TUTORIAL REVIEW

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Iodine electrophiles in stereoselective reactions: recent developments and synthetic applications

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The regio- and stereocontrolled functionalisation of carbon–carbon double bonds bears enormous potential in organic synthesis. This area has been extensively studied and reviewed as alkenes are amongst the most important starting materials for synthetic chemists, accessible in many varieties and in large quantities. We focus in this *tutorial review* only on recent developments using iodine electrophiles for the functionalisation of alkenes although transition-mediated reactions and functionalisations with chalcogen electrophiles also play an important role. New synthetic applications using this methodology showing scope and limitations of iodine-mediated processes also within the context of other electrophilic reactions are highlighted.

1 Introduction

The simple addition of electrophilic reagents to double bonds is one of the conceptually important and synthetically useful processes in organic chemistry resulting in the development of many novel reaction protocols. These reactions have emerged as very general methods for the preparation of heterocyclic compounds. Reactions performed using iodine electrophiles have been known for a long time; Bougault described the first iodolactonisation a century ago in 1904.[1] Since that time the synthesis of heterocycles by cyclisations of unsaturated substrates bearing nucleophiles and the electrophilic activation of alkenes in addition reactions have been important concepts in total synthesis. A wide range of nucleophiles can be successfully used to generate a variety of different products making the activation of double bonds by iodine a reliable transformation in synthesis. The reaction conditions described by Bougault were very

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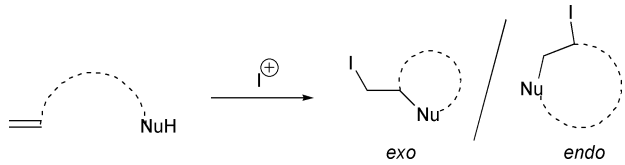
simple: the substrates were treated in an aqueous sodium carbonate solution with elemental iodine and potassium iodide. Those reaction conditions are still used nowadays but more advanced procedures have been added to the portfolio of iodine-mediated reactions which will be discussed in detail. The interaction of iodine electrophiles with double bonds leads to their activation and the addition of a nucleophile in either intermolecular or intramolecular fashion results in *trans*-addition products. New stereogenic centres can be created in such reactions and the efficient control of their formation has been the focus of extensive research efforts. The stereochemical aspects of these reactions will be analyzed in due course. The intramolecular addition to triple bonds leads to functionalised alkenes. Examples of these reactions using iodine(I) and iodine(III) reagents as the electrophile will not be discussed here. However, hypervalent iodine compounds can react with double bonds and have been successfully used as electrophilic reagents. Reactions with hypervalent iodine electrophiles will be discussed as well.

2 General strategies

The addition reactions with iodine electrophiles followed by either an intermolecular or intramolecular attack of a nucleophile can be found in a great variety of syntheses as this is a very reliable method for the functionalisation of double bonds. Stereogenic centers can be built up very easily using this methodology and many examples for their selective generation have been reported.

The stereoselective reactions can be divided into two different groups. On one side, chiral substrates or substrates attached to chiral auxiliaries have been traditionally employed in controlling the newly established stereocenters in reactions. These *substrate-controlled* stereoselective reactions represent, by far, the major route of introducing new stereogenic centers in electrophilic reactions. On the other side, chiral electrophilic reagents can be used, but they have not been intensively investigated. There are only a few examples of efficient, *reagent-controlled* stereoselective addition reactions known in literature. The preferred use of *substrate-controlled* reactions over *reagent-controlled* reactions is observed for both types of iodine electrophiles; iodine(I) reagents, being the most frequently used, and iodine(III) reagents, which are employed less frequently but allow for interesting subsequent functionalisation.

Reaction of iodine(I) electrophiles with alkenes is the initial step of an addition reaction or a cyclisation and can proceed, depending on stereochemistry and the ring size formed, in either *exo* or *endo* fashion, as shown in Scheme 1. Other factors like solvent and counterion will also have an effect on such reactions.



Scheme 1 Addition to alkenes using iodine(I) electrophiles.

The first step of any of the reactions described here is the interaction between the electrophile and the π-system of the alkene. This has been the subject of many investigations. Iodiranium intermediates of type **1** were suggested in 1937 to account for the *trans* stereochemistry observed in halogenations of double bonds.[2]

Fig. 1 Electrophile–alkene interactions.

Bromine–π complexes **2** ($E_2 = Br_2$) display a weak interaction with the alkene and have also been characterised using sterically very hindered olefins. Theoretical calculations have shown that there is almost no charge-transfer involved.[3] Kinetic investigations suggest that iodine–π complexes **2** ($E_2 = I_2$) rather than iodonium ions **1** (E = I) are involved as intermediates in at least some iodocyclisations.[4] The occurrence of intermediates **1** and **2** is also dependent on the source of the electrophile.

There are numerous ways to efficiently perform iodinations of alkenes or iodocyclisations. The traditional reaction conditions, a basic solution of elemental iodine **3** and potassium iodide are still used nowadays, but have also occasionally been replaced by other, more reactive sources of I^+. Commerically available interhalogens such as iodine monochloride **4**, or iodine monobromide **5**, have greater than two orders of magnitude higher reactivity than elemental iodine and are often employed in sluggish reactions. The simplicity of use, and low cost of these reagents make them even more attractive to the synthetic chemist. Iodonium acetate **6**, *N*-iodosuccinimide **7**, or bispyridine iodonium tetrafluoroborate **8**, can also be used as sources of I^+. Even stable iodonium ions such as **9** have been investigated.[5] Interestingly, **9** displays different kinetic behavior than the corresponding bromonium ion.

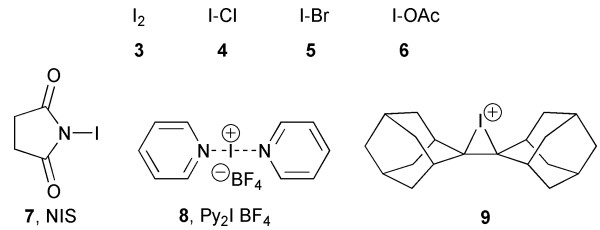


Fig. 2 Iodine(I) reagents used in electrophilic reactions.

Hypervalent iodine(III) compounds can also be used as efficient electrophiles, although these are more commonly used as metal-free, mild and selective oxidants. Simple and easily accessible iodine(III) reagents like diacetoxy iodobenzene **10**, bis(trifluoroacetoxy) iodobenzene **11** or hydroxy(tosyloxy) iodobenzene **12** (Koser's reagent) have been employed as electrophiles, but also chiral variants like **13** have been synthesised and used in stereoselective addition reactions to double bonds.

