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ENANTIOSELECTIVE HETEROCYCLE FORMATION USING CHIRAL HYPERVALENT IODINE(III)

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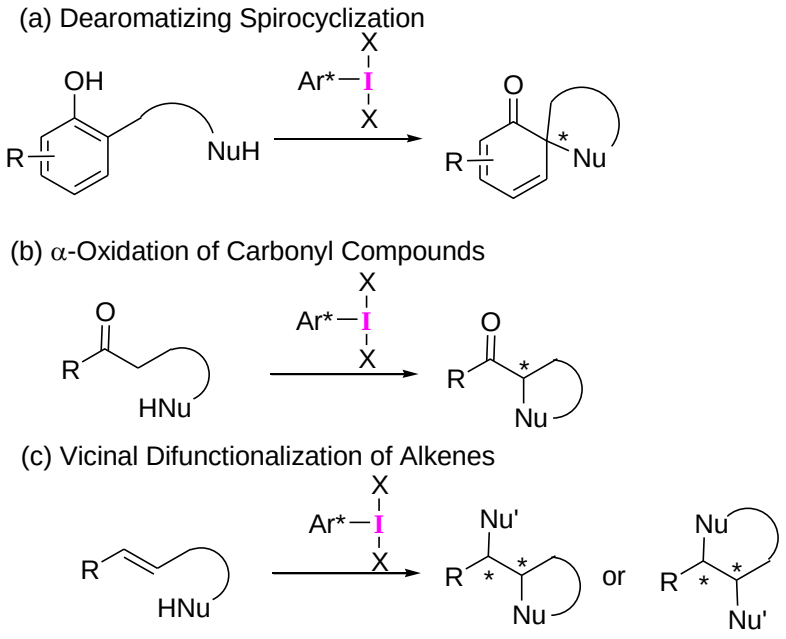
Abstract – The field of chiral hypervalent iodine chemistry has made significant progress in the past decade. This review focuses on enantioselective heterocycle formation induced by chiral hypervalent iodine reagents and catalysts. The enantioselective heterocyclizations are classified into the dearomatization of phenols (and naphthols), α-oxidation of carbonyl compounds, and oxidative vicinal difunctionalization of alkenes. As a characteristic reaction of a hypervalent iodine oxidizing reagent, the 6-*endo* selective lactonization of *ortho*-alkenylbenzoate is selected and compared with the 5-*exo* selectivity induced by other electrophilic reagents. The oxidative lactonization with 6-*endo* selectivity afforded a 4-oxyisochroman-1-one framework, which has been found in a family of polyketide metabolites. The total syntheses of 4-oxyisochroman-1-one natural products were also summarized to assess the synthetic utility of hypervalent iodine compounds.

CONTENTS

1. INTRODUCTION

The chemistry of organic hypervalent iodine compounds has been studied for over a hundred years, and these compounds still attract organic chemists owing to their unique reaction characteristics. Hypervalent iodine compounds have been used as selective oxidizing reagents under mild conditions in the field of synthetic organic chemistry. They show reactivity similar to transition metal oxidizing reagents and are considered attractive alternatives to transition metal catalysts for selective oxidations. A high level of enantiocontrol was recently achieved for several types of oxidations by using chiral hypervalent iodine reagents and catalysts. Owing to the high degree of interest in this field, some excellent reviews have been published from different viewpoints.[1,2] This review focuses on the hypervalent iodine-induced enantioselective formation of heterocyclic compounds.

The formation of heterocycles during oxidation with hypervalent iodine compounds is achieved by the participation of an intramolecular nucleophile (Scheme 1). The enantioselective variants of the heterocyclizations are categorized as dearomatizing spirocyclization (Scheme 1a), α-oxidation of carbonyl compounds (Scheme 1b), and vicinal difunctionalization of alkenes (Scheme 1c). In the case of the difunctionalization of alkenes, *exo*- and *endo*-cyclizations should be recognized as having controllable selectivity.



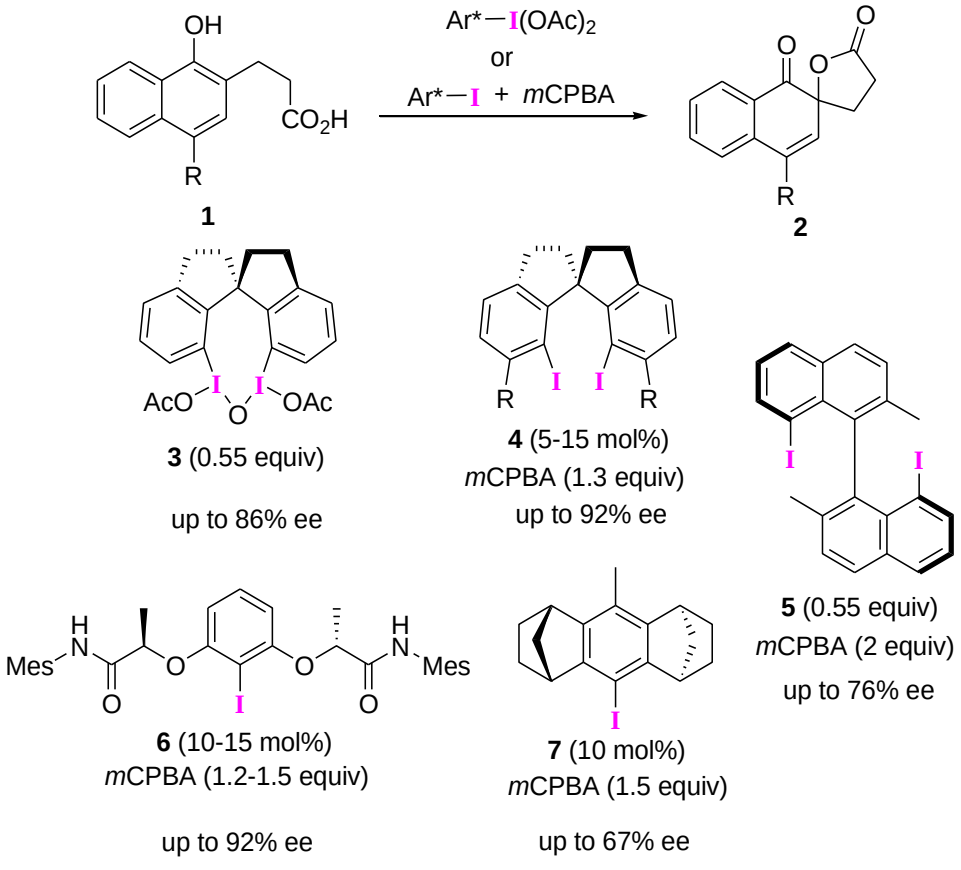
Scheme 1. Enantioselective heterocyclization using chiral hypervalent iodine

Among these heterocyclic formations mediated by hypervalent iodine compounds, the 6-*endo* selective oxylactonization of *ortho*-alkenylbenzoate is featured because electrophiles other than hypervalent iodine reagents lead to 5-*exo* lactonization. Furthermore, the 6-*endo* oxylactonization yielding 4-

oxyisochroman-1-one has been successfully applied to a crucial step in the asymmetric synthesis of 4-oxyisochromanone natural products. In this review, the synthetic uses of chiral hypervalent iodine reagents are demonstrated through concise entries into heterocyclic cores found in bioactive natural products.

2. ENANTIOSELECTIVE SPIROCYCLIZATION DURING OXIDATIVE DEAROMATIZATION WITH HYPERVALENT IODINE

Kita et al.[3] pioneered the area of enantioselective oxidation using chiral hypervalent iodine compounds and found that the oxidative dearomatization of 1-naphthol derivative **1** by using chiral spirobiindane λ^3-iodane reagent **3** afforded spirolactone product **2** with high enantiomeric excess (ee) (Scheme 2). They also succeeded in catalytic oxidation by using iodoarene **4** in the presence of *m*CPBA co-oxidant. A catalytic amount of chiral iodoarene is oxidized *in situ* to a reactive hypervalent iodine reagent, which is used as a catalyst for the enantioselective oxidation of naphthol substrate **1**. The highly stereocontrolled oxidation may be attributed to the μ-oxo bridged form of the hypervalent iodine compound. Kita[3c] also tested 8,8'-diiodo-1,1'-binaphthalene (**5**) as an asymmetric catalyst for the oxidative spirolactonization. Under stoichiometric conditions, a promising level of enantioselectivity (up to 76% ee) was demonstrated.



Scheme 2. Enantioselective spirolactonization of 1-naphthol derivatives

Ishihara et al.[4] used the flexible lactamide chiral sidechain as an iodoarene precatalyst in the enantioselective dearomatization. The C_2-symmetric structure of **6** led to the formation of desired product **2** with 92% ee under the optimal reaction conditions. Ibrahim et al.[5] tested another type of C_2-symmetric chiral iodoarene with an *anti*-dimethanoanthracene core **7** for the oxidative spirolactonization under catalytic conditions. The best enantioselectivity (67% ee) was observed in the reaction of a 4-bromo substituted naphthol substrate.

The design of a conformationally flexible chiral sidechain (Figure 1) has been tuned and tailored for the variation of oxidative dearomatization reactions (Table 1). For the dearomatization of phenol substrates, Ishihara et al.[4c] developed 2-aminoalcohol-based iodoarene precatalyst **8**. Compared with lactamide **6**, the chemical yield was improved by using newly designed precatalyst **8** in the oxidation of **10** (Table 1, entry 1). In the case of electron-deficient phenol substrate **12**, the use of **8** enabled the chemical yield and enantioselectivity to increase to 84% and 87%, respectively (entry 2). A drastic improvement was achieved in the enantioselective oxidation of 1,2-naphthohydroquinone with *O*-tethered carboxylic acid **14** (entry 3);[4d] the oxidation with precatalyst **8** gave the desired dioxolanone product **15** in 88% yield with 86% ee, whereas the use of lactamide **6** decreased the chemical yield and enantioselectivity. By contrast, the use of lactamide precatalyst **6** afforded higher enantioselectivity than the use of **8** in the oxidation of *para*-hydroquinone type substrate **16** (entry 4).[4d] Ishihara et al.[4d] further improved the enantioselectivity of the oxidation of a *para*-hydroquinone type substrate to 89% ee by employing a silyl-substituted substrate and a modified lactamide precatalyst. Highly enantioselective spirolactone **19** was obtained in the oxidation of 2-naphthol substrate **18** by using precatalyst **8** (entry 5).[4e] Ciufolini et al.[6] prepared a new chiral iodoarene **9** and used this as an asymmetric precatalyst for the oxidative cycloetherification of naphtholic alcohols **20** (entry 6). Newly designed precatalyst **9** has conformationally flexible chiral side chains, in which a stereogenic carbon center locates adjacent to the amide NH group. Precatalyst **9**

