JOC The Journal of Organic Chemistry

Article

Enantioselective Halolactonization Reactions using BINOL-derived Bifunctional Catalysts: Methodology, Diversification, and Applications

Daniel W. Klosowski, John Caleb Hethcox, Daniel H Paull, Chao Fang, James R. Donald, Christopher Ryan Shugrue, Andrew David Pansick, and Stephen F. Martin

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b00490 • Publication Date (Web): 02 May 2018

Just Accepted

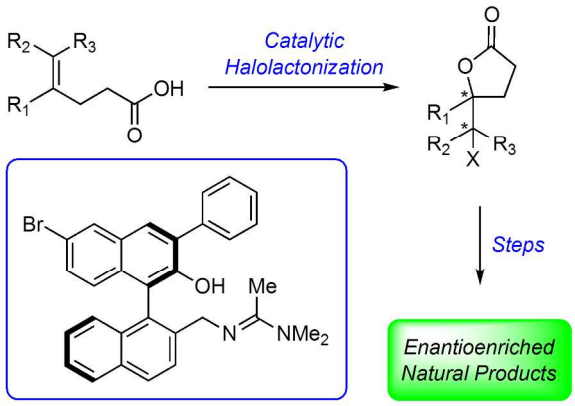
ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Enantioselective Halolactonization Reactions using BINOL-derived Bifunctional Catalysts: Methodology, Diversification, and Applications

Daniel W. Klosowski, J. Caleb Hethcox, Daniel H. Paull,[a] Chao Fang,[b] James R. Donald,[c] Christopher R. Shugrue, Andrew D. Pansick, and Stephen F. Martin*

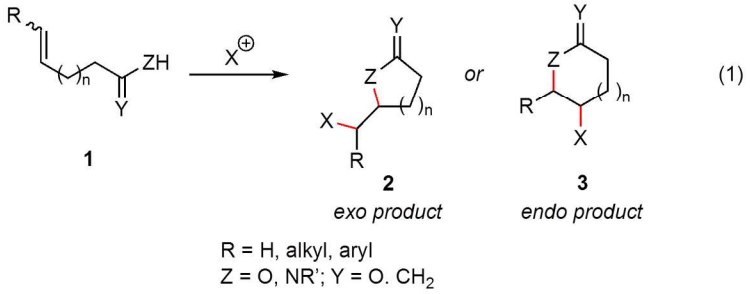
Department of Chemistry, The University of Texas at Austin, Austin, Texas 78712



ABSTRACT: A general protocol is described for inducing enantioselective halolactonizations of unsaturated carboxylic acids using novel bifunctional organic catalysts derived from a chiral binaphthalene scaffold. Bromo- and iodolactonization reactions of diversely substituted, unsaturated carboxylic acids proceed with high degrees of enantioselectivity, regioselectivity, and diastereoselectivity. Notably, these BINOL-derived catalysts are the first to induce the bromo- and iodolactonizations of 5-alkyl-4(*Z*)-olefinic acids via 5-*exo* mode cyclizations to give lactones in which new carbon–halogen bonds are created at a stereogenic center with high diastereo- and enantioselectivities. Iodolactonizations of 6-substituted-5(*Z*)-olefinic acids also occur via 6-*exo* cyclizations to provide δ-lactones with excellent enantioselectivities. Several notable applications of this halolactonization methodology were developed for desymmetrization, kinetic resolution, and epoxidation of *Z*-alkenes. The utility of these reactions is demonstrated by their application to a synthesis of precursors of the F-ring subunit of kibdelone C and to the shortest catalytic, enantioselective synthesis of (+)-disparlure reported to date.

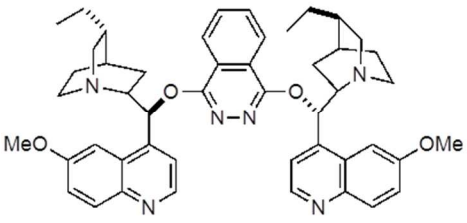
INTRODUCTION

Cyclizations via halofunctionalization of olefins **1** represent an important class of reactions for the construction of heterocyclic compounds with carbon-halogen bonds (C–X) outside (*exo*) or inside (*endo*) the newly formed ring as in **2** and **3**, respectively (Equation 1). Consequently, the development of catalytic, enantioselective halocyclization reactions is a burgeoning field, and, although there have been a plethora of advances over the past six years,[1] significant gaps in the methodology remain.

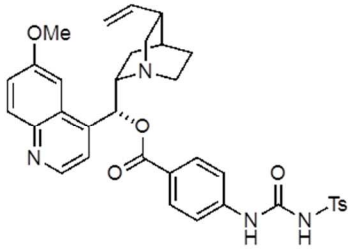


Enantioselective halocyclizations of α,ω-hydroxy alkenes **1** (Y = H_2; Z = O)[2] and α,ω-amino alkenes **1** (Y = H_2; Z = NR')[3] have been reported, although the majority of the work in the area of enantioselective halofunctionalizations of olefins has been focused on enantioselective halolactonization reactions (Y = O, Z = OH).[4–6] Borhan described the first highly enantioselective (up to 95:5 er) chlorolactonizations of a series of 4-aryl-substituted-4-pentenoic acids to generate the corresponding chlorolactones using the commercially-available, cinchona alkaloid derivative $(DHQD)_2PHAL$ (**4**) as the catalyst (Figure 1).[4a] There have been only two other catalysts capable of effecting enantioselective chlorolactonizations. Tang reported catalyst **5**, which promoted chlorolactonizations 4-aryl-substituted-4-pentenoic acids,[4b] and Zhou reported a *cinchonine*-squarimide catalyst that promotes chlorolactonizations of vinylbenzoic acids.[4d]

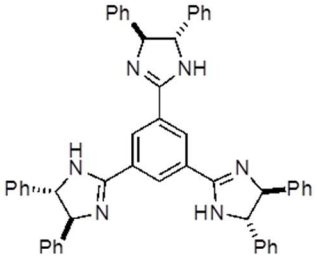
Enantioselective bromo- and iodolactonization reactions have attracted greater attention than any other cyclization involving halofunctionalization of olefins. For example, the C_3-symmetric trisimidazoline catalyst **6** was first reported to induce 6-exo bromolactonizations of 5-aryl-substituted-5-hexenoic acids to deliver δ-lactones,[5f] and it has since been shown to work equally well with tri- and tetrasubstituted olefinic acids.[5g] In 2010 Yeung showed that the quinidine-derived thiocarbamate **7** catalyzed enantioselective bromolactonizations of 4-aryl-substituted-4-pentenoic acids,[5b] and by making slight changes in the quinidine catalyst, he was able to induce the enantioselective bromolactonizations of a variety of other substrates.[5c–e] Yeung later developed several proline derived catalysts **8** for the enantioselective bromolactonizations of 4-substituted-4-pentenoic acids and 5-substituted-5-hexenoic acids, but each substrate class required catalyst optimization.



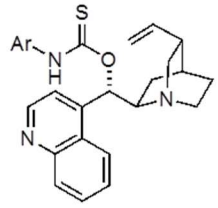
4
Borhan[4a] - Chlorolactonization
Armstrong[5h] - Bromolactonization



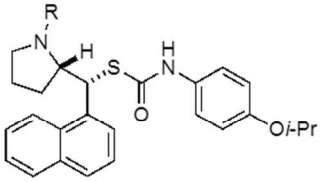
5
Tang[4b] - Chlorolactonization



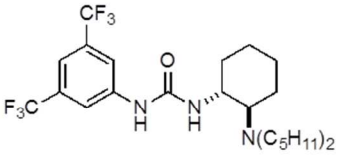
6
Fujioka[5f] - Bromolactonization



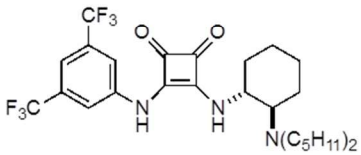
7
Yeung[5b] - Bromolactonization



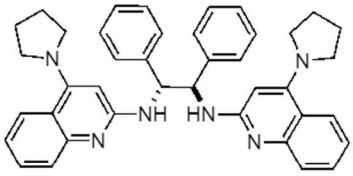
8
Yeung[5e] - Bromolactonization



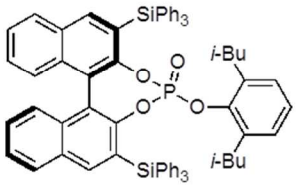
9
Jacobsen[6a] - Iodolactonization



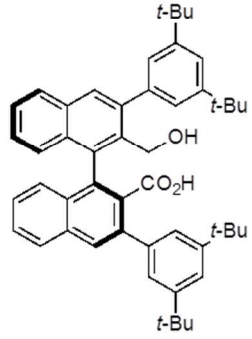
10
Hansen[6b] - Iodolactonization



11
Johnston[6e] - Iodolactonization



12
Ishihara[6h] - Iodolactonization



13
Hamashima[7b] - Fluorolactonization

Figure 1. Halolactonization catalysts.

Jacobsen's tertiary aminourea catalyst **9** promoted enantioselective iodolactonizations of 5-substituted-5-hexenoic acids with moderate to excellent selectivities.[6a] Subsequently, Hansen disclosed that the squarimide variant **10** also induced iodolactonization reactions, although the selectivities were lower than with **9**.[6b] The catalyst **11**, which was developed by Johnston, effected the iodolactonizations of 5-substituted-5-hexenoic acids with generally high enantioselectivities.[6c] Ishihara reported that iodolactonizations of benzyl-substituted-4-pentenoic acids in the presence of the binaphthyl **12** formed γ-butyrolactones with good enantioselectivities.[6h]

The first example of a catalytic, enantioselective fluorolactonization was reported by Rueping, who utilized a combination of $(DHQ)_2PHAL$ (**4**) and Selectfluor® to generate a fluorinated isobenzofuran in modest yield (50%) and with low enantioselectivity (27% ee).[7a] The only catalytic, highly enantioselective fluorolactonization using an electrophilic fluorine source reported thus far was achieved using the binaphthyl derivative **13**, although the substrate scope was somewhat limited.[7b] The methylene spacer between the naphthol and hydroxyl group was found to be critical because the naphthol based catalyst gave racemic product. Jacobsen recently reported a method for asymmetric fluorolactonization using a chiral aryl iodide catalyst and a nucleophilic fluoride source that delivered fluorinated isochromanones with generally high enantioselectivity.[7c]

Several chiral Lewis acid-derived catalysts have also been used to promote enantioselective halolactonizations,[6e,f,g] but these catalysts have some notable limitations. Specifically, halolactonizations of olefinic acids bearing an alkyl group on the double bond often led to lower enantioselectivities compared to aryl-substituted olefinic acids, and most catalytic systems appear to be limited to a specific halogen atom.

Despite the many advances in catalysts that have been developed to promote enantioselective halolactonizations, the substrate scope of each is typically limited, especially for chloro- and iodolactonizations. Although there were several gaps in the methodology when we initiated our work, a major deficiency in the contemporaneous art was the lack of any example of a halolactonization that proceeded via an exo mode of ring closure to give a lactone bearing a new C–X bond at a stereogenic secondary carbon atom (*e.g.,* **2**, R = alkyl, aryl; Z = Y = O). This was somewhat surprising because several examples of the corresponding exo halocyclizations of hydroxy alkenes **1** (R = alkyl or aryl; Y = H_2, Z = O) to furnish the corresponding tetrahydrofurans were known.[2a–d] The sole example of a halolactonization that created a stereogenic carbon atom bearing a halogen atom involved an *endo* cyclization mode.[5c] It should be noted that during the course of our studies, Yeung reported the use of **4** to catalyze the

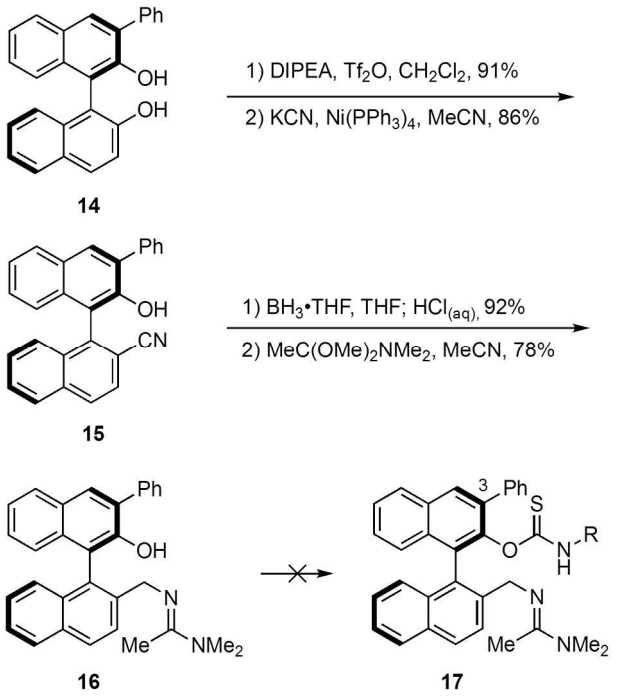
bromolactonization of several 5-substituted-4(*Z*)-pentenoic acids in an *exo* fashion to give stereogenic C–X bonds at secondary carbons.[5d] Herein we report the details of our methodological studies directed toward the design and development of novel organic catalysts for enantioselective bromo- and iodolactonizations,[8] as well as the applications of these enantioselective halolactonizations to solving several synthetic problems in this account.[9]

RESULTS AND DISCUSSION

Catalyst Design and Conditions: Bromolactonizations. The difficulty associated with developing an enantioselective bromocyclization reaction arises, in part, from the reversibility of bromonium ion formation and its propensity to transfer Br^+ to another olefin prior to intramolecular capture by a pendant nucleophile.[10] In order to address this problem, most successful known catalysts are bifunctional containing both Lewis/Brønsted acid and Lewis/Brønsted base functionalities (Figure 1). This critical attribute enables the catalyst to coordinate with the substrate as well as with the brominating reagent or bromonium ion. When we began designing a catalyst for bromolactonizations, we envisioned that established bifunctional motifs found in some of the known catalysts (*e.g.,* **4**–**9**, Figure 1) could be mounted on a chiral binaphthyl backbone, which despite its near ubiquity in the field of enantioselective reactions had not yet been applied to halocyclization reactions.

The initial goal was to develop analogs of the bifunctional catalyst **17**, which bear amidine and thiocarbamate groups as the requisite Lewis base and acid motifs appended to a BINOL-derived scaffold. An amidine group was selected rather than a tertiary amine because bromine was well-known to rapidly oxidize benzylic tertiary amines.[11] Having a phenyl group at the 3-position of **17** was designed to increase steric bulk around the proposed catalophore, a tactic known to enhance the enantioselectivity of reactions catalyzed by BINOL derivatives.[12]

Toward the synthesis of **17**, the known (*R*)-BINOL **14**[13] was first converted into **15** by monotriflation followed by nickel-mediated cross-coupling with potassium cyanide (Scheme 1). Reduction of the nitrile and amidine formation provided **16**. Unfortunately, all of our efforts to convert the phenol moiety into the thiocarbamate **17** were unsuccessful.



