JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

Dissecting the Stereocontrol Elements of a Catalytic Asymmetric Chlorolactonization: *Syn* Addition Obviates Bridging Chloronium

Roozbeh Yousefi,[†] Kumar Dilip Ashtekar,[†] Daniel C. Whitehead,[‡] James E. Jackson,*[,†] and Babak Borhan*[,†]

[†]Department of Chemistry, Michigan State University, East Lansing, Michigan 48824, United States

[‡]Department of Chemistry, Clemson University, Clemson, South Carolina 29634, United States

Supporting Information

ABSTRACT: We report absolute and relative stereochemistry of addition in enantioselective chlorolactonizations of 4-phenyl-4-pentenoic acid and its related *t*-butyl ester, catalyzed by $(DHQD)_2PHAL$. Predominant *syn* addition of the chlorenium and the nucleophile across the olefin is observed. As shown by isotopic labeling, NMR spectroscopy, and derivative studies, the two new stereocenters formed by addition across the double bond are set independently and influenced by different factors. These findings suggest a stepwise process via an intermediate capable of lactone closure with either stereochemistry, in contradistinction to the more familiar scenario in which *anti* addition is dictated by a bridging chloronium ion intermediate.

Halocyclization of alkenes is a robust, versatile route to a wide range of heterocycles. Typical textbook halocyclization mechanisms invoke electrophilic halogen attack to form a three-membered halonium ion intermediate; ring closure then ensues (Figure 1, path a) via intramolecular S_N2 attack on the halonium ion. This scenario predicts *anti* relative addition across the double bond. Until recently, however, control of absolute stereochemistry at the newly formed sp^3 centers was lacking, its development hindered by the following challenges: (a) To be useful, the catalyzed, stereocontrolled process must outcompete stereorandom noncatalyzed background reactions. Thus, the halenium donor must react with the olefin on a practical time scale, but only when these components are activated by catalysts. (b) The catalyst must survive the presence of such an electrophilic halogenating agent while directing reactions to specific olefin faces. (c) Assuming a stepwise process, high alkene face selectivity in the initial electrophilic attack is no guarantee of ultimate enantioinduction; the putative carbocation (whether or not it equilibrates with a bridged halonium ion) may undergo bond rotation, erasing configurational memory at the cationic site. Thus catalyst control of the final ring closure is essential. (d) Finally, recent sophisticated studies of bromo- and iodocyclizations have uncovered olefin-to-olefin halenium transfer, another potential mode of stereorandomization prior to ring closure.[1] The analogous exchanges in chlorenium ions, however, were ruled out, confirming earlier gas-phase and computational studies and consistent with results described herein.

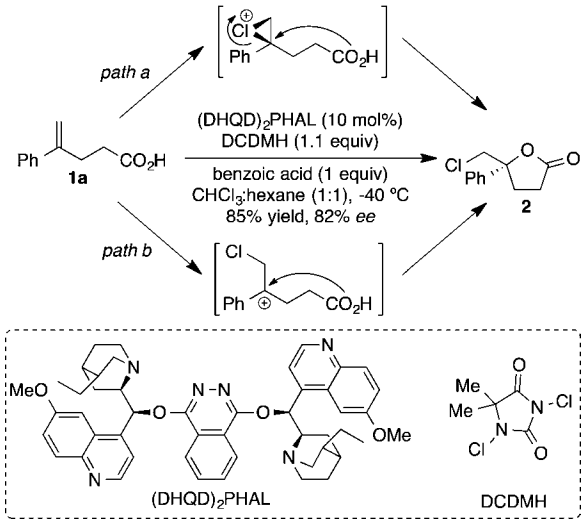

Figure 1. $(DHQD)_2PHAL$-catalyzed chlorolactonization process. Carbocation or a bridged chloronium species represent potential intermediates is in question.