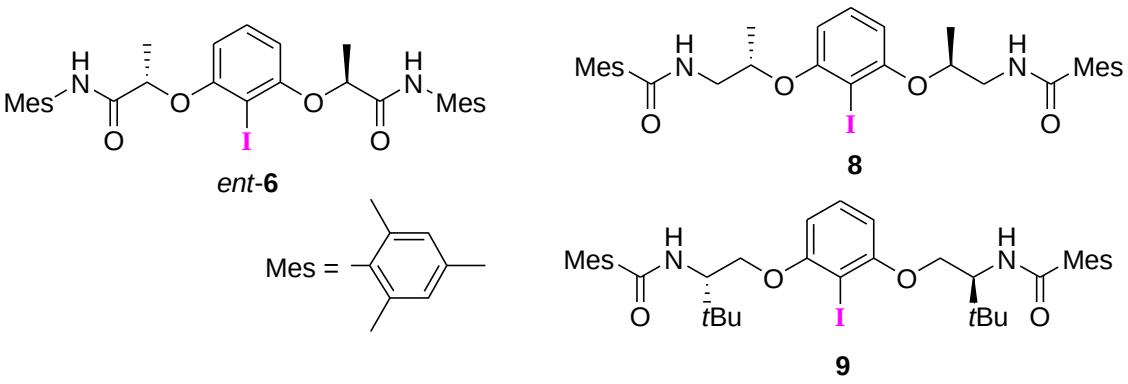
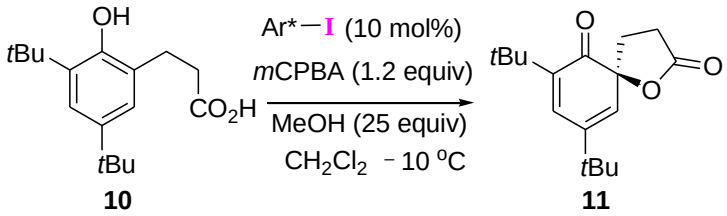
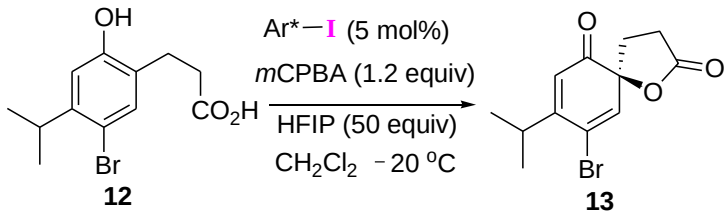
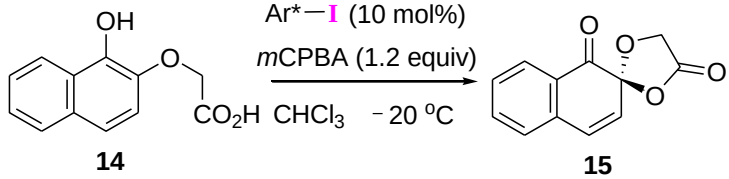
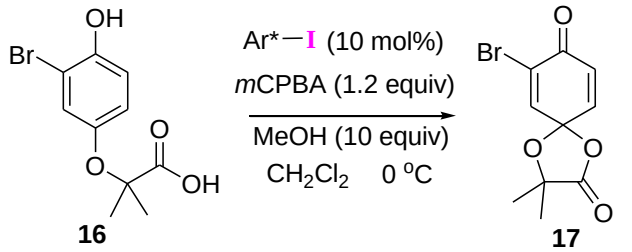
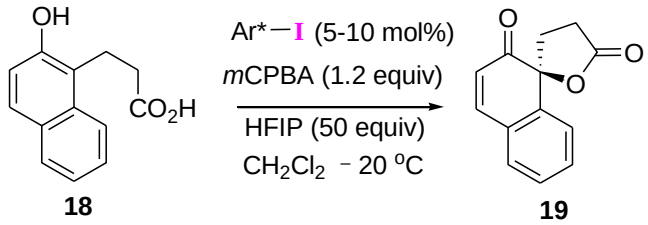
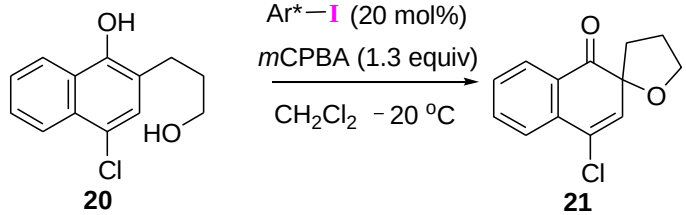
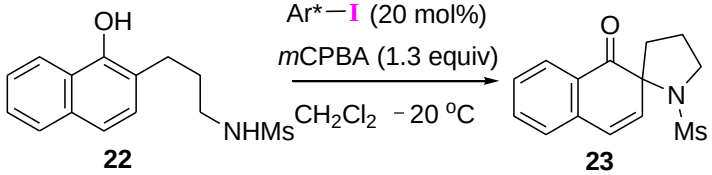


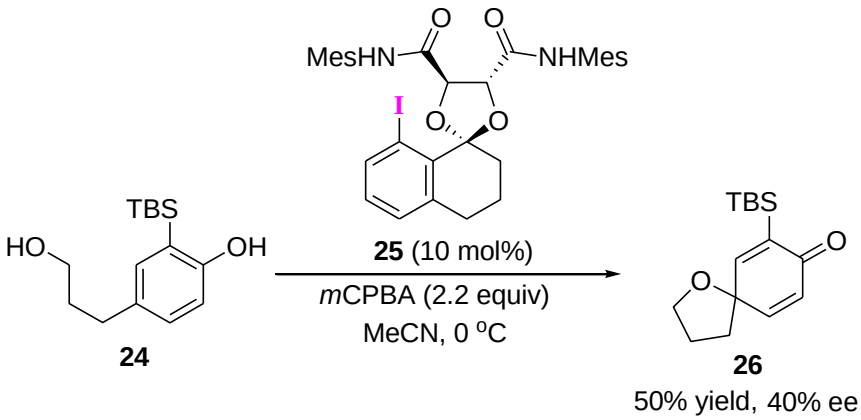
Figure 1. Chiral iodoarene precatalysts for spirocyclization

Table 1. Oxidative spirocyclization reactions catalyzed by chiral iodoarenes, *ent*-**6**, **8**, and **9**

entry	reaction	Ar*—I	% yield, % ee = *ent*-**6**	**8**	**9**
1	 **10** → **11**	Ar*—I (10 mol%), *m*CPBA (1.2 equiv), MeOH (25 equiv), CH_2Cl_2, −10 °C	30% yield 92% ee	90% yield 92% ee	
2	 **12** → **13**	Ar*—I (5 mol%), *m*CPBA (1.2 equiv), HFIP (50 equiv), CH_2Cl_2, −20 °C	34% yield 79% ee	84% yield 87% ee	
3	 **14** → **15**	Ar*—I (10 mol%), *m*CPBA (1.2 equiv), $CHCl_3$, −20 °C	22% yield 61% ee	88% yield 86% ee	
4	 **16** → **17**	Ar*—I (10 mol%), *m*CPBA (1.2 equiv), MeOH (10 equiv), CH_2Cl_2, 0 °C	49% yield 46% ee	68% yield 24% ee	
5	 **18** → **19**	Ar*—I (5-10 mol%), *m*CPBA (1.2 equiv), HFIP (50 equiv), CH_2Cl_2, −20 °C	50% yield 79% ee	89% yield 94% ee	
6	 **20** → **21**	Ar*—I (20 mol%), *m*CPBA (1.3 equiv), CH_2Cl_2, −20 °C	62% yield 65% ee	65% yield 90% ee	79% yield 93% ee
7	 **22** → **23**	Ar*—I (20 mol%), *m*CPBA (1.3 equiv), CH_2Cl_2, −20 °C		20% yield 46% ee	20% yield 67% ee

provided the best yield and enantioselectivity in the oxidative cycloetherification among the three precatalysts **6**, **8**, and **9**. Iodoarene **9** was also used for the enantioselective oxidative cyclization of naphtholic sulfonamide **22** (entry 7).[6]

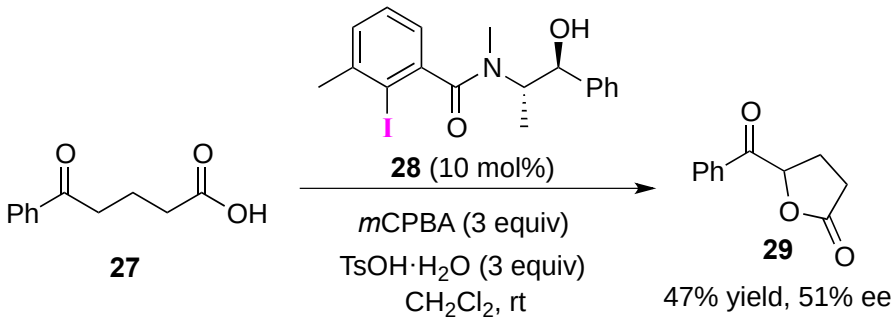
Harned[7] found that an *ortho*-silyl substitution increased the enantioselectivity of the oxidative dearomatization of phenol substrate **24**, where tricyclic iodoarene precatalyst **25** was employed as a new lead structure for stereoinduction (Scheme 3).



Scheme 3. Seminal study on enantioselective oxidative dearomatization of phenols at *para*-position

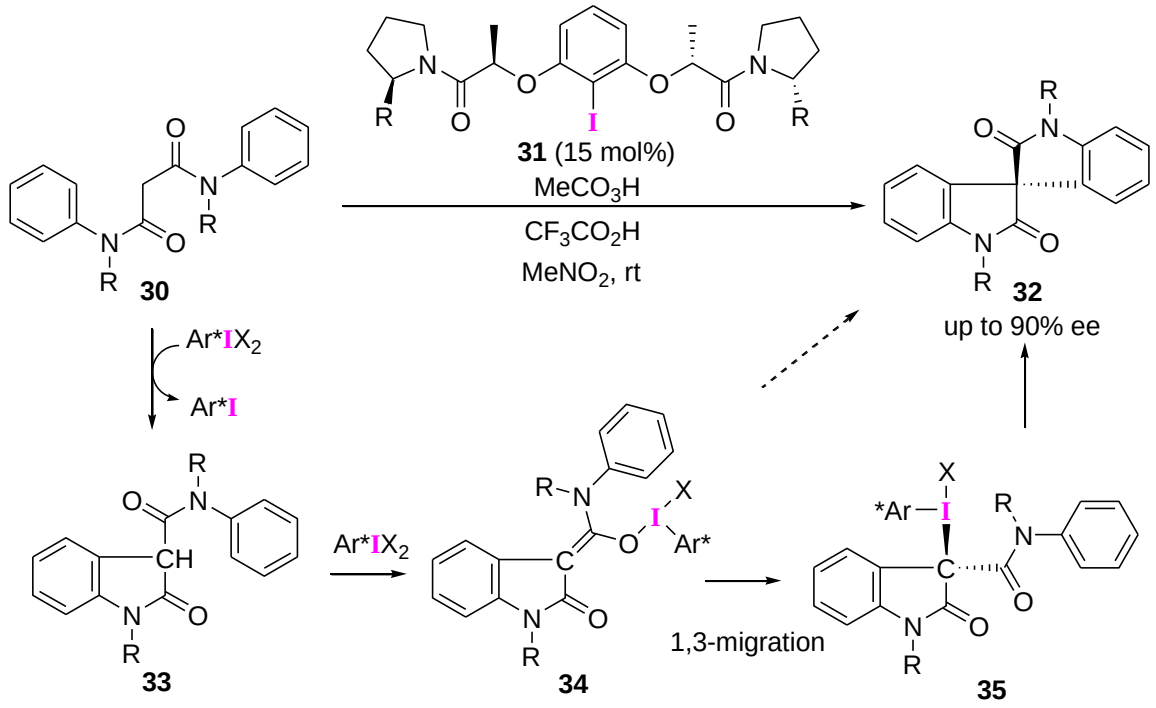
3. ENANTIOSELECTIVE OXIDATIVE CYCLIZATION AT THE α-POSITION OF CARBONYL COMPOUNDS WITH HYPERVALENT IODINE

Hypervalent iodine(III) reagents oxidize carbonyl compounds to yield α-functionalized products; a nucleophile attaches to the α-position of the carbonyl group during the oxidation. With an intramolecular nucleophile involved, a cyclization product should be obtained. Moran et al.[8] reported the enantioselective formation of a heterocycle during the oxidation of 5-oxo-5-phenylpentanoic acid (**27**), which afforded 5-benzoyldihydrofuran-2(3*H*)-one (**29**) with moderate enantiomeric excess in the presence of chiral iodoarene precatalyst **28** (Scheme 4).