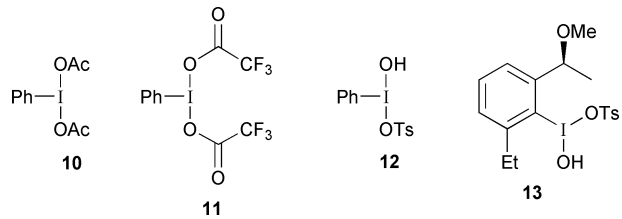


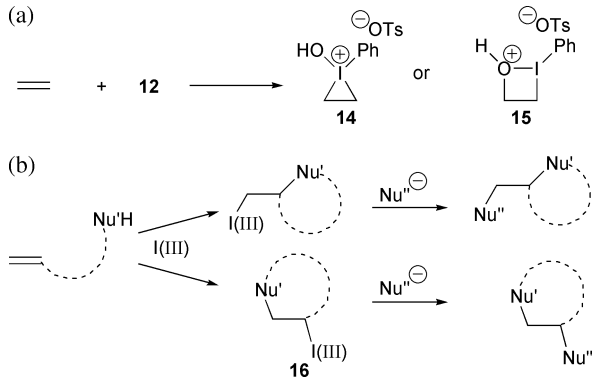
Fig. 3 Hypervalent iodine(III) reagents.

The intermediates in reactions of double bonds with iodine(III) reagents are only speculated upon and might involve cyclic, positively-charged intermediates **14** or **15** as they undergo further reactions due to the extremely good leaving group ability of the hypervalent iodine moiety in **16**.[6] The potential of a second nucleophilic addition has already been used in stereoselective synthesis and will be discussed later.

3 Regiochemical and stereochemical control

The generalised mechanisms for iodine(I) and iodine(III) initiated functionalisations of alkenes are shown in Schemes 1 and 2. The mechanistic pathways generally involve an activated intermediate and might vary depending on the substrate and other external factors.

The regiochemistry of simple electrophilic additions is controlled by electronic factors (Markovnikov rule) and by steric factors, whereas additional conformational and entropic factors can influence the course of intramolecular electrophilic heteroatom cyclisations. A general preference for *exo* cyclisations over *endo*



Scheme 2 Reaction of alkenes with iodine(III) electrophiles.

cyclisations can be observed. Since several of the steps in the addition reactions may be reversible under the reaction conditions, it is not always clear whether kinetic or thermodynamic control of a given reaction leads to the observed stereochemistry. The factors controlling the stereochemistry will, furthermore, be dependent on whether the addition of the electrophile or the nucleophilic addition (or cyclisation) is the rate-limiting step. Most double bond functionalisations with iodine electrophiles result in stereospecific *anti* additions across the double bond. In the case of iodine(III) electrophiles, the hypervalent moiety is replaced in a nucleophilic substitution as shown in Scheme 2, which results in an overall *syn* addition of the two nucleophiles.

Oxygen is probably the nucleophile used most frequently in such reactions, but nitrogen, sulfur and carbon nucleophiles can be used as well and give access to a range of differentially substituted compounds.

4 Substrate-controlled stereoselective reactions

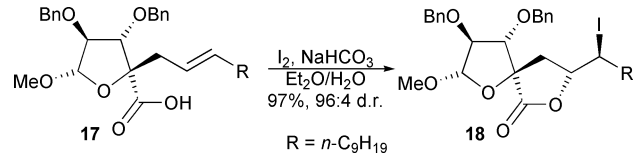
Substrates containing stereogenic centers are most frequently used in reactions with iodine electrophiles. Depending on the oxidation state of the iodine electrophile, the subsequent reactions can take different paths. Therefore, iodine(I) and iodine(III) electrophiles will be discussed separately. For iodine(I) electrophiles, subsequent reactions are grouped into three main categories; radical reactions, elimination reactions, and substitution reactions. Examples of each are presented. Iodine(III) electrophile reactions typically take advantage of the very high leaving group ability of the iodine(III) reagent and do primarily substitution reactions.

Iodine(I) electrophiles: synthetic applications and subsequent reactions

Lactone formation. The earliest, most common, and most well-known nucleophiles used in iodocyclisations are carboxylic acids and their derivatives, esters and amides. The resulting iodolactones are structurally useful moieties, and are present in the preparation of innumerable natural products. There are a host of examples of stereoselective iodolactonisations, only a few can be highlighted here. Of note is the effect of substrate regio- and stereochemistry on the regio- and stereochemical outcome of the lactonisation, especially in the formation of bicyclic lactones. Also of note is the wide variety of subsequent reactions on the resulting iodolactone products; from simple de-iodinations to further stereoselective manipulations.

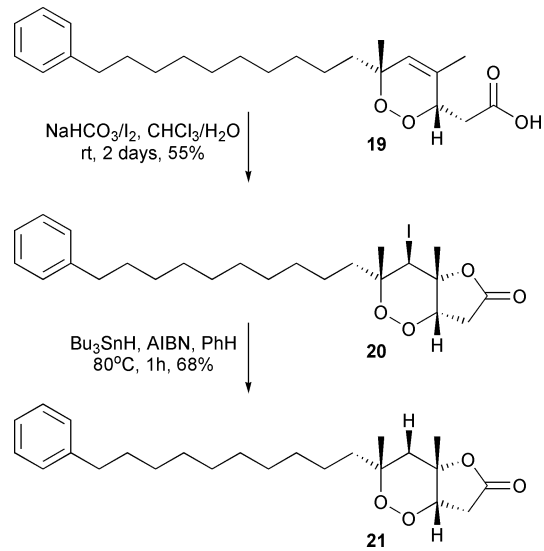
Rizzacasa's synthesis of the phospholipase A2 inhibitor, (−) cinatrin B, closed a lactone moiety in a 5-*exo* iodolactonisation of the suitably protected, arabinose-derived alkenyl acid **17**, which gave a high yield of the iodolactone **18** with good diastereomeric ratio (94 : 6).[7] Radical de-iodination provided fast access to an intermediate in the synthesis of the natural product.

Jung and coworkers synthesised 6-epiplakortolide E **21**, a potent anti cancer target, using an iodolactonisation of a cyclic peroxide, **19**.[8] Exposure to iodine and sodium hydrogen carbonate, in



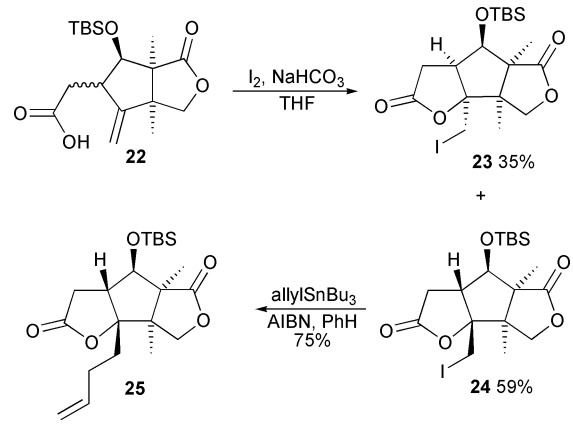
Scheme 3 Key step in Rizzacasa's synthesis of (−) cinatrin B.

chloroform–water gave good yields of the cyclic peroxylactone **20**. The iodolactonisation of this cyclic peroxide shows the mild nature of this reagent combination. Subsequent radical de-iodination gave the target compound, 6-epiplakortolide E **21**, in good yield.