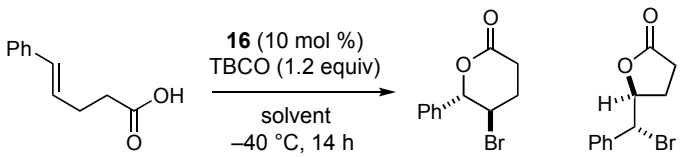
Scheme 1. Attempted synthesis of catalyst **17**

The initial disappointment notwithstanding, we queried whether **16**, which has an acidic phenolic hydroxyl group, might itself serve as a suitable catalyst for bromolactonizations.8[a] The first step toward testing this hypothesis involved identifying reaction conditions that gave minimal amounts of background reaction. In our initial screenings, we discovered that stirring solutions of 5-phenyl-4(*E*)-pentenoic acid (**18**) in PhMe/CH_2Cl_2 (1:1) containing 2,4,4,6-tetrabromobenzo-quinone (TBCO) at temperatures less than –40 °C for 14 h gave negligible amounts of racemic lactones **19a** and **19b**.

Having discovered conditions under which a background reaction was insignificant, a solvent screen was performed for the bromolactonization of the olefinic acid **18** promoted by TBCO in the presence of **16** (10 mol %) (Table 1) to identify conditions that provided **19a** with high regioselectivity and enantiomeric ratio (er). Although reactions in pure toluene or THF proceeded with low conversion and regioselectivity (Table 1, entries 1 and 2), use of CH_2Cl_2 led to furnished **19a** in good yield and with good enantioselectivity (Table 1, entry 3). We then examined mixtures of toluene and CH_2Cl_2 (Table 1, entries 4–6) and discovered that a mixture (2:1) of toluene and CH_2Cl_2 provided **19a** with excellent regioselectivity (15:1) and a high enantioselectivity (97:3 er) (Table 1, entry 5). Notably, similar combinations of a polar solvent (CH_2Cl_2 or

$CHCl_3$) and a nonpolar solvent (toluene or hexane) have been used in a number of other enantioselective halolactonizations.[5,6]

Table 1. Solvent Screening for Bromolactonization[a]

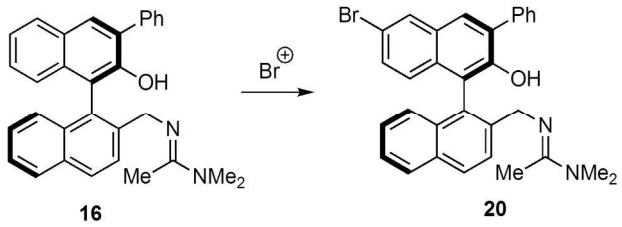


18 **19a** **19b**

Entry	Solvent	Yield (%)[b]	**19a:19b**	er[d]
1	PhMe	trace	4:1	ND
2	THF	ca. 20	1:1	ND
3	CH_2Cl_2	64	15:1	91:9
4	PhMe/CH_2Cl_2 (1:1)	75	15:1	96:4
5	PhMe/CH_2Cl_2 (2:1)	95	15:1	97:3
6	PhMe/CH_2Cl_2 (4:1)	50	15:1	97:3

[a]Reactions run on 0.1 mmol scale. [b]Yield of mixture of **19a**,**b**. [c]Regioselectivity determined by ^{1}H NMR spectra of the crude reaction mixtures. [d]er determined by chiral HPLC; absolute stereochemistry of **19a** was assigned based upon correlation of optical rotation with reported value;5[c] the absolute stereochemistry of **19b** was assigned based upon working model (*vide infra*); ND = not determined.

Subsequent to these exploratory studies, we found that *N*-bromosuccinimide (NBS) and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) could also be employed as brominating agents to furnish **19a** with similarly high enantioselectivities and yields. The fact that the enantioselectivity of bromolactonization with catalyst **16** is independent of the brominating reagent is unlike what is observed with other organic catalysts.5 Moreover, this observation has mechanistic implications and suggests that the intermediate bromonium ion might be formed by delivery of Br^+ from an *N*-bromo amidine that is generated *in situ* rather than directly from the original brominating reagent (*vide infra*).[14] When we sought to recover **16** for reuse, we were somewhat surprised to isolate the 6-bromo analog **20** rather than the original catalyst **16**. Because **16** underwent facile bromination to give **20** under the conditions for bromolactonization, we believe that **20** is the dominant active catalyst in bromolactonization reactions. This fortuitous finding led to the identification of **20** as an effective organic catalyst to promote enantioselective brominations, although we rarely prepared and used it for this purpose, and iodolactonizations (*vide infra*).8[b]



(2)

Modification of Original Catalyst Design. Although we established that **16** catalyzed the bromolactonization of **18** to give **19a** with high regio- and enantioselectivity, we found that it promoted the bromolactonization of **21**, a common test substrate for bromolactonizations,[5] to give **22** with reduced enantioselectivity (86:14 er) (Table 2, entry 1). Perhaps not surprisingly, we also showed that preformed **20** catalyzed the bromolactonization of **21** with the same enantioselectivity as **16** (Table 2, entry 2). In order to identify analogs of **16** and **20** that might be superior catalysts, we prepared the series of analogs **23a–i** (Figure 2), and surveyed their suitability for promoting the enantioselective bromolactonization of **21**.

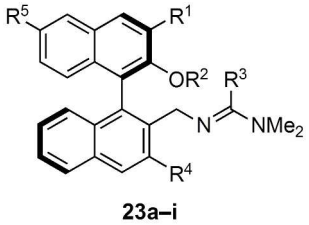
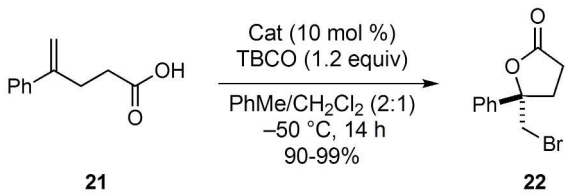


Figure 2. General design for analogs of catalyst **16**.

Table 2. Effects of Catalyst Modifications[a]



21 **22**

Entry	Cat.	R^1	R^2	R^3	R^4	R^5	er[b]
1	**16**	Ph	H	Me	H	H	86:14
2	**20**	Ph	H	Me	H	Br	86:14
3[c]	**23a**	Ph	H	Me	H	NO_2	NR
4	**23b**	H	H	Me	H	H	84:16
5	**23c**	Ph_3Si	H	Me	H	H	74:26
6	**23d**	TRIP[d]	H	Me	H	H	50:50
7	**23e**	Ph	H	Me	Ph	H	85:15
8	**23f**	Ph	H	Ph	H	H	82:18
9	**23g**	H	H	Ph	H	H	87:13
10	**23h**	H	H	*t*-Bu	H	H	62:38
11	**23i**	H	Me	Me	H	H	50:50

[a]Reactions run on 0.1 mmol scale, and all reactions gave >90% conversion. [b]er determined by chiral HPLC; the absolute stereochemistry of **22** was assigned based upon correlations of optical rotation with those previously reported values.[5b,6a] [c]NR = no reaction. [d]TRIP: 2,4,6-triisopropylphenyl.

We first evaluated the effect of placing an electron withdrawing group on the binaphthyl scaffold, and we found that **23a**, the 6-nitro analog of **16**, did not catalyze the bromolactonization of **21** (Table 2, entry 3). We then probed the consequence of varying the steric requirements of substituents at the 3- and 3'-positions of the binaphthyl moiety as well as on the amidine group (Figure 2). In our initial design of catalyst **16**, the phenyl ring was incorporated at C3 to help create a sterically biased catalytic pocket, which we believed would be important for obtaining high enantioselectivities. However, we discovered that bromolactonization of **21** with **23b** (R^1 = H, Table 2, entry 4), which lacks the phenyl group at the 3-position, gave **22** with nearly identical selectivity as **16** (84:16 er vs. 86:14 er) (Table 2, entry 3). On the other hand, increasing the size of the R^1 substituent to triphenylsilyl (**23c**, Table 2, entry 5) or 2,4,6-triisopropylphenyl (**23d**, Table 2, entry 6) led to a significant erosion of enantioselectivity. Introducing a phenyl group at the 3-position adjacent to the amidine group led to **23e**, which catalyzed the bromolactonization of **21** with selectivities comparable to that of the parent catalyst **16** (Table 2, entry 7)

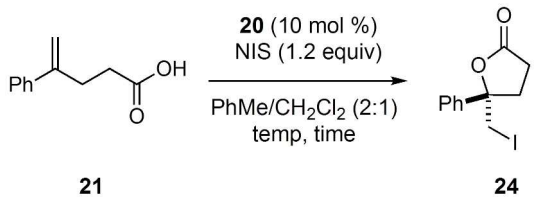
We also briefly examined the effects of altering the substituent R^3 on the amidine group upon the bromolactonization of **21**. Although replacing the methyl group in **16** (Table 2, entry 8) and **23b** (Table 2, entry 9) with a phenyl group did not significantly affect the enantioselectivities, the presence of a *tert*-butyl group **23h** (R^3 = *t*-Bu) led to significant drop in selectivity (62:38 er, Table 1, entry 10). In order to assess whether the bifunctional nature of the catalyst was critical for inducing enantioselectivity, the acidic phenolic group in **23b** was methylated to give **23i**. This modification led to complete loss of enantioselectivity (Table 2, entry 11), an observation that suggests that the acidic proton in the catalyst is imperative for enantioselectivity. Although screening a number of analogs of **16** led to several catalysts that promote the bromolactonization of **21** with comparable enantioselectivities, there were instances where **16** was superior, so it was used uniformly in subsequent experiments.

Application to Other Halolactonizations. At the time of our investigations, no catalyst was known to promote enantioselective halolactonizations with more than one halogen. We were thus inspired to ascertain whether **16** might catalyze other enantioselective halolactonizations. Chlorolactonization of **21** was first examined using **16** and **20** with *N*-chlorosuccinimide (NCS) and 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) in a variety of solvents. However, consistent with other literature reports, the reactions proceeded with low conversions and poor enantioselectivities.[5b,d] Owing to the poor enantioselectivity in these preliminary experiments, we did not further pursue chlorolactonizations.

We then turned our attention to iodolactonizations, and gratifyingly we discovered that the iodolactonization of **21** with *N*-iodosuccinimide (NIS) in the presence of **16** in a mixture (2:1) of toluene and CH_2Cl_2 at –40 °C delivered the iodolactone **24** (93:7 er). Although this reaction was sluggish, we found that the corresponding reaction with the brominated catalyst **20** was somewhat faster (Table 3, entry 1). Because of the operational advantage associated with using **20** as the catalyst, we screened several temperatures and conditions to identify a standard set of reaction parameters to establish the scope of this process. We discovered that iodolactonizations of **21** with NIS in the presence of **20** proceeded with comparable yields and enantioselectivities at temperatures between –10 and –40 °C, but there was a slight erosion in enantioselectivity when the reaction was performed at 0 °C (Table 3, entries 1–4). Not surprisingly, reaction times decreased significantly with increasing temperature. Because Jacobsen had reported that use of iodine as an additive had a beneficial effect on iodolactonizations using **9** as the catalyst,[6a] we tested the effects of adding catalytic amounts of iodine. However, the presence of iodine (1 or 10 mol %) had little effect on the enantioselectivity of the iodolactonization of **21** (Table 3, entries 6 and 7).

It is notable, however, that the effect of iodine as an additive was not consistent, and some reactions benefited from the addition of iodine.

Table 3. Optimization of Iodolactonization[a]



21 24

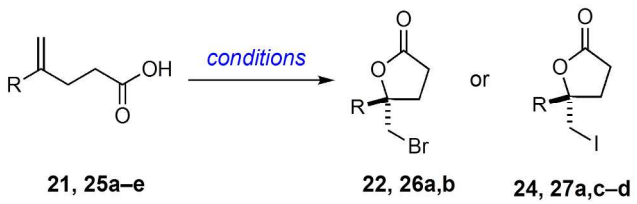
Entry	Temp (°C)	Time (h)	Yield (%)	er[b]
1	−40	38	89	93:7
2	−20	14	86	93:7
3	−10	1.5	87	92:8
4	0	0.75	87	90:10
5[c]	−20	14	99	92:8
6[c]	−20	14	86	93:7

[a]Reactions run on 0.1 mmol scale. [b]er determined by chiral HPLC; absolute stereochemistry of iodolactone **24** was assigned by correlation of optical rotation with previously reported values.[5b,6a] [c]Results obtained with 10 mol % I_2.

Substrate Scope of Halolactonizations. Having established that **16** and/or **20** catalyze highly regio- and enantioselective bromo- and iodolactonizations, we elucidated the scope of these reactions. 4-Substituted-4-pentenoic acids are commonly employed as test substrates to demonstrate the efficacy of enantioselective halolactonizations,[5,6] so we examined the bromo- and iodolactonizations, respectively, of **21** and **25a–e** (Table 4). Notably, the enantioselectivities obtained in these reactions with our new BINOL-derived catalysts are comparable to those obtained with other catalysts.[5b,6a] Although we did not fully evaluate electronic effects, the presence of an electron-withdrawing group on the aromatic ring appears to lead to a slight increase in enantioselectivity in bromolactonizations (Table 4, entries 1, 3, and 5); however, this effect was not observed for iodolactonizations (Table 4, entries 2 and 4). On the other hand, an electron-donating group (R = *p*-MeO-Ph, **25c**) led to a significant reduction in enantioselectivity of the iodolactonization (Table 4, entry 6). This finding is consistent with literature reports that chlorolactonization[4a] and bromolactonization[5b] of **25c** are even less enantioselective. In contrast to what we observed in the iodolactonization of **21** (*vide supra*) but consistent with the observations of Jacobsen,[6a] cyclization of **25c** proceeded with somewhat higher enantioselectivity (er = 82:18) in the presence of iodine

(Table 4, entry 6). This 4-Alkyl-4-pentenoic acids also underwent facile iodolactonizations, but steric effects are important, and the enantioselectivity is better for larger alkyl groups (Table 4, entries 7 and 8).

Table 4. Halolactonization of 4-Substituted-4-Pentenoic Acids[a]



21, 25a–e **22, 26a,b** **24, 27a,c–d**

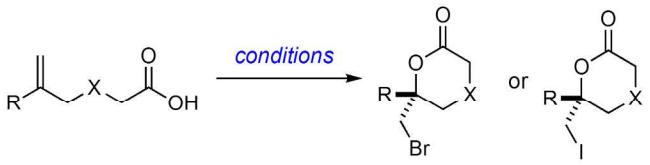
Entry	Acids	R	Product	Yield (%)	er[b]
1	**21**	Ph	**22**	99	86:14
2	**21**	Ph	**24**	89	93:7
3	**25a**	*p*-NC-Ph	**26a**	92	94:6
4	**25a**	*p*-NC-Ph	**27a**	73	90:10
5	**25b**	*m*-NC-Ph	**26b**	89	91:9
6[c]	**25c**	*p*-MeO-Ph	**27c**	90	74:26
7	**25d**	Me	**27d**	96	65:35
8	**25e**	*t*-Bu	**27e**	91	83:17

[a]Reactions run on 0.10 mmol scale. Conditions for bromolactonization: 10 mol % **16**, 1.2 equiv TBCO in PhMe/CH_2Cl_2 (2:1) at –50 °C. Conditions for iodolactonization: 10 mol % **20**, 1.2 equiv NIS in PhMe/CH_2Cl_2 (2:1) at –20 °C. [b]er determined by chiral HPLC; absolute stereochemistry of **22** and **24** were assigned by correlation of optical rotations with previously reported values,[5b,6a] and other assignments are based upon analogy. [c]Results obtained with 10 mol % I_2, 93% yield, 82:18 er.

