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Enantioselective Oxidation of Alkenylbenzoates Catalyzed by Chiral Hypervalent Iodine(III) To Yield 4-Hydroxyisochroman-1-ones

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In this study, the enantioselective oxylactonization of *ortho*-alk-1-enylbenzoates with chiral hypervalent iodine(III) reagents yielded 3-alkyl-4-hydroxyisochroman-1-ones with high enantiomeric purity (ca. 90 % *ee*). The enantioselective oxidation was also performed under catalytic conditions, in which a catalytic amount (10 mol-%) of a chiral iodoarene was oxidized to the hypervalent iodine species in situ using a stoichiometric co-oxidant, *m*-chloroperbenzoic acid (*m*CPBA). The catalytic oxidation mediated by chiral hypervalent iodine(III) species yielded enantiocontrolled *syn* products, while the direct oxidation of the substrate with *m*CPBA occurred as background oxidation to give racemic *anti* products. Under optimized conditions, the catalytic oxylactonization led to high levels of enantioselectivity (ca. 90 % *ee*) and improved *syn*/*anti* selectivities (ca. 80 % *syn*). The product distribution indicated that the lactate side-chain on the chiral iodoarene precatalyst plays an important role in enhancing both the enantioselectivity and the catalytic efficiency in the oxylactonization.

Introduction

The 4-hydroxyisochromanone motif is found in many natural products (Figure 1), most of which belong to a family of polyketide metabolites isolated from fungal and bacterial sources.[1–7] These oxyisochromanones show interesting biological activities such as antifungal, antibacterial, and cytotoxic effects. Despite the simple structures and promising biological properties of the oxyisochromanones, the synthesis of this class of natural products remains a significant challenge, and only a few successful total syntheses have been reported.[8–10]

Two strategies have been reported for the synthesis of 4-hydroxyisochroman-1-one derivatives: 1) the hetero-Diels–Alder cycloaddition of *ortho*-quinone dimethides followed by oxidation[11] (the first pathway in Scheme 1); and 2) the oxidative rearrangement of isobenzofurans followed by reduction[12] (the second pathway). However, an enantioselective transformation has not been achieved using either of these strategies. Meanwhile, we have recently presented a third method for the selective preparation of 4-oxyisochroman-1-ones using hypervalent iodine(III) reagents (the third pathway in Scheme 1).[13] Using lactate-based chiral hypervalent iodine reagents led to high levels of enantioselectivity in the oxylactonization of *ortho*-alkenylbenzoate **1**. The *endo* selectivity achieved in the oxylactonization with hypervalent iodine contrasts with the *exo* selectivity observed in the reaction with conventional oxidizing reagents.[14,15] The unprecedented regioselectivity in the oxylactonization with hypervalent iodine opens up a powerful

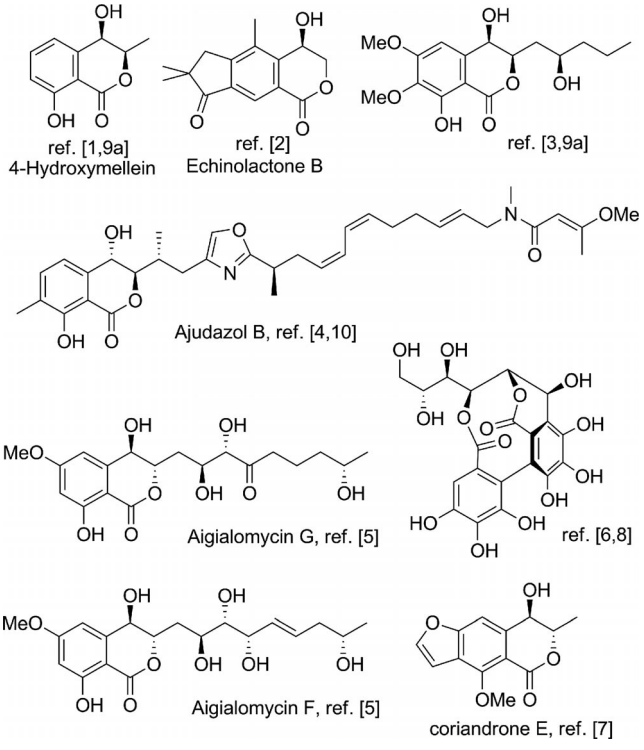

Figure 1. Natural products containing the 4-hydroxyisochroman-1-one motif.

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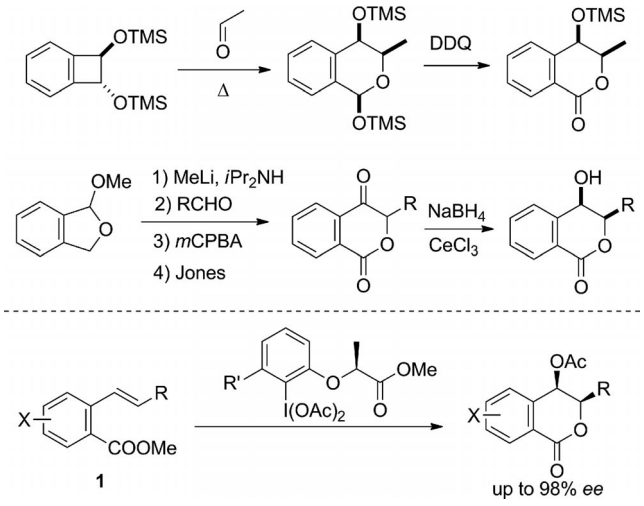
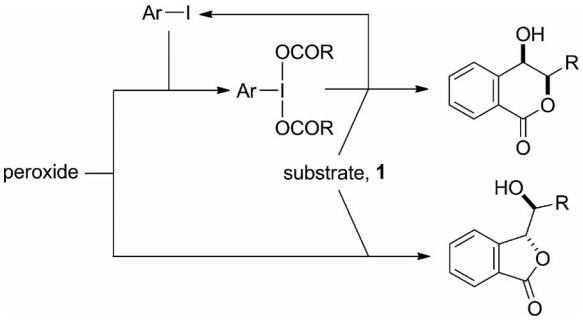
approach to the synthesis of 4-hydroxyisochroman-1-one natural products. In fact, the oxylactonization strategy using hypervalent iodine has been applied to the asymmetric synthesis of more than four types of 4-oxyisochroman-1-one natural products, including 4-hydroxymellein and a fusarentin-related compound.[9,13]



Scheme 1. Synthetic routes to 4-oxyisochroman-1-ones.