Scheme 4 Jung's synthesis of 6-epiplakortolide E **21**.

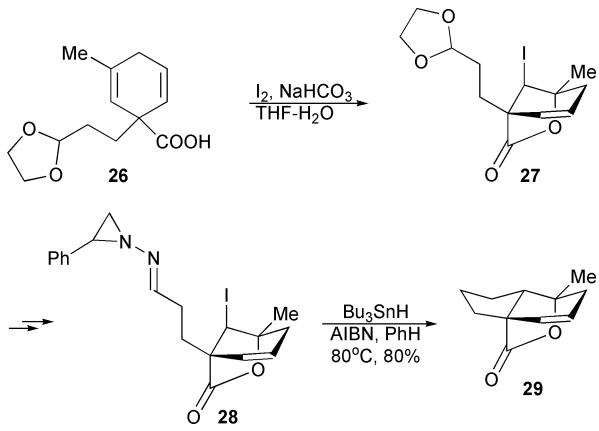
In the total synthesis of (±)-merrilactone A, a pentacyclic dilactone sesquiterpene and potent neurotropic factor, Danishefski and Birman constructed the second lactone moiety *via* a 5-*exo* iodolactonisation of an alkenyl acid precursor, **22**.[9] The resulting dilactone was obtained as roughly 2 : 1 ratio of stereoisomers, **23** and **24**. The iodide of **24** was subjected to radical allylation to give **25**.



Scheme 5 Danishefski's synthesis of merrilactone A intermediate **25**.

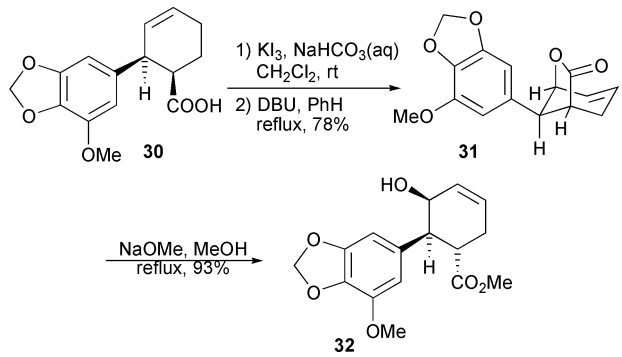
Hart and co-workers, in their synthesis of a *trans*-fused perhydroindan analog of hispidospermidin,[10] performed a 5-*endo* iodolactonisation of a dihydrobenzoic acid, **26**. Reaction with iodine and sodium hydrogen carbonate in aqueous THF afforded iodolactone **27** in high yield. After ketal hydrolysis and hydrazone formation, a radical cyclisation of the iodide **28** to make the *trans*-fused indan ring in **29** was performed, using the method of Kim.[11]

In Kim's synthesis of pancreastatin, the stereochemistry of a hydroxy group is established by a 5-*exo* iodolactonisation,



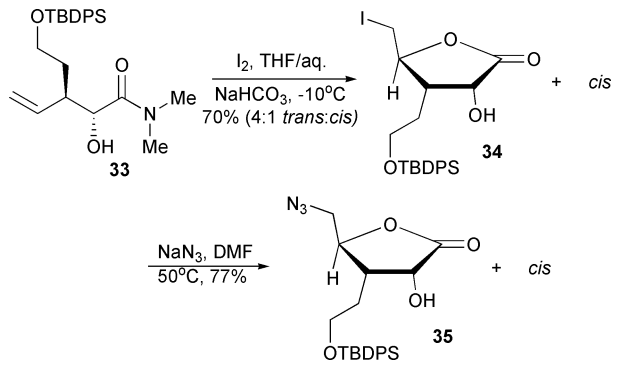
Scheme 6 Hart's hispidospermidin synthesis *via* iodolactonisation/radical cyclisation strategy.

elimination and a subsequent hydrolysis/epimerisation sequence.[12] Thus, the unsaturated acid **30** was cyclised to the bicyclic iodolactone which was subjected to an elimination of hydrogen iodide to give alkenyl lactone **31**. The epimerised hydroxy alkenyl ester **32** was then formed after methanolysis.



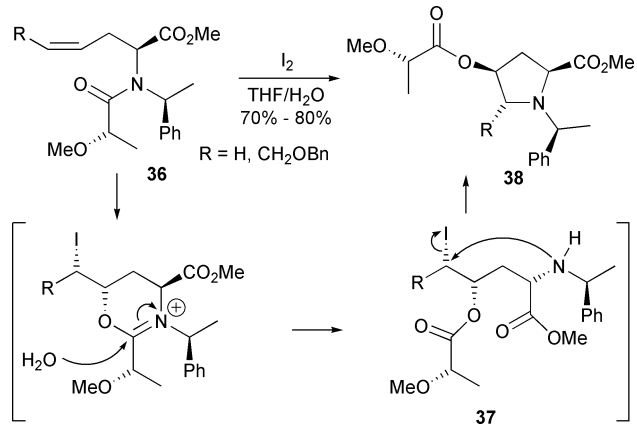
Scheme 7 Kim's synthesis of pancreastatin intermediate **32**.

Rozners and Liu, in their synthesis of an amide-linked RNA mimic performed an iodolactonisation of the unsaturated dimethylamide **33**.[13] Interestingly, the authors report sluggish reactions of the corresponding ester moiety, but good yields with the amide, as a 4 : 1 mixture of *trans* : *cis* isomers **34**. Attempts to optimize this reaction with respect to this ratio failed, suggesting a thermodynamically controlled reaction. The resulting iodide was displaced with azide in good yield to give **35**.



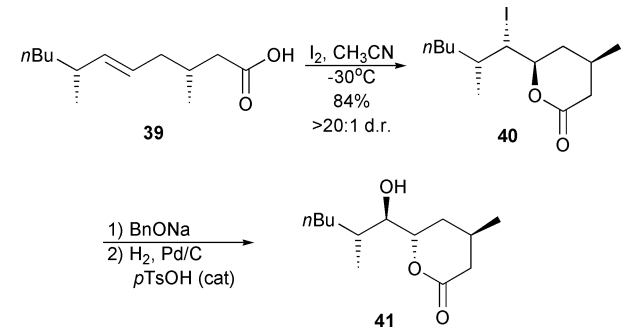
Scheme 8 Rozners and Liu's synthesis of RNA mimic **35**.

