Recent Cyclofunctionalizations by Intramolecular Attack of O, N, S, and Se Nucleophiles to Haliranium and Halirenium Ions

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Abstract. This review deals with preparing oxygen, nitrogen, sulfur, and selenium-containing heterocycles mediated by nucleophilic addition to haliranium and halirenium ions. The examples are reported starting from the year 2010, particularly emphasizing the regio- and stereoselection of the process, and demonstrate that the halocyclofunctionalization of alkenes and alkynes is a wide-scope methodology, useful for the synthesis of biologically active molecules and complex natural products.
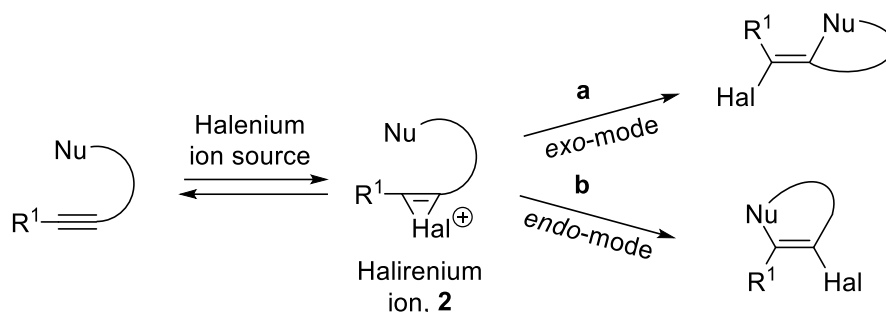
1. Introduction

A double bond, in the presence of a species able to generate a halenium ion [1-7], can be converted to a haliranium ion 1 [8-9], whose evidence was obtained from NMR measurements [10-13], whereas a triple bond can give a halirenium ion 2 [8-9]. Then, in the presence of a nucleophilic functional group containing oxygen, nitrogen, sulfur, or selenium tethered on the chain, the cyclization can proceed in endo- or exo-mode, providing a variety of heterocyclic compounds [14-20]. The appropriate choice of substrate geometry, nucleophilic functionality placed on the chain, and the activating electrophile leads to a cyclic product where the newly generated functional groups lie vicinal, and the introduced carbon-halogen bond is suitable for the introduction of other useful functional groups [21-22].
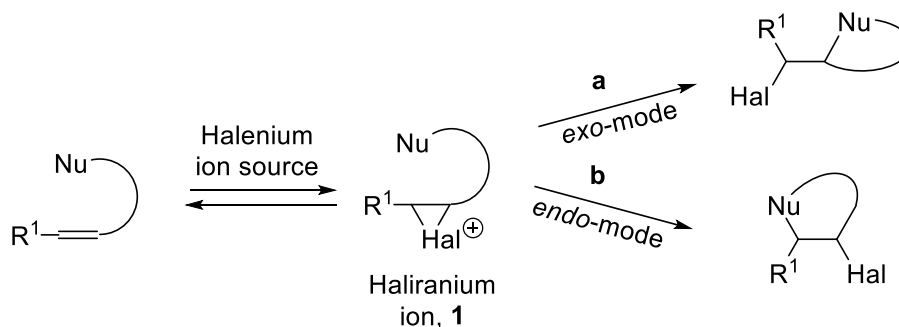
For this methodology since 1976, the term "cyclofunctionalization" was introduced by Clive [23-24], Cardillo [25-26], and Bartlett [27], and then many successful reactions in this class were disclosed. This review covers significant methods published starting from 2010, where an electron-rich heteroatom such as oxygen, nitrogen, sulfur, or selenium acting as a nucleophile attacks a haliranium or a halirenium ion generated by chlorenium, bromenium, and iodenium donors to provide heterocyclic products.