The total synthesis of natural products incorporating the 4-hydroxyisochroman-1-one motif has attracted the attention of synthetic chemists, and this field has been advancing rapidly. Recently, the total synthesis of ajudazol B (Figure 1) was completed by Menche's group,[10] and many research groups targeting this compound have reported syntheses of different ajudazol fragments.[12,16] The selective formation of the 4-hydroxyisochroman-1-one core is one of the most difficult steps in the total synthesis. Indeed, the deoxy forms of these products have previously been synthesized, which avoids the difficulties inherent in the lactonization step.[17,18] In Menche's synthetic route,[10] a highly selective and sensitive protection and deprotection of the vicinal hydroxy groups was required in the lactonization step to obtain the desired hydroxyisochromanone without the formation of the phthalide product, which is thermodynamically more stable but undesirable.[19] The establishment of a more reliable and efficient route to the 4-hydroxyisochroman-1-one core is needed, and further research is directed towards the syntheses of this class of natural products and its analogs.

Recent developments in the area of asymmetric transformations induced by chiral hypervalent iodine reagents have contributed to powerful new strategies for stereoselective oxidation.[20–25] A breakthrough in the design of a chiral reagent for high stereoselectivity came with the arrival of conformationally rigid 1,1-spiroindanone reagents[22,25d] and conformationally flexible lactate-based reagents.[9,13,23,24b,24c] The lactate-based hypervalent iodine reagent has been used for several types of highly stereoselective oxidation since we first reported it.[23a] Oxidation reactions using hypervalent iodine species may operate catalytically.[26,27] Many enantioselective oxidations using chiral hypervalent iodine reagents have been performed under catalytic conditions[22,24,25] in which a catalytic amount of a chiral iodoarene was oxidized to give a hypervalent iodine species in situ using a stoichiometric co-oxidant, as shown in Scheme 2. In the catalytic variant of the reaction, it is no longer necessary to prepare reactive hypervalent iodine compounds, and only a catalytic amount of a chiral iodoarene is used as a precursor. Thus, the catalytic route provides simpler and more efficient protocols than traditional reactions based on a stoichiometric amount of the hypervalent iodine reagent. A fundamental requirement for success in a catalytic reaction is that direct oxidation of the substrate by the stoichiometric co-oxidant occurs at a significantly lower rate than its oxidation by the catalytic hypervalent iodine species. In the case of the reaction of alkenylbenzoate substrate **1**, as illustrated in Scheme 2, the direct oxidation reaction must yield by-products (e.g., Scheme 4). To date, success in catalytic enantioselective oxidation reactions mediated by chiral hypervalent iodine has been limited almost exclusively to the α-oxidation of ketones[25] and the dearomatization of phenols (naphthols).[22,24] The oxidative double cyclization of 2-(4-hydroxybut-1-enyl)benzoates is the only current example of the catalytic enantioselective oxidation of an alkene.[9,28] However, many research groups have recently attained high enantioselectivity in the oxidation of an alkene using a stoichiometric amount of a lactate-based chiral hypervalent iodine derivative.[13,23] If the structural requirements for a successful chiral catalyst are clarified, the catalytic system may be extended to various reactions, including those that have already been reported using stoichiometric asymmetric induction.



Scheme 2. Catalytic cycle involving hypervalent iodine(III).

In this paper, a simple route to optically active 4-hydroxyisochroman-1-ones, biologically relevant building blocks, is achieved by the oxylactonization of alkenylbenzoate with a lactate-based chiral hypervalent iodine catalyst generated in situ. This reaction system is suitable for evaluating the efficiency of the catalytic cycle that includes the hypervalent iodine intermediate, because the relative contributions of the catalytic oxidation and the direct oxidation can be evaluated from the diastereomeric ratio of the oxidation products.

Results and Discussion

Stoichiometric Oxylactonization

First, we present the results of the reaction using a stoichiometric amount of a chiral hypervalent iodine reagent. The catalytic cycle illustrated in Scheme 2 includes the oxylactonization of alkenylbenzoate **1** with a hypervalent iodine reagent as an important elementary process of the cycle. This elementary process was performed separately using isolated hypervalent iodine reagents (Figure 2).

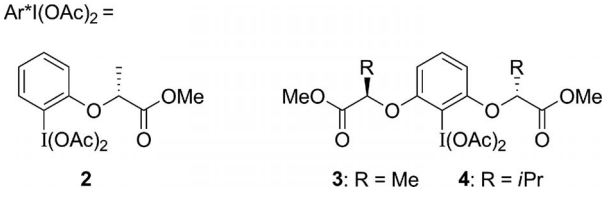
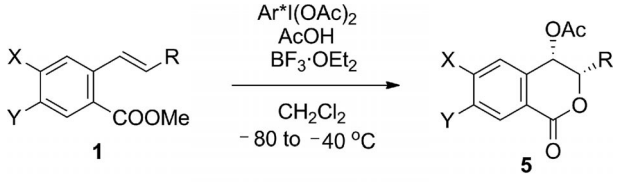


Figure 2. Chiral hypervalent iodine(III) reagents.

First, we studied the acetoxylactonization of a series of alkenylbenzoates **1** with a stoichiometric amount of lactate-based chiral hypervalent iodine(III) reagents (Table 1). The acetoxylactonization was performed under reaction conditions similar to those reported in the preliminary account.[13] Boron trifluoride diethyl etherate could activate the hypervalent iodine reagent to promote immediate acetoxylactonization at low temperatures. The reaction selectively delivered the acetoxy group onto the benzylic carbon atom of the alkene substrate to give 4-acetoxyisochroman-1-one **5**, but without the formation of the γ-lactone product [i.e., 3-(1-oxyalkyl)phthalide]. Various alkenylbenzoate substrates were subjected to the acetoxylactonization reaction, but Table 1 contains only those substrates selected for the catalytic reaction described below.[29] Substrates bearing an electron-donating substituent are not included in Table 1, although they have been used for a key step in the synthesis of natural products.[9] With the substrates shown in Table 1, high levels of enantioselectivity were obtained, especially in the reactions of substrates incorporating electron-withdrawing groups such as CF_3 (i.e., **1c**; Table 1, entry 3). When reagent **3**, bearing two lactate groups, was used, the enantioselectivity was enhanced (Table 1, entries 5 and 7).

In the acetoxylactonization, the *cis*-isochromanone product (i.e., **5**) was obtained from the *E*-substrate. In other words, the addition of two oxygen nucleophiles onto the C=C double bond of the substrate proceeded with *syn* selectivity, as can be explained by the mechanism shown in Scheme 3. The activated hypervalent iodine species electrophilically attacked at the C=C double bond of the alkene substrate, and this was followed by nucleophilic displacements by acetate and by the internal methoxycarbonyl group. These two consecutive substitution steps proceeded with inversion of configuration and so resulted in a *syn* selectivity. Enantiopure hypervalent iodine reagents **2**–**4** showed good differentiation between the enantiofaces of the alkene substrate; thus these reagents must have preferentially attacked the *si* face of the alkene substrate.