Sandri and co-workers' synthesis of the unnatural amino acids *cis*-4-hydroxyproline and bulgecinine centered on the cyclisation of the corresponding enantiopure alkenylamide ester **36**, with iodine in aqueous THF.[14] This double cyclisation reaction takes advantage of the iodocyclisation to its fullest; 6-*endo* cyclisation of the amide moiety onto the alkene, followed by a second cyclisation *via* displacement of the resulting iodide to give the protected pyrrolidine product. The mechanism of this reaction is proposed to be *via* a hydrolysis product, iodoester **37**, which was observed as an intermediate in the reaction. Continued stirring at elevated temperatures resulted in the cyclisation to the proline derivatives **38**.



Scheme 9 Mechanism of cyclisation to form proline derivatives **38**.

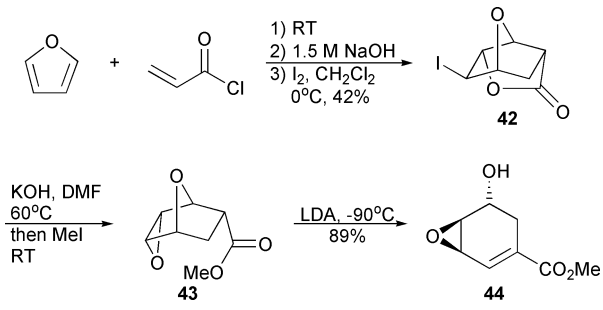
In the synthesis of fumonisin B_2 (FB_2) Kishi and coworkers have used a 6-*exo* iodolactonisation of the chiral unsaturated acid **39** to the lactone **40** to set up two new stereogenic centers in a high diastereomeric ratio (> 20 : 1), because Sharpless asymmetric dihydroxylation of the corresponding (*Z*)-alkene failed completely (1 : 1 dr). In order to replace the iodine by an oxygen atom with simultaneous inversion of both stereogenic centers, a known sequence was employed. The lactone was opened with sodium benzylate, which underwent a subsequent epoxide formation by displacing the iodide. The benzyl ester was then cleaved by hydrogenation resulting again in lactone formation with epoxide opening, to generate the building block **41** used for the synthesis of the mycotoxin FB_2.[15]



Scheme 10 Iodolactonisation with subsequent inversion of the stereogenic centers as a formal *anti*-dihydroxylation of a double bond in Kishi's FB_2 synthesis.

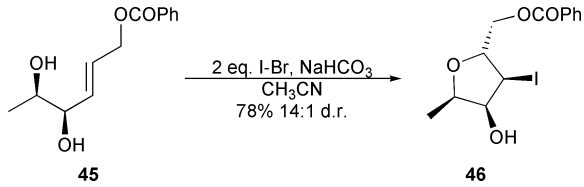
Hayashi and co-workers began their synthesis of epoxyquinals A and B, new anti-angiogenic natural products, using an iodolactonisation of an *in situ*-generated bicyclic ether acid salt.[16] Using the same strategy of iodolactone-opening with subsequent epoxide formation, **42** was treated under basic conditions, then methylated to form the epoxy ester **43**. This adduct was then treated with LDA, to facilitate ether cleavage, to generate the substituted cyclohexenol **44**.

Iodoetherifications. Iodoetherifications, where the nucleophile is an alcohol, ether or carbonyl oxygen atom, are also common and have been extensively studied by a number of groups, and applied to a number of interesting syntheses. Subsequent reactions range from eliminations and substitutions to oxidations. Knight and co-workers have devoted significant time to understanding the *endo* iodocyclisation of alkenyl alcohols to generate tetrahydrofurans.[17] In the synthesis of the aplasmomycin tetra-



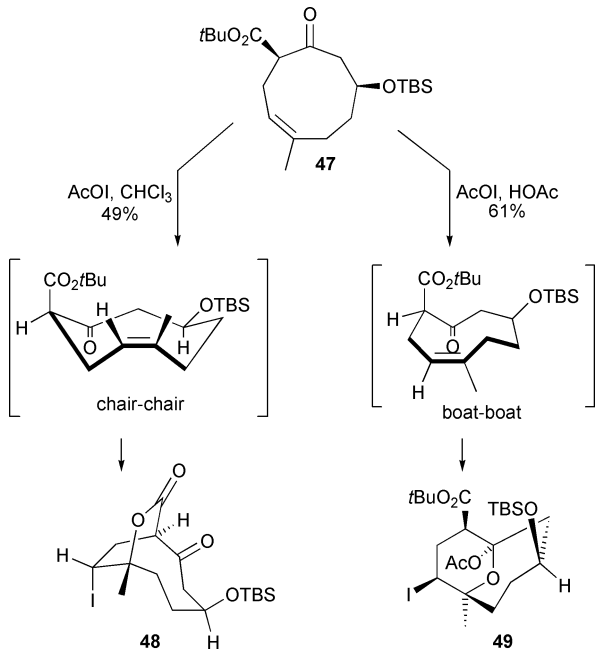
Scheme 11 Hayashi's synthesis of epoxyquinals A and B.

hydrofuran subunit, iodine monobromide was used in the cyclisation of dihydroxy ester **45**.[18] Cyclisation went exclusively in a 5-*endo* fashion in good yield with a diastereomeric ratio of 14 : 1 reported for tetrahydrofuran **46**.



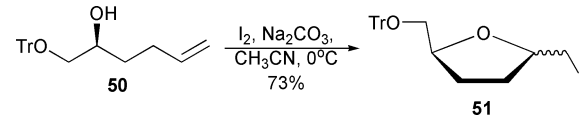
Scheme 12 Knight's synthesis of the aplasmomycin tetrahydrofuran subunit.

Clarke and co-workers, in the synthesis of the DF-ring of hexacyclinic acid, noted a significant solvent effect in treating the keto ester **47** with iodonium acetate.[19] The authors note that use of iodine under these conditions gave mixtures of numerous products. In chloroform, presumably through a chair–chair conformation which places the ester in close proximity to the alkene, a lactonisation led to the formation of bicyclic lactone **48** as the only product. Alternatively, the reaction of **47** in acetic acid, proceeding through a boat–boat transition state which places the carbonyl in close proximity to the alkene, gave iodotetrahydropyran **49** as an entirely different, but desired product. Deprotection of the silyl ether and ester hydrolysis resulted in the formation of a lactone, providing the hexacyclinic acid DF-ring subunit.