Scheme 4. Oxidative lactonization of **27**

When propiophenone was used instead of **27**, α-oxytosylation occured under the same reaction conditions, thus resulting in poor enantioselectivity.[8] The asymmetric lactonization of **27** was based on Moriarty's non-stereocontrolled reaction using a stoichiometric amount of hydroxy(tosyloxy)iodobenzene.[9] The non-stereocontrolled lactonization of **27** was also conducted under catalytic conditions by using iodobenzene and *m*CPBA.[10] A high level of enantioselectivity was successfully achieved in a cascade oxidative cyclization of diphenylmalonamides **30**, which afforded optically active spiro-bisoxindoles **32** (Scheme 5).[11] The racemic product formation of the spiro-bisoxindole was previously reported by Zhao, Du, and coworkers.[12] Gong et al.[11] used lactate-based chiral iodoarene precatalyst **31** for the enantioselective oxidation, where the enolizable sp^3 carbon with two acidic hydrogen atoms was replaced by the two intramolecular aryl groups.

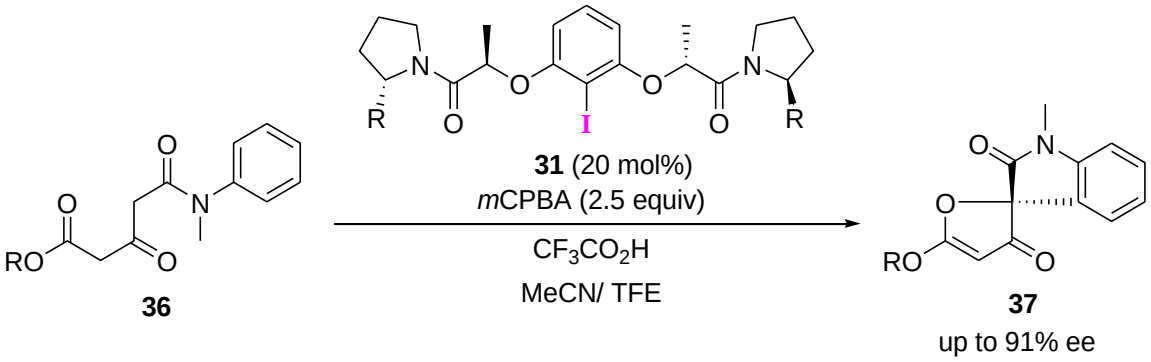


Scheme 5. Spirocyclization of diphenylmalonamide

Sunoj et al.[13] reported theoretical calculations on the enantioselective spiro-bisoxindole formation. The oxidation of diphenylmalonamide **30** proceeds via a sequential two-step cyclization; an initial cyclization yields mono-oxindole **33**, which finally undergoes another cyclization to afford spiro-bisoxindole product **32**. A stereogenic center is created at the stage of mono-oxindole **33**, but this chirality should be lost during the deprotonation that yields *O*-iodonium enolate **34**. The direct ring closure of the *O*-iodonium enolate (**34**→**32**) was noted to have high activation energy. A low energy barrier was calculated for the reaction pathway via *C*-iodonium enolate **35**, which was generated by the 1,3-migration of the chiral

iodonio group in the *O*-iodonium enolate **34**. These calculations suggest that the enantioselectivity is determined by the activation energy of the 1,3-migration step (**34**→**35**) because the following ring closure (**35**→**32**) proceeds stereospecifically.

Stimulated by the success of the enantioselective variant of the spiro-bisoxindole formation, Du et al.[14] employed alkyl 3-oxopentanedioate monoamide derivatives **36** for enantioselective spirocyclization to spirofurooxindole **37** (Scheme 6). Similar to the spirocyclization of diphenylmalonamide **30**, proline-attached chiral iodoarene precatalyst **31** gave significantly high enantioselectivity. The reaction of unsymmetrical substrate **36** is postulated to proceed via *O*-cyclization followed by *C*-cyclization.



Scheme 6. Formation of spirofurooxindole **37**

4. OXIDATIVE VICINAL DIFUNCTIONALIZATION OF ALKENES WITH HYPERVALENT IODINE

The oxidation of alkenes with hypervalent iodine compounds introduces two vicinal functional groups onto the carbon–carbon double bond. The use of an intramolecular nucleophile enables the formation of heterocyclic products. Given that alkene substrates have two reaction sites, various types of heterocyclic products are accessible from the alkene oxidation. For the enantioselective oxidation of alkenes, several chiral hypervalent iodine reagents have been developed; representative chiral reagents are summarized in Figure 2. The enantioselective formation of an oxolane ring was achieved during the oxidation of 4-benzoyloxybut-1-ene (**42a**) with lactate-based chiral hypervalent iodine reagent **38a** (Scheme 7).[15] The silyl-substituted substrates **42b**,**c** also underwent the oxidative cyclization without elimination of the silyl group to yield oxolane product **43** stereospecifically. The maximum ee of the product amounted to 64%.[15a] The stereospecific cyclization can be explained by the reaction mechanism involving a 1,3-dioxan-2-yl cation intermediate,[16] which is proposed using ^{18}O isotope label experiments.[16a] During the oxidative cyclization, the internal acyloxy group may nucleophilically participate in the formation of the dioxanyl cation intermediate and then migrate to the 3-position of oxolane product **43**.

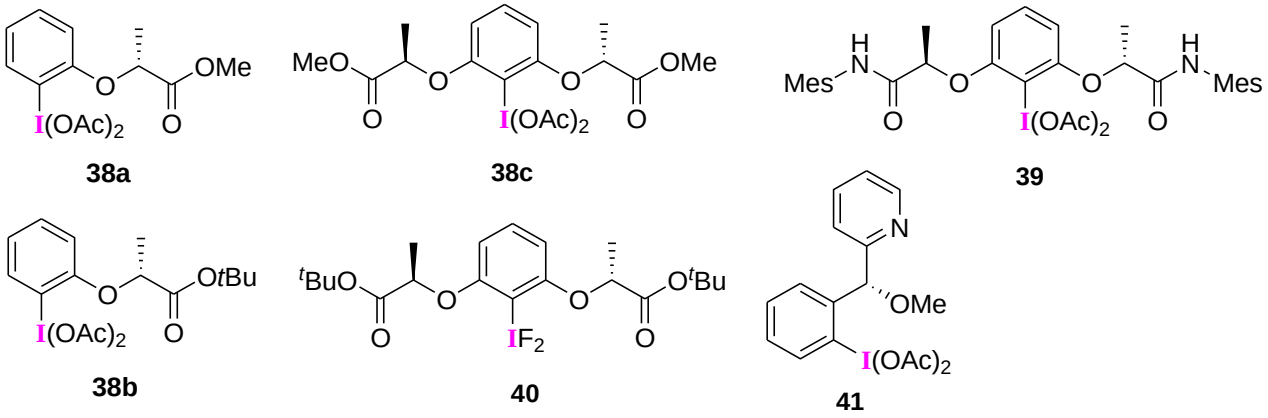
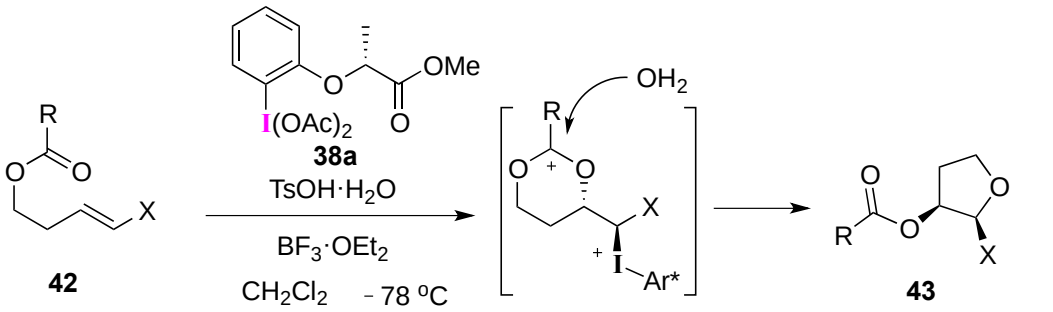
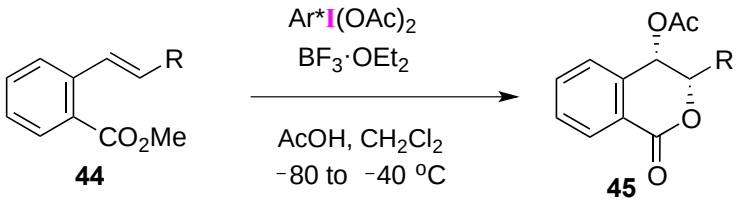


Figure 2. Chiral hypervalent iodine reagents



Scheme 7. Oxolane ring formation from acyloxybutene

The same lactate-based chiral hypervalent iodine reagent **38a** was subjected to the oxidation of *ortho*-alkenylbenzoates **44a**–**d** (Scheme 8). The oxidation yielded 4-acetoxyisochroman-1-ones **45a**–**d** in an enantiocontrolled manner (75 to 90% ee). The use of bislactate reagent **38c** increased the enantioselectivity (90 to 97% ee).[17] The *endo* selective lactonization is unique to hypervalent iodine reagents, and contrasts with the *exo* selectivity provided by conventional oxidants and electrophiles. Selectivity in these oxidative lactonizations of *ortho*-alkenylbenzoates is detailed in the next chapter.

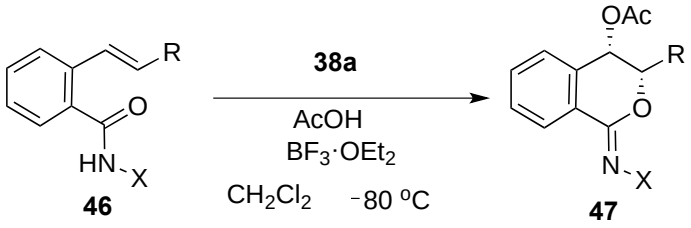


Ar*I(OAc)$_2$ =	**38a**	**38c**
a: R = H	73% yield, 75% ee	72% yield, 90% ee
b: R = CH_2OMe	80% yield, 84% ee	60% yield, 97% ee
c: R = *i*-Pr	64% yield, 87% ee	63% yield, 96% ee
d: R = C_5H_{11}	63% yield, 90% ee	

Scheme 8. *Endo*-oxylactonization of alkenylbenzoate

Endo selective cyclization was also achieved in the oxidation of alkenylbenzamide substrates **46** by using lactate-based chiral hypervalent iodine reagent **38a** in the presence of boron trifluoride diethyl etherate (Table 2).[18] Under these reaction conditions, *O*-attack cyclization preferentially occured over *N*-attack cyclization yielding lactam products. The enantioselectivity of these amide substrates **46** was similar to that of the corresponding ester substrates **44**, and it was not significantly affected by the type of *N*-substituent.

