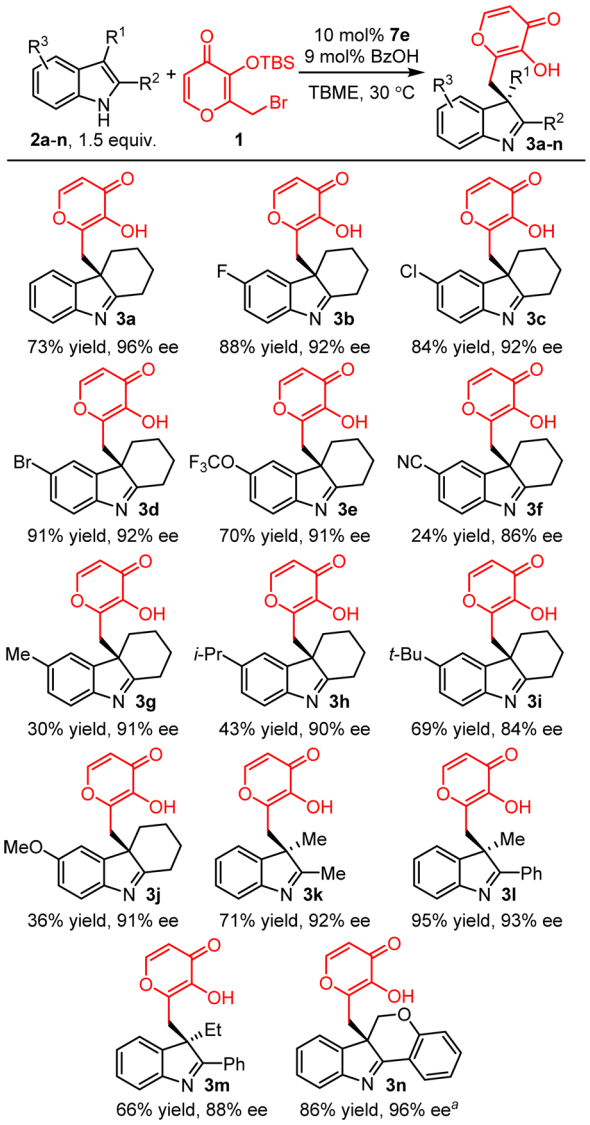


Conditions: [**1**] = 0.05 M, 3 days. All reactions were conducted on a 0.05 mmol scale. Isolated yields are reported. Enantioselectivities of the O-mesylated derivative of **3a** were determined by HPLC analysis on commercial chiral columns. See the Supporting Information for details. [a]No BzOH was added.

Received: August 19, 2014
Published: September 12, 2014

 © 2014 American Chemical Society

Table 2. Substrate Scope of Indole−Pyrone Additions



Conditions: [**1**] = 0.05 M, 3 days. Products were derivatized to the corresponding *O*-mesylates (3 equiv of RSO_2Cl, 5 equiv of NEt_3, CH_2Cl_2, overnight) for isolation and ee determination. Products **3b** and **3l** were derivatized to *O*-tosylates. Isolated yields of the corresponding sulfonates are reported. All reactions were conducted on a 0.1 mmol scale. Enantioselectivities were determined by HPLC analysis on commercial chiral columns. See the Supporting Information for details. [a]The reaction was conducted on a 0.05 mmol scale with 1.09 equiv of indole.

(Figure 1).[6,7] We describe here the successful development of this strategy.

Using the benzoic acid-catalyzed reaction of pyrone precursor **1** and 1,2,3,4-tetrahydrocarbazole (**2a**) as a model,[8] we evaluated several chiral urea and thiourea derivatives that have been utilized previously with success in Brønsted acid-cocatalyzed reactions.[5] While promising levels of enantioselectivity and reactivity were obtained with different classes of neutral hydrogen-bond-donor catalysts (Table 1),[9] particularly high ee's were observed with thiourea derivatives bearing a *t*-leucine arylpyrrolidino amide component (**7**).[10] Through a systematic investigation of such substituted arylpyrrolidino derivatives, we found that new catalysts bearing the *m*-terphenyl motif[11] promoted the indole−pyrone addition with >95% ee

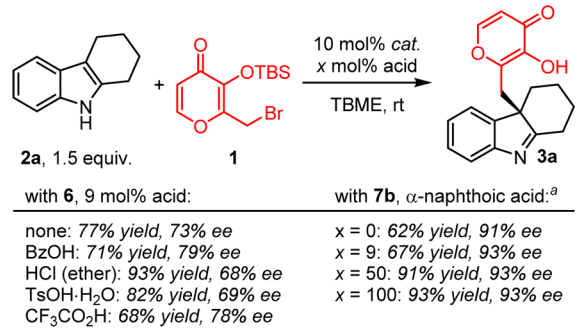


Figure 2. Variation of the Brønsted acid cocatalyst. Conditions: [**1**] = 0.05 M, 3 days. [a]The reaction was conducted at 0 °C. Isolated yields are reported. Enantioselectivities of the O-mesylated derivative of **3a** were determined by HPLC analysis on commercial chiral columns. See the Supporting Information for details.