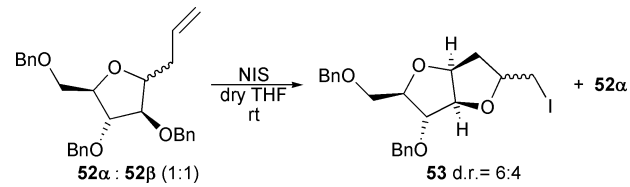
Scheme 13 Effect of solvent on iodocyclisation of olefinic keto ester **47**.

Castillon has exploited the iodoetherification strategy on a number of natural product syntheses. In his synthesis of 1′-C-fluoromethyl-2′,3′-dideoxycytidine, the 5-*exo* iodocyclisation of the trityl-protected 5-hexen-1,2-diol **50**, with iodine and sodium carbonate in acetonitrile, gave good yields of the iodotetrahydrofuran **51** as an equal mixture of diastereomers.[20] The resulting iodide was eliminated to the corresponding exocyclic olefin with potassium *tert*-butoxide, which was used without purification in the coupling to cytidine to give the target compound.



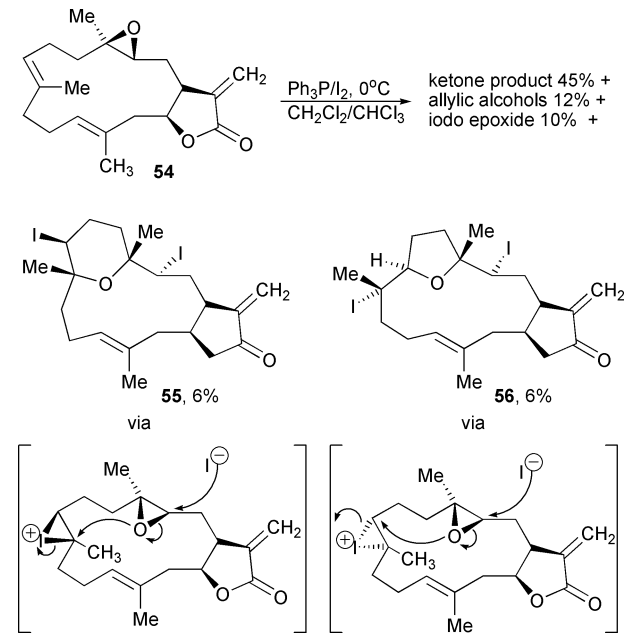
Scheme 14 Castillon's iodoetherification reaction for the synthesis of dideoxynucleotides.

The iodocyclisation of an alkenylbenzyl ether is the key reaction in Peri and Nicotra's synthesis of bicyclic sugar derivatives used for the construction of $\alpha_v\beta_3$-selective RGD peptides.[21] Under the reaction conditions, a 1 : 1 mixture of alkenyl ether **52α** and **52β** was exposed to *N*-iodosuccinimide in dry THF. 5-*exo* Cyclisation with the adjacent benzyl ether oxygen, and simultaneous debenzylation formed the bicyclic iodo ether **53**. It is most interesting to note that this cyclisation was, in fact, a resolution of diastereomeric starting materials; only the β-anomer cyclised, forming a *cis*-fused ring, while the α-anomer was recovered from the reaction mixture. The iodide was later displaced with azide ion.



Scheme 15 Peri and Nicotra's synthesis of bicyclic sugar derivative *via* iodoetherification reaction.

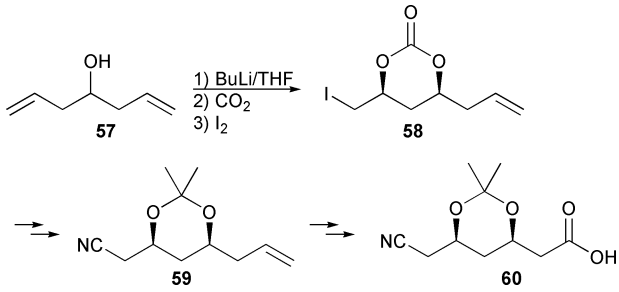
One example of an epoxide serving as the nucleophile in an iodoetherification reaction comes from the work of Rodriguez and co-workers and their reaction of iodine/triphenylphosphine on cembranoids.[22] Of particular note is the reaction described below, the reaction of euniolide **54**, which contains an olefinic epoxide structure. Among the varied epoxide opened products isolated and characterised, were two diiodo ethers, **55** and **56**. The stereochemistry of the diiodides suggests that iodonium ion formation



Scheme 16 Novel diiodoetherification of euniolide **54**.

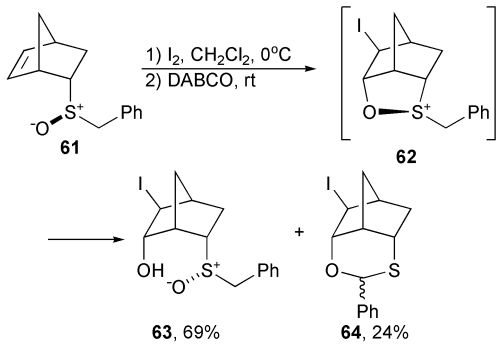
from the top face leads to tetrahydropyran formation by a 6-*endo* cyclisation, while attack of iodine from the bottom face results in the formation of the tetrahydrofuran *via* a 5-*exo* cyclisation.

Other oxygen nucleophiles. Many oxygen nucleophiles have been used in iodocyclisations, demonstrating the broad applicability of this method of constructing ring systems. In the synthesis of atorvastatin, and its analogs, the synthesis of the sidechain has been carried out *via* an iodocyclisation where the nucleophile is an *in situ*-generated alkenyl carbonate. Rádl and co-worker's racemic synthesis of this sidechain,[23] following a patented procedure,[24] established the relative stereochemistry of the second oxygen functionality in **58** by a desymmetrisation of **57**. After cyclisation, and cyclic ketal formation, the resulting iodide was displaced with cyanide, to give **59**, which after oxidative cleavage, gave the desired sidechain **60**, in a protected form.



Scheme 17 Racemic synthesis of atorvastatin sidechain intermediate.

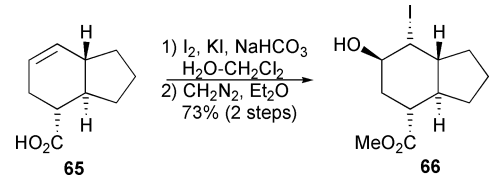
Abe and Harayama used sulfoxides as nucleophiles which underwent a subsequent Pummerer rearrangement to the 1,3-oxathianes, albeit in low yield.[25] Reaction of bicyclic alkenyl sulfoxide **61** underwent a 5-*exo* cyclisation to provide the tricyclic sulfoxy intermediate **62**. Hydrolysis of the cyclised intermediate, to give the inverted sulfoxide **63**, competes with the Pummerer rearrangement to form **64**. This reaction leads to mixtures of products, but the effectiveness of the sulfoxide to act as a nucleophile is clearly demonstrated.