The next set of substrates examined was a small collection of 5-substituted-5-hexenoic acid derivatives that cyclize via 6-exo cyclizations to give δ-lactones (Table 5). Under the standard conditions, bromolactonization of 5-phenyl-5-hexenoic acid (**28a**) proceeded with 75% yield and 62:38 er (Table 5, entry 1), whereas the iodolactone **30a** was obtained from **28a** in slightly better enantioselectivity (76:24 er, Table 5, entry 2). Consistent with findings of Jacobsen,[6a] addition of iodine (10 mol %) led to a modest increase in enantioselectivity (85:15 er) to provide **30a**. It should be noted at this juncture, however, that the presence of iodine did not always increase the selectivity of iodolactonizations catalyzed by **20** (*vide*

infra). Although Jacobsen observed that the 6-exo cyclization of **28a** and the 5-exo cyclization of **21** with **9** proceeded with *opposite* facial selectivities,[6a] use of **20** as a catalyst for these cyclizations gave products **24** and **30a** that have the same absolute configuration. The 6-exo bromo- and iodolactonization of **28b** delivered the bromolactone **29b** and iodolactone **30b** in 82:18 and 79:21 er, respectively (Table 5, entries 3 and 4); addition of iodine had little effect on the enantioselectivity of the iodolactonization. Halolactonization of **28c** occurred to give bromo- and iododioxanones in 85:15 and 84:16 er, respectively, with a slight increase in selectivity being observed when iodine was present (Table 5, entries 5 and 6).

Table 5. Halolactonization of 5-Substituted-5-Hexenoic Acids[a]



28a–c **29a–c** **30a–c**

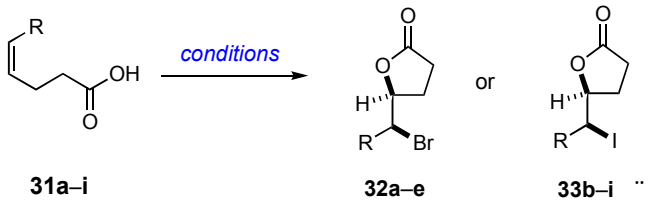
Entry	Acids	R	X	Product	Yield (%)	er[b]
1	**28a**	Ph	CH_2	**29a**	78	62:38
2[c]	**28a**	Ph	CH_2	**30a**	98	76:24
3	**28b**	Me	CH_2	**29b**	90	82:18
4[d]	**28b**	Me	CH_2	**30b**	89	79:21
5	**28c**	Ph	O	**29c**	94	85:15
6[e]	**28c**	Ph	O	**30c**	91	84:16

[a]Reactions run on 0.10 mmol scale. Conditions for bromolactonization: 10 mol % **16**, 1.2 equiv TBCO in PhMe/CH_2Cl_2 (2:1) at –50 °C. Conditions for iodolactonization: 10 mol % **20**, 1.2 equiv NIS in PhMe/CH_2Cl_2 (2:1) at –20 °C. [b]er determined by chiral HPLC; absolute stereochemistry of **30a** was assigned by correlation of optical rotation with previously reported value,[6a] and the other assignments are based upon analogy. [c]Results obtained with 10 mol % I_2, 95% yield, 85:15 er. [d]Results obtained with 10 mol % I_2, 90% yield, 80:20 er. [e]Results obtained with 10 mol % I_2, 89% yield, 90:10 er.

In our initial exploratory studies, we discovered that **16** promoted the highly enantioselective cyclization of **18** to give **19a** (**Table 1**). Although **19a** contains a new stereocenter bearing a bromo group, the formation of similar chiral alkyl bromides via a 6-endo cyclization mode was known.[5c] However, enantioselective halolactonizations in which a new C–X bond is produced at a secondary carbon atom via a 5-exo cyclization was unprecedented. It is thus notable that the bromo- *and* iodolactonizations of a representative selection of 5-alkyl-4(*Z*)-pentenoic acids **31a–e** catalyzed by **16** and **20** proceeded via a 5-exo cyclization to furnish the corresponding γ-lactones **32a–e** and **33b–e** in generally high yields and enantioselectivities (≥95:5 er) (Table 6, entries 1–9). The unsaturated acid **31a** (R = Et, Table 6, entry 1) was the only substrate tested that cyclized with a modest er (85:15), suggesting that branching on the carbon atom attached directly to the double bond might play a role in determining selectivity. The γ-lactones **32a–e** and **33b–e** contain two contiguous stereogenic centers, one of which bears a carbon-halogen bond. The *Z*-olefin geometry appears to be an important prerequisite for high enantioselectivity because the corresponding 5-alkyl substituted-4(*E*)-pentenoic acids cyclized with only 50:50 to 78:22 er. The set of 5-aryl-4(*Z*)-pentenoic acids **31f–i** also underwent facile iodolactonization via a 5-exo cyclization pathway to form γ-iodolactones **33f–i** with high enantioselectivity (er ≥98:2) (Table 6, entries 10–13). Collectively, the cyclizations of **31a–i** represent the first examples halolactonizations that occur via a 5-exo mode of ring closure to give products in which new C–O and C–X bonds are formed at contiguous stereogenic centers.

One might anticipate that the *Z*-alkenes **31f–i**, like the *E*-alkene **18**, would be electronically biased to cyclize via a 6-endo mode. However, the observation that *cis*-aryl olefinic acids **31f–i** underwent selective exo cyclizations is consistent with the transition state **35** that is favored relative to **34**, because the unfavorable steric interaction depicted in **34** prevents benzylic stabilization of the putative iodonium ion, or the nascent carbocation, by the π electrons of the aryl group (Figure 3).[15] Cyclization of conformer **35** through the 5-exo mode is thus favored for steric and entropic reasons. The regiochemical outcome in these cyclizations are consistent with those observed by Denmark in related bromoetherifications.[2d,f]

Table 6. Halolactonization of 5-Substituted-4(*Z*)-Pentenoic Acids[a]



31a–i **32a–e** **33b–i**

Entry	Acids	R	Product	Yield (%)	er[b]
1	**31a**	Et	**32a**	90	85:15
2	**31b**	*i*-Pr	**32b**	94	97:3
3	**31b**	*i*-Pr	**33b**	93	97:3
4	**31c**	*i*-Bu	**32c**	87	95:5
5	**31c**	*i*-Bu	**33c**	94	98:2
6	**31d**	*t*-Bu	**32d**	97	97:3
7	**31d**	*t*-Bu	**33d**	99	97:3
8	**31e**	Cy	**32e**	94	98.5:1.5
9	**31e**	Cy	**33e**	97	98:2
10	**31f**	Ph	**33f**	93	98.5:1.5
11	**31g**	*p*-NC-Ph	**33g**	95	99:1
12	**31h**	*p*-Cl-Ph	**33h**	89	98:2
13	**31i**	2-Np	**33i**	94	98:2

[a]Reactions run on 0.10 mmol scale. Conditions for bromolactonization: 10 mol % **16**, 1.2 equiv TBCO in PhMe/CH_2Cl_2 (2:1) at –50 °C. Conditions for iodolactonization: 10 mol % **20**, 1.2 equiv NIS in PhMe/CH_2Cl_2 (2:1) at –20 °C. [b]er determined by chiral HPLC; absolute stereochemistry of **32d, 33d,** and **33f** were determined by X-ray crystallography, and other assignments are based upon analogy.

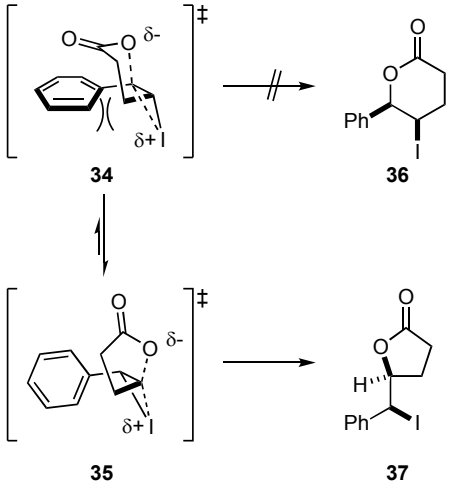
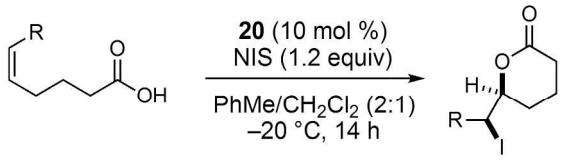


Figure 3. The 6-endo product **36** is disfavored because the phenyl ring in **34** cannot adopt a conformation that stabilizes the transition state leading to **36**, thereby leading preferentially to the formation of the 5-exo product **37**.

In a closely related set of experiments, we examined the iodolactonizations of 6-substituted-5(*Z*)-hexenoic acids **38a–d** and found that the corresponding iodo δ-lactones **39a–d** were produced in high yields and enantioselectivities of ≥98:2 (Table 7). These cyclizations are also notable in that two adjacent stereogenic centers, one of which is a C–I bond, are generated.

Table 7. Iodolactonization of 6-Substituted-5(*Z*)-Hexenoic Acids[a]



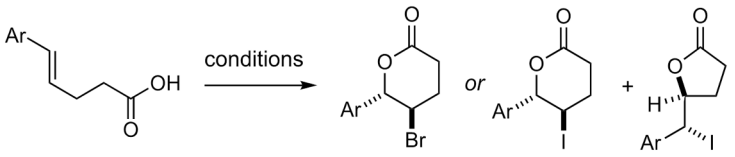
38a–d **39a–d**

Entry	Acids	R	Product	Yield (%)	er[b]
1	**38a**	Ph	**39a**	89	99:1
2	**38b**	*p*-NC-Ph	**39b**	88	99:1
3[c]	**38c**	2-Np	**39c**	93	98.5:1.5
4[c]	**38d**	*t*-Bu	**39d**	98	98:2

[a]Reactions run on 0.10 mmol scale. [b]er determined by chiral HPLC; absolute stereochemistry assigned based on analogy with **33d** and **33f**. [c]Results obtained after 38 h at –20 °C.

We then investigated halolactonizations of a set of 5-aryl-4(*E*)-pentenoic acids comprising **18** and **40a–d**. Unsaturated acids **18**, **40a**, and **40b** underwent bromolactonizations in the presence of **16** and TBCO by 6-endo cyclizations to form the δ-lactones **19a**, **41a**, and **41b** with high yields and enantioselectivities (Table 8, entries 1–3). On the other hand, iodolactonization of **18** afforded an inseparable mixture (1:1.3) of 6-endo and 5-exo products **42a** and **43a**, respectively (Table 8, entry 4). Iodolactonization of **40c** (Ar = *p*-MeO-Ph) selectively gave the 6-endo product **42c** (>20:1) with moderate enantioselectivity (86.5:13.5 er, Table 8, entry 5), whereas iodolactonization of **40d** (Ar = *p*-NC-Ph) afforded the 5-exo product **43d** with poor enantioselectivity (Table 8, entry 6). With the exception of the iodolactonization of **18**, the preferred regioselectivity in these cyclizations is consistent with electronic effects.

Table 8. Halolactonization of 5-Aryl-4(*E*)-Pentenoic Acids[a]



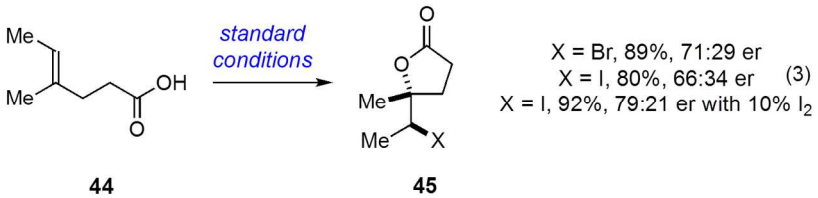
18, 40a–d **19a, 41a,b** **42a,c** **43a,d**

Entry	Acids	Ar	Product	Yield (%)	er[b]
1	**18**	Ph	**19a**	94[d]	98:2
2	**40a**	2-Np	**41a**	97	96:4
3	**40b**	2-thienyl	**41b**	92	94:6
4	**18**	Ph	**42a+43a**	89[e]	95:5[e]
5	**40c**	*p*-MeO-Ph	**42c**	89	87:13
6[f]	**40d**	*p*-NC-Ph	**43d**	94	58:42

[a]Reactions run on 0.10 mmol scale. Conditions for bromolactonization: 10 mol % **16**, 1.2 equiv TBCO in $PhMe/CH_2Cl_2$ (2:1) at –50 °C. Conditions for iodolactonization: 10 mol % **20**, 1.2 equiv NIS in $PhMe/CH_2Cl_2$ (2:1) at –20 °C. [b]er determined by chiral HPLC; absolute stereochemistry of **19a**, **41a**, and **41b** were assigned by correlation of optical rotations with previously reported values,5[c] whereas absolute stereochemistry of iodolactones assigned based on analogy. [c]The absolute stereochemistry of **43a** and **43d** (major enantiomer) were assigned based upon working model (*vide infra*). [d]Reaction run at –60 °C. [e]Combined yield; ratio of 1.0:1.3 for **42a**/**43a** based upon ^{1}H NMR analysis; er shown in parentheses is for **42a**, and er for **43a** is 52:48. [f]Reaction performed for 14 h at –20 °C and 48 h at –10 °C in CH_2Cl_2/PhMe (1:1).

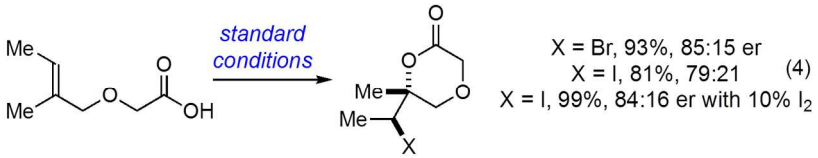
Inducing enantioselective halolactonizations of tri-substituted olefinic acids presents some significant challenges relative to 1,1- and 1,2-disubstituted substrates with only one report of a highly selective

bromolactonization to date.[5g] For example, subjection of **44** and **46** to standard bromo- and iodolactonization conditions furnished the corresponding bromo- and iodolactones **45** (X = Br and I) and **47** (X = Br and I) in very good yields but with only moderate enantioselectivities (Equations 3 and 4). The enantioselectivity of the 6-exo cyclizations of **46** are slightly better than the 5-exo cyclizations of **44**. The addition of 10 mol % iodine also led to modest increases in the enantioselectivities of the iodolactonizations of **44** and **46**. The absolute stereochemistry of **45** and **47** is tentatively assigned based upon analogy with the cyclizations of other 4,4- and 5,5-disubsitituted olefinic acids (see Tables 4,5).



44 **45**

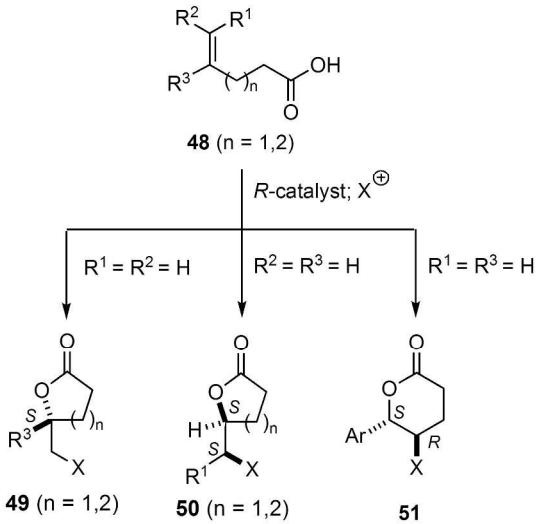
X = Br, 89%, 71:29 er
X = I, 80%, 66:34 er (3)
X = I, 92%, 79:21 er with 10% I_2



46 **47**

X = Br, 93%, 85:15 er
X = I, 81%, 79:21 (4)
X = I, 99%, 84:16 er with 10% I_2

Working Model. It is evident from the foregoing discussions that we have established **16** and **20** as novel bifunctional catalysts to promote bromo- and iodolactonizations of a rather diverse set of substituted olefinic acids **48** to give the respective lactones **49–51**, typically with excellent regio- and stereoselectivity (Scheme 2). Based on these results coupled with previous mechanistic proposals,[1h,2f] we have developed a tentative working model to rationalize the stereochemical outcomes for these processes.