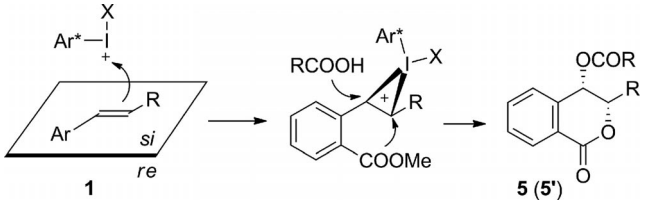
Table 1. Enantioselective acetoxylactonization of **1**.[a]



a: R = *n*-C_5H_{11}, X = Y = H
b: R = *n*-C_5H_{11}, X = H, Y = Br
c: R = *n*-C_5H_{11}, X = CF_3, Y = H
d: R = CH_2OMe, X = Y = H
e: R = *i*Pr, X = Y = H
f: R = *i*Pr, X = H, Y = F

Entry	Substrate	$Ar^*I(OAc)_2$	**5**	
			Yield [%]	*ee* [%][b]
1[c]	**1a**	**2**	63	90
2	**1b**	**2**	72	88
3	**1c**	**2**	71	96
4[c]	**1d**[d]	**2**	80	84
5[c]	**1d**	**3**	60	97
6	**1e**	**2**	64	87
7	**1e**	**3**	63	96
8	**1f**	**2**	72	88

[a] **1** (0.10 mmol), $Ar^*I(OAc)_2$ (0.12 mmol), $BF_3{\cdot}OEt_2$ (1.3 mmol), CH_2Cl_2 (5 mL), acetic acid (0.3 mL). The reaction was started at –80 °C by the addition of $BF_3{\cdot}OEt_2$. The mixture was gradually warmed up to –40 °C over 1 h, and then quenched by the addition of water at that temperature. [b] Determined by GC analysis on a chiral stationary phase. [c] The data have previously been reported in ref.[13] [d] When the corresponding carboxylic acid substrate was used, **5d** was obtained in 84% yield with 84% *ee*.[13]



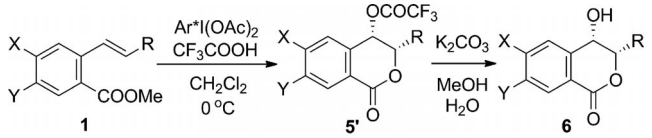
Scheme 3. Plausible mechanism for oxylactonization with hypervalent iodine.

Acetoxylactonization product **5** was subjected to hydrolysis to give 4-hydroxyisochroman-1-one **6**, which is widely found as the core structure in natural products, as shown in Figure 1. The hydrolysis was performed in aqueous methanol containing K_2CO_3 at 0 °C. Unfortunately, partial translactonization (isomerization) into γ-lactone **7** took place during the hydrolysis. The product ratio of **6**/**7** obtained depended on the electronic properties of the substituent on the aromatic ring of the isochromanone. Unsubstituted compounds **5a** and **5e** isomerized to a small degree (**6a**/**7a** = 8:2; **6e**/**7e** = 9:1), but the presence of electron-withdrawing substituents in **5b** and **5c** led to greater degrees of isomerization (**6b**/**7b**, **6c**/**7c** = 3:7). In the latter case, rearranged product **7** was already observed in the early stage of the hydrolysis of **5**. The rearrangement to the thermodynamically more stable product (i.e., **7**) may occur by hydrolysis of the δ-lactone moiety. The rate of hydrolysis of the lactone must be affected by the electronic properties of the substituents on the aromatic ring; an electron-withdrawing

group enhances the rate of hydrolysis, while an electron-donating group reduces it. In fact, selective hydrolysis without translactonization into the γ-lactone was achieved for a 4-acetoxyisochroman-1-one with electron-donating substituents on the aryl moiety during our total synthesis of natural products.[9] The selective deacetylation of electron-withdrawing isochromanones to give **6** may be difficult to achieve without translactonization, and so the products of acetoxylactonization cannot be counted as general precursors for the preparation of 4-hydroxyisochroman-1-ones.

Trifluoroacetoxylactonization may be suitable for the selective preparation of **6**, because the trifluoroacetoxy group is more readily hydrolyzed than the acetoxy group. Similarly to boron trifluoride diethyl etherate, trifluoroacetic acid (TFA) activated the hypervalent iodine reagent to promote oxylactonization and functioned as a nucleophile to give trifluoroacetoxylactonization product **5′** (Table 2). The reaction proceeded smoothly at 0 °C. Product **5′** was detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixture, but was too labile to purify by silica gel column chromatography. Thus, isolation of the product was performed after hydrolysis of the crude reaction mixture containing **5′** by treatment with potassium carbonate/methanol/H_2O. Notably, this hydrolysis reaction yielded **6** cleanly, even in the presence of an electron-withdrawing group (**6b**/**7b** > 20:1, **6c**/**7c** = 12:1).

Table 2. Enantioselective trifluoroacetoxylactonization of **1**.[a]



1 **5′** **6**

a: R = *n*-C_5H_{11}, X = Y = H
b: R = *n*-C_5H_{11}, X = H, Y = Br
c: R = *n*-C_5H_{11}, X = CF_3, Y = H
d: R = CH_2OMe, X = Y = H
e: R = *i*Pr, X = Y = H
f: R = *i*Pr, X = H, Y = F

Entry	Substrate	$Ar^*I(OAc)_2$	Time [h]	**6**	
				Yield [%]	*ee* [%][b]
1	**1a**	**3**	3.5	52	68
2	**1a**	**4**	20	57	80
3[c]	**1a**	**3**	40	69	96
4[d]	**1a**	**2**	1	72	86
5	**1b**	**3**	17.5	51	74 (94)
6[c,e]	**1b**	**3**	139	44	74
7	**1c**	**3**	44	56	76 (99)
8	**1d**	**3**	3	76	84 (91)
9	**1e**	**3**	1	43	78 (99)
10[c]	**1e**	**3**	67	62	94
11	**1f**	**3**	2.5	65	61 (96)

[a] **1** (0.10 mmol), $Ar^*I(OAc)_2$ (0.16 mmol), CF_3COOH (0.1 mL), CH_2Cl_2 (4 mL), 0 °C, unless otherwise noted. [b] Determined by GC analysis on a chiral stationary phase. The value in parentheses corresponds to the *ee* value after crystallization. [c] The reaction was carried out at –80 °C. [d] The reaction was started at –80 °C by the addition of $BF_3{\cdot}OEt_2$ (0.16 mL). The mixture was gradually warmed up to –40 °C over 1 h, and then quenched by the addition of water at –40 °C. [e] CF_3COOH (0.4 mL).

