

Published in final edited form as:

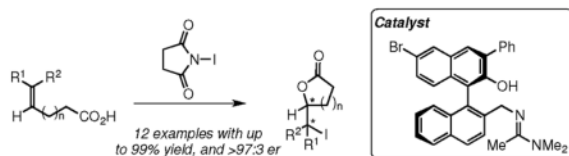
Org Lett. 2012 December 21; 14(24): 6290–6293. doi:10.1021/ol3030555.

Enantioselective Iodolactonization of Disubstituted Olefinic Acids Using a Bifunctional Catalyst

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Abstract



The enantioselective iodolactonizations of a series of diversely-substituted olefinic carboxylic acids are promoted by a BINOL-derived, bifunctional catalyst. Reactions involving 5-alkyl- and 5-aryl-4(*Z*)-pentenoic acids and 6-alkyl- and 6-aryl-5(*Z*)-hexenoic acids provide the corresponding γ - and δ -lactones having stereogenic C–I bonds in excellent yields and >97:3 er. Significantly, this represents the first organocatalyst that promotes both bromo- and iodolactonization with high enantioselectivities. The potential of this catalyst to induce kinetic resolutions of racemic unsaturated acids is also demonstrated.

Electrophilic halocyclizations of α,ω -functionalized alkenes represent an important class of reactions in organic chemistry.¹ In particular, halolactonizations of unsaturated acids have been widely used in organic chemistry to prepare intermediates in the synthesis of biologically active natural products and other compounds having potential utility.² Given the importance of these cyclizations, there has been considerable interest in developing enantioselective variants, and a number of notable advances in developing enantioselective bromolactonizations of unsaturated acids **1** to give lactones **2** (X = Br, Figure 1) have been recently reported.³ However, the corresponding catalytic, enantioselective chloro-^{3f,4} and iodolactonizations⁵ to give **2** (X = Cl and I, Figure 1) are less common and much more restrictive in substrate scope.

The first catalytic, enantioselective iodolactonization was reported in 2004 by Gao, who used quaternary ammonium salts derived from cinchonidine to promote cyclizations of 5-aryl-4(*E*)-pentenoic acids. However, these reactions proceeded with only moderate enantioselectivity, and mixtures of γ - and δ -lactones were often obtained.^{5a} Gao and coworkers later found that a salen-Co(II) complex catalyzed enantioselective iodolactonizations of several 4-aryl-4-pentenoic acids to give γ -lactones with up to 92:8 er.^{5b} Veitch and Jacobsen recently discovered that 5-aryl-5-hexenoic acids undergo enantioselective iodolactonizations, typically with >95:5 er, in the presence of a tertiary aminourea catalyst.^{5c} Most recently Dobish and Johnston utilized a chiral Brønsted acid catalyst to promote enantioselective iodolactonizations of an extensive series of 5-aryl-5-

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 Supporting Information Available: Experimental procedures, characterization of new compounds, and Xray crystal data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

hexenoic acids, usually with >98:2 er.^{5d} Despite these achievements, there are a number of significant limitations to existing methods. In particular, there are few examples of iodolactonizations of olefinic acids bearing alkyl groups on the double bond,^{5b-d} and these cyclizations invariably have occurred with lower enantioselectivity than their aryl counterparts. Moreover, there are no examples of iodolactonizations that generate new C–I bonds at stereogenic centers. Because the products of such cyclizations may bear two new stereocenters, existing iodolactonization methods are not applicable to the direct synthesis of compounds containing multiple stereocenters.

We envisioned that these and other gaps in prevailing methods might be addressed by adapting our recently reported protocol for enantioselective bromolactonizations that are catalyzed by **3**.³ⁱ In particular, we queried whether **4**, which is formed quantitatively in situ by bromination of **3** under conditions used for bromolactonization, might promote highly enantioselective iodolactonizations. We thus discovered that **4** catalyzed the iodolactonizations of various disubstituted olefinic acids with *N*-iodosuccinimide (NIS) to deliver iodolactones in excellent yields and enantioselectivities.⁶ To our knowledge, this is the first instance where the same organocatalyst is highly effective for both bromo- and iodolactonizations. Herein we report the details of some of our findings.

