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

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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 stereo-centers 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 SN2 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 sp3 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.

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 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?

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Figure 1. (DHQD)2PHAL-catalyzed chlorolactonization process. Carbocation or a bridged chloronium species represent potential intermediates is in question.
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 carboxylation should be energetically preferred, as seen in Olah’s seminal work on chloronium intermediates of similarly substituted olefins. Previous studies 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 single 1,1-dialkyl alkene, such as 2-methylpropene. Thus, an open halomethyl carbocation (Figure 1, path b) would be the intermediate expected from halonium 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 carbocation intermediate, the absolute stereochemistry defined by asymmetric delivery of the chloronium 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 chloronium 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 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). NOEY 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 (H₆) and trans (H₇) to the phenyl ring. Conversion of deuterated (SR)-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 (H₆). With the deuterion cis to the phenyl group, the carbon bearing it was assigned the S-configuration, implying the R-configuration for the CHDCl group in the (SR) 2-D from which epoxide 3-D was formed via intramolecular S₈2 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 CH₂Cl 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 conditions. Though 1a-D was a 83:5:12 mixture of E:Z:H₃ isotomers, 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. Inclusion of quinuclidine as an achiral catalyst (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 overall sequence capable of multiple stereochemical outcomes. Reaction with quinuclidine does introduce an overall sequence capable of multiple stereochemical outcomes.
tained, and suggests that in systems beyond 1,1-disubstituted olefins, nonbridged chlorenium mechanisms may also apply when the Cl−C bonds form enantioselectively.

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. Stereocenters at both new sp² 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 SS enantiomer in the above reaction also showed a strong preference for the R stereocenter at the CHDCI 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 SS isomer weakly predominant, at 20% ee (Figure 4). These 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 surprising 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.
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. 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 \((\text{DHQD})_2\text{PHAL}\), 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 SR over the SS lactone by a factor of \(>10:1\), regardless of the original Cl' delivery path. Thus, the two sites’ stereo-pREFERENCES

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| 9.0 kcal/mol. See SI for details of calculations and structures. (9) Although dichlorodiphenyl hydantoin yields slightly higher ee, 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 \(\text{S}_2\text{C}\) nucleophilic reaction to yield the dominant syn chlorolactonization product. However, the diversity of stereocchemical 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 stereocatalysis of the catalyst. |