An Organocatalytic Asymmetric Chlorolactonization

Daniel C. Whitehead, **Roozbeh Yousefi**, **Arvind Jaganathan**, and **Babak Borhan**
Department of Chemistry, Michigan State University, East Lansing, MI 48824

Catalytic asymmetric oxidations, most notably dihydroxylations,[1] epoxidations,[2-4] and aminohydroxylations,[5] have proven to be versatile transforms for the installation of chiral functionality onto non-chiral alkene substrates. In all three cases, the methodology has progressed and matured to the extent that the transformations are routinely applied in organic synthesis.

Notably absent from this arsenal of transformations are examples of synthetically useful, conceptually related asymmetric electrophilic olefin halogenation reactions. With the intention of addressing this long-standing problem, we instituted a program geared towards the development of a reagent-controlled asymmetric halogenation of olefins.

Recently, a polyene cascade induced by a stoichiometric chiral iodonium source was disclosed in an elegant work by Ishihara *et al*.[6a] An efficient Co-salen catalyzed iodoetherification has also been reported by Kang *et al*.[6b] Nonetheless, an efficient *catalytic* asymmetric halolactonization reaction has been elusive. In contrast to the number of examples of substrate controlled stereoselective halolactonizations,[7] reagent controlled processes are rare, and have only begun to emerge recently. The development of such a methodology would provide access to richly functionalized chiral halolactones in one step from achiral alkenoic acids.

The first reagent controlled enantioselective halolactonization was reported in 1992 by the Taguchi group, where an alkenoic acid was cyclized by action of iodine and a *stoichiometric* equivalent of a chiral titanium complex, returning an iodolactone in 65% *ee*.[8] Subsequently, a number of examples have appeared that employ stoichiometric or super-stoichiometric amounts of chiral amine promoters. Typically, these methodologies employ a dimeric iodonium salt as the chiral halogen source (i.e. [(L*)2I+]Y-, where L* is a chiral amine).[8-12] Two of the most selective examples of this strategy were presented by Wirth[11,12] and Rousseau.[9] Aside from the disadvantage of committing up to ~5 equiv of chiral promoter, these approaches were marred by low enantioselectivities (15 to 45% *ee*). Interestingly, all of these disclosures produce iodolactones. Reports on chloro and bromolactonizations are absent, except for a single example where a bromolactone was produced in 5% *ee* with a chiral bromonium/pyridine dimer.[13]

Recently, Gao and coworkers reported the only catalytic protocol for the iodolactonization of alkenoic acids, whereby *trans*-5-aryl-4-pentenoic acids were cyclized in the presence of iodine and 30 mol% of a cinchonidine-derived quaternary ammonium salt under PTC conditions.[14] Iodolactones were returned in a nearly 1:1 ratio of δ and γ isomers with marginal enantioselectivities (δ = 16% *ee*, γ = 31% *ee*).

ak@chemistry.msu.edu .

We now report the discovery of an organocatalytic enantioselective protocol for the chlorolactonization of 4-substituted 4-pentenoic acids. This methodology represents the first example of a catalytic process that returns chiral halolactones in synthetically useful enantioselectivities.

We were encouraged by the discovery that $(DHQD)_2PHAL$[15-17] provided good conversions and modest enantioselectivity in the bromolactonization of alkenoic acid **1** (Table 1, entry 1). When **1** was treated with 10 mol % of $(DHQD)_2PHAL$ in the presence of NBS in CH_2Cl_2, the desired bromolactone was isolated in quantitative yield with a modest 22% *ee*. Although lowering the reaction temperature to −20 °C produced an inferior result (entry 2), an exhaustive solvent screen subsequently revealed that $CHCl_3$ was optimal, returning the bromolactone with an improved selectivity of 35% *ee* (entry 3).

A substantial improvement in selectivity was realized when the analogous chlorolactonization was investigated, employing NCS in lieu of NBS. In this case, reaction with 10 mol % of catalyst in $CHCl_3$ returned the desired chlorolactone with a dramatically enhanced selectivity of 65% *ee* (entry 5). Analogous to the bromolactonization, chlorolactonization in DCM returned the chlorolactone with an eroded 39% *ee* (entry 4).