Despite the above pitfalls, the last three years have witnessed great progress,[2] highlighted by the discovery of several efficient catalytic asymmetric halocyclizations with excellent enantioselectivity.[3] As more examples emerge, tools to probe the origins of stereocontrol will be essential to provide mechanistic insight and guidance to the field.

In recently disclosed efforts, we showed that cinchona alkaloid dimers, such as $(DHQD)_2PHAL$, can catalyze efficient, stereoselective chlorolactonization of alkenoic acids **1a**, as depicted in Figure 1.[2g,4] Furthermore, the same alkaloid has demonstrated proficiency in several other catalytic asymmetric halocyclizations.[2f,5] To understand this system's effectiveness and generality as a path to chiral heterocyclic frameworks, we have explored its stereochemical details.

Key questions to address are: (a) Is the chlorenium delivered in a face-selective manner? (b) What stereochemical relationship, if any, exists between the chlorenium delivery and the nucleophilic attack? (c) For a stepwise process, what would be the likely nature of the reactive intermediate, i.e., a bridged chloronium or a carbocation as in Figure 1?

Received: July 15, 2013
Published: September 11, 2013

dx.doi.org/10.1021/ja4072145 | J. Am. Chem. Soc. 2013, 135, 14524−14527

The literature offers a start on this last question. For substrates like **1a**, halocyclization may be a polar, stepwise process, as in the textbook scenario. However, the open carbocation should be energetically preferred, as seen in Olah's seminal work on chloronium intermediates of similarly substituted olefins.[6] Previous studies[7] and our own quantum chemical modeling support this view; even in the "gas phase" where bridging is the only available mode of charge delocalization, no cyclic chloronium ion energy minimum deep enough to lock in stereochemistry is seen from **1a** (or any α-alkylstyrene) or even from a simple 1,1-dialkyl alkene, such as 2-methylpropene.[8] Thus, an open halomethyl carbenium ion (Figure 1, path b) would be the intermediate expected from halenium attack on a 1-aryl-1-alkylalkene substrate **1a**.

Halocyclization of the 1,1-disubstituted olefin **1a** forms lactone **2** with a single stereocenter; the chlorine resides on a nonstereogenic carbon, with no record of its attack path on the alkene. In the expected planar carbenium ion intermediate, the absolute stereochemistry defined by asymmetric delivery of the chlorenium to the olefin would be lost, so the reaction's enantioselectivity would then be determined at the (presumably catalyst controlled) ring-closing step. Notably, if the reaction were to involve a bridged chloronium (i.e., a species in which both ends are stereochemically committed), stereochemical definition would be preserved as the carboxylate closed the ring. Enantioselectivity would be controlled in parallel with the initial asymmetric chlorenium delivery, yielding *anti* addition.

To probe the scenarios described above, we required a labeled substrate that could report on the stereochemical fate of the chlorine atom, without sacrificing the structural uniqueness of the 1,1-disubstituted carboxylic acid substrate. Accordingly, the *E*-deuterated analog **1a-D** was synthesized in short order, as shown in Figure 2a. The chlorolactonization of **1a-D** under standard catalytic asymmetric conditions yielded the corresponding deuterated product **2-D**. As described below, the absolute stereochemistry of the CHDCl group in the major