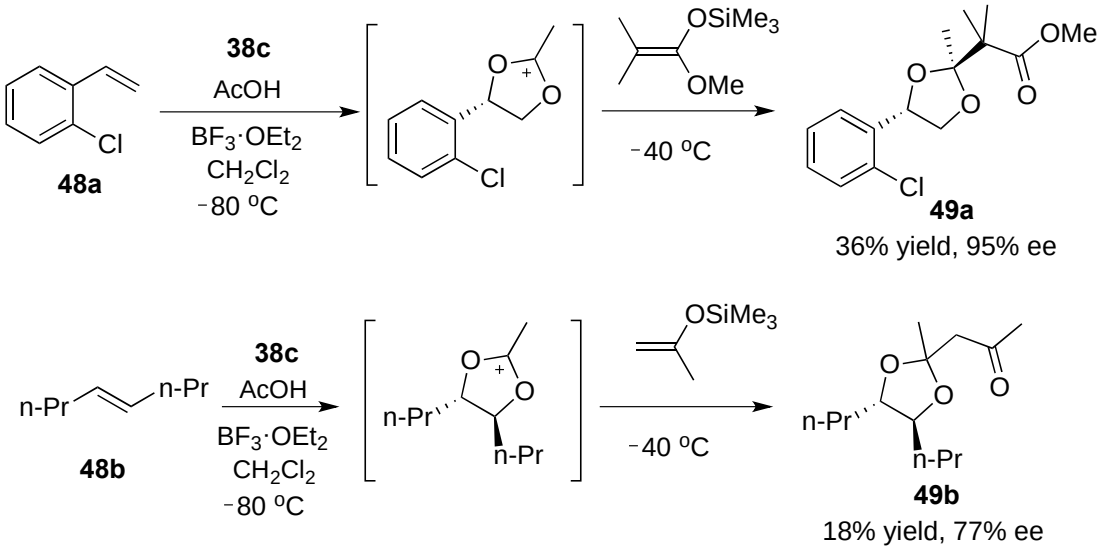
Table 2. Oxidation of alkenylbenzamide



R	X	yield (%)	ee (%)
H	Ts	66	81
H	OMe	62	78
H	OAc	79	84
H	NHCOPh	70	83
n-pentyl	Ts	73	82
n-pentyl	OAc	61	82
n-pentyl	OMe	50	88
n-Pr	OMe	71	90

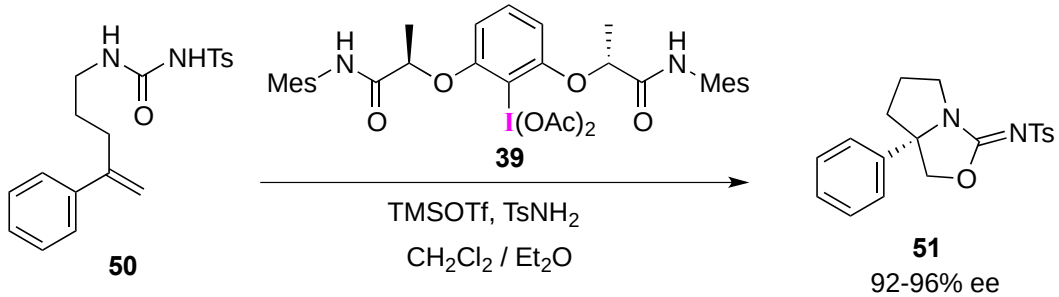
A dioxolane ring was formed during oxidative annulations of alkenes **48** and acetic acid (Scheme 9).[19] The electrophilic addition of lactate-based chiral hypervalent iodine reagent **38c** to the olefins **48** is followed by the nucleophilic substitution of acetic acid. The attached acetate moiety participates

nucleophilically to generate the 1,3-dioxolan-2-yl cation intermediates, which are trapped at the 2-position by ketene silyl acetal or silyl enol ether to yield **49**. The enantioselective formation of the dioxolanyl cation intermediate was confirmed by the formation of enantiomerically enriched **49**. Therefore, acetic acid acts as a bidentate nucleophile to promote the annulation.



Scheme 9. Dioxolane formation by annulation between alkene and acetic acid

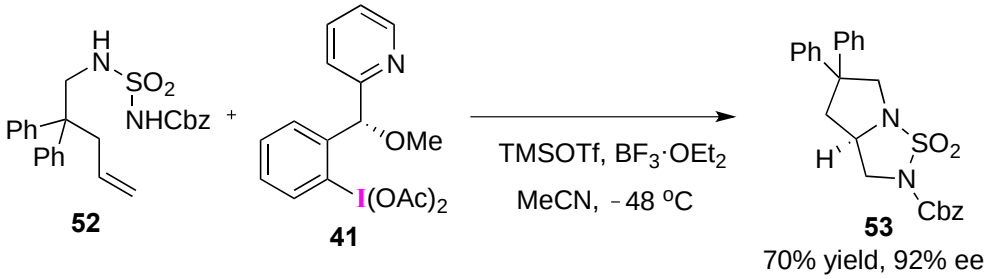
Intramolecular bidentate nucleophiles led to the formation of bicyclic products. A urea group induced bicyclic product formation during the oxidation of an alkene with a hypervalent iodine reagent.[20] Wirth et al.[21] reported an enantioselective variant of the bicycle formation by using lactamide-based chiral hypervalent iodine reagent **39** (Scheme 10). Under the optimized reaction conditions, cyclic isourea product **51** was formed with a high level of enantioselectivity.



Scheme 10. Bicycle formation induced by urea group

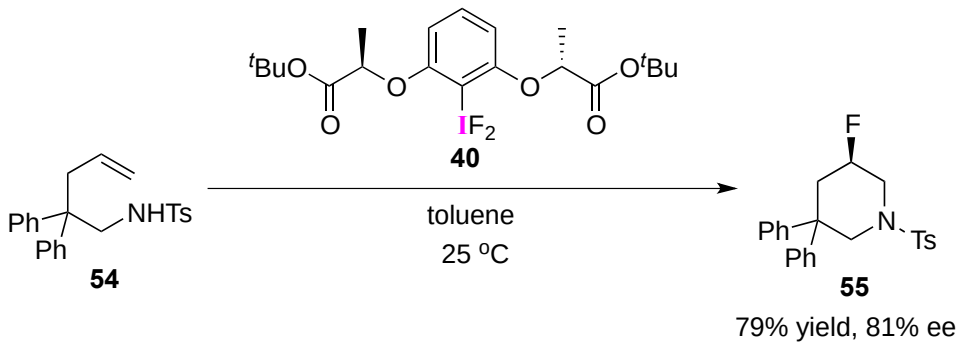
Wirth et al.[22] expanded the bidentate nucleophile to sulfodiamines **52**; this was employed for enantioselective oxidation to yield diamination bicyclic product **53** (Scheme 11). When lactamide

hypervalent iodine reagent **39** was used for the oxidation of **52**, the enantioselectivity was poor (10% ee). Novel chiral hypervalent iodine reagent **41** with a pyridine moiety was developed for use in a highly enantiocontrolled diamination cyclization.



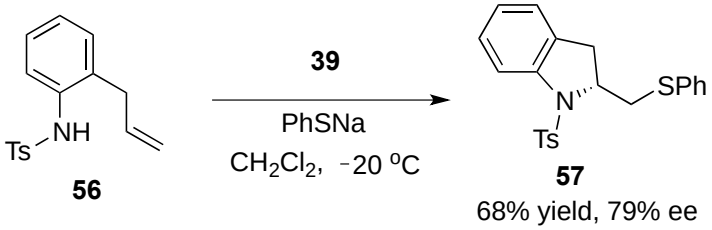
Scheme 11. Bicycle formation induced by sulfodiamine

Nevado et al.[23] reported the enantioselective aminofluorination of **54** using lactate-based chiral hypervalent iodine reagent **40** (Scheme 12). The aminocyclization proceeded with *endo* selectivity to yield fluorinated piperidine product **55** with 81% ee. The aminofluorination of **54** also proceeded under catalytic conditions, where 2,2'-diiodobinaphthyl was used as an enantiocontrolled precatalyst in the presence of *m*CPBA and hydrogen fluoride.[24] Desired product **55** was obtained with 70% ee.



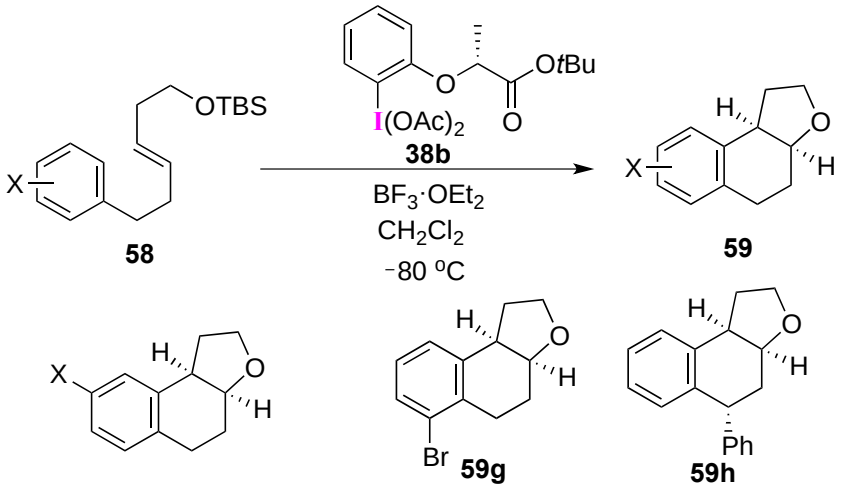
Scheme 12. Aminofluorination

The attachment of a sulfur nucleophile was also achieved during enantioselective aminocyclization (Scheme 13). Wirth et al.[25] reported the thioamination of *ortho*-allylaniline **56** with lactamide-based hypervalent iodine reagent **39**.



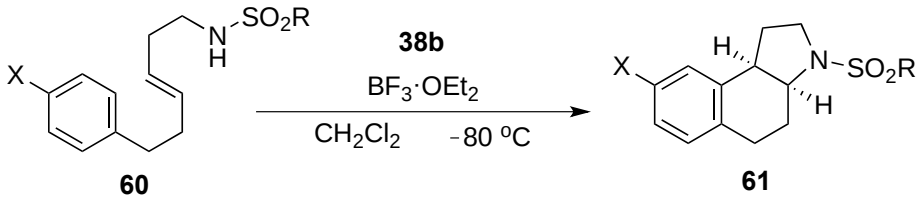
Scheme 13. Thioamination

Recently, a cascade cyclization involving a carbon nucleophile was reported by Fujita et al.[26] The oxidation of 6-phenylhex-3-en-1-oxy silyl ether **58** using lactate-based hypervalent iodine reagent **38b** yielded oxolane-fused tetralin product **59** with high enantioselectivity.[26a] The silyl ether did not act as a protection group, but promotes the nucleophilic oxycyclization. As shown in Scheme 14, a wide range of both electron-rich and electron-deficient arenes were found to participate in the oxidative arylation. Aminoarylation also proceeded to yield hexahydrobenz[*e*]indoles **61** with a moderate ee (Scheme 15).[26a] The hexahydrobenz[*e*]indole framework is found in candidate agonists/antagonists for dopamine and serotonin receptors.



[a] **38c** was employed instead of **38b**.

Scheme 14. Oxyarylation



60 **61**

X = H, R = Me 85% y, 80% ee[a]

X = H, R = 2-$NO_2C_6H_4$ 93% y, 72% ee

X = CF_3, R = Me 56% y, 62% ee[b]

X = CF_3, R = 2-$NO_2C_6H_4$ 78% y, 62% ee

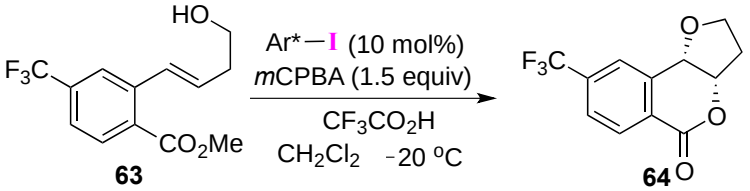
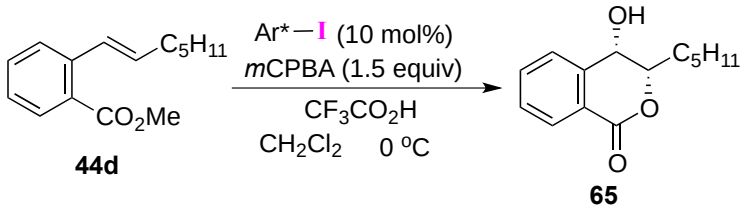
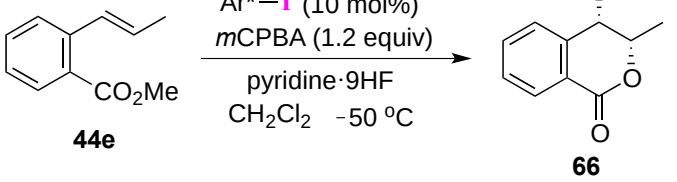
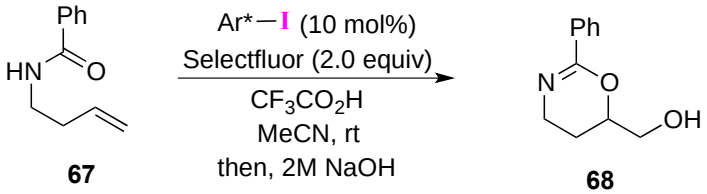
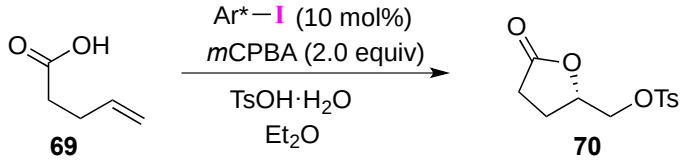
[a] $(C_6F_5)_3B$ was used instead of $BF_3{\cdot}OEt_2$. [b] TMSOTf was used instead of $BF_3{\cdot}OEt_2$.