Scheme 2. Summary of enantioselective halolactonizations catalyzed by **16** and **20**

As a starting point, we recognize that the bridged halonium ion intermediate could be stabilized by a Lewis acid/base interaction with either the basic amidine moiety or the naphthalenoxide ion of the catalyst **16** or **20**. However, we are aware of no models for catalytic halocyclizations in which the halonium ion is stabilized by a phenoxide ion, whereas there are a number of mechanistic models wherein this ion is stabilized by a basic nitrogen atom. Indeed, amidines are known to transfer bromine from NBS to olefins.[14] Accordingly, we presently prefer a model for halolactonizations catalyzed by **16** or **20** in which the halonium ion is stabilized by the amidine moiety, and there is a Brønsted acid/base interaction between the carboxylate group of the olefinic acid and the naphthol moiety. Assuming that these are the key ionic interactions in the transition states for the halolactonization, one may envision the competing transition states for the enantioselective cyclizations that deliver **49**–**51** as those shown in Figure 4**A**–**C,** respectively.

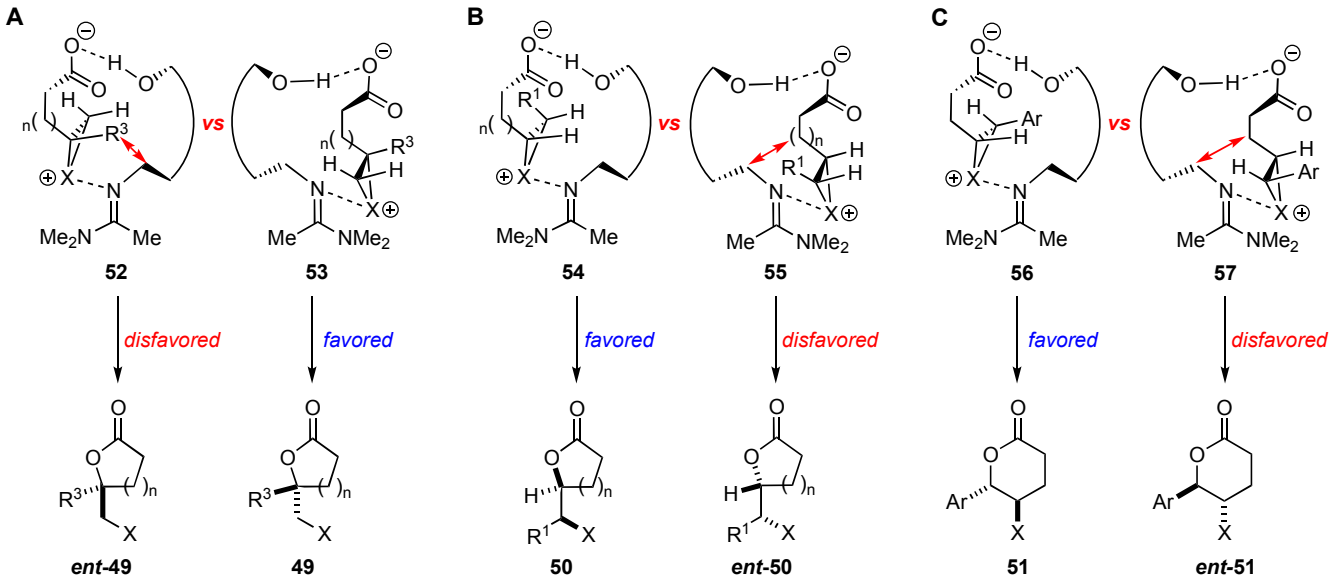


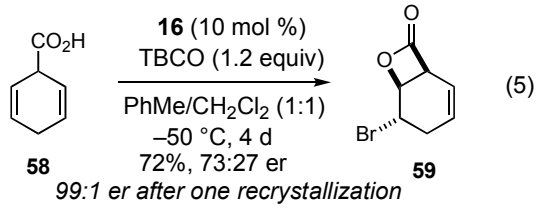
Figure 4. Tentative working stereochemical model for halolactonization reactions of **48** (see Scheme 2) catalyzed by **16** and **20** showing adverse steric interactions (red double headed arrow) in disfavored transition states. (A) Competing transition states for halolactonizations of acids **48** (n = 1,2; $R^1 = R^2 = H$). (B) Competing transition states for halolactonizations of acids **48** (n = 1,2; $R^2 = R^3 = H$). (C) Competing transition states for halolactonizations of acids **48** (n=1; $R^1 = R^3 = H$).

An inspection of models of these transition states reveals dominating steric interactions between the benzylic methyene group that is attached to the amidine substituent and either the olefinic R^3 group (*e.g.*, **52,** Figure 4A) or the allylic methylene group in the chain linking the double bond with the carboxylic acid

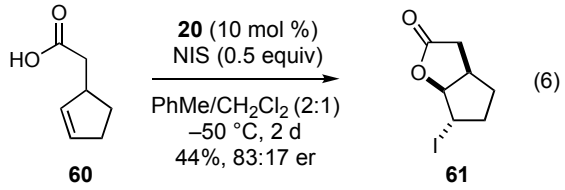
moiety (*e.g.,* **55** and **57**, Figure 4B, C) in the disfavored transition states. The transition states **53, 54**, and **56** leading to the observed products do not suffer such unfavorable steric interactions. In a recent study of bromocycloetherifications of 5-aryl-4(*E*/*Z*)-pentenols, Denmark noted that the catalyst directed the electrophilic bromine ion to one face of the olefin, irrespective of olefin geometry.[2d,f] Similarly, we find that the electrophilic bromo or iodo species is preferentially delivered from the same face of the olefin in all cyclizations of unsaturated pentenoic and hexenoic acids that lack a substituent on the olefinic carbon atom proximal to the carboxyl group (*i.e.,* **48**, n = 1,2 and R^3 = H) (see Tables 6–8 and Figure 4B,C). When the internal carbon atom of the olefin is geminally substituted (*i.e.,* **48**, n = 1,2 and R^3 = alkyl, aryl) (see Tables 4,5), however, attack of the electrophilic halogen moiety is from the opposite face.

Applications to Methodological Problems. At the outset of our studies, we identified a number of synthetic challenges that needed to be addressed in the context of enantioselective halolactonizations. The first of these was to induce transformations that created new C–Br of C–I at stereogenic centers exo to a ring; we had now achieved that goal. However, other problems that needed to be solved involved desymmetrization of prochiral substrates and kinetic resolution of racemic substrates, although there have been several reports of alternative solutions since we completed our own work.[16]

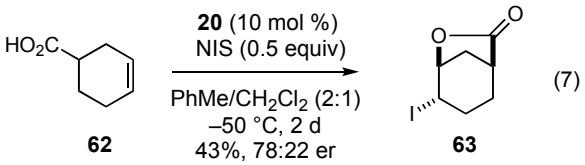
The potential of **16** as a catalyst to induce desymmetrization reactions is exemplified by the bromolactonization of 1,4-dihydrobenzoic acid (**58**) in the presence of **16** to furnish lactone **59** in 73:27 er (Equation 5). Although the enantioselectivity in this reaction was modest, the enantiopurity of **59** was easily improved to 99:1 er after a single recrystallization. This process was then applied in the syntheses of several synthons of the F ring subunit of the natural product kibdelone C (*vide infra*).[9a] Iodolactonization of **58** could be effected using catalyst **20**, but the resultant iodolactone was unstable. On the other hand, the utility of **20** as a catalyst to promote kinetic resolutions of racemic olefinic acids is illustrated by the iodolactonizations of **60** and **62** to deliver the corresponding bicyclic iodolactones **61** and **63** in 83:17 er and 78:22 er, respectively (Equations 6 and 7). Both **61** and **63** are important intermediates for the syntheses of several natural products,[17] including sieboldine A[17b] and phyllanthocin.[17d]



(5)

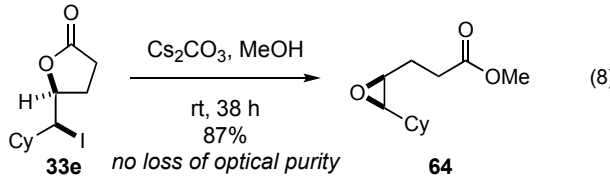


(6)



(7)

Another important extension of our halolactonization methodology is to the synthesis of enantioenriched *cis*-1,2-disubstituted epoxides. The direct epoxidation of *Z*-disubstituted olefins without directing groups remains a significant challenge,[18] but we discovered that 4(*Z*)-alkenoic acids can be readily converted into the corresponding epoxides by a facile two-step process. For example, iodolactone **33e**, which was obtained from the *cis*-disubstituted olefinic acid **32e** (Table 6, entry 9), was converted to *cis*-epoxide **64** with no loss of enantiopurity simply upon treatment with Cs_2CO_3 in MeOH (Equation 8). A similar iodolactonization-epoxidation sequence was utilized in our concise enantioselective synthesis of (+)-disparlure (*vide infra*).9[b]

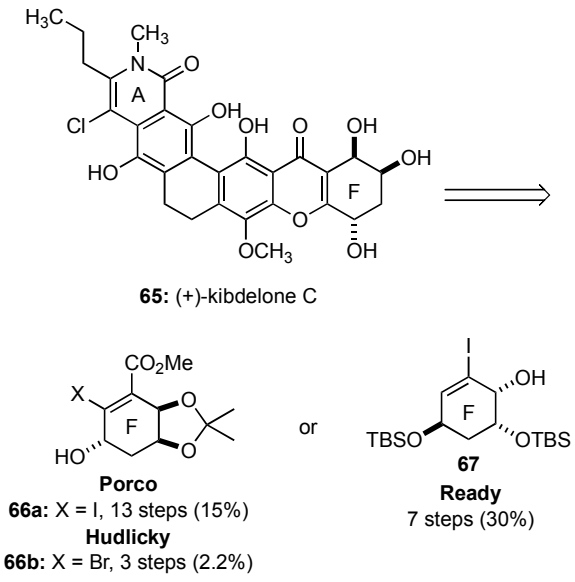


(8)

Application to Natural Product Synthesis: F-Ring Fragments of Kibdelone C.

First isolated in 2007 by Capon and coworkers, kibdelone C (**65**) is a member of a novel family of polycyclic xanthone natural products that is produced by *Kibdelosporangium* sp, a rare soil actinomycete.[19] Collectively, compounds belonging to this class possess an array of potentially useful biological activities that include low nanomolar GI_{50}'s against a panel of human cancer cell lines as well as potent antibacterial

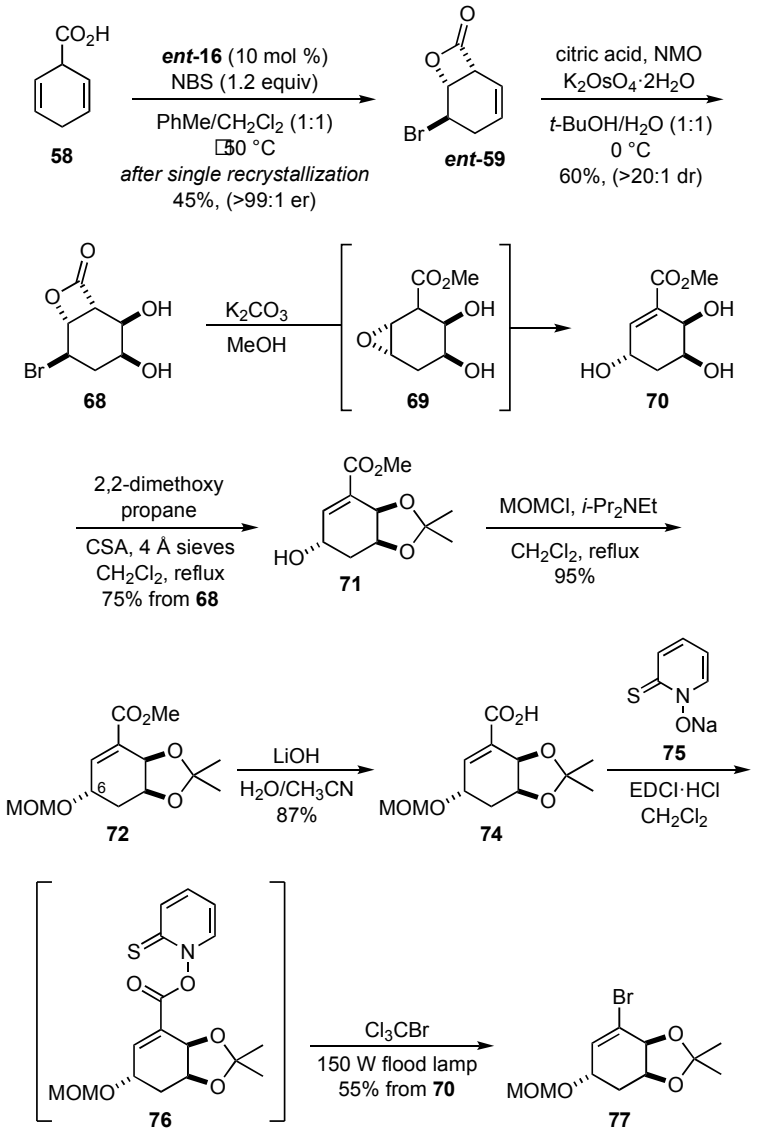
and nematocidal properties. The promising biological activity of **65** coupled with its complex polycyclic architecture sparked considerable interest in the synthetic community, culminating in two successful enantioselective syntheses, (+)-kibdelone C completed by Porco,[20] and (–)-kibdelone C completed by Ready.[21] A key challenge for both groups was the synthesis of the chiral polyhydroxylated F ring (Scheme 3). Toward this end, for his synthesis of (+)-kibdelone C, Porco utilized **66a**, which was prepared in 13 steps and 15% overall yield.[20] Hudlicky subsequently reported an enzymatic approach that provided the related F ring precursor **66b** in three steps, albeit in only 2.2% overall yield.[22] Ready's approach to (–)-kibdelone C required the use of fragment **67**, which was in prepared in seven steps and 30% overall yield.[21]



Scheme 3. F-ring fragments of kibdelone C used by Porco and Ready

With the view of developing a short entry to cyclohexene derivatives related to **66a,b** and **67**, we envisioned that the lactone ***ent*-59** might be a viable intermediate (Scheme 4). Drawing from earlier work directed toward developing modified catalysts (*vide supra*), we initially queried whether the simplified catalyst ***ent*-23b** might deliver ***ent*-59** with selectivity comparable to that of ***ent*-16** (see Equation 5). However, desymmetrization of **58** using ***ent*-23b** afforded ***ent*-59** with slightly diminished enantioselectivity (63:37 er), so we were relegated to using ***ent*-16.** In our initial experiments to desymmetrize **58** via an enantioselective bromolactonization using ***ent*-16**, the reaction was performed on a relatively small scale (100 mg) at low concentrations (0.03 M). However, we found this reaction was readily scalable to multigram quantities (2.5 g) at higher concentrations (0.1 M). Moreover, we discovered

that the less expensive brominating agent *N*-bromosuccinimide (NBS) gave ***ent*-59** in comparable yield and enantioselectivity to TBCO.