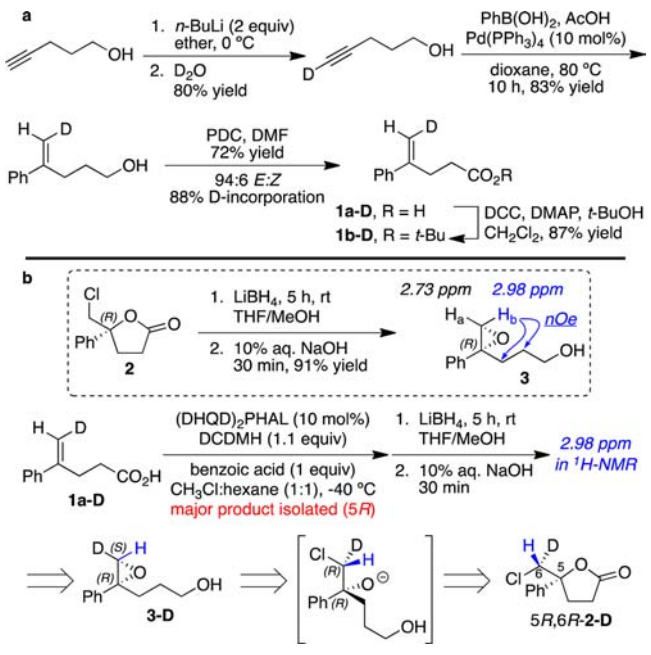

Figure 2. (a) Synthesis of deuterated substrates **1a-D** and **1b-D**. (b) Absolute stereochemical assignment of the deuterated product **2-D** via conversion to the epoxide **3-D**.

isolate was straightforwardly established via NOE analysis of epoxide **3-D** obtained from the chemically transformed chlorolactone product **2-D**. Lithium borohydride reduction of lactone **2**-(*R*), followed by sodium hydroxide mediated cyclization of the resulting chlorohydrin intermediate, returned the 1,1-disubstituted epoxy alcohol **3** in good yield (Figure 2b). NOESY analysis of **3** showed a pronounced correlation between the epoxy proton at 2.98 ppm and the methylene protons of the alkyl chain, indicating that the protons at 2.73 and 2.98 ppm are, respectively, *cis* (H_a) and *trans* (H_b) to the phenyl ring. Conversion of deuterated (5*R*)-lactone **2-D** (91:9 *er* from catalytic asymmetric chlorolactonization of **1a-D** with $(DHQD)_2PHAL$ to the corresponding epoxy alcohol **3-D** yielded a ^1H NMR spectrum with the major epoxy CH resonance (90%) at 2.98 ppm (H_b). With the deuteron *cis* to the phenyl group, the carbon bearing it was assigned the *S*-configuration, implying the *R*-configuration for the CHDCl group in the (5*R*) **2-D** from which epoxide **3-D** was formed via intramolecular S_N2 chloride displacement. This result, in turn, allowed assignment of the ^1H resonances from the pro-*R* (3.74 ppm) and pro-*S* (3.83 ppm) diastereotopic hydrogens of the CH_2Cl group in **2** and CHDCl in **2-D** (see SI). The latter assignment enables identification of all four isomers obtained via chlorolactonization of **1a-D** and **1b-D**.

Figure 3 depicts the results obtained from the chlorolactonization of **1a-D** under $(DHQD)_2PHAL$ catalyzed reaction

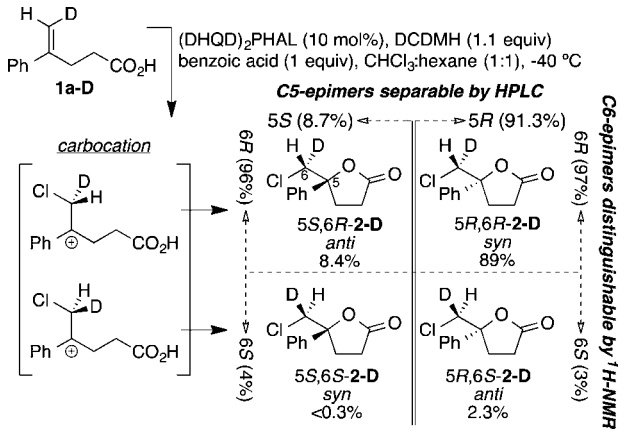

Figure 3. Reaction of deuterated substrate **1a-D** under standard catalytic asymmetric reaction conditions with $(DHQD)_2PHAL$ provided four isomeric products. The anticipated 5*R* product was the major HPLC isolate (~91:9 5*R*:5*S*). The level of C-6 stereoisomerism (6*R*:6*S* = 97:3 for 5*R*, 96:4 for 5*S*) was quantified by ^1H NMR analysis of crude and HPLC purified fractions.