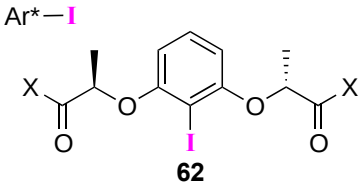
Scheme 15. Aminoarylation

Oxidative cyclization of alkene substrates has been conducted under catalytic conditions, where a catalytic amount of chiral iodoarene **62** is oxidized *in situ* to hypervalent iodine and used for the enantioselective oxidation of alkene substrates (Table 3). The cascade cyclization of *ortho*-(4-hydroxybut-1-enyl)benzoate **63** occured under catalytic conditions using bislactate **62a** precatalyst and *m*CPBA to yield oxolane-fused isochromanone product **64** with 91% ee (entry 1).[27] The catalytic oxidation conditions were applied to the *endo*-selective oxylactonization of *ortho*-alkenylbenzoate **44d** (entry 2).[28] The oxidation of **44d** using bislactate precatalyst **62a** yielded **65** with 68% ee. The use of sterically bulky ester **62c** at low temperature increased enantioselectivity to 94% ee, whereas amide precatalyst **62e** (= **6**) resulted in low selectivity. In the presence of hydrogen fluoride/pyridine, alkenylbenzoate substrate **44e** underwent fluorolactonization to give 4-fluoroisochroman-1-one **66** (entry 3).[29] High enantioselectivity was achieved with lactate-based iodoarenes **62a** and **62d**.

Moran et al.[30] used Selectfluor as a co-oxidant for the catalytic oxidation of *N*-(but-3-enyl)amide **67**, yielding dihydrooxazine **68** (entry 4). Chiral iodoarene precatalyst **62f** with dimethyl lactamide motifs gave higher enantioselectivity than ester **62b** and mesityl amide **62e** (= **6**). Masson et al.[31] reported sulfonyllactonization of pent-4-enoic acid (**69**) under the stereocontrol of lactate-based precatalyst **62** (entry 5). In contrast to poor enantioselectivity using ester precatalyst **62a**, amide precatalysts **62e** (= **6**) and **62g** improved the chemical yield and enantioselectivity in the oxidative lactonization of **69**.

Table 3. Oxidative heterocycle formation catalyzed by chiral iodoarene

entry	reaction	% yield, % ee		
1	 **63** → **64**	**62a**: X = OMe 46% yield 91% ee		
2	 **44d** → **65**	**62a**: X = OMe 67% yield 68% ee	**62c**: X = OMenthyl 71% yield 94% ee (at –40 °C)	**6 = 62e**: X = NHMes 30% yield 37% ee
3	 **44e** → **66**	**62a**: X = OMe 68% yield 94% ee	**62d**: X = OBn 86% yield 95% ee	
4	 **67** → **68**	**62b**: X = OEt 23% yield 44% ee	**6 = 62e**: X = NHMes 53% yield 50% ee	**62f**: X = NMe_2 86% yield 64% ee
5	 **69** → **70**	**62a**: X = OMe 6% yield 6% ee	**6 = 62e**: X = NHMes 50% yield 64% ee	**62g**: X = NPh_2 49% yield 60% ee

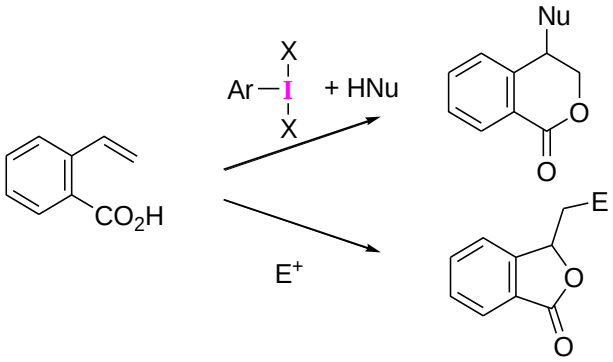


62

62a: X = OMe
62b: X = OEt
62c: X = OMenthyl
62d: X = OBn
6 = 62e: X = NHMes
62f: X = NMe_2
62g: X = NPh_2

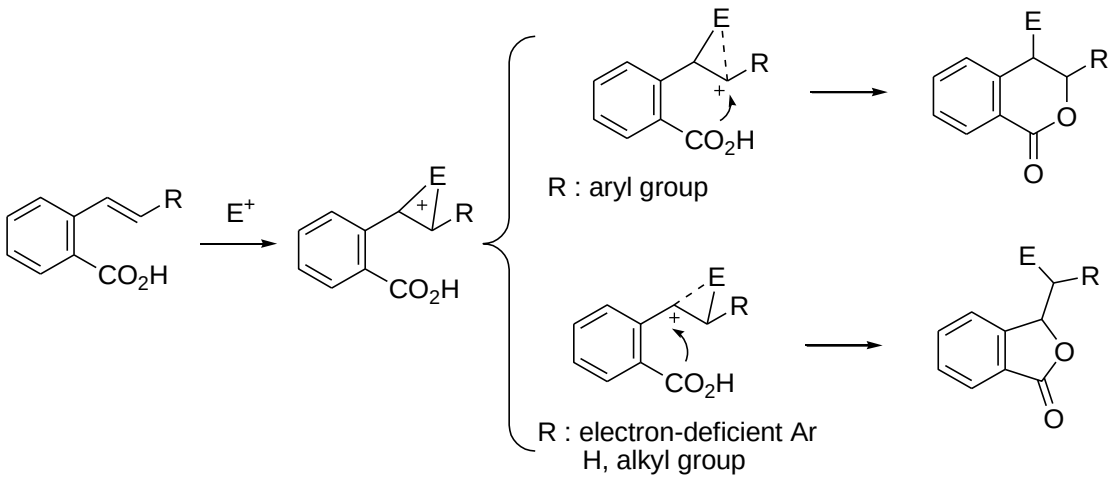
5. FEATURE SELECTIVITY OF HYPERVALENT IODINE REAGENT: 6-*ENDO*-LACTONIZATION OF *ORTHO*-ALKENYLBENZOIC ACID OR *ORTHO*-ALKENYLBENZOATE LEADING TO OXYISOCHROMANONE

Hypervalent iodine(III) reagents exhibit unique selectivity in the oxidative lactonization of *ortho*-alkenylbenzoates. The oxylactonization with hypervalent iodine proceeds with 6-*endo* selectivity to yield 4-oxyisochroman-1-one, whereas oxidations with conventional electrophiles derive a five-membered phthalide product as a result of 5-*exo* lactonization (Scheme 16).



Scheme 16. Regioselectivity in oxidative lactonization of alkenylbenzoic acid

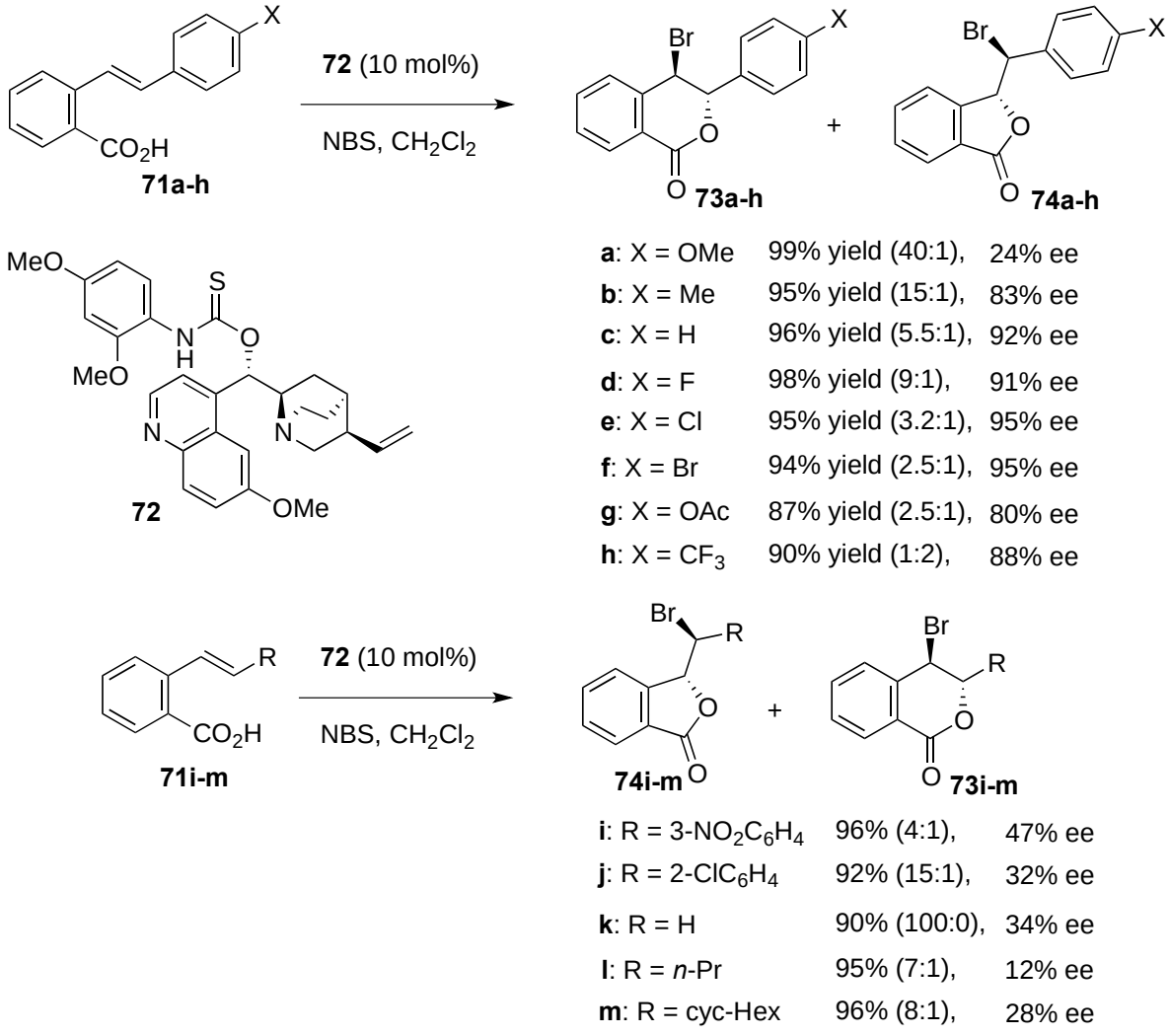
Regioselectivity in the lactonization using conventional electrophiles is strongly influenced by the electronic properties of the alkene substituent. The substrate bearing an aryl group at the β-position underwent 6-*endo* lactonization to produce an isochromanone product owing to the localization of positive charge at the carbon atom adjacent to the aryl group (upper part in Scheme 17).