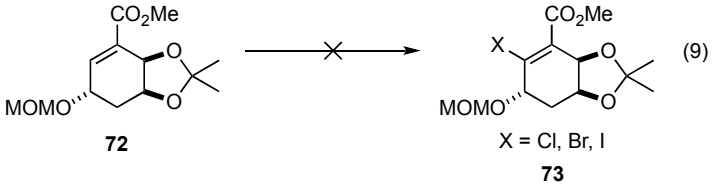


Scheme 4. Synthesis of F-ring fragments of kibdelone C

Our initial foray to induce dihydroxylation of ***ent*-59** was problematic because ***ent*-59** was unstable in the basic media typical of standard Sharpless or Upjohn reaction conditions,[23] so **68** was isolated in <35% yield and only <4:1 dr. After screening a variety of conditions, we discovered that dihydroxylation of ***ent*-59** in the presence of citric acid proceeded with high selectivity from the less hindered face to deliver **68** in 60% yield (>20:1 dr).[24] Treating the lactone **68** with methanol and potassium carbonate initiated a multistep cascade of reactions involving sequential transesterification and formation of the epoxide **69**

that underwent spontaneous β-elimination to deliver triol **70**, which was used without further purification. Formation of the acetonide moiety of the vicinal diol in **70** then gave **71**, and subsequent protection of the distal hydroxyl group furnished **72** in 71% yield over three steps. Although we did not pursue the possibility, it is notable that **71**, which is available in only four steps and 19% overall yield from 1,4-dihydrobenzoic acid (**58**) is also a potential F-ring precursor of (+)-kibdelone C.

Our initial plan was to directly install a halogen atom at the β-position of the enoate **72** to provide **73** (Equation 9), but numerous attempts to induce this transformation were unavailing. For example, treatment of **72** with a variety of reagents such as Br_2 and triethylamine,[25] NBS, NIS, or $I(coll)_2PF_6$ gave no detectable amounts of the desired product **73**. Another approach to prepare **73** was inspired by Bartlett's synthesis of (–)-2-chloroshikimic acid,[26] but preliminary efforts to apply this procedure to the problem at hand were unsuccessful. A change of plan was needed, and we turned our attention to the synthesis of **77**, a putative F-ring fragment similar to **67**.

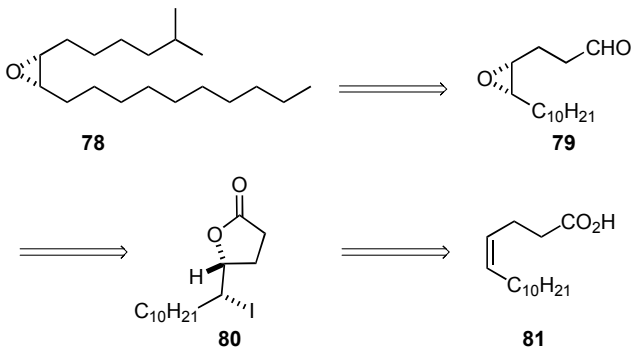


(9)

In the event, the methyl ester moiety of **72** was saponified to deliver the carboxylic acid **74** in 87% yield (Scheme 4). The use of CH_3CN as solvent in this reaction proved to be critical, because when aqueous solvent mixtures of THF or MeOH were used, unavoidable epimerization of the C6 stereocenter was observed. Carbodiimide mediated coupling **74** with **75** afforded the intermediate thiohydroxamate ester **76** that was immediately subjected to a Barton–Hunsdiecker[27] halodecarboxylation by irradiation in bromotrichloromethane to provide vinyl bromide **77** in 55% overall yield from **74**. We thus completed a short synthesis of **77**, an alternate F-ring synthon of kibdelone C, in eight steps and 9% overall yield from 1,4-dihydrobenzoic acid (**58**).

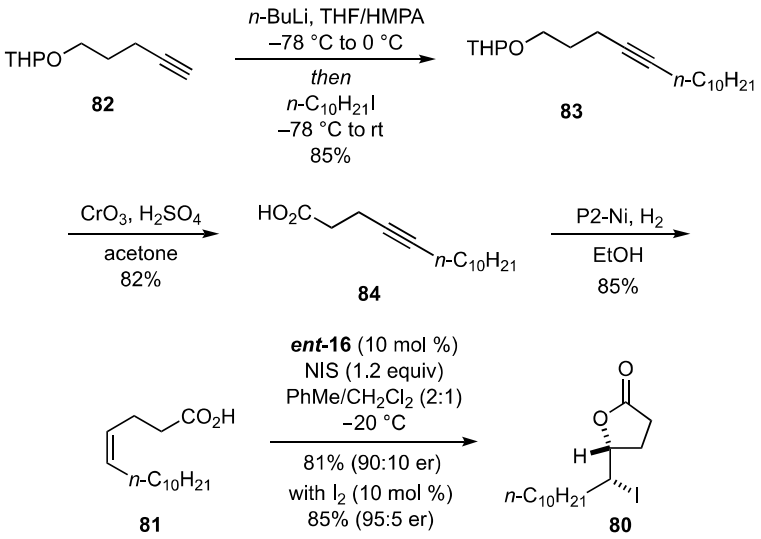
Applications to Natural Product Synthesis: (+)-**Disparlure (78).** The gypsy moth, *Lymantria dispar*, ranks as one of the most devastating forest pests because of the extensive deforestation it causes during outbreaks in North America, Europe, and Asia. Because the resultant defoliation has serious ecological and economic ramifications, the gypsy moth has become a target for eradication.[28] Disparlure, (*Z*)-7,8-epoxy-2-methyloctadecane, was identified in 1970 by Bierl as the sex pheromone emitted by the female gypsy moth,[29] and it was later shown that (+)-disparlure (**78**) is the major component.[30] Since that time, (+)-disparlure has been widely used as an attractant in traps as a means of controlling and managing gypsy moth populations. However, owing to its scarcity from natural sources, it has been necessary to rely upon synthesis to ensure adequate quantities of synthetic (+)-disparlure are available. Accordingly, (+)-disparlure has been the target of innumerable chemical investigations, and more than 50 syntheses of racemic and enantiopure disparlure have been reported.[31] Despite these many successes, there remains significant opportunity for improvements that may result from advances in enantioselective synthesis. It thus occurred to us that an enantioselective iodolactonization/epoxide forming sequence might be applied to a concise enantioselective synthesis of (+)-disparlure.

Based upon the chemistry that is summarized in Equation 8, we envisaged that (+)-disparlure (**78**) could be prepared from the *cis*-epoxide **79**, which would be produced upon the reductive opening of the enantioenriched iodolactone **80** followed by epoxide formation (Scheme 5). This plan was predicated upon the ability of our BINOL-derived catalyst ***ent*-16** to convert the unsaturated acid **81** to the corresponding iodolactone with a high degree of enantioselectivity. At the outset of our studies, however, it was unclear whether **81** would be a suitable substrate, because we had previously observed that unbranched, alkyl-substituted *cis*-alkenoic acids such as **31a** cyclized to iodolactones with only moderate enantioselectivity (85:15 er) (Table 6, Entry 1). Accordingly, the key question that needed to be resolved whether a long, *n*-alkyl chain in **81** might behave differently from the mere ethyl group in **31a**.



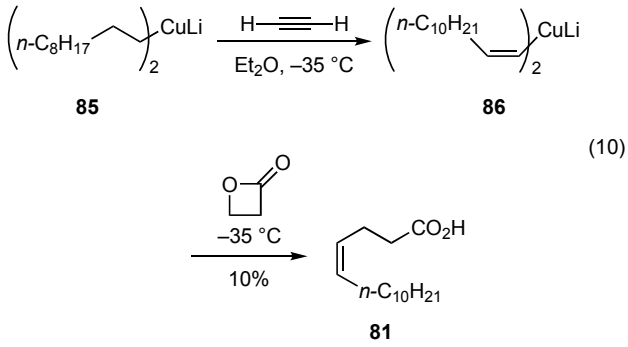
Scheme 5. Approach to (+)-disparlure (**78**)

Our first generation approach to prepare (+)-disparlure via **81** commenced with the alkylation of the lithiated alkyne **82** with 1-iododecane to give **83** in 85% yield (Scheme 6).[32] When **83** was subjected to the conditions of the Jones oxidation, the tetrahydropyran (THP) protecting group was removed, and the resulting alcohol underwent direct oxidation to the carboxylic acid **84** in 82% yield. Initial attempts to partially reduce the alkyne moiety of **84** with Lindlar's catalyst gave inseparable mixtures of *cis*- and *trans*-isomers of **81** (~10:1 *cis*:*trans*). However, semi-hydrogenation of **84** with P2-Ni and dihydrogen cleanly gave the desired *cis*-olefinic acid **81** without any contamination by the *trans*-isomer. Gratifyingly, the enantioselective iodolactonization of **81** in the presence of ***ent*-16** proceeded to give the iodolactone **80** in 81% yield and 90:10 er. Inclusion of I_2 (10 mol %) further enhanced the enantioselectivity of the reaction, furnishing **80** with 95:5 er. Although these experiments established critical proof-of-principle for the highly enantioselective iodolactonization of **81**, we viewed the sequence as too lengthy, so we then sought to streamline the synthesis of the key *Z*-olefinic acid **81**.



Scheme 6. Enantioselective iodolactonization of **81**

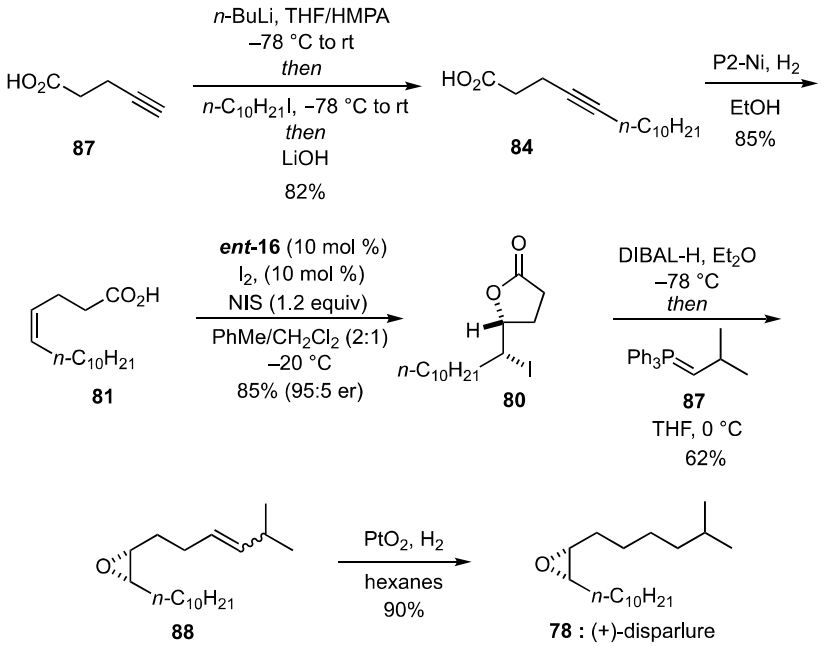
A more appealing approach to **81** was inspired by a previously reported one-step procedure for the synthesis of (*Z*)-4-alkenoic acids by a carbocupration of acetylene followed by reaction of the intermediate vinylcuprate with β-propiolactone (Equation 10).[33] However, despite extensive experimentation using the cuprate **86**, we were not able to reliably prepare **81** in acceptable yield, so we abandoned this route.



(10)

A reliable, two-step route to **81** was then developed that commenced with alkylation of the dianion generated from **87** with 1-iododecane (Scheme 7). Because it was necessary to employ an excess of 1-iododecane to optimize *C*-alkylation, considerable amounts of the corresponding ester by-product were unavoidably formed. However, any ester was saponified *in situ* upon completion of the reaction to provide **84** (82% yield), which was elaborated to **80** as shown in Scheme 6. The transformation of **80** into the epoxide **88** was then achieved in 62% overall yield using a simple one-pot process that involved sequential

reduction of the lactone moiety with DIBAL-H and a Wittig reaction of the intermediate cyclic hemiacetal. Consistent with literature precedent,[34] we discovered that selective reduction of the double bond in **88** by catalytic hydrogenation was problematic because reductive opening of the epoxide was a significant side reaction. After some experimentation with different catalysts and conditions, however, we eventually solved the problem by hydrogenating **88** using PtO_2 as a catalyst and hexanes as solvent to deliver **78** in 90% yield. Notably, this synthesis of (+)-disparlure proceeded in 33% overall yield in only five steps from commercially available **87**, making this the shortest catalytic enantioselective synthesis of **78** to date.[35]



Scheme 7. Synthesis of (+)-disparlure (**78**)

SUMMARY

In summary, we have discovered and developed **16** and **20** as novel bifunctional organic catalysts to promote highly enantioselective and regioselective bromo- and iodolactonizations of a diverse array of olefinic acids. The only other catalyst reported to promote enantioselective halolactonizations with different halogens is $(DHQD)_2PHAL$ (**4**).[4a,5h] Catalysts **16** and **20**, which uniquely incorporate a phenolic moiety as a Brønsted acid (or base) in the bifunctional catalyst design, were the first to incorporate a binaphthyl moiety as a chiral scaffold, although several such catalysts have been reported subsequently.[6h,7b]

Significantly, these organic catalysts were the first to induce enantioselective halolactonizations via exo cyclization modes to give halolactones having carbon–halogen bonds at newly created stereogenic centers exocyclic to the lactone. Notable applications of this halolactonization methodology include desymmetrization, kinetic resolution, and epoxidation of simple *Z*-alkenes. For example, we showed that the desymmetrization of **58** could be performed on multigram scale, leading to short enantioselective syntheses of two potential F-ring synthons of kibdelone C. The utility of **16** was also exemplified by its application to the enantioselective synthesis of (*Z*)-1,2-alkyl epoxides from iodolactones generated from 4(*Z*)-pentenoic acids, and this process was applied to the shortest catalytic enantioselective synthesis of the insect pheromone (+)-disparlure to date.

Experimental

General

Solvents were purified before use as follows unless otherwise noted. Dichloromethane (CH_2Cl_2) and benzene were distilled from calcium hydride immediately prior to use. Tetrahydrofuran and diethyl ether were dried by filtration through two columns of activated, neutral alumina according to the procedure described by Grubbs.[36] Methanol (MeOH), acetonitrile (MeCN), and dimethylformamide (DMF) were dried by filtration through two columns of activated molecular sieves, and toluene was dried by filtration through one column of activated, neutral alumina followed by one column of Q5 reactant. These solvents were determined to have less than 50 ppm H_2O by Karl Fischer coulometric moisture analysis. Chloroform and acetone were distilled from $CaSO_4$ and stored over 4 Å molecular sieves. Reagents were reagent grade and used without purification unless otherwise noted. Trifluoromethanesulfonic anhydride (Tf_2O) was freshly distilled from P_2O_5. Alkyl halides were passed through a plug of silica and distilled. KCN was crushed and heated at 80 °C under vacuum for 3 h prior to use. Zinc powder was activated and stored under argon. Triethylamine (Et_3N), ethylene diamine, diisopropylethylamine (Hünig's base), and diisopropylamine were refluxed with, distilled from, and stored over KOH. In nickel(0), palladium(0), and copper(I)-catalyzed reactions, all solvents were freed from oxygen by three freeze-pump-thaw cycles prior to use. All reactions were performed in flame-dried glassware under nitrogen or argon; reaction temperatures refer to the temperature of the cooling/heating bath.