conditions. Though **1a-D** was a 83:5:12 mixture of *E*:*Z*:H_2 isotopomers, numbers provided in Figure 3 are corrected to the pure *E* value (see SI). Noncatalyzed cyclization of **1a-D** in the presence of DCDMH yielded a racemic mixture of the two diastereomeric products in a 1:1 *dr*.[9] Inclusion of quinuclidine as an achiral catalyst (at 20 mol %, to equal the concentration of amine sites in $(DHQD)_2PHAL$ at 10 mol %) led to a 5:1 *anti*:*syn dr* (see SI). Formation of both diastereomers excludes reaction via a single, stereospecific pathway, requiring instead an overall sequence capable of multiple stereochemical outcomes. Reaction with quinuclidine does introduce an *anti* stereopreference, consistent with the idea of enhanced carboxylate nucleophilicity in the presence of the quinuclidine; in the suggested carbocation pathway, the cation would then be

dx.doi.org/10.1021/ja4072145 | J. Am. Chem. Soc. 2013, 135, 14524−14527

trapped fast enough to retain some conformational memory of the orientation of chlorenium delivery.

Olefin-to-olefin chlorenium ion transfer, already noted by Denmark et al. as least probable,[1] is a conceivable stereorandomizing factor. This possibility is largely eliminated by the following observations: (a) For the catalyzed process in Figure 3, the 6*R* stereopreference is 96:4, allowing for a randomization process of at most 4%. (b) Quantum chemical models without catalyst find an open (unbridged) chloromethyl carbenium ion whose low barrier (<3.5 kcal/mol) for CHDCl rotation indicates that the newly attached Cl atom exerts no stereochemical control over bond formation at C-5.[8] (c) Even the slowest of the above reactions shows no loss of stereochemical integrity for the labeled olefinic carbon of recovered starting material **1a-D**. Since chlorenium ion loss from the conformationally mobile carbocation would scramble label in the alkenoic acid, this finding implies that cyclization is faster than any reversible chlorenium transfer. (d) Cyclization is also irreversible; control experiments were run using pure enantiomers (isolated by HPLC) of the *p*-OMe phenyl analogs of chlorolactone **2**. This substrate, chosen for its potential ability to form a stabilized benzylic carbenium ion, showed no loss of stereochemical integrity, even in the presence of reacting components. Thus, there is no reversibility in the ring closure step (see SI for details).

Considering the diversity of stereochemical outcomes above, it appears likely that in the presence of the $(DHQD)_2PHAL$, the conversion of **1a** to **2** also proceeds through the intermediacy of a carbocation intermediate. If so, the high enantioselectivity of the final lactone product must be the result of high facial selectivity in the ring-closing step. However, the observed *ee* of the product need not reflect the facial selectivity, if any, for the chlorenium transfer to the olefin. Using the *E*-deuterated analog **1a-D** and NMR assignments outlined above to probe both absolute stereochemistry at the CHDCl site and the relative addition stereochemistry of the chlorine and the carboxylate nucleophile, this hypothesis was readily tested.

Chlorolactonization of **1a-D** was carried out under optimized reaction conditions (Figure 2). The proportions of the four stereoisomeric products **2-D**, depicted in Figure 3, were quantified as follows: chiral HPLC separation of C-5 epimers enabled isolation of the expected major product, the 5*R* diastereomeric mixture. The C-6 CHDCl epimer ratios of the two C-5 antipodes could then be quantified through NMR analysis of crude products and HPLC isolates of major and minor fractions (details in SI).