2. Intramolecular attack of nucleophiles to haliranium ions

2.1. O-C(sp^3) bond formation by the attack of oxygen nucleophiles.

2.1.1. Bromo and iodolactones from carboxylic acids and esters.

Halolactones 5 are an important class of organic products of particular interest to synthetic chemists since the lactone ring functionality that arises from halogen and oxygen addition across a double bond occurs in many bioactive natural products, whereas the halogen substituent is suitable for ready conversion to other useful functional groups, mainly by nucleophilic substitution [28]. The synthesis of halolactones can be carried out under kinetic conditions, using a base in a protic solvent to generate a carboxylate anion. A haliranium ion is formed, and eventually nucleophilic attack by carboxylate occurs, 3 (Path A). On the other hand, when the reaction is performed under thermodynamic conditions in an aprotic solvent, the addition of the halogen and the carboxylate oxygen to the double bond takes place in a concerted manner, 4, and the generated oxonium ion is eventually deprotonated or dealkylated by the halide ion (Path B) [28-30].
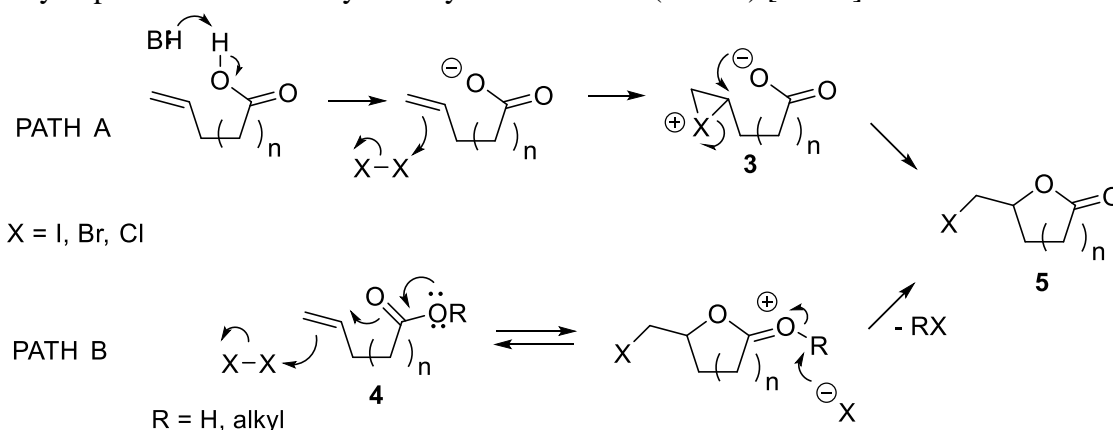

The importance of halolactonization is evidenced by the large number of applications to the synthesis of useful building blocks and biologically active molecules. Moreover, over the past decades, a number of methods were used to construct enantiopure lactones, and the reaction can be enantioselective when an appropriate chiral catalyst is used, leading to selective delivery of the halogen to the double bond exploiting ion pairing, hydrogen bonding, or Lewis and Brønsted-Lowry acid/base interactions between the catalyst, the substrate and the halenium source [31-41].

2.1.1.1. Without asymmetric induction.

The chief drawback of the cyclofunctionalization reactions involving haliranium ions was the use of halogens and halogen donors [42]. With the aim of avoiding the direct presence of halogens, new "green" methodologies were recently reported exploiting halide ions that were converted in situ into halogens. In fact, the iodide anion was oxidized to iodine by using 1,4-benzoquinone in the presence of 4-pentenoic acid, but the corresponding iodolactone 6 was isolated only in poor yield [43].
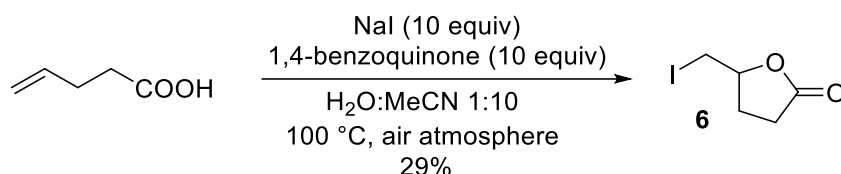

However, a bromide ion was oxidized to bromine by sulfoxide 8, and bromolactonization of alkenoic acids 7 provided lactones 9 in moderate to good yield [44].