Analytical HPLC separations were performed using a Pirkel Covalent (*S*,*S*) Whelk-O1 (Regis Technologies, Inc.), Chiralcel OD-H (Daicel Chemical Industries, Ltd.), Chiralcel OB (Daicel Chemical Industries, Ltd.) column, as indicated. Infrared (IR) spectra were obtained either neat on sodium chloride or as solutions in the solvent indicated and reported as wavenumbers (cm^{-1}). Proton nuclear magnetic resonance (^1H NMR) and proton-

decoupled, carbon nuclear magnetic resonance (^{13}C NMR) spectra were obtained at the indicated field as solutions in $CDCl_3$ unless otherwise indicated. Chemical shifts are referenced to the deuterated solvent (*e.g.,* for $CDCl_3$, δ = 7.26 ppm and 77.0 ppm for ^{1}H and ^{13}C NMR, respectively) and are reported in parts per million (ppm, δ) relative to tetramethylsilane (TMS, δ = 0.00 ppm). Coupling constants (*J*) are reported in Hz and the splitting abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; comp, overlapping multiplets of magnetically nonequivalent protons; br, broad; app, apparent.

The catalysts **16** and **20**, and the bromolactones **22**, **26a,b**, **29c**, **32a–e**, **19a**, **41a,b**, **45** (X=Br), and **47** (X=Br) were prepared according to our previously reported procedures[8a] as were the iodolactones **33b–i**, **39a–d**, **42a+43a**, **42c, 43d**, and **57**.[8b] The kibdelone fragments **67** and **73**[9a] and (+)-disparlure (**74**)[9b] were synthesized according to our previously reported procedures.

General Procedure for Enantioselective Bromolactonization

(*S*)-5-((*S*)-1-Bromo-2-methylpropyl)dihydrofuran-2(*3H*)-one (32b). A solution of TBCO (0.197 g, 0.480 mmol) in CH_2Cl_2 (4 mL) was added dropwise to a solution of (*Z*)-6-methylhept-4-enoic acid **31b** (0.057 g, 0.400 mmol) and catalyst **16** (0.018 g, 0.040 mmol) in toluene (8 mL) at –50 °C, and the solution was stirred for 14 h. The reaction was quenched with saturated aqueous Na_2SO_3 (10 mL), and the mixture was warmed to room temperature with vigorous stirring. The mixture was diluted with Et_2O (40 mL) and water (10 mL), and the organic fraction was washed with 5% aqueous Na_2CO_3 (2 × 20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography, eluting with CH_2Cl_2/toluene (2:1) to give 0.083 g (94%) of **32b** as a clear, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.76–4.71 (m, 1 H), 3.87 (dd, *J* = 6.0, 3.6 Hz, 1 H), 2.76–2.66 (m, 1 H), 2.59–1.48 (m, 1 H), 2.44–2.33 (m, 1 H), 2.22–2.06 (comp, 2 H), 1.10 (d, *J* = 6.4 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz)δ 176.4, 79.9, 66.8, 32.8, 28.3, 26.7, 21.2, 20.3; IR (neat) 2966, 2933, 2876, 1769, 1176, 1022, 908 cm^{-1}; HRMS (ESI/Q-TOF) *m/z* [M + Na]$^+$ Calcd for $C_8H_{13}BrNaO_2$ 242.9991; found 242.9992; $[\alpha]^{25}_D$ +53.0 (c = 1.0, $CHCl_3$); HPLC (210 nm): Whelk-O1 (20% *i*-PrOH / hexanes, 1.2 mL/min) 17.4 min (minor), 20.3 min (major); 97:3 er.

General Procedure for Enantioselective Iodolactonization

(*S*)-5-(Iodomethyl)-5-phenyldihydrofuran-2(*3H*)-one (24). NIS (0.027 g, 0.12 mmol) (and I_2 (0.0026 g, 0.010 mmol) for reactions with addition of 10 mol % iodine) was added to a solution of 4-phenyl-4-pentenoic acid **21** (0.018 g, 0.100 mmol) and catalyst **20** (0.005 g, 0.010 mmol) in toluene (2 mL) and CH_2Cl_2 (1 mL) at –20 °C, and the solution was stirred for 14 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (1 mL), and

the mixture was warmed to room temperature with vigorous stirring. The two layers were separated, and the aqueous layers were extracted with CH_2Cl_2 (2 × 5 mL), and the combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography, eluting with hexanes/EtOAc (5:1, v/v) to give 0.027 g (89%) of **24** as a clear, colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42–7.33 (comp, 5 H), 3.65 (d, *J* = 11.1 Hz, 1 H), 3.61 (d, *J* = 11.1 Hz, 1 H), 2.83–2.68 (comp, 2 H), 2.66–2.45 (comp, 2 H),; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.3, 140.6, 128.8, 128.6, 124.8, 86.0, 33.9, 29.2, 16.2; IR (neat) 2924, 2853, 1779, 1448, 1151, 700 cm^{-1}; HRMS (CI/Magnetic Sector) *m/z* [M + H]$^+$ Calcd for $C_{11}H_{12}IO_2$ 302.9882; Found 302.9881; $[\alpha]^{24}_D$ –15.3 (c = 1.0, $CHCl_3$); HPLC (214 nm): OD-H (5% *i*-PrOH / hexanes, 1.0 mL/min) 19.0 min (minor), 23.8 min (major); 93:7 er.

(*S*)-4-(2-(Iodomethyl)-5-oxotetrahydrofuran-2-yl)benzonitrile (27a). Isolated 0.024 g (73%) of **27a** as a white solid: mp 154 °C (decomposition); ^{1}H NMR ($CDCl_3$, 300 MHz)δ 7.72 (d, *J* = 8.4 Hz, 2 H), 7.54 (d, *J* = 8.4 Hz, 2 H), 3.60 (s, 2 H), 2.85–2.74 (comp, 2 H), 2.64–2.51 (comp, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.4, 145.9, 132.6, 125.8, 118.1, 112.7, 85.3, 33.8, 29.0, 14.6; IR (neat) 2921, 2230, 1783, 1413, 1164, 1028, 841 cm^{-1}; HRMS (CI/Magnetic Sector) *m/z* [M + H]$^+$ Calcd for $C_{12}H_{11}NO_2I$ 327.9835; Found 327.9835; $[\alpha]^{25}_D$ –10.6 (c = 1.0, $CHCl_3$); HPLC (231 nm): Whelk-O1 (3% CH_3CN / 20% *i*-PrOH / hexanes, 1.2 mL/min) 17.5 min (minor), 20.2 min (major); 90:10 er.

(*S*)-5-(Iodomethyl)-5-(4-methoxyphenyl)dihydrofuran-2(*3H*)-one (27c). Isolated 0.030 g (90%) of **27c** as a colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34-7.31 (m, 2 H), 6.93-6.90 (m, 2 H), 3.83 (s, 3 H), 3.62 (d, *J* = 11.1 Hz, 1 H), 3.58 (d, *J* = 11.1 Hz, 1 H), 2.77–2.48 (comp, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.4, 159.6, 132.3, 126.2, 114.1, 86.0, 55.3, 33.7, 29.3, 16.6; IR (neat) 2957, 2837, 1779, 1514, 1253, 1178, 1029, 928, 834 cm^{-1}; HRMS (CI/Magnetic Sector) m/z: [M + H]$^+$ Calcd for $C_{12}H_{14}O_3I$, 332.9988; Found 332.9991; $[\alpha]^{25}_D$ –8.3 (c = 1.0, $CHCl_3$); HPLC (230 nm): Whelk-O1 (3% CH_3CN / 20% *i*-PrOH / hexanes, 1.2 mL/min) 10.3 min (minor), 12.7 min (major); 74:26 er.

(*R*)-5-(Iodomethyl)-5-methyldihydrofuran-2(*3H*)-one (27d). Isolated 0.023 g (96%) of **27d** as a colorless oil; spectra was consistent with previsouly reported data for racemic **27d**.[37] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.42 (d, *J* = 10.5 Hz, 1 H), 3.37 (d, *J* = 10.5 Hz, 1 H), 2.71–2.64 (comp, 2 H), 2.38–2.78 (m, 1 H), 2.19–2.09 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.7, 83.8, 32.9, 29.4, 25.9, 14.1; IR (neat) 2976, 1769, 1158 cm^{-1}; HRMS (ESI) *m/z* calcd for $[C_6H_9O_2INa]^+$ (M+Na), 262.9539; found 262.9537; $[\alpha]^{25}_D$ –21 (c = 1.0, $CHCl_3$); HPLC (254 nm): Whelk-O1 (20% *i*-PrOH / hexanes, 1.2 mL/min) 17.8 min (minor), 19.2 min (major); 65:35 er.

(*S*)-5-(*tert*-Butyl)-5-(iodomethyl)dihydrofuran-2(3H)-one (27e). Reaction executed on 0.128 mmol scale. Isolated 0.033 g (91%) of **27e** as a colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.83 (d, *J* = 11.2 Hz, 1 H), 3.47 (d, *J* = 10.8 Hz, 1 H), 2.85–2.76 (m, 1 H), 2.55–2.36 (comp, 2 H), 2.16–2.08 (m, 1 H) ; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.5, 89.9, 38.2, 30.2, 28.4, 25.3, 16.4; IR (neat) 2969, 1762, 1469, 1166, 986 cm^{-1}; HRMS (ESI/Q-TOF) *m/z* $[M + Na]^+$ Calcd for $C_9H_{15}O_2INa$ 305.0009; Found 305.0008; $[\alpha]^{25}_D$ –35 (c = 1.0, $CHCl_3$); HPLC (256 nm): Whelk-O1 (20% *i*-PrOH / hexanes, 1.2 mL/min) 11.0 min (minor), 12.0 min (major); 83:17 er.

(*S*)-6-(Bromomethyl)-6-phenyltetrahydro-2H-pyran-2-one (29a). Reaction executed on a 0.2 mmol scale. Isolated 0.042 g (75%) of **29a** as a colorless oil, spectra consistent with the previously reported data.[5e] HPLC (217 nm) OD-H (1% *i*-PrOH / hexanes, 1 mL/min) 53.3 min (major), 71.5 min (minor); 62:38 er.

(*R*)-6-(Bromomethyl)-6-methyltetrahydro-2H-pyran-2-one (29b). Reaction executed on a 0.2 mmol scale. Isolated 0.037 g of **29b** as a colorless oil, spectra consistent with the previously reported data.[5e] HPLC (217 nm) OD-H (1% *i*-PrOH / hexanes, 1 mL/min) 62.28 min (minor), 64.89 min (major); 82:18 er.

(*S*)-6-(Iodomethyl)-6-phenyltetrahydro-*2H*-pyran-2-one (30a). Isolated 0.031 g (98%) of **30a** as a clear, colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.41–7.35 (m, 5 H), 3.58 (s, 2 H), 2.50–2.44 (comp, 2 H), 2.40-2.34 (comp, 2 H), 1.87–1.79 (comp, 1 H), 1.64–1.55 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.4, 140.2, 129.0, 128.4, 125.2, 84.4, 32.0, 29.0, 17.6, 16.5; IR (neat) 2958, 1738, 1257, 1179, 1037, 701 cm^{-1}; HRMS (ESI/Q-TOF) *m/z* $[M + Na]^+$ Calcd for $C_{12}H_{13}NaIO_2$, 338.9852; Found 338.9853; $[\alpha]^{26}_D$ +12.3 (c = 1.0, $CHCl_3$); HPLC (214 nm): Whelk-O1 (20% *i*-PrOH / hexanes, 1.2 mL/min) 20.4 min (minor), 27.2 min (major); 76:24 er.

(*R*)-6-(Iodomethyl)-6-methyltetrahydro-*2H*-pyran-2-one (30b). Isolated 0.024 (89%) of **30b** as clear, slightly yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.4 (dd, J = 10.5, 14.5 Hz, 2 H), 2.62–2.42 (comp, 2 H), 2.16-2.02 (m, 1 H), 1.95–1.82 (comp, 3 H), 1.59 (s, 3 H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 170.4, 81.9, 31.9, 29.4, 26.5, 16.9, 15.3; IR (neat) 2955, 1730, 1275, 1215, 1183, 1050 cm^{-1}; HRMS (CI/Magnetic Sector) *m/z* $[M + H]^+$ Calcd for $C_7H_{11}IO_2$ $(M+H)^+$, 254.9882; Found 254.9872; $[\alpha]^{25}_D$ –32 (c = 1.0, $CHCl_3$); HPLC (259 nm): Whelk-O1 (20% *i*-PrOH / hexanes, 1.2 mL/min) 22.5 min (minor), 27.3 min (major); 79:21 er.

(*R*)-6-(Iodomethyl)-6-phenyl-1,4-dioxan-2-one (30c). Isolated 0.029 g (91%) of **30c**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.35 (comp, 5 H), 4.43 (d, *J* = 17.7 Hz, 1 H), 4.32 (d, *J* = 12.9 Hz, 1 H), 4.28 (d, *J* = 17.7 Hz, 1 H), 4.19 (d, *J* = 12.9 Hz, 1 H), 3.70 (d, *J* = 11.2 Hz, 1 H), 3.66 (d, *J* = 11.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 138.0, 129.0, 128.9, 125.1, 83.0, 69.6, 65.4, 10.7; HRMS (CI/Magnetic Sector) *m/z* $[M + H]^+$

Calcd for $C_{11}H_{11}IO_3$ 317.9753; Found 317.9753; HPLC (210 nm): Whelk-O1 (20% *i*-PrOH / hexanes, 1.2 mL/min) 19.5 min (minor), 24.3 min (major); 84:16 er (without I_2), 90:10 er (with 10 mol % I_2)

(*R*)-5-((*S*)-1-Iodoethyl)-5-methyldihydrofuran-2(3*H*)-one (45, X = I**).** Isolated 0.020 g (80%) of **45-I** as a clear, colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.29 (q, *J* = 7.0 Hz, 1 H), 2.70-2.64 (comp, 2 H), 2.35-2.13 (comp, 2 H), 1.97 (d, *J* = 7.0 Hz, 3 H), 1.59 (s, 3 H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 176.1, 88.7, 34.8, 34.6, 29.7, 23.6, 21.7; IR (neat) 2978, 2931, 1777, 1240, 1176, 1073 cm^{-1}; HRMS (ESI/Q-TOF) *m/z* [M + Na]$^+$ Calcd for $C_7H_{11}INaO_2$276.9696, Found 276.9695; $[\alpha]^{25}_D$ –35.3 (c = 0.5, $CHCl_3$); HPLC (259 nm): Whelk-O1 (20% *i*-PrOH/ hexanes, 1.2 mL/min) 14.4 min (minor), 17.4 min (major); 68:32 er.

(*R*)-6-((*S*)-1-Iodoethyl)-6-methyl-1,4-dioxan-2-one (47, X = I**).** Isolated 0.026 g (81%) of **47-I** as a clear, colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.41 (q, *J* = 7.1 Hz, 1 H), 4.31 (s, 2 H), 4.05 (d, *J* = 12.6 Hz, 1 H), 3.96 (dd, *J* = 56.7, 12.6 Hz, 2 H), 3.87 (d, *J* = 12.6 Hz, 1 H), 2.02 (d, *J* = 7.1 Hz, 3 H), 1.61 (s, 3 H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 166.6, 84.1, 71.8, 65.5, 28.2, 22.5, 19.0; IR (neat) 2985, 2932, 2872, 1749, 1273, 1102 cm^{-1}; HRMS (ESI/Q-TOF) *m/z* [M + Na]$^+$ Calcd for $C_7H_{11}INaO_3$ 292.9645; Found 292.9644; $[\alpha]^{24}_D$ +5.3 (c = 0.5, $CHCl_3$); HPLC (259 nm): Whelk-O1 (20% *i*-PrOH / hexanes, 1.2 mL/min) 10.7 min (minor), 12.8 min (major); 79:21 er.