The enantiomeric purity of **6** was determined by GC analysis on a chiral stationary phase. At 0 °C, the product was formed with an unsatisfactory enantiomeric purity (61–84% *ee*), but enantiomerically enriched 4-hydroxyisochroman-1-ones were obtained after recrystallization from ethyl acetate/hexane. The oxylactonization reaction using TFA proceeded even at –80 °C, but a prolonged reaction time (2–3 d) was necessary for the substrate to be consumed (Table 2, entries 3 and 10). The reaction at low temperatures gave higher enantioselectivities. The reaction of an electron-deficient substrate (i.e., **1b**) at –80 °C (Table 2, entry 6) barely proceeded in the presence of an increased amount of TFA, but the enantioselectivity was moderate. The trifluoroacetoxylactonization reaction at low temperatures could be accelerated by the addition of boron trifluoride diethyl etherate in the presence of TFA (Table 2, entry 4). The enantioselectivity (86% *ee*) was comparable with that obtained in the acetoxylactonization reaction under similar conditions (90% *ee*; Table 1, entry 1). Thus, trifluoroacetoxylactonization with the chiral hypervalent iodine reagent is reliable for the preparation of optically active 4-hydroxyisochroman-1-ones.

Catalytic Oxylactonization

To simplify the oxylactonization protocol with hypervalent iodine, we examined catalytic conditions in which a catalytic amount of a chiral iodoarene was oxidized to the hypervalent iodine species in situ using a stoichiometric co-oxidant. It was not necessary to isolate the reactive hypervalent iodine compounds; only a catalytic amount of chiral iodoarene was used as a precursor. In the stoichiometric reaction, lactate-based hypervalent iodine reagents **2–4** gave high enenatioselectivities. In addition to enantioselectivity, catalytic efficiency must be taken into account in the catalytic reaction. To examine the relationship between the structure of the precatalyst and the catalytic efficiency, we used various iodoarene precatalysts **10a**–**u**, including achiral compounds (Figure 3). Methyl 2-[(*E*)-hept-1-enyl]benzoate (**1a**) was selected as a benchmark substrate for the optimization of the reaction conditions, and the results are summarized in Table 3.

First, the reaction in the absence of an iodoarene precatalyst was examined as a control test (Table 3, entry 1). Substrate **1a** was subjected to oxidation with *m*-chloroperbenzoic acid (*m*CPBA) in the presence of TFA in dichloromethane at 0 °C. Only the *anti* products (i.e., **8a** and **9a**) were obtained, which suggests that these products were formed by epoxidation followed by acid-catalyzed nucleophilic displacement (Scheme 4).[30] The diastereoselectivity (*anti*) in the direct oxidation with *m*CPBA contrasts with the *syn* selectivity observed in the oxidation with hypervalent iodine derivatives (Scheme 3). During the catalytic reaction, the direct oxidation with *m*CPBA must occur as a background oxidation. Ideally, the *syn*/*anti* ratio of the oxidation products should correspond to the ratio of the catalytic oxidation to the direct oxidation. The appropriateness of this

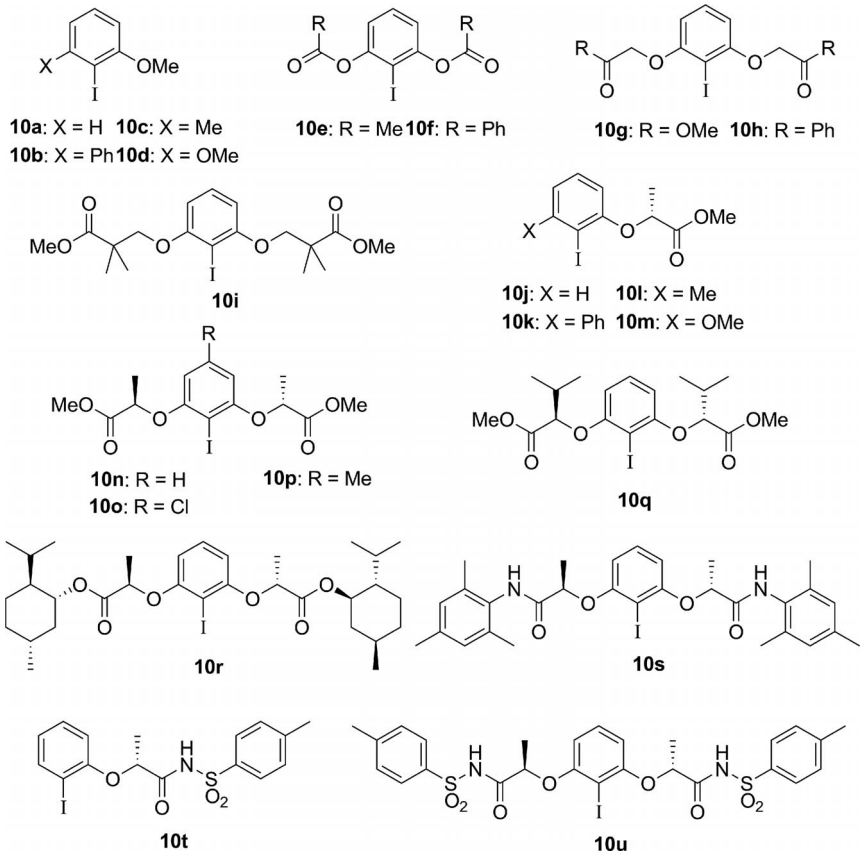
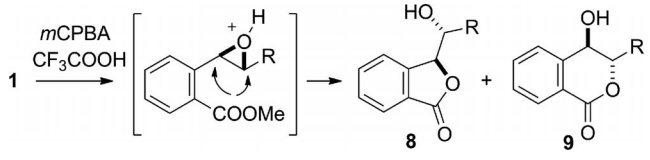


Figure 3. Iodoarene precatalysts.

proposal can be judged from the result of an enantioselective catalytic reaction. A representative example of a gas chromatogram of products of enantioselective catalytic oxidation is shown in Figure 4. Four pairs of enantiomers of hydroxylactonization products **6a**, **7a**, **8a**, and **9a** were separated to give eight peaks. In the chiral GC trace, *anti* products **8a** and **9a** were nearly racemic, whereas *syn* products **6a** and **7a** showed significant enantiomeric excesses. This is consistent with the above proposal, i.e., the direct oxidation must yield racemic *anti* products, while the catalytic oxidation must yield enantiocontrolled *syn* products. The *ee* value of the minor *syn* product (i.e., **7a**) was slightly different from that of the major product (i.e., **6a**). This difference can be explained as being due to experimental errors in the determination of the *ee* value of **7a** owing to the small amount of **7a** and/or to some contribution from an S_N1 mechanism to the acid-catalyzed transformation of the epoxide into the lactone. For **6a**, the *ee* value (68% *ee*; Table 3, entry 15) obtained in the catalytic reaction is consistent with that obtained in the stoichiometric oxidation under the corresponding reaction conditions (68% *ee*; Table 2, entry 1). Thus, at least **6a** must have resulted from a catalytic cycle involving chiral hypervalent iodine. Essentially, the *syn*/*anti* ratio can be used as an indicator of catalytic efficiency, even when an achiral iodoarene precatalyst is used.