R^1 = H, 94%; R^1 = CH$_3$, 84%, R^1 = C$_6$H$_5$, 68%
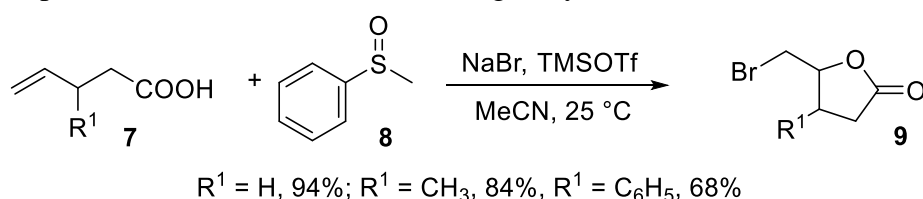
Bromide and iodide ions were also oxidized with (diacetoxyiodo)benzene (PIDA), and the corresponding halolactones 11a,b were isolated in good yield starting from alkenoic acid 10 [45].

**A**: KI; **a.** X = I, 83%; **B**: LiBr; **b.** X = Br, 80%
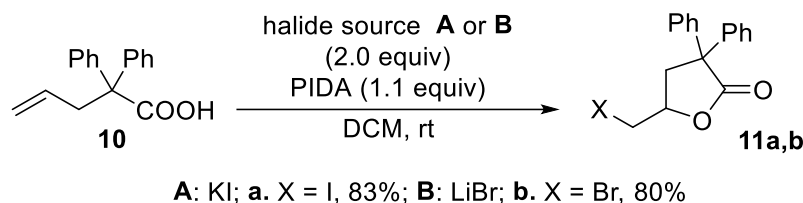
In addition, in the presence of a catalytic amount of V2O5, oxidation of bromide ion to bromine was efficiently performed using the hydrogen peroxide-urea system, and unsaturated acids 12 were converted to bromolactones 13 in good to moderate yield [46-47].

R^1 = C$_6$H$_5$, 90%; R^1 = 4-CH$_3$OC$_6$H$_4$, 96%; R^1 = 4-CH$_3$C$_6$H$_4$, 87%; R^1 = H, 50%
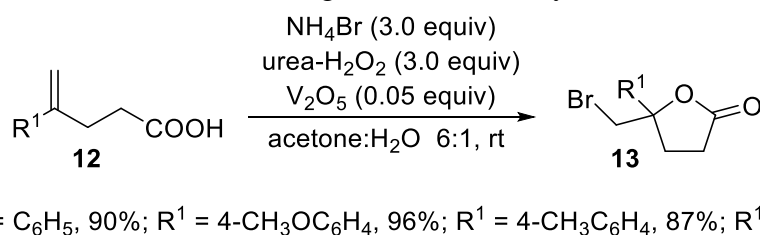
Moreover, in an undivided electrochemical cell, oxidative umpolung of the bromide anion allowed the generate of a haliranium ion, and the alkenoic acids 14 provided the corresponding bromolactones 15 in moderate to excellent yield [48].