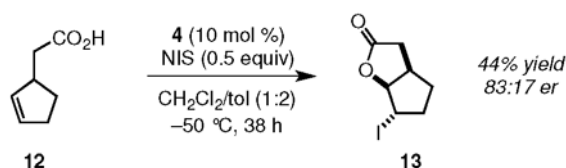
We found that both 5-alkyl-4(*Z*)-pentenoic acids **5a–d** and 5-aryl-4(*Z*)-pentenoic acids **5e–h** undergo iodolactonization in the presence of **4** (10 mol %) and NIS (1.2 eq) at –20 °C to furnish the γ -lactones **6a–h** as the only isolable products in >97:3 er and in excellent yield (Table 1, entries a–h). The reaction with **5a** was also ran on 0.5 mmol scale to give the iodolactone product **6a** in 95% yield and 97.5:2.5 er (Table 1, entry a). These cyclizations proceed via an *exo* mode of ring closure with high regioselectivity to generate products with two contiguous stereogenic centers. Diastereomeric products were observed only when the starting *Z*-alkene contained detectable amounts of the inseparable *E*-isomer. The presence of electron withdrawing groups on the aromatic ring is well tolerated, but the products obtained from substrates having electron rich aromatic rings, such as *p*-methoxyphenyl, are unstable and suffer extensive decomposition during isolation and purification. In the reactions of *cis*-aryl olefinic acids **5e–h**, no products arising from a 6-*endo* cyclization pathway were observed. We tentatively attribute this observation to the difficulty of achieving the planar arrangement in the transition state necessary for maximum stabilization of the developing positive charge at the benzylic position.⁷

The utility of organocatalyst **4** is further exemplified by the enantioselective iodolactonizations of 6-aryl- and 6-alkyl-5(*Z*)-hexenoic acids such as **7a–d** to provide the corresponding δ -lactones **8a–d** in high yields and up to 99:1 er (Table 2). No regioisomeric products were observed, and diastereomeric products were detected only if the starting *Z*-alkene contained discernable amounts of *E*-isomer. Although an electron-withdrawing group slowed the iodolactonization reaction, the selectivity was not adversely affected (Table 2, entry b).

In contrast to the high enantioselectivities observed for 5-substituted-4(*Z*)-pentenoic acids **5a–h**, iodolactonizations of 5-alkyl-4(*E*)-pentenoic acids are somewhat less selective, as exemplified by the cyclization of **9a** to give **10a** (Table 3, entry a). The divergent levels of enantioselectivity in the iodolactonizations of 5-alkyl-4(*E*)- and 5-alkyl-4(*Z*)-pentenoic acids mirrors the related bromolactonizations,³ⁱ and it may reflect a preferential side-on approach of the olefin during formation of the iodonium ion in analogy with known enantioselective epoxidations of olefins.⁸ The iodolactonization of **9b** was not regioselective, giving an inseparable mixture (1.3:1.0) of the γ - and δ -lactones **10b** and **11b** via 5-*exo* and 6-*endo* cyclization pathways, respectively (Table 3, entry b). For other 5-aryl-4(*E*)-pentenoic acids, we find, like Gao,^{5a} that the electronic nature of substituents on the aromatic ring has a

marked effect upon the regioselectivity of the iodolactonization (Table 3, entries c,d). For example, **9c** undergoes both regio- and enantioselective iodolactonization preferentially via an *endo* mode of ring closure (6-*endo*:5-*exo* >20:1) to give **11c** with 86.5:13.5 er. The presence of an electron-withdrawing group favors iodolactonization by an *exo* mode of closure that is not very enantioselective (Table 3, entry d).