(1*S*,4*S*,5*S*)-4-Iodo-6-oxabicyclo[3.2.1]octan-7-one (63). Reaction executed according to the general iodolactonization procedure with 0.5 equiv NIS. Isolated 0.011 g (43%) of **63** as a clear, colorless oil. Spectra consistent with the previously reported data.[38] HPLC (210 nm) Chiracel OB (0.5% *i*-PrOH / hexanes, 1.05 mL/min) 12.0 min (major), 13.0 min (minor); 78:22 er.

AUTHOR INFORMATION

Corresponding Author

* sfmartin@mail.utexas.edu

Present Addresses

[a]Department of Chemistry and Physics, Florida Gulf Coast University, Fort Myers, Florida 33965

[b]Arrakis Therapeutics, Waltham, Massachusetts 02451

[c]Department of Chemistry, University of York, Heslington, York YO105DD, North Yorkshire, United Kingdom

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

ACKNOWLEDGMENT

We thank the National Institutes of Health (GM31077) and the Robert A. Welch Foundation (F-0652) for generous support of this research. DHP thanks the NIH for a postdoctoral fellowship (GM 96557). CRS thanks the NSF for support via an NSF-REU grant (CHE-1003947). We also thank Jonathan Kim (The University of Texas) for assistance with catalyst synthesis and Dr. Vincent Lynch (The University of Texas) for X-ray crystallography.

ASSOCIATED CONTENT

Supporting Information. characterization of new compounds, and X-ray crystal data. This material is available free of charge via the Internet at http://pubs.acs.org.

REFERENCES

1. For reviews, see: (a) Chen, G.; Ma, S. Enantioselective Halocyclization Reactions for the Synthesis of Chiral Cyclic Compounds. *Angew. Chem. Int. Ed.* **2010**, *49*, 8306–8308. (b) Tan, C. K.; Zhou, L.; Yeung, Y. Y. Organocatalytic Enantioselective Halolactonizations: Strategies of Halogen Activation. *Synlett* **2011**, 1335–1339. (c) Snyder, S. A.; Treitler, D. S.; Brucks, A. P. Halonium-Induced Cyclization Reactions; **2011**; *44*, 27–40 (d) Denmark, S. E.; Kuester, W. E.; Burk, M. T. Catalytic, Asymmetric Halofunctionalization of Alkenes-a Critical Perspective. *Angew. Chem. Int. Ed.* **2012**, *51*, 10938–10953. (e) Murai, K.; Fujioka, H. Recent Progress in Organocatalytic Asymmetric Halocyclization. *Heterocycles* **2013**, *87*, 763–805. (f) Nolsøe, J. M. J.; Hansen, T. V. Asymmetric Iodolactonization: An Evolutionary Account. *Eur. J. Org. Chem.* **2014**, *2014*, 3051–3065. (g) Kalyani, D.; Kornfilt, D. J.-P.; Burk, M. T.; Denmark, S. E. Lewis Base Catalysis: A Platform for Enantioselective Addition to Alkenes Using Group 16 and 17 Lewis Acids (N → Σ*). In *Lewis Base Catalysis in Organic Synthesis*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2016; pp 1153–1212. (h) Gieuw, M. H.; Ke, Z.; Yeung, Y. Y. Lewis Base Catalyzed Stereo- and Regioselective Bromocyclization. *Chem. Rec.* **2017**, *17*, 287–311.

2. (a) Kang, S. H.; Lee, S. B.; Park, C. M. Catalytic Enantioselective Iodocyclization of γ-Hydroxy-*Cis*-Alkenes. *J. Am. Chem. Soc.* **2003**, *125*, 15748–15749. (b) Huang, D.; Wang, H.; Xue, F.; Guan, H.; Li, L.; Peng, X.; Shi, Y. Enantioselective Bromocyclization of Olefins Catalyzed by Chiral Phosphoric Acid. *Org.*

Lett. **2011**, *13*, 6350–6353. (c) Hennecke, U.; Müller, C. H.; Fröhlich, R. Enantioselective Haloetherification by Asymmetric Opening of Meso -Halonium Ions. *Org. Lett.* **2011**, *13*, 860–863. (d) Denmark, S. E.; Burk, M. T. Enantioselective Bromocycloetherification by Lewis Base/Chiral Brønsted Acid Cooperative Catalysis. *Org. Lett.* **2012**, *14*, 256–259. (e) Zhao, Y.; Jiang, X.; Yeung, Y.-Y. Catalytic, Enantioselective, and Highly Chemoselective Bromocyclization of Olefinic Dicarbonyl Compounds. *Angew. Chem. Int. Ed.* **2013**, *52*, 8597–8601. (f) Denmark, S. E.; Burk, M. T. Development and Mechanism of an Enantioselective Bromocycloetherification Reaction via Lewis Base/ Chiral Brønsted Acid Cooperative Catalysis. *Chirality* **2014**, *26*, 344–355. (g) Ke, Z.; Tan, C. K.; Chen, F.; Yeung, Y. Y. Catalytic Asymmetric Bromoetherification and Desymmetrization of Olefinic 1,3-Diols with C2-Symmetric Sulfides. *J. Am. Chem. Soc.* **2014**, *136*, 5627–5630. (i) Ke, Z.; Tan, C. K.; Liu, Y.; Lee, K. G. Z.; Yeung, Y. Y. Catalytic and Enantioselective Bromoetherification of Olefinic 1,3-Diols: Mechanistic Insight. *Tetrahedron* **2016**, *72*, 2683–2689. (j) Böse, D.; Denmark, S. E. Investigating the Enantiodetermining Step of a Chiral Lewis Base Catalyzed Bromocycloetherification of Privileged Alkenes. *Synlett* **2018**, *29*, 433–439.

3. (a) Zhou, L.; Chen, J.; Tan, C. K.; Yeung, Y. Y. Enantioselective Bromoaminocyclization Using Amino-Thiocarbamate Catalysts. *J. Am. Chem. Soc.* **2011**, *133*, 9164–9167. (b) Chen, F.; Tan, C. K.; Yeung, Y. Y. C2-Symmetric Cyclic Selenium-Catalyzed Enantioselective Bromoaminocyclization. *J. Am. Chem. Soc.* **2013**, *135*, 1232–1235. (c) Egart, B.; Lentz, D.; Czekelius, C. Diastereoselective Bromocyclization of O-Allyl-N-Tosyl-Hydroxylamines. *J. Org. Chem.* **2013**, *78*, 2490–2499. (d) Zhou, L.; Tay, D. W.; Chen, J.; Leung, G. Y. C.; Yeung, Y.-Y. Enantioselective Synthesis of 2-Substituted and 3-Substituted Piperidines through a Bromoaminocyclization Process. *Chem. Commun.* **2013**, *6*, 4412–4414. (e) Mizar, P.; Burrelli, A.; Günther, E.; Söftje, M.; Farooq, U.; Wirth, T. Organocatalytic Stereoselective Iodoamination of Alkenes. *Chem. Eur. J.* **2014**, *20*, 13113–13116. (f) Tripathi, C. B.; Mukherjee, S. Catalytic Enantioselective Halocyclizations Beyond Lactones: Emerging Routes to Enantioenriched Nitrogenous Heterocycles. *Synlett* **2014**, *25*, 163–169. (g) Cai, Y.; Zhou, P.; Liu, X.; Zhao, J.; Lin, L.; Feng, X. Diastereoselectively Switchable Asymmetric Haloaminocyclization for the Synthesis of Cyclic Sulfamates. *Chem. Eur. J.* **2015**, *21*, 6386–6389. (h) Liu, W.; Pan, H.; Tian, H.; Shi, Y. Enantioselective 6-*exo*-Bromoaminocyclization of Homoallylic *N*-Tosylcarbamates Catalyzed by a Novel Monophosphine-Sc(OTf)$_3$ Complex. *Org. Lett.* **2015**, *17*, 3956–3959. (i) Jiang, H. J.; Liu, K.; Yu, J.; Zhang, L.; Gong, L. Z. Switchable Stereoselectivity in Bromoaminocyclization of Olefins: Using Brønsted Acids of Anionic Chiral Cobalt(III) Complexes. *Angew. Chem. Int. Ed.* **2017**, *56*, 11931–11935.

4. For chlorolactonizations, see: (a) Whitehead, D. C.; Yousefi, R.; Jaganathan, A.; Borhan, B. An Organocatalytic Asymmetric Chlorolactonization. *J. Am. Chem. Soc.* **2010**, *132*, 3298–3300. (b) Zhang, W.; Liu, N.; Schienebeck, C. M.; Decloux, K.; Zheng, S.; Werness, J. B.; Tang, W. Catalytic Enantioselective Halolactonization of Enynes and Alkenes. *Chem. Eur. J.* **2012**, *18*, 7296–7305. (c) Yousefi, R.; Ashtekar, K.

D.; Whitehead, D. C.; Jackson, J. E.; Borhan, B. Dissecting the Stereocontrol Elements of a Catalytic Asymmetric Chlorolactonization: *Syn* Addition Obviates Bridging Chloronium. *J. Am. Chem. Soc.* **2013**, *135*, 14524–14527. (d) Han, X.; Dong, C.; Zhou, H. B. C3-Symmetric Cinchonine-Squaramide-Catalyzed Asymmetric Chlorolactonization of Styrene-Type Carboxylic Acids with 1,3-Dichloro-5,5-Dimethylhydantoin: An Efficient Method to Chiral Isochroman-1-Ones. *Adv. Synth. Catal.* **2014**, *356*, 1275–1280. (e)Denmark, S. E.; Ryabchuk, P.; Burk, M. T.; Gilbert, B. B. Toward Catalytic, Enantioselective Chlorolactonization of 1,2-Disubstituted Styrenyl Carboxylic Acids. *J. Org. Chem.* **2016**, *81*, 10411–10423. (f) Ashtekar, K. D.; Vetticatt, M.; Yousefi, R.; Jackson, J. E.; Borhan, B. Nucleophile-Assisted Alkene Activation: Olefins Alone Are Often Incompetent. *J. Am. Chem. Soc.* **2016**, *138*, 8114–8119. (g) Salehi Marzijarani, N.; Yousefi, R.; Jaganathan, A.; Ashtekar, K. D.; Jackson, J. E.; Borhan, B. Absolute and Relative Facial Selectivities in Organocatalytic Asymmetric Chlorocyclization Reactions. *Chem. Sci.* **2018**, *9*, 2898–2908.

5. For bromolactonizations, see: (a) Zhang, W.; Zheng, S.; Liu, N.; Werness, J. B.; Guzei, I. A.; Tang, W. Enantioselective Bromolactonization of Conjugated (*Z*)-Enynes. *J. Am. Chem. Soc.* **2010**, *132*, 3664–3665. (b) Zhou, L.; Tan, C. K.; Jiang, X.; Chen, F.; Yeung, Y. Y. Asymmetric Bromolactonization Using Amino-Thiocarbamate Catalyst. *J. Am. Chem. Soc.* **2010**, *132*, 15474–15476. (c) Tan, C. K.; Zhou, L.; Yeung, Y. Amino-Thiocarbamate Catalyzed Asymmetric Bromolactonization of 1,2- Disubstituted Olefinic Acids. *Org. Lett.* **2011**, *13*, 2738–2741. (d) Tan, C. K.; Le, C.; Yeung, Y.-Y. Enantioselective Bromolactonization of C*is*-1,2-Disubstituted Olefinic Acids Using an Amino-Thiocarbamate Catalyst. *Chem. Commun.* **2012**, *48*, 5793–5795. (e) Jiang, X.; Tan, C. K.; Zhou, L.; Yeung, Y. Y. Enantioselective Bromolactonization Using an *S*-Alkyl Thiocarbamate Catalyst. *Angew. Chem. Int. Ed.* **2012**, *51*, 7771–7775. (f) Murai, K.; Matsushita, T.; Nakamura, A.; Fukushima, S.; Shimura, M.; Fujioka, H. Asymmetric Bromolactonization Catalyzed by a C3-Symmetric Chiral Trisimidazoline. *Angew. Chem. Int. Ed.* **2010**, *49*, 9174–9177. (g) Murai, K.; Nakamura, A.; Matsushita, T.; Shimura, M.; Fujioka, H. C3-Symmetric Trisimidazoline-Catalyzed Enantioselective Bromolactonization of Internal Alkenoic Acids. *Chem. Eur. J.* **2012**, *18*, 8448–8453. (h) Armstrong, A.; Braddock, C. D.; Jones, A. X.; Clark, S.; Braddock, D. C.; Jones, A. X.; Clark, S. Catalytic Asymmetric Bromolactonization Reactions Using $(DHQD)_2PHAL$-Benzoic Acid Combinations. *Tetrahedron Lett.* **2013**, *54*, 7004–7008. (i) Aursnes, M.; Tungen, J. E.; Hansen, T. V. Enantioselective Organocatalyzed Bromolactonizations: Applications in Natural Product Synthesis. *J. Org. Chem.* **2016**, *81*, 8287–8295.

6. For iodolactonizaions, see: (a) Veitch, G. E.; Jacobsen, E. N. Tertiary Aminourea-Catalyzed Enantioselective Iodolactonization. *Angew. Chem. Int. Ed.* **2010**, *49*, 7332–7335. (b) Tungen, J. E.; Nolsøe, J. M. J.; Hansen, T. V. Asymmetric Iodolactonization Utilizing Chiral Squaramides. *Org. Lett.* **2012**, *14*, 5884–5887. (c) Dobish, M. C.; Johnston, J. N. Achiral Counterion Control of Enantioselectivity in a

Bronsted Acid-Catalyzed Iodolactonization. *J. Am. Chem. Soc.* **2012**, *134*, 6068–6071. (d) Oderinde, M. S.; Hunter, H. N.; Bremner, S. W.; Organ, M. G. Iodolactonization: Synthesis, Stereocontrol, and Compatibility Studies. *Eur. J. Org. Chem.* **2012**, 175–182. (e) Arai, T.; Kajikawa, S.; Matsumura, E. The Role of Ni-Carboxylate during Catalytic Asymmetric Iodolactonization Using PyBidine-Ni$(OAc)_2$. *Synlett* **2013**, *24*, 2045–2048. (f) Arai, T.; Sugiyama, N.; Masu, H.; Kado, S.; Yabe, S.; Yamanaka, M. A Trinuclear $Zn_3(OAc)_4$-3,3'-bis(aminoimino)binaphthoxide Complex for Highly Efficient Catalytic Asymmetric Iodolactonization. *Chem. Commun.* **2014**, *50*, 8287–8290. (g) Filippova, L.; Stenstrøm, Y.; Hansen, T. V. An Asymmetric Iodolactonization Reaction Catalyzed by a Zinc Bis-Proline-Phenol Complex. *Tetrahedron Lett.* **2014**, *55*, 419–422. (h) Nakatsuji, H.; Sawamura, Y.; Sakakura, A.; Ishihara, K. Cooperative Activation with Chiral Nucleophilic Catalysts and *N*-Haloimides: Enantioselective Iodolactonization of 4-Arylmethyl-4-Pentenoic Acids. *Angew. Chem. Int. Ed.* **2014**, *53*, 6974–6977. (i) Kristianslund, R.; Aursnes, M.; Tungen, J. E.; Hansen, T. V. Squaramide Catalyzed Enantioselective Iodolactonization of Allenoic Acids. *Tetrahedron Lett.* **2016**, *57*, 5232–5236.