Scheme 4. Lactonization by way of epoxidation.

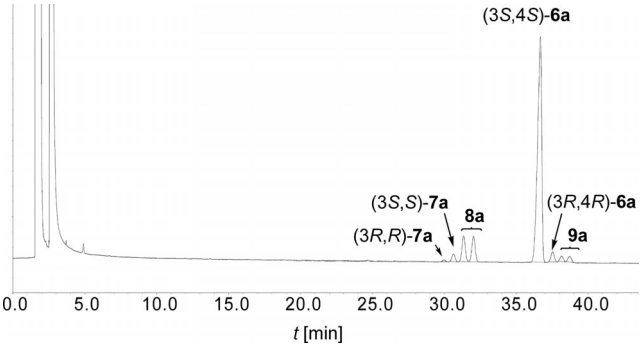
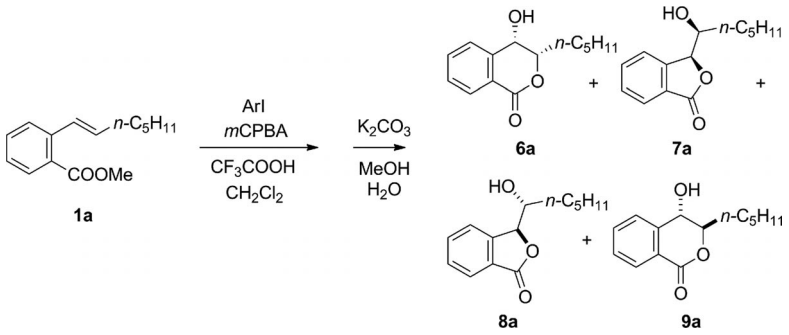
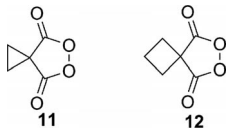


Figure 4. GC trace of the products of the catalytic oxidation reaction of **1a** with **10r** at –40 °C (Table 3, entry 29); injection after treatment with trimethylsilylimidazole, DEX-CB column at 170 °C. **6a**: 92% *ee*, **7a**: 72% *ee*, **8a**: 0% *ee*, **9a**: 4% *ee*. Ratio of the peak areas **6a**/**7a**/**8a**/**9a** = 80:2:14:4 agrees well with that determined by ^{1}H NMR spectroscopy (77:3:14:6).

Table 3. Hydroxylactonization of **1a** under catalytic conditions.[a]



Entry	Cat.	Time [h]	Yield [%] (**6a**/**7a**/**8a**/**9a**)[b]	*ee* [%] of **6a**[c]
1	–	5[d]	59 (0:0:76:24)	
2	**10a**	7	65 (47:4:35:14)	
3	**10b**	5	67 (54:4:29:13)	
4	**10c**	18	53 (38:6:40:16)	
5	**10d**	10	70 (20:5:51:24)	
6	**10e**	22	[e] (0:2:73:25)	
7	**10f**	19	[e] (1:2:73:24)	
8	**10g**	3	80 (57:3:23:17)	
9	**10h**	3	68 (58:4:21:17)	
10	**10i**	8	60 (25:4:48:23)	
11	**10j**	5	72 (48:3:32:17)	58
12	**10k**	10.5	68 (29:4:47:20)	30
13	**10l**	3	60 (46:2:34:18)	58
14	**10m**	6	63 (50:3:32:15)	56
15	**10n**	2	67 (74:3:14:9)	68
16[f]	**10n**	3	50 (70:3:17:10)	66
17[g]	**10n**	11	43 (63:3:18:16)	70
18[h]	**10n**	6	70 (62:6:25:7)	48
19[i]	**10n**	48.5	51 (3:5:64:28)	70
20[j]	**10n**	20.5	55 (43:6:36:15)	70
21[k]	**10n**	35	59 (16:4:54:26)	65
22[l]	**10n**	41	53 (46:20:23:11)	72
23[m]	**10n**	47	76 (60:20:14:6)	67
24	**10o**	2	79 (41:4:35:20)	64
25	**10p**	3	73 (61:5:21:13)	74
26	**10q**	4	79 (48:4:32:16)	84
27	**10r**	2.5	70 (67:4:20:9)	76
28[n]	**10r**	6	70 (69:3:17:11)	80
29[o]	**10r**	35	46 (77:3:14:6)	92
30[n,o]	**10r**	32	64 (51:3:32:14)	96
31[p]	**10r**	38 + 24	71 (78:3:14:5)	94
32	**10s**	18.5	30 (7:2:66:25)	37
33	**10t**	31	51 (15:3:60:22)	26
34	**10u**	20.5	48 (8:3:65:24)	30



[a] **1** (0.10 mmol), **10** (0.01 mmol), *m*CPBA (0.15 mmol), CF_3COOH (0.1 mL), CH_2Cl_2 (4 mL), 0 °C, unless otherwise noted. The reaction mixture was treated with K_2CO_3 in aqueous methanol at 0 °C for 10 min. [b] Isolated yield of a mixture of **6a**, **7a**, **8a**, and **9a**. The value in parentheses is the product ratio determined by ^1H NMR spectroscopy. [c] Determined by GC analysis on a chiral stationary phase. [d] In CH_2Cl_2 (3 mL) containing CF_3COOH (0.2 mL). [e] Not determined. [f] **1a** was slowly added using a syringe pump over 2 h. [g] Reaction carried out at –20 °C. [h] Reaction carried out in $CHCl_3$. [i] Reaction carried out in MeCN. [j] Reaction carried out in CH_2Cl_2/AcOH (9:1). [k] Reaction carried out in CH_2Cl_2/AcOH (1:1). [l] Co-oxidant **11** was used. [m] Co-oxidant **12** was used. [n] *m*CPBA was slowly added using a syringe pump over 3.5 h (entry 28) or 11 h (entry 30). [o] Reaction carried out at –40 °C. [p] The reaction was carried out at –80 °C for 38 h, and then at –40 °C for 24 h.