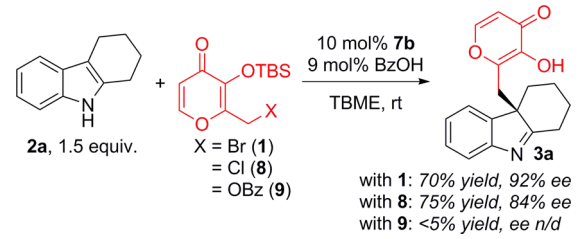


Figure 3. Variation of the pyrone precursor. Conditions: [**1**] = 0.05 M, 3 days. Isolated yields are reported. Enantioselectivities of the O-mesylated derivative of **3a** were determined by HPLC analysis on commercial chiral columns. See the Supporting Information for details.

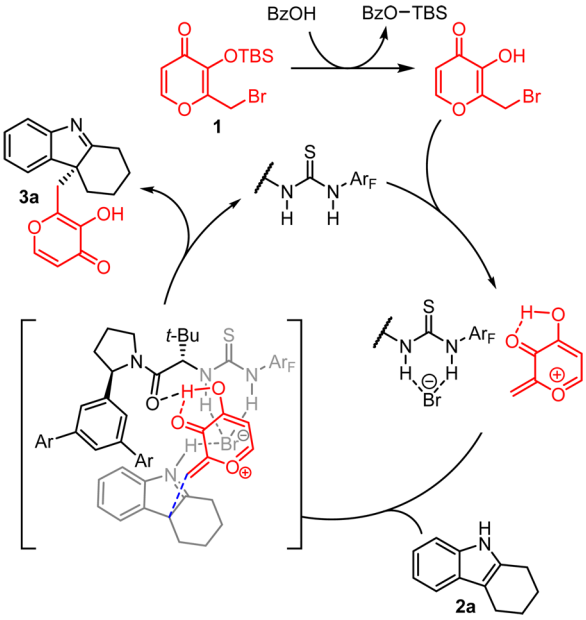


Figure 4. Proposed catalytic cycle.

(**7d** and **7e**). Thiourea **7e** was ultimately selected for further evaluation in the addition of various indole nucleophiles to γ-pyrone precursor **1** (Table 2). Both electron-withdrawing (**3b**−**f**) and electron-donating (**3g**−**j**) substituents on the indole ring were well-tolerated, indicating that the nucleophilicity of the reactive 3-position of the indole is not critical for high enantioselectivity.[12] Variation of both the 2- and 3-substituents on the indole was also possible (**3k**−**m**), although substitution at the 3-position was necessary to avoid rearomatization to an

achiral product. The absolute configuration of (*R*)-**3a** was established unambiguously by X-ray crystallography, and all of the derivatized adducts were assigned by analogy.

Several experiments were carried out with the goal of shedding light on the mechanism of catalysis and enantioinduction in this indole−pyrone addition reaction. Variation of the identity or the amount of the Brønsted acid cocatalyst had remarkably little effect on the reaction outcome (Figure 2), suggesting that the acid does not participate directly in the enantiodetermining step. In contrast, variation of the leaving group on the pyrone precursor was found to impact the enantioselectivity, as the chlorinated analogue **8** underwent the reaction to afford adduct **3a** with 84% ee using catalyst **7b** while the benzoyl derivative **9** proved unreactive (Figure 3). Finally, the N-methylated analogue of **2a** reacted with **1** in the presence of chiral thiourea **7e** to afford only racemic cycloaddition product, revealing a crucial role of the indole N−H in the catalytic mechanism. Taken together, these findings are most consistent with an enantiodetermining step involving specific interactions between the catalyst and both the pyrone leaving group and the indole N−H moiety. We propose that **1** undergoes desilylation in the presence of the Brønsted acid. A cationic quinone methide-like intermediate is then generated by anion abstraction by the thiourea catalyst, with general base activation of the indole in the stereodetermining addition step (Figure 4).[13] Additional attractive interactions (e.g., $\pi-\pi$ or C−H−π) between the cationic electrophile and the catalyst pyrrolidine substituent are suggested by the dependence of the reaction enantioselectivity on the nature of that aromatic group.[11] A mechanistic picture emerges that bears resemblance to that invoked previously in the ring-opening reaction of episulfonium ions with indole nucleophiles,[5b] thereby suggesting a possible general principle for enantioselective additions of indoles to cationic electrophiles.