Scheme 17. Regioselectivity in oxidative lactonization of alkenylbenzoic acid

The ratio of the 6-*endo* cyclization product decreases as the electron-withdrawing ability of the aryl group increases, and the 5-*exo* lactonization product predominantly forms in the cases of highly electron-deficient aryl group and alkyl group (lower part in Scheme 17).

A good example of changeover in the regioselectivity was found in enantioselective bromolactonization with NBS in the presence of quinidine-derived amino-thiocarbamate organocatalyst **72** by Yeung et al.[32] (Scheme 18).

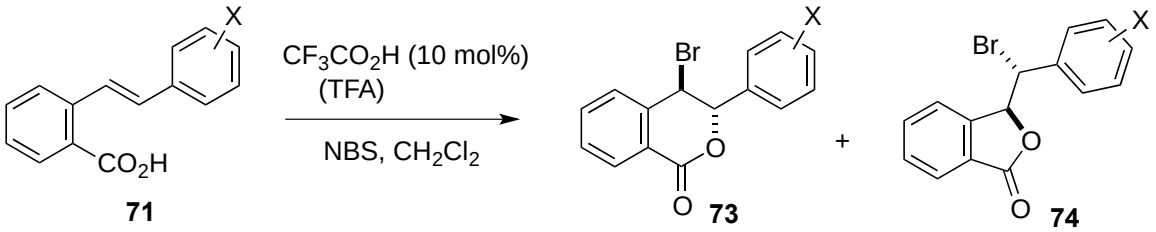


Scheme 18. Effect of electronic properties on bromolactonization

The same group reported that the presence of TFA increases the ratio of the 6-*endo* cyclization product in the bromolactonization of 2-styrylbenzoic acid derivatives **71** (Table 4).[33] The association of carboxylic acids decreased the nucleophilicity of the internal carboxylic acid. Most of the 2-styrylbenzoic acid derivatives **71a**–**g** underwent *endo*-lactonization to yield isochromanone **73** as the major regioisomeric product. In the case of electron-withdrawing CF_3 substituted substrate **71h**, the major product was

phthalide **74h**. Similarly, the reaction of electron-withdrawing aromatic substrates **71i**,**j** yielded phthalide products **74i**,**j** as a major regioisomer. Simple aliphatic alkenylbenzoic acid substrates **71k**–**m** also preferentially gave phthalide products **74k**–**m**. The regioselectivity can be reasonably explained within the positive charge distribution in the bromonium ion intermediate illustrated in Scheme 17. Thus, the alkenylbenzoic acid substrates, except for the styryl type, underwent 5-*exo* bromolactonization to yield the phthalide product.

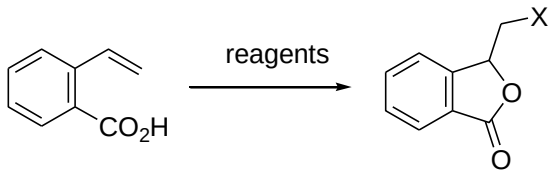
Table 4. Bromolactonization



entry	substrate X	73 : 74 with TFA	73 : 74 without TFA
1	H	>99 : 1	3.8 : 1
2	4-F	>99 : 1	4.6 : 1
3	4-Cl	>99 : 1	1.1 : 1
4	4-Me	>99 : 1	5 : 1
5	4-MeO	>99 : 1	9 : 1
6	2-Me	>99 : 1	2.5 : 1
7	3-Me	>99 : 1	1.6 : 1
8	2-Cl	11 : 1	1 : 3
9	3-NO_2	2 : 1	1 : 12
10	4-CF_3	4 : 1	1 : 3.3

In addition to the bromolactonization,[34] the preferential formation of the 5-*exo* cyclization product has been observed in several types of electrophilic addition: oxylactonization,[35] iodolactonization,[36] chlorolactonization,[37] fluorolactonization,[38] aminolactonization,[39] thiolactonization,[40] trifluoromethyllactonization,[41] and selenolactonization.[42] Representative reactions of alkenylbenzoic acids and alkenylbenzoates are summarized in Tables 5–7. The reactions of vinylbenzoic acid (Table 5) and α-substituted vinylbenzoic acids (Table 6) proceeded with 5-*exo* selectivity in all cases. Only a styrylbenzoic acid substrate gave the 6-membered lactone product (Table 7).

Table 5. Oxidative lactonization of vinylbenzoic acid



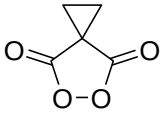
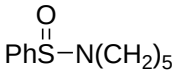
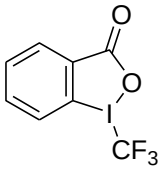
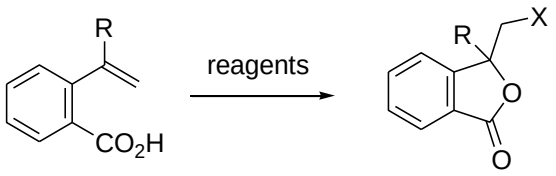
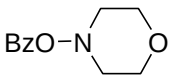
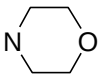
reagents	product	ref.
$Pb(OCOAr)_4$	X = OCOAr	35g
	X = $OCOC(CH_2)_2CO_2H$	35i
I_2	X = I	36
	X = SPh	40
$NH_2SO_3CH_2CCl_3$ $Rh_2(OCOR)_4$ $PhI(OCO^tBu)_2$	X = $NHSO_3CH_2CCl_3$	39c
 $(MeCN)_4CuPF_6$	X = CF_3	41a

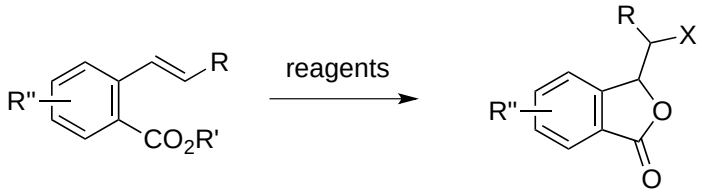
Table 6. Oxidative lactonization of α-substituted vinylbenzoic acid

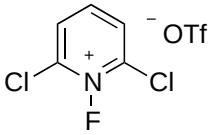
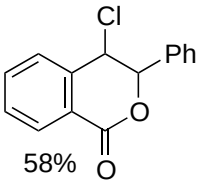
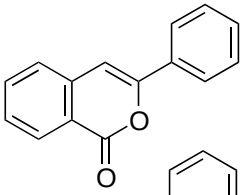
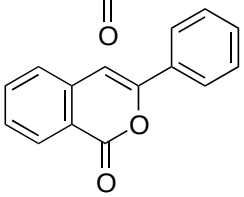
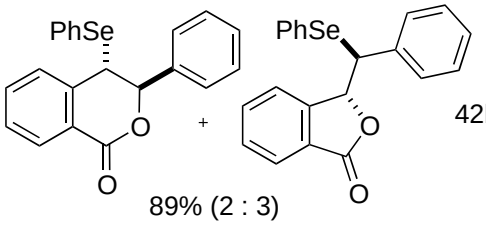


substrate	reagents	product	ref.
R = Me, Ph	$PhCO_3H$	X = OH	35a
R = Ar[a]	*m*CPBA	X = OH	35d
R = Ar	1,3-dichloro-5,5-dimethylhydantoin	X = Cl	37b
R = Me	1,3-dichloro-5,5-dimethylhydantoin + cat.	X = Cl 83% ee	37c
R = H, Me, aryl	Selectfluor	X = F	38a
R = Ar	Selectfluor + cat.	X = F 70 - 94% ee	38b
R = alkyl, aryl	$FN(SO_2Ph)_2$ CuCl (10 mol%)	$X = N(SO_2Ph)_2$	39a
R = H, Me, aryl	 $Cu(OTf)_2$(10 mol%)	X = 	39b
R = H, Me, Ph	PhSeCl, DABCO	X = SePh	42a
R = H, Me, aryl	$BrCF_2CO_2Et$ *fac*-[Ir(ppy)$_3$] blue LEDs	$X = CF_2CO_2Et$	41b

[a] Benzyl ester of 2-alkenyl-3-methoxybenzoic acid was used as substrate.

Table 7. Oxidative lactonization of alkenylbenzoic acid or alkenylbenzoate

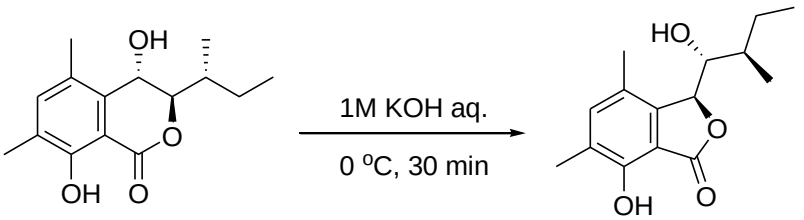


substrate[a]	reagents	product	ref.
R = *n*-Pr	H_2O_2 AcOH	X = OH	35c
R = Me R' = Me R'' = 4,6-$(OBn)_2$	AD-mix-b	X = OH 75%	35e
R = *n*-Pr R' = Me R'' = 6-BnO	AD-mix-b	X = OH 92%	35f
R = H, Me		X = F	29
R = Ph	1,3-dichloro-5,5-dimethylhydantoin	 58%	37a
R = Ph	PhSe—N$(COCH_2)_2$		42c
R = Ph	PhSeSePh $PhI(OCOCF_3)_2$		42d
R = Ph	PhSeCl	 89% (2 : 3)	42b

[a] R' = R'' = H, otherwise noted.

The thermodynamic stability of isochromanone and phthalide compounds was studied using natural products isolated from a marine-derived fungus *Chrysosporium articulatum*.[43] Isomerization between the

isochromanone natural product and the phthalide product was conducted under basic conditions. The six-membered chrysoarticulin A (**75**) was readily converted to the five membered chrysoarticulin C (**76**) during hydrolysis in the presence of KOH (Scheme 19). By contrast, no isomerization of **76** to **75** was observed under the same basic conditions with a prolonged reaction time (22 h). These results indicate that the isochromanone structure is less stable than the phthalide.



chrysoarticulin A (**75**) chrysoarticulin C (**76**)

Scheme 19. Thermodynamic stability between phthalide and isochromanone natural products

6. ASYMMETRIC TOTAL SYNTHESIS OF 4-OXYISOCHROMAN-1-ONE NATURAL PRODUCTS

The 4-oxyisochroman-1-one motif is present in many bioactive polyketide natural products isolated from several fungal sources.