R^1 = C$_6$H$_5$, 96%; R^1 = 4-F-C$_6$H$_4$, 84%; R^1 = 4-CH$_3$O-C$_6$H$_4$, 63%
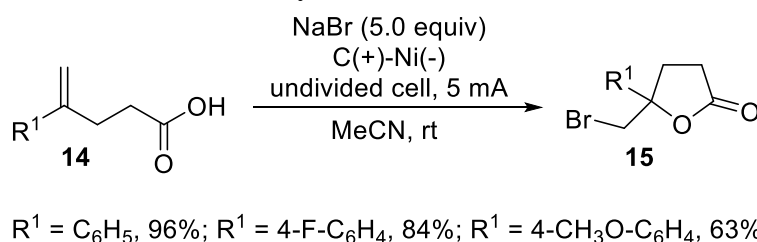
Eventually, exploiting the vanadium-dependent chloroperoxidase from Curvularia inaequalis (CiVCPO), a chemoenzymatic method was devised for in situ generation of hypohalites, and halolactones 16 were obtained in moderate yield starting from unsaturated acids 17 [49].
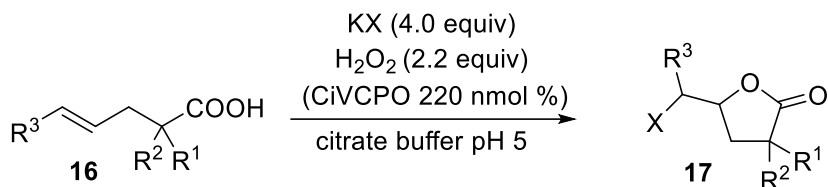
X = Br, $R^1 = R^2 = R^3$ = H, 67%; $R^1 = R^2 = CH_3$, R^3 = H, 72%; $R^1 = R^2$ = H, $R^3 = CH_3$, 57%;
X = I, $R^1 = R^2 = R^3$ = H, 67%; $R^1 = R^2 = CH_3$, R^3 = H, 68%; $R^1 = R^2$ = H, $R^3 = CH_3$, 56%

Five-membered iodolactones were useful intermediates for the preparation of six-membered hydroxylactams. In fact, in the presence of a small amount of iodide anion that was converted under oxidizing conditions into iodine, alkenoic acids 18 gave the intermediate iodolactones 19. These compounds first reacted with an appropriate amine to give by substitution the amino lactones 20, regenerating the iodide anion that underwent oxidation again, whereas subsequent attack of the amino group to the lactone functionality gave the six-membered hydroxy lactams 21 in good yield [50-51].
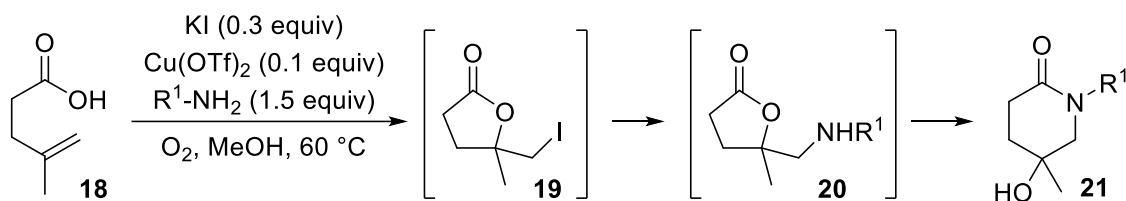

R^1 = 3-CH_3O-C_6H_4-CH_2, 78%; R^1 = 4-Br-$C_6H_4CH_2$, 84%;
R^1 = cyclohexyl, 60%; $R^1 = CH_2CH(CH_3)_2$, 72%

In a novel synthetic approach, the cyclization of alkenoic acids 22 providing bromolactones 23 in very high yield was performed using mechanical force under solvent- and catalyst-free conditions using a mixer mill [52].
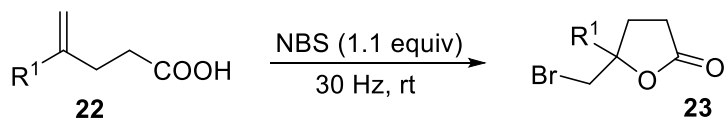