In summary, we have uncovered a highly enantioselective method for the addition of 3-substituted indoles to γ-pyrone-derived electrophiles, providing a route to simplified pleiomaltinine analogues bearing a defined quaternary stereocenter. Investigation of the biological activity of these unusual structures is underway. In addition, identification of the *m*-terphenyl group as the optimal substituent in this class of chiral thiourea catalysts is new;[10] we are currently exploring the specific transition-state interactions associated with this aromatic framework in an effort to elucidate the basis for the stereoinduction in this reaction.

■ ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures, characterization data, additional discussion of catalyst optimization and substrate scope, and crystallographic information (CIF) for compound (*R*)-**3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

porco@bu.edu

jacobsen@chemistry.harvard.edu

Author Contributions

[§]C.S.Y. and R.E.Z. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the National Institutes of Health (GM-099920 to J.A.P. and GM-43214 to E.N.J.), a postdoctoral fellowship from NSERC (C.S.Y.), and a graduate fellowship from Vertex Pharmaceuticals, Inc. (R.E.Z.) are gratefully acknowledged. We thank Professor Scott Schaus and Neil Lajkiewicz (Boston University) for helpful discussions, Won Seok Ham and Dennis Dobrovolsky (Harvard University) for experimental assistance, and Dr. Shao-Liang Zheng (Harvard University) for crystal structure determination. Research at the Center for Chemical Methodology and Library Development at Boston University (CMLD-BU) was supported by NIH Grant GM-067041.

■ REFERENCES

(1) Tan, S.-J.; Choo, Y.-M.; Thomas, N. F.; Robinson, W. T.; Komiyama, K.; Kam, T.-S. *Tetrahedron* **2010**, *66*, 7799−7806.

(2) Ziegler, R. E.; Tan, S.-J.; Kam, T.-S.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2012**, *51*, 9348−9351.

(3) For examples, see: (a) Alden-Danforth, E.; Scerba, M. T.; Lectka, T. *Org. Lett.* **2008**, *10*, 4951−4953. (b) Lv, H.; Jia, W.-Q.; Sun, L.-H.; Ye, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 8607−8610. (c) Izquierdo, J.; Orue, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2013**, *135*, 10634−10637. (d) Luan, Y.; Schaus, S. E. *J. Am. Chem. Soc.* **2012**, *134*, 19965−19968. (e) El-Sepelgy, O.; Haseloff, S.; Alamsetti, S. K.; Schneider, C. *Angew. Chem., Int. Ed.* **2014**, *53*, 7923−7927. For a review of transition-metal-catalyzed approaches, see: (f) Pathak, T. P.; Sigman, M. S. *J. Org. Chem.* **2011**, *76*, 9210−9215.

(4) For reviews analyzing different aspects of anion-binding catalysis, see: (a) Brak, K.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2013**, *52*, 534−561. (b) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187−1198. (c) Phipps, R. J.; Hamilton, G. L.; Toste, F. D. *Nat. Chem.* **2012**, *4*, 603−614. (d) Mahlau, M.; List, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 518−533. For specific examples of enantioselective reactions proceeding via anion-binding pathways and catalyzed by thioureas and related dual H-bond donors, see: (e) Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 7198−7199. (f) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404−13405. (g) Raheem, I. T.; Thiara, P. S.; Jacobsen, E. N. *Org. Lett.* **2008**, *10*, 1577−1580. (h) Peterson, E. A.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6328−6331. (i) Knowles, R. R.; Lin, S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 5030−5032. (j) Brown, A. R.; Kuo, W.-H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 9286−9288. (k) Birrell, J. A.; Desrosiers, J.-N.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 13872−13875. (l) Burns, N. Z.; Witten, M. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 14578−14581. (m) Schafer, A. G.; Wieting, J. M.; Fisher, T. J.; Mattson, A. E. *Angew. Chem., Int. Ed.* **2013**, *52*, 11321−11324. (n) De, C. K.; Seidel, D. *J. Am. Chem. Soc.* **2011**, *133*, 14538−14541.

(5) (a) Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. *Science* **2010**, *327*, 986−990. (b) Lin, S.; Jacobsen, E. N. *Nat. Chem.* **2012**, *4*, 817−824. (c) Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2009**, *11*, 887−890. (d) Lee, Y.; Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2011**, *13*, 5564−5567. (e) Min, C.; Mittal, N.; Sun, D. X.; Seidel, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 14084−14088. (f) Rubush, D. M.; Morges, M. A.; Rose, B. J.; Thamm, D. H.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 13554−13557. (g) Geng, Y.; Kumar, A.; Faidallah, H. M.; Albar, H. A.; Mhkalid, I. A.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2013**, *52*, 10089−10092.