Upon the addition of a catalytic amount (10 mol-%) of iodoarene (even an achiral iodoarene **10a**–**10i**), *syn* products **6a** and **7a** were obtained (Table 3, entries 2–10). The composition of the product mixtures was significantly affected by the *ortho* substituent of the iodoarene precatalyst. In particular, the systematic change of the position of the carbonyl group in **10e**–**10i** provides useful insights into the structural requirements for a catalyst (Table 3, entries 6–

10). The reaction catalyzed by 2,6-dimethoxy-1-iodobenzene (**10d**) resulted in the formation of *anti* isomers **8a** and **9a** (Table 3, entry 5) as major products. In contrast, when a β-oxo functional group was introduced into the 2- and 6-alkoxy groups in **10g** and **10h**, *syn* product **6a** was obtained as a major isomer (Table 3, entries 8 and 9). The product distribution was not greatly affected by the nature of the β-oxo-alkoxy groups, which could be either an ester (in **10g**) or a ketone (in **10h**). Notably, the oxo group at the γ-position in **10i** reduced the proportion of **6a** (Table 3, entry 10). Diacyloxy-substituted precatalysts **10e** and **10f**, which have the oxo group at the α-position, did not function as catalysts for the formation of *syn* products (Table 3, entries 6 and 7). These results suggest that the β-oxo group in the *ortho*-alkoxy side-chain is important for successful catalytic design. The chiral lactate-based catalyst has the same structural features as the β-oxo-alkoxy design, so this must result in enhancements of both the catalytic efficiency and the enantioselectivity.

Several derivatives of lactate-based iodoarenes (i.e., **10j**–**10u**) were used for the catalytic hydroxylactonization of **1a** (Table 3, entries 11–34). First, a substituent was introduced at the *ortho* position into the simple lactate-based iodoarene **10j**, and the electronic and steric effects were examined (Table 3, entries 11–15, **10j**–**10n**). Precatalyst **10n**, which has two lactate groups, resulted in the highest enantioselectivity and *syn* selectivity of all of the precatalysts **10j**–**10n**. Alternative solvents (Table 3, entries 18–21) and co-oxidants (Table 3, entries 22 and 23) were explored using **10n**, but the standard conditions (dichloromethane solvent containing *m*CPBA co-oxidant) were found to be optimal. A low enantioselectivity in chloroform solvent (Table 3, entry 18) and a low yield of the *syn* product in acetonitrile solvent (Table 3, entry 19) were obtained. When cyclic peroxides **11** and **12**[31] were used instead of *m*CPBA (Table 3, entries 22 and 23), prolonged reaction times were required (41 h and 47 h at 0 °C) for the consumption of the starting material. Furthermore, direct oxidation by the cyclic peroxides may have formed the minor *syn* γ-lactone product (i.e., **7a**) together with the *anti* products, because the *ee* value of **7a** was very low (8% *ee*).

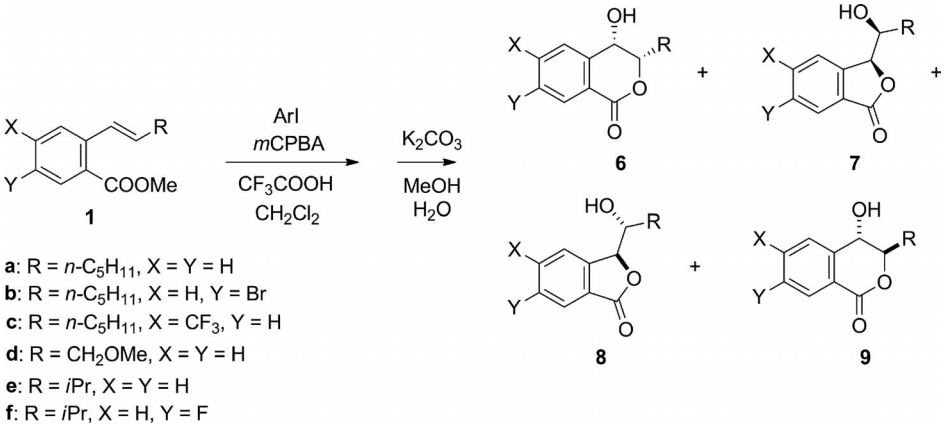
Next, based on the structure of **10n**, we examined the effect of the substituent on the aryl group (**10o** and **10p**; Table 3, entries 24 and 25) and also the effect of structural variation of the lactate moiety (**10q** and **10r**; Table 3, entries 26 and 27). Isopropyl derivative **10q** gave a high enantioselectivity (84% *ee*), but the amount of *syn* products formed was low (Table 3, entry 26). When the sterically congested menthyl group was introduced as the ester of the lactate group (**10r**), a relatively favorable result was obtained, in terms of both enantioselectivity and *syn*/*anti* ratio (Table 3, entry 27). The use of amide derivatives **10s**–**10u** as precatalysts resulted in significantly reduced enantioselectivities and *syn*/*anti* ratios (Table 3, entries 32–34). We then evaluated the influence of the reaction temperature using **10n** and **10r** as precatalysts (Table 3, entries 17, 29, and 31). The reaction with **10n** at –20 °C led to a slight increase in the enantioselectivity (Table 3, entry 17), and precatalyst **10r** significantly enhanced both the enantioselectivity (up to 94% *ee*) and the *syn* selectivity (ca. 80% *syn*) at low temperatures (Table 3, entries 29 and 31). We also examined the slow addition of substrate **1a** (Table 3, entry 16) or of the *m*CBPA (Table 3, entries 28 and 30), but no significant improvement in the selectivities was observed.

A series of other substrates were used for the catalytic variant of hydroxylactonization, and the results are summarized in Table 4. To further explore the combination of substrates and precatalysts, five selected precatalysts **10n**–**10r** were used for the exploration of the substrate scope. Carboxylic acid substrate **1′a** also gave hydroxylactonization products **6a**–**9a**, but its enantioselectivity and *syn*/*anti* ratio decreased slightly (Table 4, entry 1) compared with methyl ester substrate **1a** (Table 3, entry 15). The introduction of an electron-withdrawing substituent (5-Br for **1b** and 4-CF_3 for **1c**) onto the aryl group of the substrate was also tolerated, but it resulted in a diminished reaction rate (Table 4, entries 2–10). Pleasingly, for enantioselective induction at 0 °C, the electron-withdrawing substituents in **1b** and **1c** seemed to be slightly preferred (Table 4, entries 2–6, 8, and 10) over the standard substrate **1a**, but disappointingly, the reaction at low temperatures resulted in a decrease in enantioselectivity (Table 4, entries 7 and 9). Variation of the alkenyl side-chain of the substrate was examined (in **1d** and **1e**). The reactions of **1d** and **1e** at 0 °C (Table 4, entries 11, 13–16, 18, 20, and 21) led to higher enantioselectivities than that obtained with **1a** under the same reaction conditions, but they resulted in moderate *syn*/*anti* ratios. Relatively good results in terms of both enantioselectivity and *syn*/*anti* selectivity were obtained when menthyl derivative **10r** was used as precatalyst (Table 4, entries 16 and 21). The slow addition of *m*CBPA led to a slight improvement in the *syn*/*anti* selectivity (Table 4, entries 6 and 22). Pleasingly, the reactions of substrates **1d** and **1e** at low temperatures led to enhancements of both the enantioselectivity and the *syn*/*anti* selectivity to ca. 90% *ee* and ca. 80% *syn* (Table 4, entries 12, 17, 19, 23, and 24).