R^1 = 4-CH_3-C_6H_4, 98%; R^1 = 4-CH_3O-C_6H_4, 87%;
R^1 = 4-CF_3-C_6H_4, 98%; R^1 = 4-F-C_6H_4, 90%

Moreover, the formation rate of bromolactones 24 starting from the corresponding unsaturated alkenoic acids 25 highly increased when NBS was strongly activated by the Lewis acid selenonium cation 26 [53].
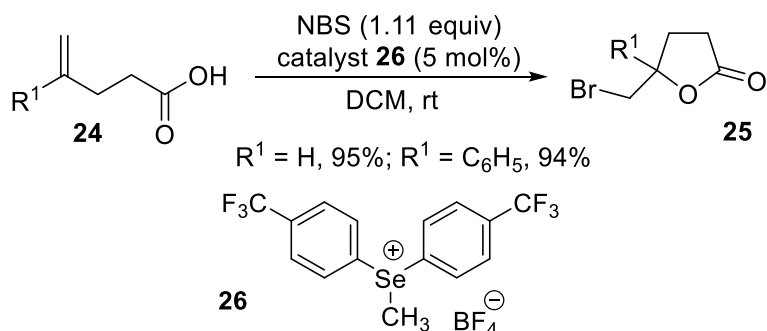
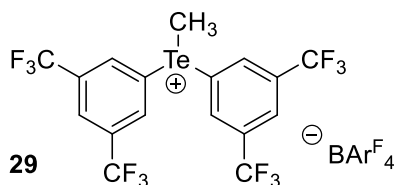R^1 = H, 95%; $R^1 = C_6H_5$, 94%

The same effect was observed when alkenoic acids 27 underwent cyclization to bromolactones 28 mediated by NBS activated by the telluronium cation 29 [54].


n = 1, 77%; n = 2, 99%; n = 3, 82%

29
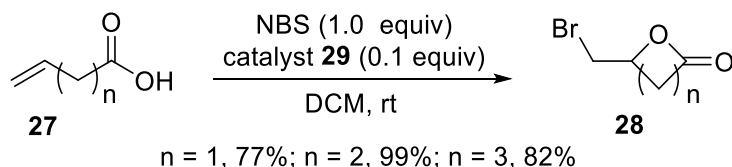
The bromocyclization rate also increased using NBS and a catalytic amount of indole 30 in an apolar solvent due to the formation of the intermediate 31 that, by exchange easily generated a bromiranium ion, eventually providing the bromolactones 33 in very good yield, starting from the alkenoic acids 32 [55].

$R^1 = C_6H_5$, 97%; $R^1 = 4\text{-}CH_3C_6H_4$, 75%; $R^1 = H$, 89%, $R^1 = CH_3$, 95%
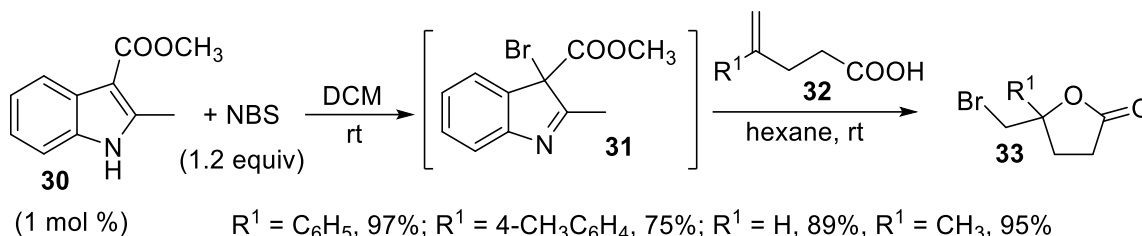
Lewis bases were found to strongly activate N-haloamides or halosuccinimides, probably due to coordination with the intermediate haliranium ions. Thus, organoselenium compound 36, acting as a Lewis base, enhanced the bromocyclization rate of alkenoic acids 34, leading to the bromolactones 35 in excellent Å yield via a 6-exo-trig closure [56].
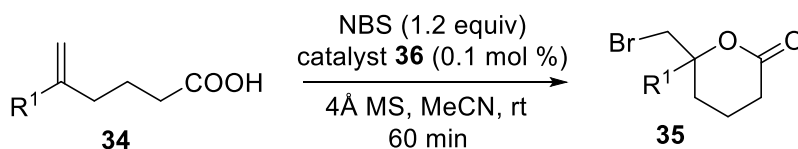
$R^1 = C_6H_5$, 96%; $R^1 = 4\text{-}F\text{-}C_6H_4$, 96%; $R^1 = 4\text{-}NO_2\text{-}C_6H_4$, 94%; $R^1 = $ cyclohexyl, 97%