In agreement with our previous results, the *R* stereochemistry of the quaternary carbon for lactone **2-D** was favored by 91% (HPLC). Interestingly, ^{1}H NMR analysis of the major fraction isolated by HPLC clearly showed one major diastereomeric product. Integration of the diastereotopic ^{1}H peaks revealed a 97:3 preference for one CHDCl epimer; assignment of the CH_2Cl group's ^{1}H resonances as discussed above and shown in Figure 2b proved this dominant form to have a CHDCl group of *R* configuration. Thus $(DHQD)_2PHAL$ strongly controls face selectivity of the initial chlorenium delivery and favors *syn* addition in the major product. This relative stereochemistry is opposite to that expected from a bridged chloronium intermediate. This high level of stereoinduction is striking and suggests that in systems beyond 1,1-disubstituted olefins, nonbridged chloronium mechanisms[10] may also apply when the Cl–C bonds form enantioselectively.[2f,5]

The face selectivity of chlorenium transfer is formally inconsequential for the enantioselectivity of lactonization with unlabeled 1,1-disubstituted alkenoic acids, such as **1a**. But revealing the new stereocenters' absolute preferences (or lack thereof) sheds light on the factors that control selectivity. Stereocontrol at both new sp^3 sites might reflect binding of the substrate to the protonated catalyst in a conformation "cocked" for formation of both new bonds, or the two bond-forming events could be independently controlled by the same catalyst. A key hint favoring the latter interpretation is that the minor 5*S* enantiomer in the above reaction also showed a strong preference for the *R* stereochemistry at the CHDCl site (i.e., net *anti* addition).

To better segregate face selectivity in chlorenium transfer from the intramolecular cyclization that yields the lactone product, the transformations of *t*-butyl esters **1b** and **1b-D** were investigated. Chlorolactonization of **1b** under standard catalytic asymmetric conditions with $(DHQD)_2PHAL$ led to **2** with the 5*S* isomer weakly predominant, at 20% *ee* (Figure 4). These

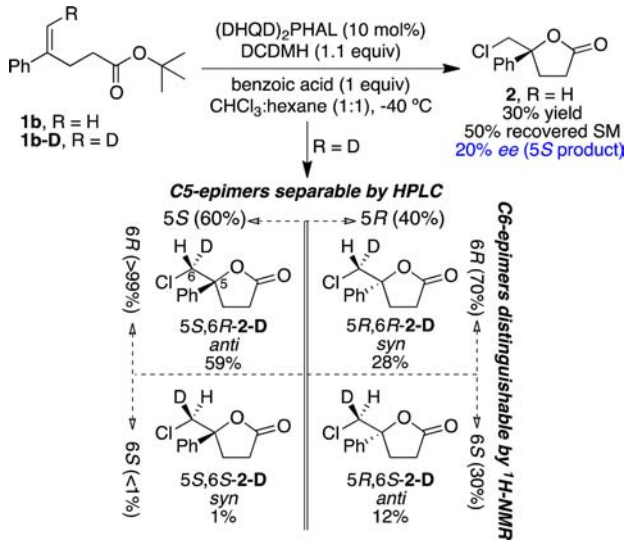

Figure 4. Chlorolactonization of the *t*-butyl ester analog **1b** under the standard catalytic asymmetric reaction conditions with $(DHQD)_2PHAL$ produces the 5*S* product in low *ee*. The deuterated analog **1b-D** yields the same C-5 product stereoisomers. ^{1}H NMR analysis of the HPLC purified fractions reveals high olefin face selectivity in chlorination in the first step as compared to poor carbocation face selectivity in the second step.

results suggest that the carboxylic acid moiety is important for achieving high enantioselectivity, presumably as a result of hydrogen bonding or ionic interactions with the chiral amine catalyst. The analogous reaction of the deuterated *E*-*t*-butyl ester analog **1b-D** under identical reaction conditions yielded a surprise: NMR analysis of the HPLC purified fractions as described above indicated a much higher facial selectivity in chlorenium transfer to the olefin (via integration of the diastereotopic protons) than for the cyclization to the lactone product. As with **1a**, the *R* configuration dominates in the C-6 CHDCl group, but this is true in both 5*S* and 5*R* enantiomers. Thus, the dominant 5*S* product **2** from **1b** actually arises from mostly *anti* addition.