Although further enhancement of the catalytic efficiency is required, the catalytic variant of the oxidation of *ortho*-alk-1-enylbenzoates successfully competed with direct oxidation by *m*CPBA to give high levels of enantioselectivity (ca. 90% *ee*). This investigation provides a synthetically attractive methodology for the preparation of 4-hydroxyisochroman-1-one natural products and related compounds. Furthermore, the reaction system seems to be useful for the evaluation of the catalytic efficiency of organocatalytic oxidations mediated by hypervalent iodine.

Finally, we would like to discuss the enantioselective catalytic cycle from a mechanistic viewpoint. The enantioselective catalytic cycle includes the enantioselective oxidation of alkenylbenzoate substrates **1** by chiral hypervalent iodine species. In other words, the enantioselectivity in the catalytic reaction can be compared with that in the stoichiometric oxidation. The enantioselectivities observed in the stoichiometric oxidations (Table 2) are consistent with those obtained in the catalytic reactions (Tables 3 and 4). This

Table 4. Other substrates in the catalytic hydroxylactonization.[a]



Entry	Subst.	Cat.	Time [h]	Yield [%] (**6**/**7**/**8**/**9**)[b]	*ee*[%] of **6**[c]
1	**1′a**[d]	**10n**	1	56 (56:1:25:18)	64
2	**1b**	**10n**	5	75 (59:15:17:9)	78
3	**1b**	**10o**	15	67 (57:6:17:20)	76
4	**1b**	**10p**	4.5	77 (39:15:30:16)	80
5	**1b**	**10r**	5	81 (61:9:17:13)	74
6[e]	**1b**	**10r**	10	65 (69:4:11:16)	74
7[f,g]	**1b**	**10r**	83	79 (82:0:9:9)	58
8	**1c**	**10n**	24	67 (56:4:21:19)	82
9[h]	**1c**	**10n**	2 + 17	53 (55:5:10:30)	67
10	**1c**	**10o**	19	45 (46:13:18:23)	72
11	**1d**	**10n**	13.5	56 (64:18:16:2)	84
12[f]	**1d**	**10n**	20	49 (70:4:25:1)	90
13	**1d**	**10o**	10	47 (59:17:23:1)	82
14	**1d**	**10p**	17.5	42 (29:5:59:7)	68
15	**1d**	**10q**	33	61 (56:10:30:4)	89
16	**1d**	**10r**	15	61 (74:12:13:1)	82
17[f]	**1d**	**10r**	69	70 (76:8:16:0)	88
18	**1e**	**10n**	17.5	66 (41:2:45:12)	82
19[i]	**1e**	**10n**	24	66 (68:2:22:8)	80
20	**1e**	**10p**	18	33 (54:4:28:14)	78
21	**1e**	**10r**	5	59 (54:4:33:9)	86
22[e]	**1e**	**10r**	8	59 (66:2:23:9)	88
23[i]	**1e**	**10r**	13	60 (65:3:26:6)	88
24[g,j]	**1e**	**10r**	65 + 21	53 (76:1:22:1)	98
25	**1f**	**10n**	4	56 (54:5:23:18)	62

[a] **1** (0.10 mmol), **10** (0.01 mmol), *m*CPBA (0.15 mmol), CF_3COOH (0.1 mL), CH_2Cl_2 (4 mL), 0 °C, unless otherwise noted. The reaction mixture was treated with K_2CO_3 in aqueous methanol at 0 °C. [b] Isolated yield of a mixture of **6**, **7**, **8**, and **9**. The value in parentheses is the product ratio determined by ^1H NMR spectroscopy. [c] Determined by GC analysis on a chiral stationary phase. [d] The substrate was 2-[(*E*)-hept-1-enyl]benzoic acid (**1′a**). [e] *m*CPBA was slowly added using a syringe pump over 5 h (entry 6) or 3 h (entry 22). [f] Reaction carried out at –40 °C. [g] CF_3COOH (0.3 mL). [h] The reaction was carried out in the presence of $BF_3{\cdot}OEt_2$ (0.1 mL) and CF_3COOH (0.3 mL) at –80 °C for 2 h, and then at –40 °C for 17 h. [i] Reaction carried out at –20 °C. [j] The reaction was carried out at –80 °C for 65 h, and then at –40 °C for 21 h.

indicates that the presence of *m*CPBA and its reduced form does not affect the enantioselectivity. Thus, the enantioselectivity in the catalytic reaction can be discussed along the lines of the stoichiometric oxidation mechanism.

Apart from the enantioselectivity, the catalytic efficiency is an important issue in the catalytic cycle. The lactate moieties of **10n** seem to enhance the catalytic efficiency compared with **10d** (Table 3, entries 5 and 15), as mentioned above. To confirm the effect of the lactate groups, the following control experiments were conducted. A mixture of **10n** and **10d** was used as a precatalyst for the oxidation of **1a**, as shown in Figure 5.[32] The total amount of these two iodoarenes was fixed at 10 mol-%, and the amount of **10n** was decreased. The *ee* value of the major *syn* product (i.e., **6a**) decreased as the amount of **10n** in the mixed precatalysts decreased (open circles), whereas the *ee* value of **6a** remained constant (68% *ee*) when the amount of **10n** added was decreased without the addition of achiral **10d** (filled circles). Achiral **10d** worked as a precatalyst to give racemic **6a** and resulted in a decrease in the *ee* value. The results in Figure 5 indicate that these two precatalysts have different catalytic efficiencies. If the two precatalysts **10n** and **10d** had had the same catalytic efficiency, the *ee* value would have decreased linearly to half of 68% at 5 mol-% **10n** and 5 mol-

% **10d**. The actual *ee* value is above the line. This is consistent with the independent experimental results (i.e., Table 3, entries 5 and 15), and indicates that **10n** is more efficient than **10d**.

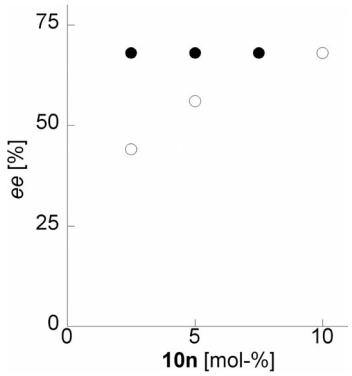


Figure 5. Dependence of the enantiomeric excess of **6a** on the amount of precatalyst **10n**. The reaction conditions were the same as those in Table 3. Either only **10n** was used as the precatalyst (filled circles), or chiral **10n** and achiral **10d** were mixed; **10n** + **10d** = 10 mol-% (open circles).