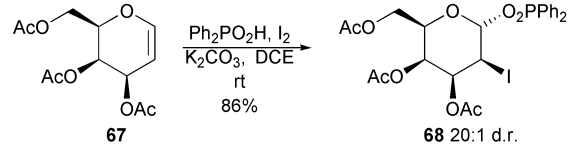
Scheme 18 Iodocyclisation with sulfoxide nucleophile followed by Pummerer rearrangement or hydrolysis.

In Clive's synthesis of the bicyclic core of ottelione B,[26] an antitumor agent, reaction of unsaturated acid **65** with iodine, potassium iodide, and sodium hydrogen carbonate produced iodohydrin **66** rather than a bicyclic lactone. The authors suggest that the required β-face iodonium ion formation results in a strained boat-like transition state which would lead to a strained lactone product. Alternatively, formation of the iodonium ion by attack on the α-face avoids these interactions, and thus, *trans* diaxial opening with water or hydroxide leads to the product **66**.

Togo and co-workers performed an iodophosphorylation on alkenes and alkynes, including glycals.[27] For example, iodophosphorylation of glycal **67** using diphenylphosphinic acid as nucleophile with iodine/potassium carbonate yielded **68** in up to 86% (with up to 20 : 1 selectivity for the α-anomer).

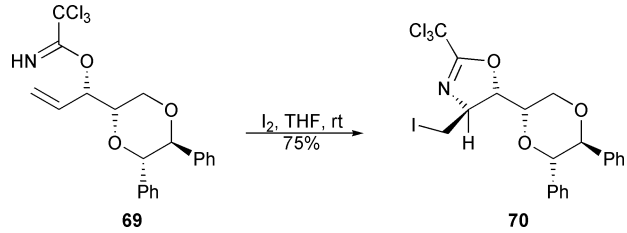


Scheme 19 Clive's synthesis of bicyclic core of ottelione B.



Scheme 20 Iodophosphorylation of glycals.

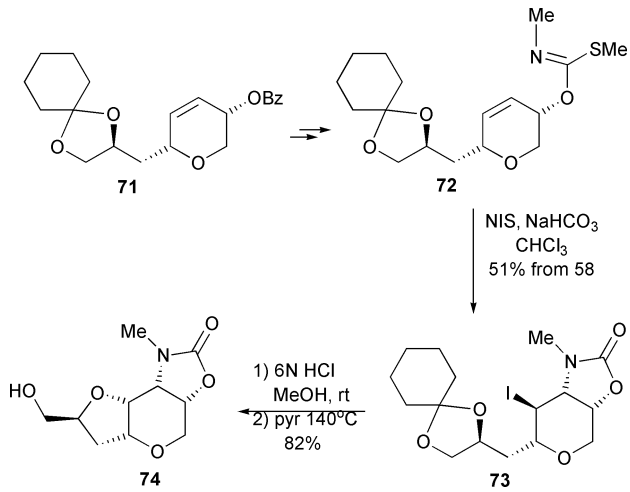
Nitrogen nucleophiles. In the synthesis of (+)-polyoxamic acid,[28] Kim and co-workers performed a cyclisation with a trichloroacetimidate as the nucleophile. Thus, regioselective and stereoselective cyclisation of the alkenyl trichloroacetimidate **69** with iodine at room temperature in THF, gave the iodo-1,3-oxazoline **70** in good yield.



Scheme 21 Iodocyclisation with trichloroacetimidate as nucleophile.

In this synthesis the iodide was then converted to a carboxylic acid functionality by hydrolysis with Amberlite®IRA-900 carbonate resin and oxidation.

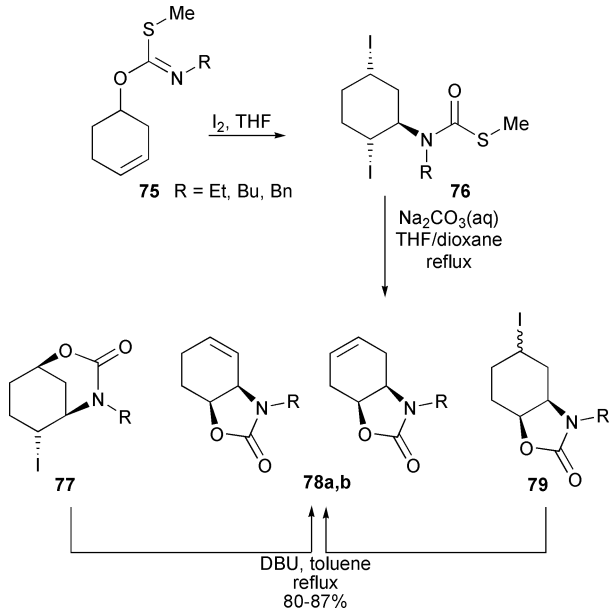
Kang and Lee synthesised (−)-dysiherbaine using three successive cyclisations.[29] The dihydropyran ring in **71** was formed using an alkoxymercuration protocol which was converted to the carbonimidothioate **72**. An iodocyclisation of **72** using *N*-iodosuccinimide and sodium hydrogen carbonate in chloroform was used to close the oxazolidinone ring of this drug candidate and the resulting iodide in **73** was displaced, after deprotection of the diol, to form the tetrahydrofuran ring **74**, completing the synthesis of the key intermediate of (−)-dysiherbaine.



Scheme 22 Kang and Lee's synthesis of (−)-dysiherbaine intermediate.

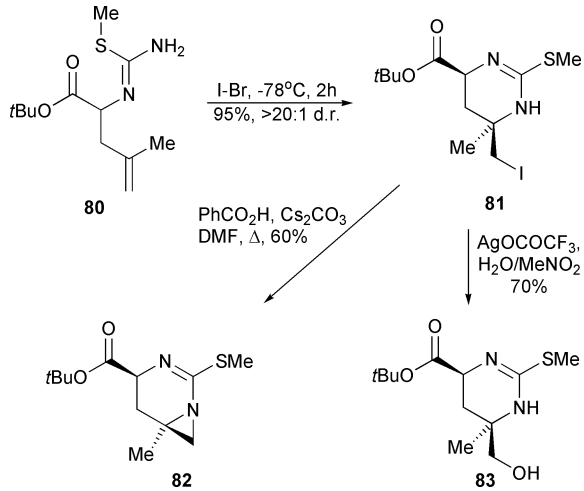
Delgado and co-workers performed a similar iodocyclisation of this functional group, this time on *O*-(3-cyclohexenyl) thiocarbami-

date **75**.[30] Reaction with iodine in THF followed by a sodium sulfite quench, gave an interesting result. While the bicyclic adduct was expected, the product obtained was, in fact, a 65–79% yield of the diiodide **76**, presumably by the attack of the nascent bicycle by iodide. Hydrolysis of this product resulted in different products, depending on the *N*-substituent. A large substituent, like benzyl or butyl, resulted in significant formation of the desired 1,3-adduct **77**, whereas *N*-ethyl substituents resulted in formation of the eliminated tetrahydrobenzoxazolones **78**. It is also interesting to note that treatment of either **77** or **79** with DBU in refluxing toluene gave excellent yields of the isomeric tetrahydrobenzoxazolones **78**. Hydrolysis with aqueous sodium hydroxide in ethanol afforded *cis*-1,2-amino alcohols in excellent yields.