Although we were initially discouraged by the sluggish chlorolactonization when the temperature of the reaction was lowered to −40 °C (no lactone was detected by TLC, entry 6), we were emboldened by the discovery that the more reactive 1,3-dichloro-5,5-dimethylhydantoin (**3**, DCDMH) afforded a faster and more stereoselective reaction at −40 °C (entry 8, quant. conversion, 83% *ee*; for absolute stereochemical assignment of product see Supporting Information). The reaction at room temperature was less stereoselective (entry 7). Extensive parallel additive and co-solvent screens revealed that both 1.0 equiv of benzoic acid additive (entry 9) and a $CHCl_3$/hexane (1:1) solvent system (entry 10) each independently increased the selectivity of the chlorolactonization to 86% *ee*. When the co-solvent and additive effects were combined, the desired lactone was produced in 89% *ee* (entry 11). This selectivity was maintained when the analogous DCDPH (**4**)[18] was applied as the terminal chlorine source (entry 12). We deferred to DCDPH, since it returned higher isolated yields during the course of scale-up experiments. Importantly, it appears that the N,N-dichlorohydantoins are uniquely situated between NBS and NCS in reactivity. They are reactive enough relative to NCS to allow for reaction at low temperature yet are attenuated relative to NBS, thus quelling a prevailing non-selective background reaction.

Next, a panel of *p*-substituted pentenoic acids was subjected to the optimal reaction conditions (Table 2). Phenyl substituted lactone **6a** was generated in 86% yield and 89% *ee*. The quasienantiomeric $(DHQ)_2PHAL$ returned the enantiomeric lactone **6b** in a reduced 75% yield and 77% *ee*. The reduced selectivity in the latter case is likely due to the diastereomeric relationship between the DHQD and DHQ catalysts. Lactone **6c** was returned in nearly quantitative yield, but with essentially no selectivity. Evidently, the *p*-methoxy substituent promotes the facile ring opening of the putative chloronium intermediate, precluding a high degree of selectivity. Lactone **6d**, harboring a less donating *p*-methyl group, was returned with a much improved 80% *ee*. Chloro and fluoro substituted lactones **6e** and **6f** were generated in good yield with 88% and 89% *ee*, respectively. Paratrifluoromethyl substituted **6g** was isolated with 90% *ee*. Biphenyl substituted substrate **5h** returned chlorolactone **6h** in 83% *ee*. Larger aryl substituents resulted in reduced selectivities. Namely, 2-naphthyl lactone **6i** was returned in 72% *ee*. Finally, replacing the 4-aryl substituent in **5** with a cyclohexyl group returned lactone **6j** in 55% yield with a substantially lower 43% *ee*.

We have also evaluated the transformation when 0.01 equiv of $(DHQD)_2PHAL$ was employed for a selection of the substrates in Table 2. Even with a low catalyst loading of just 1 mol %,

lactones **6d**, **6f**, **6h**, and **6i** were returned in 82%, 86%, 80%, and 72% *ee*, respectively (Table 2, values in parentheses). In each case the enantioselectivities approximately match those realized with 10 mol % catalyst.

During the study, a few nuances regarding the mechanism of the transformation have come to light. Early on, we noted that the selectivity of the process was influenced by the gross structural features of the achiral terminal halogen source. Two interesting trends emerged. First, an increase in selectivity was realized as the steric demand of the C-5 substituents on the terminal chlorine source increased. While lactone **6f** was generated in 81% *ee* by action of unsubstituted **7**, the selectivity steadily increased on employing the dimethyl (**3**, 84% *ee*), methylphenyl (**8**, 85% *ee*), and diphenyl (**4**, 89% *ee*) chlorine sources (Scheme 1).

These results seem to belie any cursory mechanistic musings that conceptualized the process hinging on the transfer of an active chlorenium equivalent from the hydantoin to the alkaloid prior to delivery to the substrate. One would expect that such a process ought to return **6f** with roughly the same degree of stereoinduction irrespective of the gross structure of the terminal chlorenium source. Conversely, the results in Scheme 1 may indicate a more intimate relationship between the terminal halogen source and the catalyst.

Indeed, we were able to observe an associative complex between unsubstituted hydantoin **7** and the catalyst in a stoichiometric ^{1}H NMR experiment (Scheme 2). In the event, the equivalent C-5 protons of **7** (s, 4.35 ppm) were split into a clean AB quartet (4.30 ppm, J_{AB} = 16.5 Hz) on incubation with an equivalent of (DHQD)$_2$PHAL and benzoic acid (2 equiv) in CDCl$_3$ at −40 °C. This result clearly indicates an association between the N,N-dichlorohydantoin chlorine source and the chiral catalyst. On slowly warming the sample to RT, the association collapses and the AB quartet converges to the expected singlet at 4.35 ppm.

Although premature, we are tempted to suggest complex **11a**, invoking a hydrogen bond mediated association between the protonated catalyst and the chlorenium source. Alternatively one might imagine a tight ion-pair between the chlorinated catalyst and the monochloro anion of the hydantoin chlorine source (see structure **11b**). Although the putative reactive complex awaits further investigation, we believe that the associative complex between catalyst and N,N-dichlorohydantoin disclosed herein is a crucial element in the asymmetric delivery of the chlorine atom.