Catalytic enantioselective transformations may be applied to kinetic resolutions, which can provide an enantiomerically pure product from a racemic starting material. There are, however, fewer examples of such processes with organic catalysts than with metal or enzyme catalysts. Although there is a recent report of a kinetic resolution of a racemic, unsaturated acid by bromolactonization,⁹ we are aware of no example of a kinetic resolution by an iodolactonization. It is thus notable that **4** promotes the kinetic resolution of commercially available 2-cyclopentene-1-acetic acid (**12**) to give bicyclic iodolactone (+)-**13** in 44% yield (88% of theoretical) in 83:17 er (eq 1).¹⁰ Compound (+)-**13** and its enantiomer are important intermediates in the syntheses of a number of targets.¹¹



(1)

As mentioned previously, halolactones are useful intermediates for the synthesis of a number of other compounds. One important application of their utility is exemplified by their conversion into epoxides. Although there are some excellent methods for the enantioselective synthesis of epoxides,¹² there remain some gaps in methods for preparing epoxides having certain substitution patterns. For example, enantioselective epoxidation of unconjugated, *cis*-1,2-dialkyl alkenes lacking suitable directing groups is not well-documented.¹³ It is thus significant that treatment of **6d** with Cs₂CO₃ in MeOH afforded the corresponding epoxy ester **14** in 87% yield with essentially complete retention of enantiopurity (eq 2). Application of this iodolactonization-epoxidation sequence therefore provides a practical approach to the enantioselective synthesis of *cis*-epoxides that were heretofore not accessible.



(2)

In summary, we have discovered that the BINOL-derived catalyst **4** is a useful bifunctional catalyst for promoting the highly enantioselective iodolactonizations of a wide array of olefinic acids. Moreover, to our knowledge **4** is the first organocatalyst that is capable of promoting both highly enantioselective bromo- and iodolactonizations. The iodolactonizations of 5-substituted-4(*Z*)-pentenoic and 6-substituted-5(*Z*)-hexenoic acids

typically proceed with >97:3 er to give the corresponding γ - and δ -lactones having two contiguous stereogenic centers. Indeed, these reactions represent the first examples where new C–I bonds are formed with high enantioselectivity by iodolactonizations. The potential of **4** and analogs thereof for effecting enantioselective syntheses of iodolactones by kinetic resolution is also demonstrated. Moreover, the product lactones can be converted into epoxides, thereby enabling the highly enantioselective preparation of certain substituted epoxides that were heretofore inaccessible. The utility of **4** and related catalysts to promote highly enantioselective reactions as key steps in natural product synthesis is under active investigation as are studies to elucidate the mechanism and the origin of stereoinduction in these cyclizations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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). We are also grateful to Dr. Vincent Lynch (The University of Texas) for X-ray crystallography.

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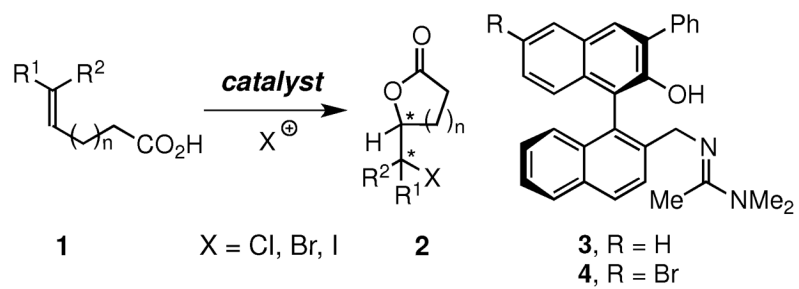
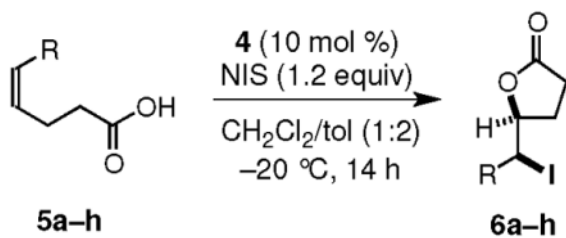