7. For fluorolactonizations, see: (a)Parmar, D.; Maji, M. S.; Rueping, M. Catalytic and Asymmetric Fluorolactonisations of Carboxylic Acids through Anion Phase Transfer. *Chem. Eur. J.* **2014**, *20*, 83–86. (b) Egami, H.; Asada, J.; Sato, K.; Hashizume, D.; Kawato, Y.; Hamashima, Y. Asymmetric Fluorolactonization with a Bifunctional Hydroxyl Carboxylate Catalyst. *J. Am. Chem. Soc.* **2015**, *137*, 10132–10135. (c) Woerly, E. M.; Banik, S. M.; Jacobsen, E. N. Enantioselective, Catalytic Fluorolactonization Reactions with a Nucleophilic Fluoride Source. *J. Am. Chem. Soc.* **2016**, *138*, 13858–13861.

8. (a) Paull, D. H.; Fang, C.; Donald, J. R.; Pansick, A. D.; Martin, S. F. Bifunctional Catalyst Promotes Highly Enantioselective Bromolactonizations to Generate Stereogenic C-Br Bonds. *J. Am. Chem. Soc.* **2012**, *134*, 11128–11131. (b) Fang, C.; Paull, D. H.; Hethcox, J. C.; Shugrue, C. R.; Martin, S. F. Enantioselective Iodolactonization of Disubstituted Olefinic Acids Using a Bifunctional Catalyst. *Org. Lett.* **2012**, *14*, 6290–6293.

9. (a) Klosowski, D. W.; Martin, S. F. Enantioselective Synthesis of F-Ring Fragments of Kibdelone C via Desymmetrizing Bromolactonization of 1,4-Dihydrobenzoic Acid. *Synlett* **2018**, *29*, 430–432. (b) Klosowski, D. W.; Martin, S. F. Synthesis of (+)-Disparlure via Enantioselective Iodolactonization. *Org. Lett.* **2018**, *20*, 1269–1271.

10. (a) Brown, R. S. Investigation of the Early Steps in Electrophilic Bromination through the Study of the Reaction with Sterically Encumbered Olefins. *Acc. Chem. Res.* **1997**, *30*, 131–137. (b) Denmark, S. E.; Burk, M. T.; Hoover, A. J. On the Absolute Configurational Stability of Bromonium and Chloronium Ions. *J. Am. Chem. Soc.* **2010**, *132*, 1232–1233. (c) Denmark, S. E.; Burk, M. T. Lewis Base Catalysis of Bromo- and Iodolactonization, and Cycloetherification. *Proc. Natl. Acad. Sci.* **2010**, *107*, 20655–20660.

11. Lee, D. G.; Srinivasan, R. The Oxidation of Benzyldimethylamine by Bromine. *Can. J. Chem.* **1973**, *51*, 2546–2554.

12. Volla, C. M. R.; Atodiresei, I.; Rueping, M. Catalytic C-C Bond-Forming Multi-Component Cascade or Domino Reactions: Pushing the Boundaries of Complexity in Asymmetric Organocatalysis. *Chem. Rev.* **2014**, *114*, 2390–2431.

13. Shi, M.; Chen, L. H.; Li, C. Q. Chiral Phosphine Lewis Bases Catalyzed Asymmetric Aza-Baylis-Hillman Reaction of *N*-Sulfonated Imines with Activated Olefins. *J. Am. Chem. Soc.* **2005**, *127*, 3790–3800.

14. Amidines are known to promote the transfer of bromine from NBS to alkenes: (a) Ahmad, S. M.; Braddock, D. C.; Cansell, G.; Hermitage, S. A.; Redmond, J. M.; White, A. J. P. Amidines as Potent Nucleophilic Organocatalysts for the Transfer of Electrophilic Bromine from N-Bromosuccinimide to Alkenes. *Tetrahedron Lett.* **2007**, *48*, 5948–5952. (b) Ahmad, S. M.; Braddock, D. C.; Cansell, G.; Hermitage, S. A. Dimethylformamide, Dimethylacetamide and Tetramethylguanidine as Nucleophilic Organocatalysts for the Transfer of Electrophilic Bromine From *N*-Bromosuccinimide to Alkenes. *Tetrahedron Lett* **2007**, *48*, 915–918.

15. (a) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. Activation of 6-*Endo* over 5-*Exo* Hydroxy Epoxide Openings. Stereoselective and Ring Selective Synthesis of Tetrahydrofuran and Tetrahydropyran Systems. *J. Am. Chem. Soc.* **1989**, *111*, 5330–5334. (b) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. Activation of 7-*Endo* over 6-*Exo* Epoxide Openings. Synthesis of Oxepane and Tetrahydropyran Systems. *J. Am. Chem. Soc.* **1989**, *111*, 5335–5340.

16. (a) Ikeuchi, K.; Ido, S.; Yoshimura, S.; Asakawa, T.; Inai, M.; Hamashima, Y.; Kan, T. Catalytic Desymmetrization of Cyclohexadienes by Asymmetric Bromolactonization. *Org. Lett.* **2012**, *14*, 6016–6019. (b Murai, K.; Matsushita, T.; Nakamura, A.; Hyogo, N.; Nakajima, J.; Fujioka, H. Kinetic Resolution of β-Substituted Olefinic Carboxylic Acids by Asymmetric Bromolactonization. *Org. Lett.* **2013**, *15*, 2526–2529. (c) Wilking, M.; Mück-Lichtenfeld, C.; Daniliuc, C. G.; Hennecke, U. Enantioselective, Desymmetrizing Bromolactonization of Alkynes. *J. Am. Chem. Soc.* **2013**, *135*, 8133–8136. (d) Hennecke, U.; Wilking, M. Desymmetrization as a Strategy in Asymmetric Halocyclization Reactions. *Synlett* **2014**, *25*, 1633–1637. (e) Wilking, M.; Daniliuc, C. G.; Hennecke, U. Monomeric Cinchona Alkaloid-Based Catalysts for Highly Enantioselective Bromolactonisation of Alkynes. *Chem. Eur. J.* **2016**, *22*, 18601–18607. (f) Knowe, M. T.; Danneman, M. W.; Sun, S.; Pink, M.; Johnston, J. N. Biomimetic Desymmetrization of a Carboxylic Acid. *J. Am. Chem. Soc.* **2018**, *140*, 1998–2001.

17. (a) Röhrig, S.; Hennig, L.; Findeisen, M.; Welzel, P.; Müller, D. Use of Winterfeldt's Template to Control the C-2' Configuration in the Synthesis of Strigol-Type Compounds. *Tetrahedron* **1998**, *54*, 3439–3456. (b) Canham, S. M.; France, D. J.; Overman, L. E. Total Synthesis of (+)-Sieboldine A. *J. Am. Chem.*

Soc. **2010**, *132*, 7876–7877. (c) Trost, B. M.; Kondo, Y. An Asymmetric Synthesis of (+)-Phyllanthocin. *Tetrahedron Lett*. **1991**, *32*, 1613–1616. (d) Martin, S. F.; Colapret, J. A.; Dappen, M. S.; Dupre, B.; Murphy, C. J. Application of Nitrile Oxide Cycloadditions to a Convergent, Asymmetric Synthesis of (+)-Phyllanthocin. *J. Org. Chem.* **1989**, *54*, 2209–2216.

18. Shi reported a modified fructose-derived ketone to promote enantioselective epoxidation of limited scope of *cis*-olefins with moderate enantioselectivity: (a) Burke, C. P.; Shi, Y. Enantioselective Epoxidation of Nonconjugated *Cis* -Olefins by Chiral Dioxirane. **2009**, *11*, 2007–2010.(b) Zhu, Y.; Wang, Q.; Cornwall, R. G.; Shi, Y. Organocatalytic Asymmetric Epoxidation and Aziridination of Olefins and Their Synthetic Applications. *Chem. Rev.* **2014**, *114*, 8199–8256.

19. Ratnayake, R.; Lacey, E.; Tennant, S.; Gill, J. H.; Capon, R. J. Kibdelones: Novel Anticancer Polyketides from a Rare Australian Actinomycete. *Chem. Eur. J.* **2007**, *13*, 1610–1619.

20. (a) Sloman, D. L.; Bacon, J. W.; Porco, J. A. Total Synthesis and Absolute Stereochemical Assignment of Kibdelone C. *J. Am. Chem. Soc.* **2011**, *133*, 9952–9955. (b) Winter, D. K.; Sloman, D. L.; Porco Jr., J. A. Polycyclic Xanthone Natural Products: Structure, Biological Activity and Chemical Synthesis. *Nat. Prod. Rep.* **2013**, *30*, 382.

21.(a)Butler, J. R.; Wang, C.; Bian, J.; Ready, J. M. Enantioselective Total Synthesis of (–)-Kibdelone C. *J. Am. Chem. Soc.* **2011**, *133*, 9956–9959. (b) Rujirawanich, J.; Kim, S.; Ma, A. J.; Butler, J. R.; Wang, Y.; Wang, C.; Rosen, M.; Posner, B.; Nijhawanc, D.; Ready, J. M. Synthesis and Biological Evaluation of Kibdelone C and Its Simplified Derivatives. *J. Am. Chem. Soc.* **2016**, *138*, 10561–10570.

22. (a) Endoma-Arias, M. A. A.; Hudlicky, T. A Short Synthesis of Nonracemic Iodocyclohexene Carboxylate Fragment for Kibdelone and Congeners. *Tetrahedron Lett.* **2011**, *52*, 6632–6634. (b) Froese, J.; Endoma-Arias, M. A. a; Hudlicky, T. Processing of *O*-Halobenzoates by Toluene Dioxygenase. The Role of the Alkoxy Functionality in the Regioselectivity of the Enzymatic Dihydroxylation Reaction. *Org. Process Res. Dev.* **2014**, *18*, 801–809.

23. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. Catalytic Asymmetric Dihydroxylation. *Chem. Rev.* **1994**, *94*, 2483–2547.

24. Dupau, P.; Epple, R.; Thomas, A. A.; Fokin, V. V.; Sharpless, K. B. Osmium-Catalyzed Dihydroxylation of Olefins in Acidic Media: Old Process, New Tricks. *Adv. Synth. Catal.* **2002**, *344*, 421–433.

25. Nicolaou, K. C.; Li, A. Total Syntheses and Structural Revision of α- and β-Diversonolic Esters and Total Syntheses of Diversonol and Blennolide C. *Angew. Chem. Int. Ed.* **2008**, *47*, 6579–6582.

26. Rich, R. H.; Lawrence, B. M.; Bartlett, P. A. Synthesis of (□)-2-Chloroshikimic Acid. *J. Org. Chem.* **1994**, *59*, 693–694.

27. (a) Barton, D.; Crich, D.; Motherwell, W. The Invention of New Radical Chain Reactions .8. Radical Chemistry of Thiohydroxamic Esters - a New Method for the Generation of Carbon Radicals From Carboxylic-Acids. *Tetrahedron* **1985**, *41*, 3901–3924. (b) Carbain, B.; Hitchcock, P. B.; Streicher, H. New Aspects of the Hunsdiecker-Barton Halodecarboxylation-Syntheses of Phospha-Shikimic Acid and Derivatives. *Tetrahedron Lett.* **2010**, *51*, 2717–2719.

28. (a) Journal, S.; Sep, N.; Liebhold, A. M.; Halverson, J. A.; Northeasternforest, G. A. E. Gypsy Moth Invasion in North America : A Quantitative Analysis. *J. Biogeogr.* **1992**, *19*, 513–520. (b) Liebhold, A. M.; Tobin, P. C. Population Ecology of Insect Invasions and Their Management. *Annu. Rev. Entomol.* **2008**, *53*, 387–408.

29. Bierl, B. A.; Beroza, M.; Collier, C. W. Potent Sex Attractant of the Gypsy Moth: Its Isolation, Identification, and Synthesis. *Science* **1970**, *170*, 87–89.

30. (a) Iwaki, S.; Marumo, S.; Saito, T.; Yamada, M.; Kazumasa, K. Synthesis and Activity of Optically Active Disparlure. *J. Am. Chem. Soc.* **1974**, *96*, 7842–7844. (b) Plettner, E.; Lazar, J.; Prestwich, E. G.; Prestwich, G. D. Discrimination of Pheromone Enantiomers by Two Pheromone Binding Proteins from the Gypsy Moth Lymantria Dispar. *Biochemistry* **2000**, *39*, 8953–8962.

31. For recent syntheses, see: (a) Garg, Y.; Kumar Tiwari, A.; Kumar Pandey, S. Enantioselective Total Synthesis of *Cis*-(+)- and *Trans*-(+)-Disparlure. *Tetrahedron Lett.* **2017**, *58*, 3344–3346. (b) Bethi, V.; Kattanguru, P.; Fernandes, R. A. Domino Recombinant γ-Isomerization and Reverse Wacker Oxidation of γ-Vinyl-γ -Butyrolactone: Synthesis of (+)-*trans*-(–)- and (+)-Disparlures. *Eur. J. Org. Chem.* **2014**, *2014*, 3249–3255.(c) Herbert, M. B.; Marx, V. M.; Pederson, R. L.; Grubbs, R. H. Concise Syntheses of Insect Pheromones Using Z-Selective Cross Metathesis. *Angew. Chem. Int. Ed.* **2013**, *52*, 310–314. (d) Kim, S. G. G. Concise Total Synthesis of (+)-Disparlure and Its *trans*-Isomer Using Asymmetric Organocatalysis. *Synthesis* **2009**, 2418–2422. (e) Prasad, K. R. R.; Anbarasan, P. Enantiodivergent Synthesis of Both Enantiomers of Gypsy Moth Pheromone Disparlure. *J. Org. Chem.* **2007**, *72*, 3155–3157.

32. Avedissian, H.; Sinha, S. C.; Yazbak, A.; Sinha, A.; Neogi, P.; Sinha, S. C.; Keinan, E. Total Synthesis of Asimicin and Bullatacin. *J. Org. Chem.* **2000**, *65*, 6035–6051.

33. Fujisawa, T.; Sato, T.; Kawara, T.; Naruse, K. One-Pot Synthesis of (*Z*)-Alkenoic Acids. *Chem. Lett.* **1980**, 1123–1124.

34. Sajiki, H.; Hattori, K.; Hirota, K. Pd/C(en)-Catalyzed Regioselective Hydrogenolysis of Terminal Epoxides to Secondary Alcohols. *Chem. Commun.* **1999**, 1041–1042.

35. To the best of our knowledge, the shortest enantioselective synthesis of (+)-disparlure was achieved in five steps through the use of a chiral sulfoxide auxiliary. Satoh, T.; Oohara, T.; Ueda, Y.; Yamakawa, K. A Novel Approach to the Asymmetric Synthesis of Epoxides, Allylic Alcohols, α-Amino Ketones, and α-

Amino Aldehydes from Carbonyl Compounds through α,β-Epoxy Sulfoxides Using the Optically Active *p*-Tolylsulfinyl Group To Induce Chirality. *J. Org. Chem*. **1989**, *54*, 3130–3136.

36. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. Safe and Convenient Procedure for Solvent Purification. *Organometallics* **1996**, *15*, 1518-1520.

37. Meng, C.; Liu, Z.; Liu, Y.; Wang, Q. 4-(Dimethylamino)pyridine-Catalysed Iodolactonisation of γ,δ-Unsaturated Carboxylic Acids. *Org. Biomol. Chem.* **2015**, *13*, 6766–6772

38 Raghavan, S.; Babu, V. S. Enantioselective Synthesis of Oseltamivir Phosphate. *Tetrahedron* **2011**, *67*, 2044–2050.