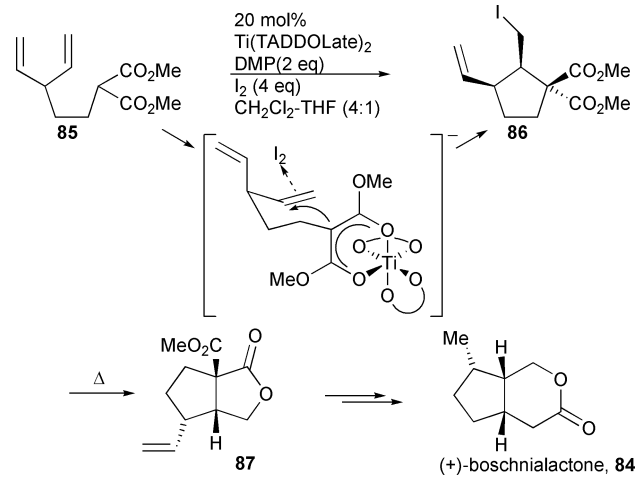
Scheme 23 Iodocyclisation of *O*-(3-cyclohexenyl)thiocarbamidate **75**.

MacKay used a diastereoselective iodocyclisation of the corresponding unsaturated isothiourea in the synthesis of the heterocyclic portion of manzacidin A and D.[31] Reaction of **80** with a variety of iodine electrophiles (I_2, NIS, I–Br, I–Cl) gave upwards of 95% yield of the amidine **81** with $>20:1$ diastereoselectivity. Treatment of the iodide with benzoic acid resulted in the formation of aziridine **82**. Solvolysis of the iodide gave the alcohol **83**, the core of the manzacidins.



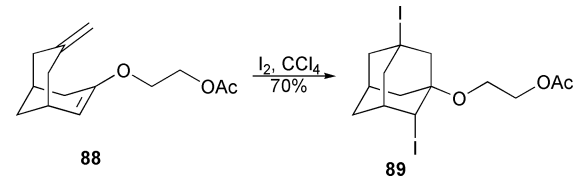
Scheme 24 MacKay's synthesis of heterocyclic portion of manzacidins.

Other nucleophiles. Taguchi and co-workers demonstrated that malonates can act as good nucleophiles in iodocarbocyclisation reactions.[32] When chiral titanium additives are included in the reaction, outstanding stereochemical control is possible. Demonstration of the practical utility of this methodolgy was made through a number of syntheses, including cyclosarkomycin, and a precursor to brefeldin A. Below is seen an application to the synthesis of (+)-boschnialactone **84** using a Ti(TADDOLate)$_2$ additive. Thus, treatment of the malonate **85** with dimethoxypyridine (DMP), iodine and the chiral titanium ligand results in a 5-*exo* carbocyclisation to the *cis* iodomethyl-cyclopentane **86** in 80% yield with 99% *ee*. The corresponding *trans* isomer of **86** is isolated in 6% yield. Heating **86** results in the cyclisation of the iodide by the *cis* ester to give the lactone **87**, eight steps from the target, boschialactone **84**. The requirement for a successful stereoselective reaction of this type is, however, the presence of a malonate moiety which allows for the efficient coordination to the Ti(TADDOLate)$_2$ ligand, generating a chiral substrate–reagent complex which reacts with iodine in a stereoselective way.



Scheme 25 Taguchi's asymmetric iodocarbocyclisation toward the synthesis of (+)-boschnialactone.

Skomorokhov and Klimochkin report an alkene acting as a nucleophile in the formation of diiodo adamantane esters.[33] In the addition of molecular iodine to bicyclic diene **88** in carbon tetrachloride, a 70% yield of the diiodoadamantane derivative **89** is obtained. It is presumed that the iodine associates with the more substituted olefin, from the bottom face, due to steric considerations. The olefin, in close proximity to the activated carbon atom attacks, forming an adamantyl cation, which is then iodinated.

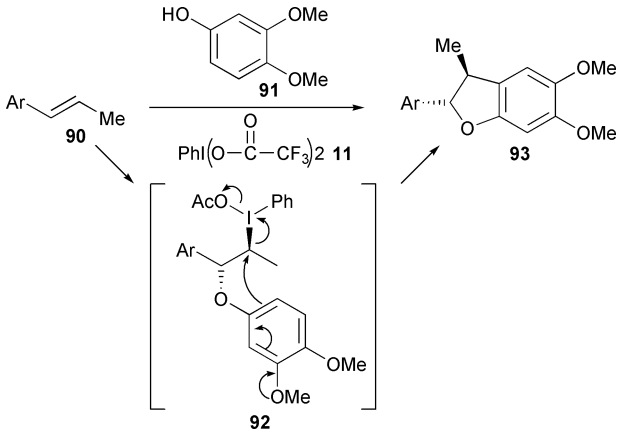


Scheme 26 Alkene as nucleophile in synthesis of adamantane derivatives.

Hypervalent iodine electrophiles: synthetic applications and subsequent reactions

The activation of double bonds using hypervalent iodine reagents as electrophiles bears a high potential but has only rarely been used in stereoselective reactions. There are, however, a wide range of oxidative cyclisations with hypervalent iodine reagents which Kita and others have used very successfully in different natural product syntheses.[34] An addition reaction of phenol **91** to the styrene derivative **90** using bis(trifluoroactoxy) iodobenzene **11** leads *via* an intermediate of type **92** and a subsequent cyclisation to the *trans*-dihydrobenzofuran **93**, indicating again the stereospecificity of the electrophilic addition reaction.[35] A different mechanism of a

1,3-dipolar cycloaddition of an oxidised species of the phenol **91** to the styrene derivative **90** can, however, not be excluded.



Scheme 27 Stereoselective synthesis of *trans*-dihydrobenzofurans.