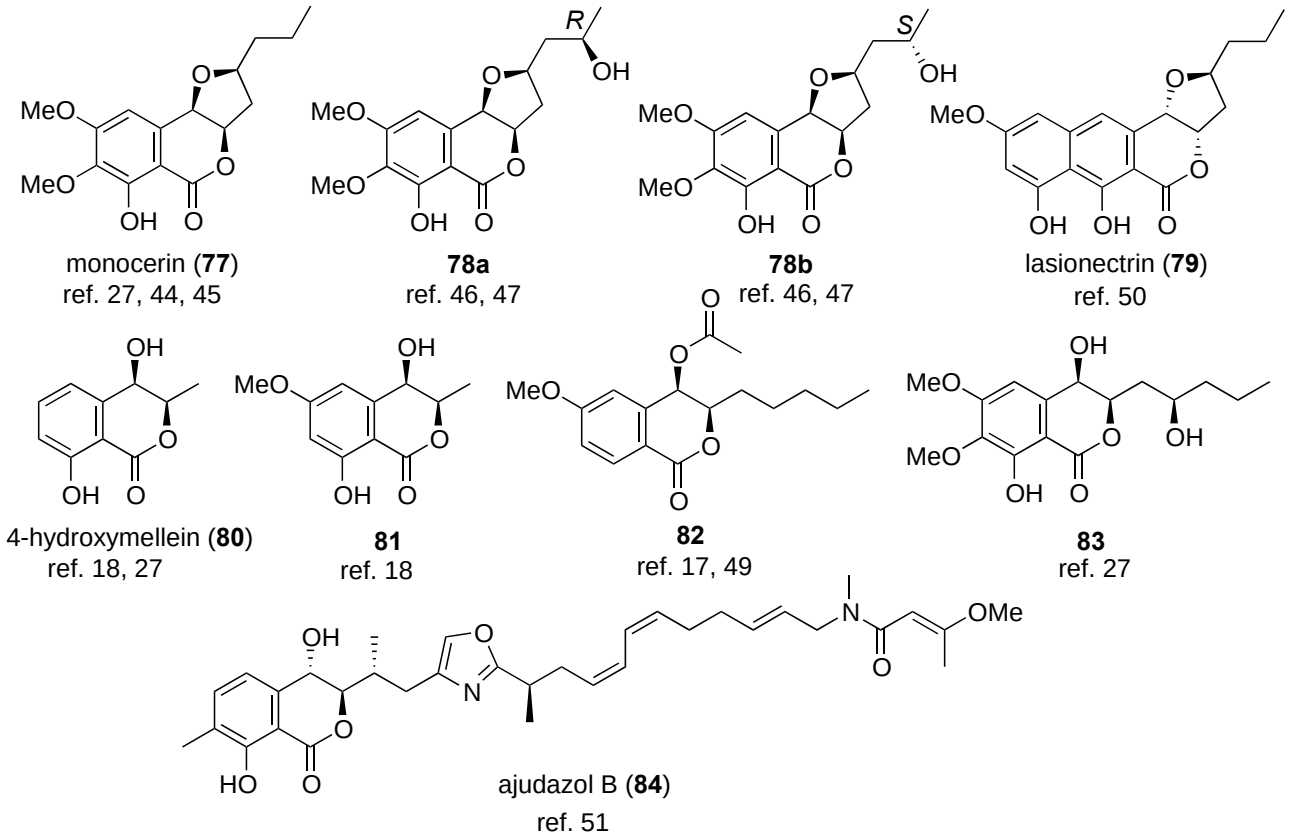
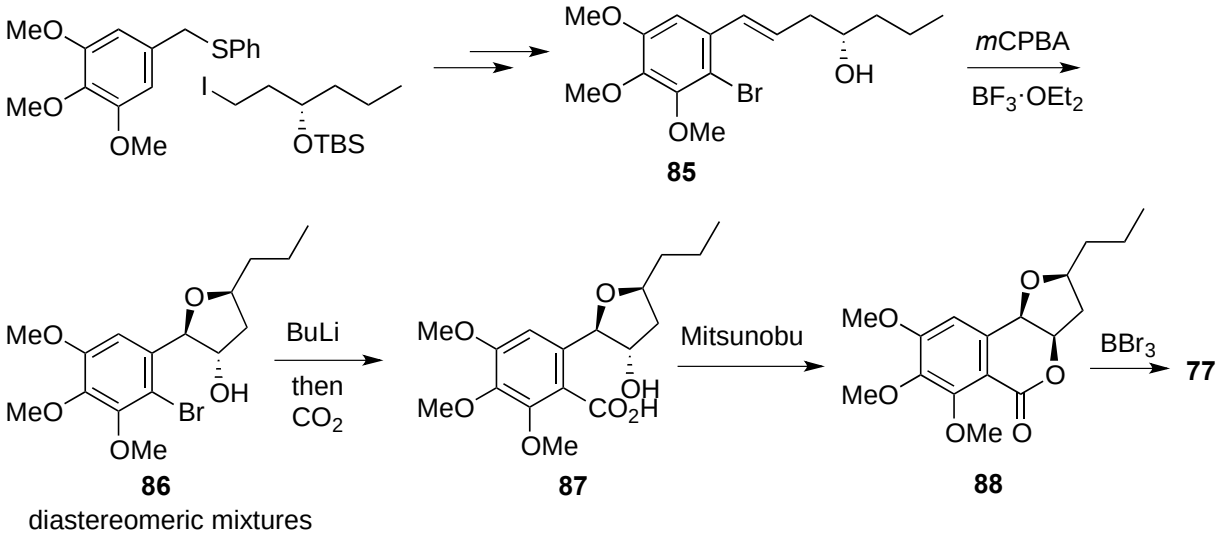


Figure 3. Natural products containing 4-oxyisochroman-1-one motif

Among this class of natural products, successful examples of total synthesis remain limited to the compounds listed in Figure 3. The preparation of the oxyisochroman-1-one core is a key step in the total syntheses. In this chapter, we disclose the superiority of the isochromanone formation using hypervalent iodine reagents.

The first total synthesis of monocerin (**77**) was reported by Mori and Takaishi[44] in 1989 (Scheme 20). The seminal synthetic work was achieved using the *m*CPBA-induced oxidative cyclization of 1-arylhept-1-en-4-ol **85** as a key step, which yielded 3-hydroxyoxolane compound **86** as a diastereomeric mixture. The hydroxy substituted oxolane ring was used as a scaffold for lactone formation via carbohydroxylation with carbon dioxide. The stereochemical configuration of lactone product **88** was adjusted by stereochemical inversion via the Mitsunobu reaction. Finally, monocerin (**77**) was obtained via selective demethylation of **86** using boron tribromide.

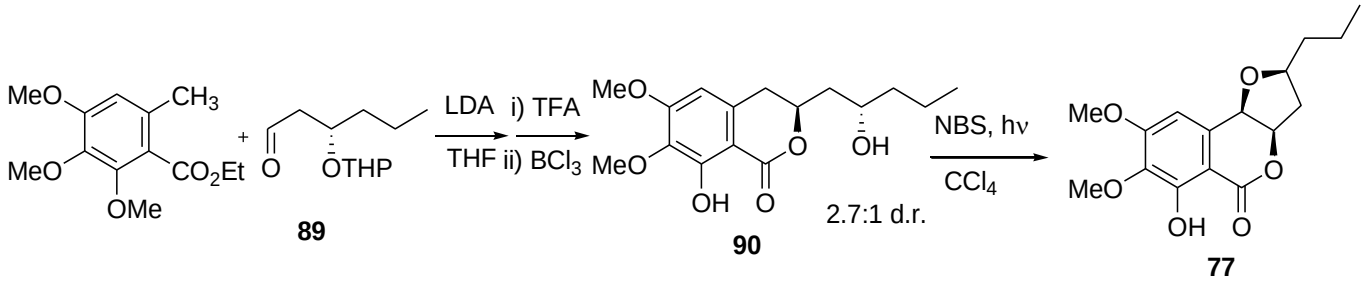


Scheme 20. The first total synthesis of monocerin

The total synthesis of monocerin has been reported by several research groups.[45] A synthetic strategy using the 3-hydroxyoxolane ring scaffold was found in most of the reports. The oxolane scaffold was selectively prepared and then used for oxolane-fused isochroman-1-one formation in a stereoselective manner.[45a–45c,45f–45h]

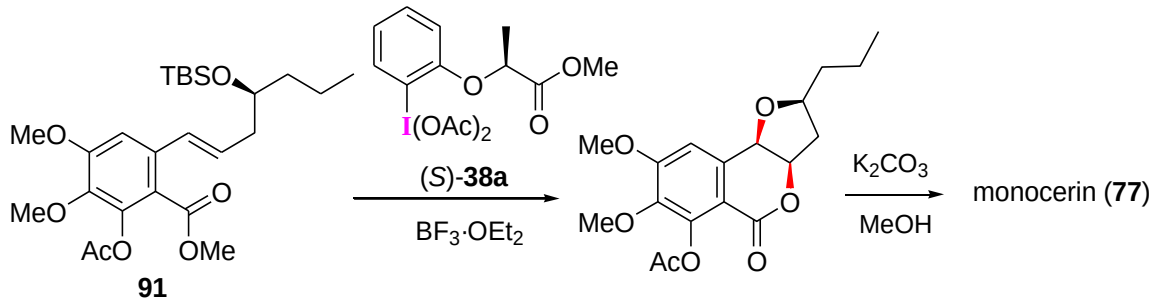
Simpson et al.[45d] achieved an elegant biomimetic synthesis of monocerin (Scheme 21). The biosynthetic route to monocerin is reasonably explained by the oxidative cyclization of the corresponding fusarentin via a quinonemethide intermediate. Simpson et al.[45d] used a radical benzylic bromination strategy, which initiates quinonemethide formation and cyclization. The starting fusarentin-type substrate **90** was prepared by anion condensation with aldehyde **89**. The final ring closure was successfully conducted

using a photoinduced radical reaction. Oxidative cyclization via a quinonemethide intermediate was also employed by the group of She.[45e]



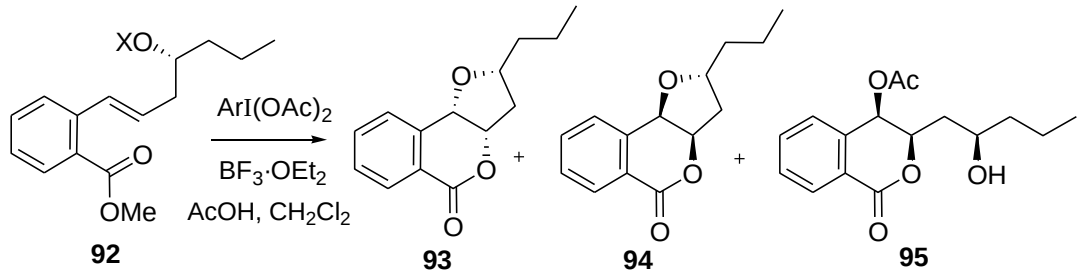
Scheme 21. Biomimetic synthesis of monocerin

Several synthetic routes to monocerin (**77**) have been reported, most of which involved the stereocontrolled preparation of a trisubstituted oxolane ring and subsequent isochromanone formation using the oxolane ring as an important scaffold. By contrast, the cascade formation of the oxolane-fused isochromanone core was achieved by using a hypervalent iodine-mediated protocol (Scheme 22).[27] The lactate-based chiral hypervalent iodine reagent (*S*)-**38a** enabled stereoselective double cyclization during the oxidation of alkenybenzoate substrate **91**. The stereoselective oxidation of olefin was used to prepare the trisubstituted oxolane scaffold, but these protocols demanded the following lactone formation steps.[44,45] Cascade dicyclization is an advantage of the hypervalent iodine-mediated protocol. It is also remarkable that the silyloxy group of substrate **91** participates as a nucleophile in the oxidative cyclization. The unexpected reactivity of the silyloxy group was examined using model substrates **92** (Table 8). The reaction of the silyl ether substrate (entries 1–3) yielded oxolane-fused isochromanone products **93** and **94** but not acetoxy product **95**. Instead, an unprotected hydroxy substrate (entries 4–6) decreased the yield of desired products **93** and **94**. The lactate-based chiral hypervalent iodine reagent **38a** strongly controlled the stereoselectivity of the oxidative dicyclization (entries 1–3).