36
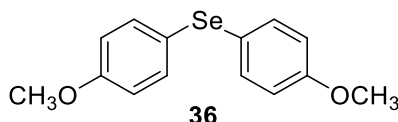
In addition, when DMAP and the same selenium compound 36 were added to the reaction mixture, alkenoic acids 37 underwent an exo-mode cyclization mediated by NBS and provided in moderate yield, but with total regio-selection, the corresponding otherwise inaccessible medium- and large-size bromolactones 38 [57].
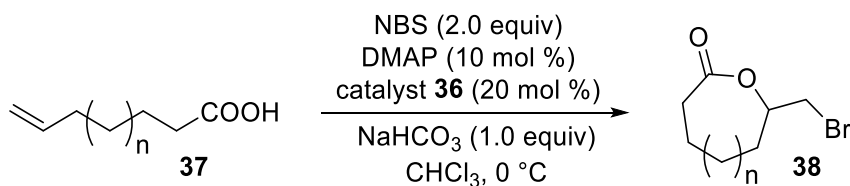
n = 0, 95%; n = 1, 64%; n = 2, 30%; n = 3, 55%; n = 4, 40%, n = 5, 65%

Accordingly, when NIS was used in the presence of Lewis base triphenylphosphine with the aim to stabilize the intermediate iodiranium ion, unsaturated silyl esters 39 gave in moderate yield iodolactones 40, the cyclization proceeding in a 5-exo mode driven by electronic factors [58].

$R^1 = C_6H_5$, 54%; $R^1 = CH_3$, 71%; $R^1 = $ cyclohexyl, 59%
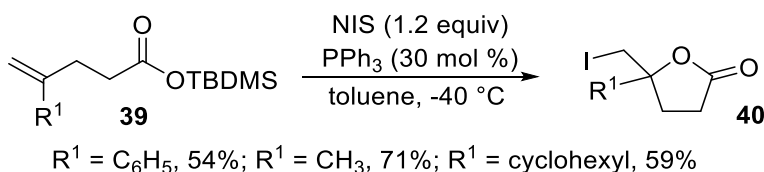
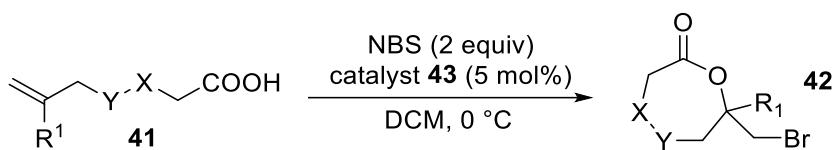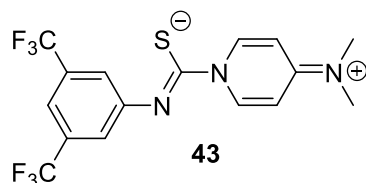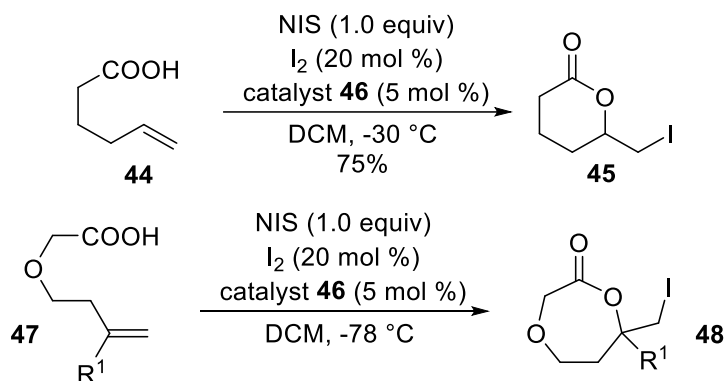Again, electronic factors directed the formation in moderate to good yield of medium-size ring bromolactones 42 starting from alkenoic acids 41, and the intermediate bromiranium ion was stabilized by the Lewis base 43 [59].