Taken together, the above findings suggest that independent events determine facial selectivity in chlorination of the olefin and cyclization of the ensuing intermediate. The high *R*-

dx.doi.org/10.1021/ja4072145 | J. Am. Chem. Soc. 2013, 135, 14524–14527

selectivity in the first step may be due to attack by the chlorinated hydantoin on the styrenic portion common to substrates **1a** and **1b**, bound by catalyst so that only the pro-*R* face is accessible.[11] The selectivity for the second step, which is so strongly modified by esterification that its stereopreference is inverted, would then be controlled by catalyst templating of the cation's conformational preferences, setting the face selectivity of the ring-closing step. Given the hydrogen binding moieties of acid **1a**, largely absent in less polar, more sterically bulky ester **1b**, it seems sensible that cyclization of the cation from **1b** should be much less strongly directed by its interaction with the polyamine catalyst.

In summary, to answer the questions raised at the outset: (a) Chlorenium delivery to alkene sites in **1a** and **1b**, catalyzed by $(DHQD)_2PHAL$, is highly face-selective. But this pro-*R* face selectivity is not a sufficient condition to ensure enantioselective lactone production. (b) Following attack of chlorenium on acid **1a**, catalyst-templated nucleophilic closure favors the 5*R* over the 5*S* lactone by a factor of >10:1, regardless of the original Cl^+ delivery path. Thus, the two sites' stereopreferences, though determined independently, lead to predominant *syn* Cl,O addition from acid **1a**. The strong pro-*R* preference of chlorenium attack, however, results in net *anti* addition in the weakly favored 5*S* product of ester **1b**.[12] (c) With the two stereochemical decisions apparently uncoupled, the reaction is most straightforwardly understood as stepwise via a carbocation intermediate. A bridged chloronium ion is both energetically and stereochemically incompatible with this and many analogous reported reaction systems. Thus, we believe that independent catalyst stereocontrol of the two new bond formation steps is ultimately responsible not only for controlling which olefin face is attacked by Cl^+ but also for guiding the final enantioselective cyclization.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, characterization data, and stereochemical assignments. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

babak@chemistry.msu.edu
jackson@chemistry.msu.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge the NSF (CHE-0957462) for funding.

■ REFERENCES

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

(2) (a) Murai, K.; Matsushita, T.; Nakamura, A.; Fukushima, S.; Shimura, M.; Fujioka, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 9174. (b) Veitch, G. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2010**, *49*, 7332. (c) Dobish, M. C.; Johnston, J. N. *J. Am. Chem. Soc.* **2012**, *134*, 6068. (d) Li, G. X.; Fu, Q. Q.; Zhang, X. M.; Jiang, J.; Tang, Z. *Tetrahedron-Asymmetry* **2012**, *23*, 245. (e) Tan, C. K.; Le, C. C.; Yeung, Y. Y. *Chem. Commun.* **2012**, *48*, 5793. (f) Jaganathan, A.; Garzan, A.; Whitehead, D. C.; Staples, R. J.; Borhan, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 2593. (g) Whitehead, D. C.; Yousefi, R.; Jaganathan, A.; Borhan, B. *J. Am. Chem. Soc.* **2010**, *132*, 3298. (h) Cai, Y. F.; Liu, X. H.; Jiang, J.; Chen, W. L.; Lin, L. L.; Feng, X. M. *J. Am. Chem. Soc.* **2011**, *133*, 5636. (i) Sakakura, A.; Ukai, A.; Ishihara, K. *Nature* **2007**, *445*, 900. (j) Zhang, W.; Zheng, S. Q.; Liu, N.; Werness, J. B.; Guzei, I. A.; Tang, W. P. *J. Am. Chem. Soc.* **2010**, *132*, 3664.