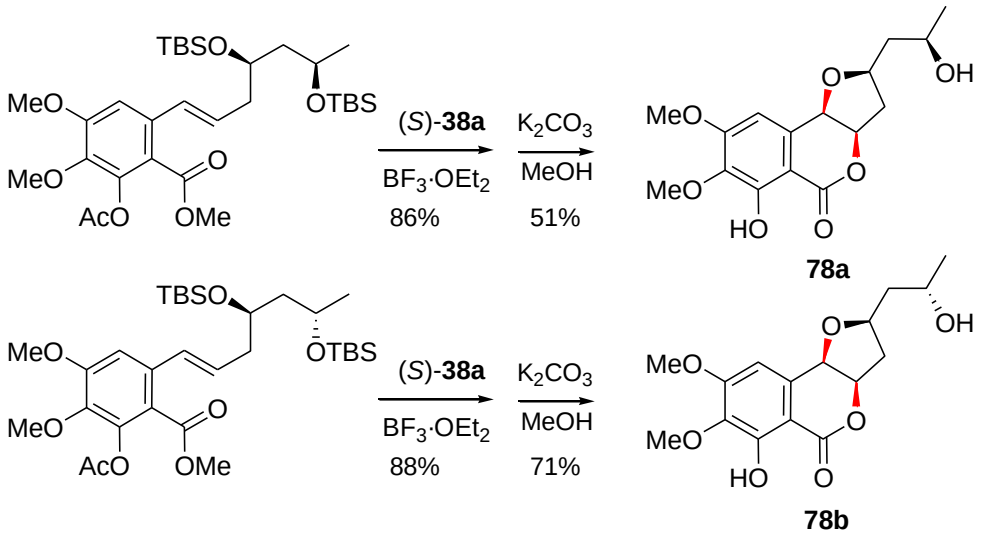
Scheme 22. Cascade preparation of monocerin using chiral hypervalent iodine

Table 8. Oxylactonization using model substrate



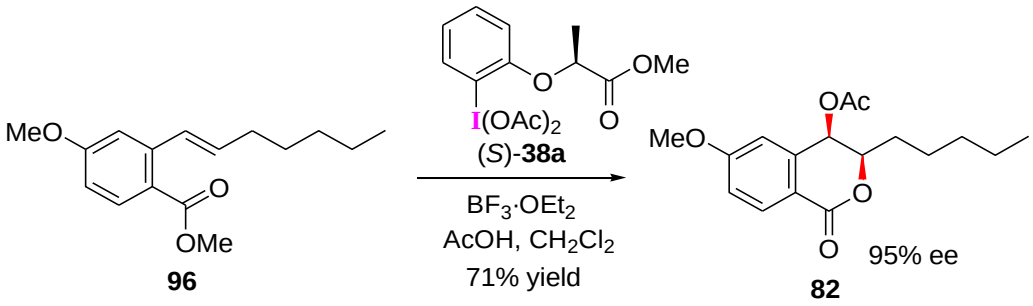
entry		ArI(OAc)$_2$		yield	
1	X = TBS	PhI(OAc)$_2$	33%	41%	
2	TBS	(*R*)-**38a**	75%		
3	TBS	(*S*)-**38a**		81%	
4	H	PhI(OAc)$_2$		32%	24%
5	H	(*R*)-**38a**	43%	17%	19%
6	H	(*S*)-**38a**		31%	54%

The hypervalent iodine-mediated protocol was applied to the total syntheses of (12*R*)- and (12*S*)-12-hydroxymonocerins **78a** and **78** (Scheme 23).[46] The 12-hydroxymonocerins were isolated from the endophytic fungi *Microdochium bolleyi*, together with monocerin. They showed antifungal, antibacterial, and antialgal activities. The first total synthesis was achieved by using stereoselective oxylactonization with a chiral hypervalent iodine reagent as a key step.[46] For another synthesis of 12-hydroxymonocerins, She et al.[47] applied the oxidative cyclization via a quinonemethide intermediate.



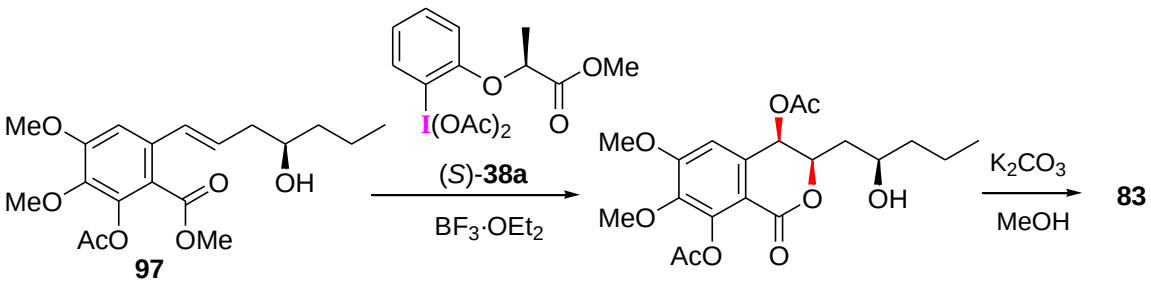
Scheme 23. Synthesis of 12-hydroxymonocerin using chiral hypervalent iodine

The hypervalent iodine-mediated protocol was used to prepare acetoxyisochromanone natural product **82** (Scheme 24).[17] Natural product **82** was isolated from *Xyris pterygoblephara* and was found to act as a selective inhibitor of aromatase.[48] The reaction of **96** with (*S*)-**38a** hypervalent iodine reagent gave the desired enantiomer of **82** with 95% ee. Venkateswarlu et al.[49] reported the second example of asymmetric synthesis of **82**, where selective protection and deprotection of the 1,2-dioxy moiety were required to construct the isochromanone framework.



Scheme 24. Enantioselective synthesis of **82**

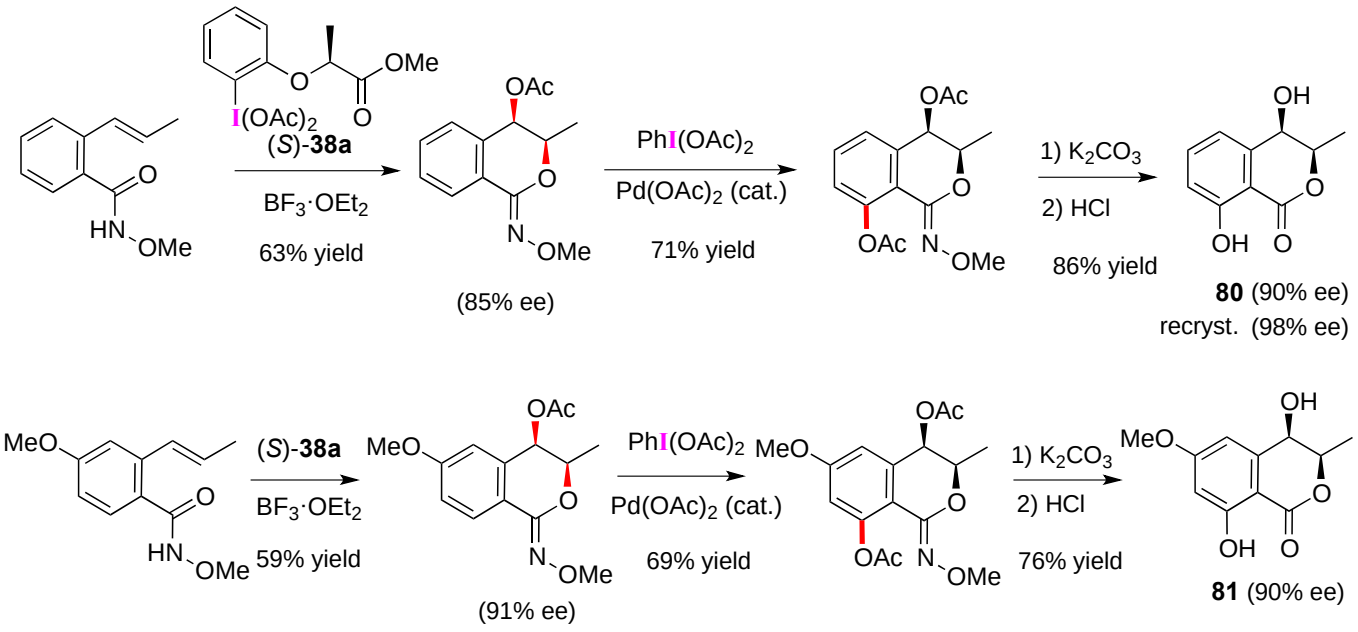
The more functionalized isochromanone natural product **83** was successfully synthesized via the acetoxylactonization of alkenylbenzoate substrate **97** (Scheme 25).[27] Target compound **83** possesses the same number of oxy functional groups at the same position as monocerin (**77**); that is, **83** belongs to the same oxidation level as that of monocerin. Both **83** and monocerin can be derived from a common olefin substrate through the hypervalent iodine-mediated oxidation protocol; thus, chemoselectivity in the oxidative lactonization should be taken into account. The chemoselective formation of **83** was achieved by using hydroxy substrate **97**, whereas monocerin was prepared from silyloxy substrate **91** (Scheme 22). The use of lactate-based hypervalent iodine reagent (*S*)-**38a** is key to the asymmetric synthesis of **83**, as examined by the model reactions in Table 8 (entry 6).



Scheme 25. Asymmetric synthesis of **83**

To introduce synthetic accessibility into 4-oxyisochroman-1-one natural products, Fujita et al.[18] developed a late–stage 8-oxy group incorporation strategy. The 8-oxy group originates from a polyketide biosynthetic route; thus, it is found in several polyketide natural products. In the synthetic strategy, 2-alkenylbenzamides underwent hypervalent iodine-induced oxylactamidation with 6-*endo* selectivity to afford isochroman-1-imine products (**47** in Table 2), which served as a scaffold for palladium catalyzed C-H acetoxylation in a regiocontrolled manner.[18] The imidate moiety acts as a removable directing group for regioselective oxygenation at the 8-position.

The oxidative cyclization using hypervalent iodine reagent proceeded for amide substrates with tosyl, methoxy, acetoxy, benzamide, and phthalimide *N*-substitution to yield the corresponding isochroman-1-imine. The oxidation with lactate-based chiral hypervalent iodine reagent **38a** afforded highly stereocontrolled products with 78%–90% ee. The following palladium catalyzed acetoxylation proceeded smoothly in the case of *N*-methoxy and *N*-acetoxy imidates. With these successful results using the model compounds, the imidate synthetic route was applied for concise synthesis of (3*R*,4*R*)-4-hydroxymellein (**80**) and (3*R*,4*R*)-4-hydroxy-6-methoxymellein (**81**) (Scheme 26). The enantioselective oxidation of *N*-methoxy-2-(prop-1-enyl)benzamide was followed by palladium catalyzed C-H acetoxylation. Targeted mellein derivatives **80** and **81** were finally obtained through deacetylation under basic conditions and subsequent acid hydrolysis of the imidate moiety. The synthetic pathway is characterized by the late-stage attachment of the 8-hydroxy group, which may affect bioactivity owing to hydrogen-bonding interactions with the 1-oxo group. The strategy using the hypervalent iodine reagent facilitates the asymmetric syntheses of isochromanone natural products and their mimics.



Scheme 26. Asymmetric syntheses of **80** and **81**

While total syntheses of lasionetrin (**79**)[50] and ajudazol B (**84**)[51] were recently achieved without using the hypervalent iodine-mediated strategy, the *endo*-selective oxylactonization using hypervalent iodine reagents have been one of attractive pathways for constructing 4-oxyisochromanone core in a stereoselective manner.

7. CONCLUSION

Hypervalent iodine compounds have served as efficient and powerful oxidizing reagents for the enantioselective formation of heterocyclic compounds. Optically active heterocycles have been prepared via the dearomatizing spirocyclization of phenols and naphthols, α-oxidation of carbonyl compounds, and vicinal functionalization of alkene substrates. Among these hypervalent iodine-mediated transformations, a unique selectivity was found in the oxidative lactonization of *ortho*-alkenylbenzoates; conventional electrophiles lead to 5-*exo* lactonization, thus giving a phthalide product, whereas hypervalent iodine reagents promote 6-*endo* lactonization to yield isochromanone products. The synthetic uses of the hypervalent iodine-mediated protocol have been demonstrated by its application to a crucial step of the asymmetric total synthesis of several isochromanone natural products.

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