Figure 1.
Enantioselective Halolactonizations

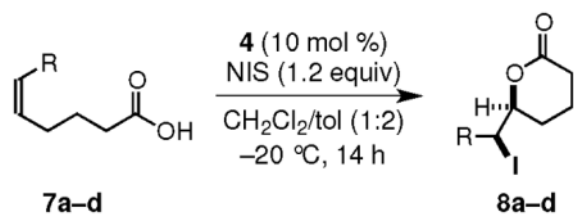
Table 1

Iodolactonization of 5-Substituted-4(*Z*)-pentenoic Acids^a

entry	R	product	yield ^b (%)	er ^{c,d}
a	<i>i</i> -Pr	6a	93 (95) ^e	97.5:2.5
b	<i>i</i> -Bu	6b	94	98:2
c	<i>t</i> -Bu	6c	99	97:3
d	<i>c</i> -Hex	6d	97	98:2
e ^f	Ph	6e	93	98.5:1.5
f	<i>p</i> -NC-C ₆ H ₄	6f	95	99:1
g ^g	<i>p</i> -Cl-C ₆ H ₄	6g	89	98:2
h ^h	2-Np	6h	94	98:2

^aReactions run on 0.1 mmol scale.^bIsolated yield after column chromatography.^cer determined by chiral HPLC.^dAbsolute stereochemistry of **6c** and **6e** established by X-ray analysis; **6a–b**, **6d**, **6f–h** were based on analogy.^eYield in parentheses obtained on 0.5 mmol scale.^f*Z/E* ratio of **5e**, 20:1.^g*Z/E* ratio of **5g**, 11:1.^h*Z/E* ratio of **5h**, 17:1.

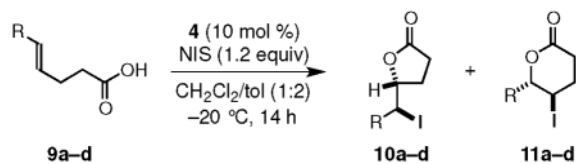
Table 2

Iodolactonization of 6-Substituted-5(*Z*)-hexenoic Acids^a

entry	R	product	yield ^b (%)	er ^{c,d}
a ^e	Ph	8a	89	99:1
b ^{f,g}	<i>p</i> -NC-C ₆ H ₄	8b	88	99:1
c ^g	2-Np	8c	93	98.5:1.5
d	<i>t</i> -Bu	8d	98	98:2

^aReactions run on 0.1 mmol scale.^bIsolated yield after column chromatography.^cer determined by chiral HPLC.^dAbsolute stereochemistry of **8a-d** are based on analogy with **6c** and **6e**.^e*Z/E* ratio of **7a**, 14:1.^f*Z/E* ratio of **7b**, 20:1.^gResults obtained after 38 h at -20 °C.

Table 3

Regiochemistry in Iodolactonization of 5-Substituted-4(*E*)-pentenoic Acids^a

entry	R	product	yield ^b (%)	er ^{c,d}
a	<i>i</i> -Pr	10a	78	67:33
b	Ph	10b+11b	89 ^e	52:48(95:5) ^f
c	<i>p</i> -MeO-C ₆ H ₄	11c	89	86.5:13.5
d ^g	<i>p</i> -NC-C ₆ H ₄	10d	94	58:42

^aReactions run on 0.1 mmol scale.^bIsolated yield after column chromatography.^cer determined by chiral HPLC.^dAbsolute stereochemistry of iodolactones was assigned based on analogy with corresponding bromolactone analogs.³¹^eCombined yield; ratio of 1.3:1.0 based upon NMR analysis.^fer shown in parentheses is for **11b**.^gReaction performed for 14 h at -20 °C and 48 h at -10 °C in CH₂Cl₂/tol (1:1).