(6) We have found that indolenines bearing γ-pyrone functionalities preferentially adopt the ring-closed form in settings where the indole nitrogen is alkylated (cf. pleiomaltinine, ref 2) and the open form when the indole lacks an N substitutent (cf. **3a**). The position of this equilibrium is expected to depend strongly on medium effects and specific hydrogen-bonding interactions.

(7) For examples of indolines containing quaternary stereocenters, see: (a) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314−

6315. (b) Kolundzic, F.; Noshi, M. N.; Tjandra, M.; Movassaghi, M.; Miller, S. J. *J. Am. Chem. Soc.* **2011**, *133*, 9104−9111. (c) Li, M.; Woods, P. A.; Smith, M. D. *Chem. Sci.* **2013**, *4*, 2907−2911. (d) Huehls, C. B.; Hood, T. S.; Yang, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 5110−5113. (e) Lin, A.; Yang, J.; Hashim, M. *Org. Lett.* **2013**, *15*, 1950−1953. For a review of pyrroloindolines containing quaternary stereocenters, see: (f) Repka, L. M.; Reisman, S. E. *J. Org. Chem.* **2013**, *78*, 12314−12320. For examples of pyrroloindolines containing quaternary stereocenters, see: (g) Movassaghi, M.; Schmidt, M. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3725−3728. (h) Furst, L.; Narayanam, J. M. R.; Stephenson, C. R. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 9655−9659. (i) Kim, J.; Movassaghi, M. *J. Am. Chem. Soc.* **2011**, *133*, 14940−14943. (j) Sun, Y.; Li, R.; Zhang, W.; Li, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 9201−9204. For examples of oxindoles containing quaternary stereocenters, see: (k) Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488−6499. (l) Hills, I. D.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3921−3924. (m) Trost, B. M.; Frederiksen, M. U. *Angew. Chem., Int. Ed.* **2005**, *44*, 308−310. (n) Kündig, E. P.; Seidel, T. M.; Jia, Y.-x.; Bernardinelli, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 8484−8487. (o) Duffey, T. A.; Shaw, S. A.; Vedejs, E. *J. Am. Chem. Soc.* **2009**, *131*, 14−15. (p) Taylor, A. M.; Altman, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 9900−9901. (q) Ma, S.; Han, X.; Krishnan, S.; Virgil, S. C.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 8037−8041. (r) He, R.; Ding, C.; Maruoka, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 4559−4561. (s) Würtz, S.; Lohre, C.; Fröhlich, R.; Bergander, K.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 8344−8345. For an example of benzofuroindolines containing quaternary stereocenters, see: (t) Liao, L.; Shu, C.; Zhang, M.; Liao, Y.; Hu, X.; Zhang, Y.; Wu, Z.; Yuan, W.; Zhang, X. *Angew. Chem., Int. Ed.* **2014**, DOI: 10.1002/anie.201405689. For a review of setting quaternary stereocenters, see: (u) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473−1482.

(8) (a) Rumbo, A.; Castedo, L.; Mourino, A.; Mascareñas, J. L. *J. Org. Chem.* **1993**, *58*, 5585−5586. (b) López, F.; Castedo, L.; Mascareñas, J. L. *Org. Lett.* **2000**, *2*, 1005−1007. (c) Rodríguez, J. R.; Castedo, L.; Mascareñas, J. L. *J. Org. Chem.* **2000**, *65*, 2528−2531. (d) López, F.; Castedo, L.; Mascareñas, J. L. *Org. Lett.* **2001**, *3*, 623−625. (e) López, F.; Castedo, L.; Mascareñas, J. L. *Chem.—Eur. J.* **2002**, *8*, 884−899.

(9) Products were derivatized to the corresponding *O*-mesylates or *O*-tosylates for isolation and ee determination. See the Supporting Information for a detailed summary of catalyst screening and optimization efforts.

(10) Catalysts with the general structure of **7** have proven effective in a wide variety of enantioselective reactions. For examples, see refs 4e, 4i, 4k, 5b, and: (a) Bergonzini, G.; Schindler, C. S.; Wallentin, C.-J.; Jacobsen, E. N.; Stephenson, C. R. J. *Chem. Sci.* **2014**, *5*, 112−116. (b) Lykke, L.; Carlsen, B. D.; Rambo, R. S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2014**, *136*, 11296−11299.

(11) *m*-Terphenyl groups have been shown to engage productively in cation−π interactions. See: Shukla, R.; Lindeman, S. V.; Rathore, R. *Chem. Commun.* **2009**, 5600−5602.

(12) The low yields obtained for certain addition products (e.g., **3g**−**j**) can be attributed to competitive homodimerization of precursor **1**.

(13) The addition step may occur through a conjugate addition mechanism, as proposed in Figure 4, to afford the observed open product directly or via a concerted [4 + 2] cycloaddition pathway with subsequent ring opening.