It is interesting to consider why lactate-based precatalyst **10n** has a higher efficiency than dimethoxy derivative **10d**. To gain a mechanistic insight into the catalytic efficiency, the course of the oxidation was monitored by ^{1}H NMR spectroscopy. The catalytic cycle consists of two oxidation steps: 1) oxidation of iodoarene **10** with *m*CPBA to give the corresponding hypervalent iodine(III) species; and 2) oxidation of the substrate with the generated hypervalent iodine(III) species. These two elementary processes were examined independently.

First, oxidations of iodoarenes **10d** and **10n** with *m*CPBA[33] were performed in CD_2Cl_2 containing TFA in an NMR tube. The time-dependent changes of the concentrations of the iodoarene and the corresponding hypervalent iodine compound are shown in Figures S1–S3 (Supporting Information). Iodoarenes **10d** and **10n** were readily oxidized within 10–20 min at room temperature, and their rates of oxidation were similar. On balance, the oxidation of the dimethoxyiodobenzene **10d** seemed to be slightly faster than that of the lactate-based **10n**. Thus, the high efficiency of the catalytic oxidation mediated by **10n** cannot be explained by a difference in the kinetics of the first elementary process.

As the second elementary process, the oxidation of substrate **1a** was examined. Isolated hypervalent iodine(III) compounds were used for stoichiometric reactions in an NMR tube (Figures S4 and S5 in the Supporting Information). The oxidation with lactate-based hypervalent reagent **3** proceeded cleanly in approximately 1 h to give oxyisochromanone product **5′a** and the corresponding iodoarene (i.e., **10n**), as shown in Figure S5. The oxidation with 2-(diacetoxyiodo)-1,3-dimethoxybenzene (**13**) also led to the formation of **5′a** at a similar reaction rate (Figure S4). Thus, the kinetics of the second elementary process do not seem to be a major reason for the difference in the catalytic efficiency. Notably, in the oxidation of **1a** by **13** (Figure S4), unidentified signals were observed together with the generation of dimethoxyiodobenzene **10d**. The same unidentified signals were also observed during the oxidation of **10d** with *m*CPBA (Figure S1). An activated hypervalent iodine compound is known to react electrophilically with an electron-donating arene to give a diaryliodonium compound.[34] Such compounds could reasonably be assumed to be the by-products observed in the NMR measurements.[35] Such a decomposition of precatalyst **10d** may cause the decrease in catalytic efficiency. The lactate moiety in precatalyst **10n** may partially stabilize the activated hypervalent species by coordination of the lactate moiety to the electron-deficient iodine atom,[13] and thus **10n** is more tolerant to decomposition and can maintain its catalytic efficiency. The difference in the catalytic efficiencies of achiral precatalysts **10g** and **10i** (Table 3, entries 8 and 10) can be explained by the contribution of the coordination of the ester group.

Conclusions

A concise route to optically active 3-alkyl-4-hydroxyisochroman-1-ones has been established using the enantioselective oxylactonization of an *ortho*-alkenylbenzoate mediated by a catalytic amount of a chiral lactate-based hypervalent iodine(III) species generated in situ. On the basis of the results presented in this paper, it is reasonable to suggest that the lactate moiety plays an important role in the enhancement of the catalytic efficiency as well as that of the enantioselectivity. These results should provide a basis for the synthesis of many 4-hydroxyisochoman-1-one natural products and their analogs, and also for further developments in the field of highly selective oxidation mediated by hypervalent iodine species.

Experimental Section

General Procedure for Acetoxylactonization: A dichloromethane solution (5 mL) containing **1** (0.10 mmol), Ar*I(OAc)$_2$ (0.12 mmol), and acetic acid (0.3 mL) under nitrogen was cooled to –80 °C using an EYELA PSL-1800 low-temperature bath with a magnetic stirrer. Boron trifluoride diethyl etherate (1.3 mmol) was added to the solution at –80 °C. The solution was gradually warmed up to –40 °C over 1 h. The reaction mixture was then quenched by the addition of water, and the mixture was extracted with dichloromethane. The organic phase was dried with Na_2SO_4 and concentrated in vacuo. The crude mixture was purified by column chromatography (SiO_2, eluent: ethyl acetate in hexane). The enantiomeric ratio of the product was determined by gas chromatography using a chiral column (Chirasil-DEX-CB or Supelco β-DEX-325).

General Procedure for Trifluoroacetoxy-lactonization: A dichloromethane solution (4 mL) containing **1** (0.10 mmol) and Ar*I(OAc)$_2$ (0.16 mmol) under nitrogen was cooled to 0 °C. Trifluoroacetic acid (0.1 mL) was added to the solution at 0 °C, and the mixture was stirred at 0 °C for 1–44 h. The reaction was monitored by TLC. After the starting material had been consumed, the reaction mixture was quenched by the addition of $NaHCO_3$ (aq.), and the mixture was extracted with dichloromethane. The organic phase was dried with Na_2SO_4 and concentrated in vacuo. The

crude mixture was analyzed by ^{1}H NMR spectroscopy, then it was hydrolyzed in aqueous methanol in the presence of K_2CO_3 at 0 °C. The hydrolyzed products were extracted with dichloromethane and purified by column chromatography (SiO_2, eluent: ethyl acetate in hexane). The enantiomeric ratio of the product was determined by gas chromatography using a chiral column (Chirasil-DEX-CB or Supelco β-DEX-325).

General Procedure for Catalytic Oxy-lactonization: A dichloromethane solution (4 mL) containing **1** (0.10 mmol), *m*-chloroperbenzoic acid (0.15 mmol), and **10** (0.010 mmol) under nitrogen was cooled to 0 °C. Trifluoroacetic acid (0.1 mL) was added to the solution at 0 °C, and the mixture was stirred at 0 °C for 2–47 h. The reaction was monitored by TLC. After the starting material had been consumed, the reaction mixture was quenched by the addition of $NaHCO_3$ (aq.), and the mixture was extracted with dichloromethane. The organic phase was dried with Na_2SO_4 and concentrated in vacuo. The crude mixture was analyzed by ^{1}H NMR spectroscopy, and then it was hydrolyzed in aqueous methanol in the presence of K_2CO_3 at 0 °C. The hydrolyzed products were extracted with dichloromethane and purified by column chromatography (SiO_2, eluent: ethyl acetate in hexane). The enantiomeric ratio of the product was determined by gas chromatography using a chiral column (Chirasil-DEX-CB or Supelco β-DEX-325).

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data for new compounds, and additional data.

Acknowledgments

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