This associative complex serves not only to impart the enantioselectivity observed in the transformation, but also to significantly accelerate the transformation. Indeed, the uncatalyzed background chlorolactonization is exceedingly slow under identical reaction conditions (effectively no conversion after 24 h). This stands in stark contrast to the catalyzed reactions, which are complete in a 30-90 min timeframe. In fact, the rate of the reaction seems to be chiefly governed by the solubility of the substrate. Remarkably, we have observed that *p*-fluoro substituted substrate **5f** is converted to lactone **6f** (89% *ee*) in less than two minutes!

Secondly, comparison of the results with DCDMH (**3**) and its N-1 and N-3 monomethylated derivatives (**9** and **10** respectively, Scheme 1) and NMR studies indicate an intriguing synergistic role of the two chlorine atoms in the dichlorohydantoin chlorine sources that prove most selective in the transformation. Monitoring the reaction with NMR, revealed that the chlorine atom from the more activated N-3 position, flanked by two carbonyls, was transferred leading to the chlorolactone, apparent from the immediate production of the N1-Cl-hydantoin side product (see supporting information). Comparison of the data for DCDMH **3** and its mono-methylated derivatives **9** and **10** highlight the importance of the less active N-1 chlorine atom. It seems that the N-1 chlorine atom in the dichlorohydantoins serves to inductively activate the N-3 chlorine towards electrophilic delivery. Replacing the N-1 chlorine with a methyl group (**9**) resulted in an inferior transformation returning **6f** in a lower yield (50%) and

enantioselectivity of 78% *ee* (Scheme 1). Further evidence suggesting that the N-1 chlorine is not readily transferred to the product lactone is the exceedingly poor yield of **6f** realized when monochlorohydantoin **10** is employed (7% yield, 72% *ee*). Taken together, these data suggest that the N-3 chlorine is delivered to the substrate exclusively, while the static N-1 chlorine serves to enhance the reactivity of the chlorine source through the inductive withdrawal of electron density.

Currently, the role played by the benzoic acid additive is less clear. Considering the hydrogen bond-mediated complex **11a** (Scheme 2), the additive might serve to ensure adequate protonation of the alkaloid, thus facilitating the formation of the hydantoin/catalyst complex. This role ought to be particularly important late in the reaction as the reduced hydantoin product consumes the acidic proton from the starting alkenoic acid. Alternatively, the benzoic acid may serve to protonate the hydantoin carbonyl, thus facilitating chlorenium transfer to the substrate (in **11a**) or to the catalyst (in **11b**).

We have evaluated the enantioselectivity of the transformation as a function of time. In the chlorolactonization of **5f** (leading to *p*-fluoro substituted **6f**) we noted that the enantioselectivity of the transformation does not change as a function of time or conversion, monitoring the reaction as early as 30 s after initiation. Additionally, a catalyst aging period of 0 min to 1 h prior to the addition of the substrate does not cause a change in the observed enantioselectivity. Finally, doping the reaction mixture with enantiopure **6f** failed to increase the observed enantioselectivity, thus ruling out autocatalysis phenomena. Taken together, these data suggest that non-linear catalysis behavior is not operative in this system.

We have also developed a convenient one-pot protocol for the transformation of these chiral chlorolactones into enantioenriched 1,1-disubstituted epoxy alcohols (Scheme 3). Lithium borohydride reduction of lactone **6f** (86% *ee*) followed by sodium hydroxide mediated cyclization of the resulting chlorohydrin intermediate returned 1,1-disubstituted epoxy alcohol **12** in good yield and importantly without any appreciable loss of enantiopurity. Significantly, 4-arylpenten-1-ols have proven to be difficult substrates for conventional asymmetric epoxidation protocols.[19]

In summary, we have discovered a novel organocatalytic asymmetric chlorolactonization that returns chiral chlorolactones by action of (DHQD)$_2$PHAL and DCDPH. This methodology represents the first example of a catalytic, enantioselective halolactonization that proceeds with synthetically useful enantioselectivities. Current efforts are aimed at understanding the mechanism of the transformation and the details of enantioselection in order to expand the substrate scope and to improve the enantioselectivity. We believe that a thorough understanding of the associative catalyst/chlorohydantoin complexation will likely allow for the development of related transformations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

1. Kolb HC, Vannieuwenhze MS, Sharpless KB. Chem. Rev 1994;94:2483.

2. Katsuki T. Adv. Synth. Catal 2002;344:131.

3. Katsuki T, Martin VS. Org. React 1996;48:1.

4. Wong OA, Shi Y. Chem. Rev 2008;108:3958. [PubMed: 18590339]

5. O'Brien P. Angew. Chem., Int. Ed 1999;38:326.

6. a Sakakura A, Ukai' A, Ishihara' K. Nature 2007;445:900. [PubMed: 17314976] b Kang SH, Lee SB, Park CM. J. Am. Chem. Soc 2003;125:15748. [PubMed: 14677957]

7. a Dowle MD, Davies DI. Chem. Soc. Rev 1979;8:171. b Cardillo G, Orena M. Tetrahedron 1990;46:3321.