(3) (a) Castellanos, A.; Fletcher, S. P. *Chem.—Eur. J.* **2011**, *17*, 5766. (b) Tan, C. K.; Zhou, L.; Yeung, Y.-Y. *Synlett* **2011**, 1335. (c) Hennecke, U. *Chem. Asian J.* **2012**, *7*, 456. (d) Chen, F.; Tan, C. K.; Yeung, Y. Y. *J. Am. Chem. Soc.* **2013**, *135*, 1232. (e) Jiang, X.; Tan, C. K.; Zhou, L.; Yeung, Y. Y. *Angew. Chem.* **2012**, *51*, 7771.

(4) Yousefi, R.; Whitehead, D. C.; Mueller, J. M.; Staples, R. J.; Borhan, B. *Org. Lett.* **2011**, *13*, 608.

(5) (a) Garzan, A.; Jaganathan, A.; Salehi Marzijarani, N.; Yousefi, R.; Whitehead, D. C.; Jackson, J. E.; Borhan, B. *Chem.—Eur. J.* **2013**, *19*, 9015. (b) Ikeuchi, K.; Ido, S.; Yoshimura, S.; Asakawa, T.; Inai, M.; Hamashima, Y.; Kan, T. *Org. Lett.* **2012**, *14*, 6016. (c) Wilking, M.; Muck-Lichtenfeld, C.; Daniliuc, C. G.; Hennecke, U. *J. Am. Chem. Soc.* **2013**, *135*, 8133.

(6) Olah, G. A.; Bollinger, J. M. *J. Am. Chem. Soc.* **1968**, *90*, 947.

(7) (a) Haubenstock, H.; Sauers, R. R. *Tetrahedron* **2004**, *60*, 1191. (b) Haubenstock, H.; Sauers, R. R. *Tetrahedron* **2005**, *61*, 8358. (c) Ohta, B. K.; Hough, R. E.; Schubert, J. W. *Org. Lett.* **2007**, *9*, 2317. (d) Solling, T. I.; Radom, L. *Int. J. Mass Spectrom.* **1999**, *185*, 263.

(8) For the $C_9H_{10}Cl^+$ ion obtained from chlorenium addition to α-methylstyrene, B3LYP/6-31G* calculations find only an open carbocation minimum. The optimized structure does find the C−Cl bond aligned with the carbocation's empty 2p orbital, but it shows a ∠CCCl angle of 109°, and the face-switching barrier to rotation of the CH_2Cl group is calculated to be only 1.6 kcal/mol in the gas phase, roughly half the value for methyl group rotation in ethane. Simulated solvation in $CHCl_3$ further lowers this value to 0.9 kcal/mol. See SI for details of calculations and structures.

(9) Although dichlorodiphenyl hydantoin yields slightly higher *ees*, we opted for the use of DCDMH because of its better solubility in the chosen solvents for this study.

(10) (a) Fahey, R. C.; McPherson, C. A. *J. Am. Chem. Soc.* **1969**, *91*, 3865. (b) Fahey, R. C.; Schubert, C. *J. Am. Chem. Soc.* **1965**, *87*, 5172.

(11) X-ray or NOE results could suggest a structural model for catalyst−substrate−DCDMH interactions; however, assiduous efforts to obtain crystals in various solvents and temperature conditions yielded only uncomplexed catalyst crystals. Likewise, detailed NMR studies failed to yield interpretable data on the relevant spatial relationships.

(12) We cannot absolutely exclude the possibility of multiple competing pathways that independently yield the four stereoisomeric products. For instance, a double inversion process can be envisioned wherein a nearby nucleophile (e.g., catalyst's phthalazine nitrogen atom) forms a covalent catalyst−substrate intermediate, which then undergoes S_N2 nucleophilic reaction to yield the dominant *syn* chlorolactonization product. However, the diversity of stereochemical outcomes in the products from **1a** and **1b** argues against such stereochemically defined intermediates, supporting instead the notion of a common carbocation which then undergoes ring closing under the stereocontrol of the catalyst.