5 Reagent-controlled stereoselective reactions

Chiral iodine(I) electrophiles

A general strategy in stereoselective synthesis are reagent-controlled reactions, where a chiral reagent induces the chirality in the product. Although they have a valuable synthetic potential, there are only very few reports on chiral iodine electrophiles. Several chiral hypervalent iodine reagents are known, but chiral iodine(I) electrophiles have appeared only recently in literature. Chiral iodine(I) reagents can be formed by coordination of the iodonium ion to one or more chiral ligands. An early example of a reagent-controlled stereoselective iodocyclisation was published by Grossman and Trupp who prepared dihydroquinidine–iodine complex **94** as a source of a chiral iodonium ion.[36] Selectivities of up to 14% *ee* in 5-*exo* iodolactonisation were achieved. Brown and Cui investigated the bromocyclisation of 4-pentene-1-ol using modified pyridines as chiral ligands for Br^+.[37] The only minor selectivites (5% *ee*) were observed using the menthol derived pyridine complex **95**.

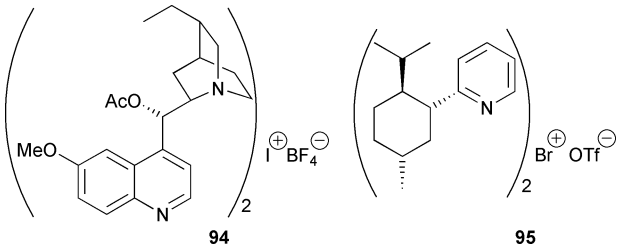
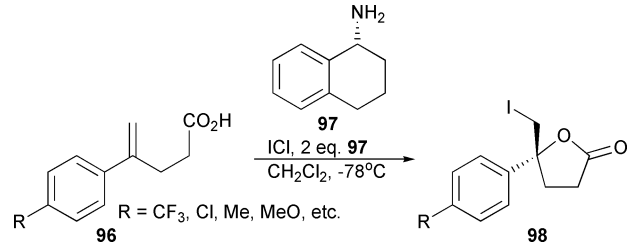


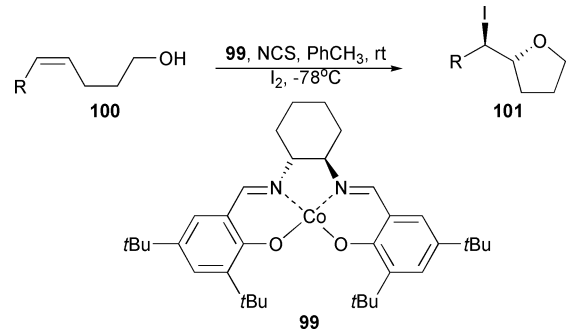
Fig. 4 First examples of chiral halonium complexes.

Wirth and co-workers studied the reagent-controlled iodolactonisation of 4-aryl-4-pentenoic acids **96**, using ICl and chiral primary amine ligands such as **97**.[38] Electron deficient aryl groups gave improved selectivities suggesting a tighter association of the chiral amine–ICl complex to an electron deficient alkene. Up to 50% *ee* were obtained in the iodolactones **98**. A study on solvent effects was also carried out and methylene chloride was found to yield significantly higher selectivities than other solvents.

The first catalytic reagent controlled iodocyclisation has been published by Kang and coworkers.[39] Chiral salen–cobalt complexes **99** were used in the enantioselective intramolecular iodoetherification of γ-hydroxy-(*Z*)-alkenes **100** to yield 2-substituted tetrahydrofurans. It was found that the addition of *N*-chlorosuccinimide further increased selectivities. Again, the choice of solvent seems to play a crucial role and reactions in toluene gave products **101** with up to 90% *ee*.



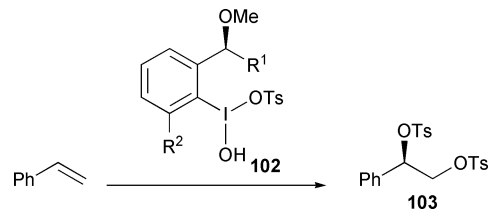
Scheme 28 Iodolactonisation of 4-aryl-4-pentenoic acids **96** with chiral amine–ICl complexes.



Scheme 29 Iodocyclisation of **100** using (*R*,*R*)-salen-Co(II) complex **99**.

Chiral hypervalent iodine electrophiles

The covalent attachment of chiral moieties on a hypervalent iodine atom is the concept mostly used for the synthesis of chiral hypervalent iodine compounds. Reagents with chiral alcohol substituents on the iodine atom have been used for stereoselective sulfide-to-sulfoxide oxidations, but Wirth and co-workers have shown that chiral compounds of type **102** can be employed for stereoselective electrophilic functionalisation of alkene double bonds.[40] Dioxytosylations of styrene and other alkenes can be performed which resulted in enantioselectivities of up to 65% *ee* in product **103**.[41]

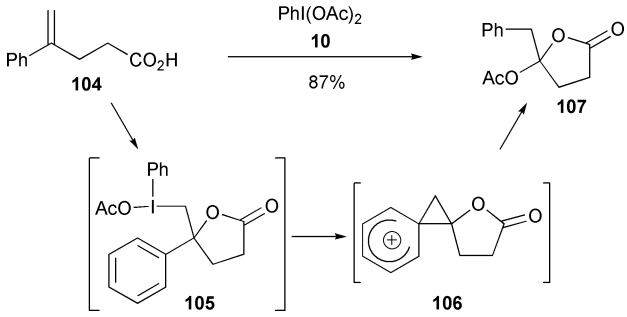


Scheme 30 Chiral hypervalent iodine reagents **102** in dioxytosylations.

The cyclisation of the unsaturated carboxylic acid **104** with diacetoxy iodobenzene **10** leads to the formation of **106** *via* the initial addition product **105**. This can be rationalised by a participation of the phenyl moiety resulting in the formation of a phenonium ion **106**. The high leaving group ability of the hypervalent iodine moiety in **105** causes this neighboring group participation. A 1,2-aryl migration accompanies the opening of the phenonium ion **106**. Chiral hypervalent iodine compounds like **13** gave, however, only very small enantioselectivities (4%) in product **107**.[42]

Conclusions and outlook

Iodine electrophiles have a long history and their potential for the functionalisation of double bonds has long been recognised. Their value, especially in stereoselective synthesis, has grown steadily and many mechanistic details of these reactions have been discovered. We have aimed to illustrate recent developments in the area of stereoselective iodine electrophiles by selected examples from the current literature. We believe that this versatile methodology will be of increasing importance for stereoselective synthesis in the future.



Scheme 31 Lactonisation *via* phenonium-ion intermediate.

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