8. Kitagawa O, Hanano T, Tanabe K, Shiro M, Taguchi T. J. Chem. Soc.-Chem. Commun 1992:1005.

9. Garnier JM, Robin S, Rousseau G. Eur. J. Org. Chem 2007:3281.

10. Grossman RB, Trupp RJ. Can. J. Chem 1998;76:1233.

11. Haas J, Bissmire S, Wirth T. Chem.-Eur. J 2005;11:5777.

12. Haas J, Piguel S, Wirth T. Org. Lett 2002;4:297. [PubMed: 11796074]

13. Cui XL, Brown RS. J. Org. Chem 2000;65:5653. [PubMed: 10970306]

14. Wang M, Gao LX, Mai WP, Xia AX, Wang F, Zhang SB. J. Org. Chem 2004;69:2874. [PubMed: 15074944]

15. Becker H, Sharpless KB. Angew. Chem., Int. Ed 1996;35:448.

16. a Li G, Chang HT, Sharpless KB. Angew. Chem., Int. Ed 1996;35:451. b Li G, Hubert HH, Sharpless KB. Angew. Chem., Int. Ed 1996;35:2813.

17. Jacobsen EN, Marko I, Mungall WS, Schroder G, Sharpless KB. J. Am. Chem. Soc 1988;110:1968.

18. Whitehead DC, Staples RJ, Borhan B. Tetrahedron Lett 2009;50:656. [PubMed: 20157342]

19. Wang B, Wong OA, Zhao MX, Shi Y. J. Org. Chem 2008;73:9539. [PubMed: 18850744]

Scheme 1.
Cyclization of **5f** with various N-chlorohydantoins.

Scheme 2.
Observation of hydantoin/catalyst complex by NMR.

Scheme 3.
One-pot conversion of **6f** to chiral epoxyalcohol **12**.

Table 1

The (DHQD)$_2$PHAL mediated halolactonization.

Entry	X$^+$ Source[a]	Solvent	Additive	°C	% ee[b]
1	NBS	CH$_2$Cl$_2$	-	RT	22
2	NBS	CH$_2$Cl$_2$	-	−20	14
3	NBS	CHCl$_3$	-	RT	35
4	NCS	CH$_2$Cl$_2$	-	RT	39
5	NCS	CHCl$_3$	-	RT	65
6	NCS	CHCl$_3$	-	−40	NR[c]
7	DCDMH	CHCl$_3$	-	RT	71
8	DCDMH	CHCl$_3$	-	−40	83
9	DCDMH	CHCl$_3$	PhCO$_2$H	−40	86
10	DCDMH	CHCl$_3$/Hex (1:1)	-	−40	86
11	DCDMH	CHCl$_3$/Hex (1:1)	PhCO$_2$H	−40	89
12	DCDPH	CHCl$_3$/Hex (1:1)	PhCO$_2$H	−40	89

[a] X = Br for entries 1-3, and Cl for entries 4-12.

[b] as judged by chiral HPLC or GC analysis.

[c] NR = no reaction after 3 hours.

Table 2

(DHQD)₂PHAL mediated asymmetric chlorolactonization.

R[b]	%yield[c]	%ee[d]	R[b]	%yield[c]	%ee[d]
Ph; **6a**	86	89	p-F-C$_6$H$_4$; **6f**	81 (78)	89 (86)
Ph; **6b** (ent-**6a**)	75	77[e]	p-CF$_3$-C$_6$H$_4$; **6g**	61	90
p-OMe-C$_6$H$_4$; **6c**	99	<5	p-Ph-C$_6$H$_4$; **6h**	59	83 (80)
p-Me-C$_6$H$_4$; **6d**	86 (82)[f]	80 (82)[f]	2-Napth; **6i**	92 (83)	72 (72)
p-Cl-C$_6$H$_4$; **6e**	80	88	Cy; **6j**	55	43

[a] Reaction times; 30 min for products **6a-6f** and **6j**, 90 min for products **6g-6i** (as judged by TLC).

[b] Stereochemistry was determined by chemical correlation (see Supplementary Information).

[c] Isolated yield after column chromatography.

[d] As judged by chiral GC or HPLC analysis.

[e] Reaction was performed with 0.1 equiv of (DHQ)₂PHAL.

[f] Values in parentheses are yields and % ee when 0.01 eq. (DHQD)₂PHAL was employed.