NBS (2 equiv)
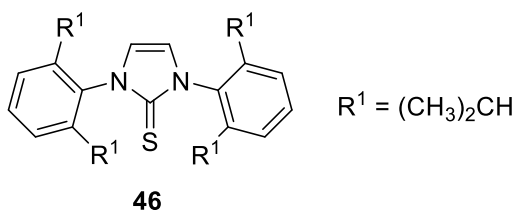catalyst **43** (5 mol%)
DCM, 0 °C

41 **42**

X = O, Y = CH$_2$, R^1 =H, 71%; X = CH$_2$, Y = O, R^1 = H, 67%; X = CH$_2$, Y = O, R^1 = CH$_3$, 85%

43

Finally, when catalytic iodine coupled with the Lewis base 46 allowed both activation of NIS and stabilization of the intermediate iodiranium ion, iodolactones 45 and 48 were prepared in high yield and total regioselection from unsaturated acids 44 and 47 according to 6-exo or 7-exo cyclization mode, respectively [60].

NIS (1.0 equiv)
I$_2$ (20 mol %)
catalyst **46** (5 mol %)
DCM, -30 °C
75%

44 **45**

NIS (1.0 equiv)
I$_2$ (20 mol %)
catalyst **46** (5 mol %)
DCM, -78 °C

47 **48**

R^1 = CH$_3$, 79%; R^1 = CH$_2$CH$_2$C$_6$H$_5$, 78%; R^1 = CH$_2$CH$_2$-2-naphthyl, 94%

R^1 = (CH$_3$)$_2$CH

46

It is worth mentioning that when cyclopropanes were present in the chain of carboxylic acids 49 in place of double bonds, lactones 50 were prepared in moderate to good yield by homohalolactonization, and 1,3-dibromo-5,5-dimethylhydantoin (1,3-DBDMH) was found to be the best haliranium source [61]. The yields further increased when the Lewis basic sulfide 53 was added, and the reaction was carried out in the dark in order to avoid a radical side mechanism triggered by light [62].

1,3-DBDMH (1.2 equiv)
DCM, rt

49 **50**
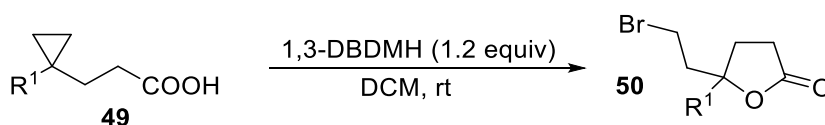
R^1 = C$_6$H$_5$, 88%; R^1 = 4-t-C$_4$H$_9$-C$_6$H$_4$, 68%; R^1 = 4-CH$_3$-C$_6$H$_4$, 64%
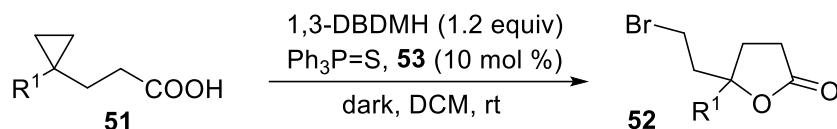
R¹ = C₆H₅, 89%; R¹ = cyclohexyl, 93%; R¹ = 2-naphthyl, 91%

In the event, by reaction with NIS, the carboxylic acid 54 containing a cyclopropane ring yielded an equimolar diastereomeric mixture of lactones 55 with total regioselection, whereas the triple bond remained completely unaffected under the reaction conditions [63].

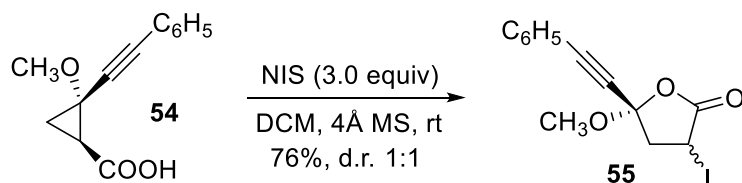2.1.1.2. With internal asymmetric induction

Studies on the stereochemistry of the reaction evidenced that addition proceeds stereospecifically, and the back-side nucleophilic opening of the haliranium ion leads to the observed anti-addition [64-66]. With the aim to generate stereoisomers with high regio- and stereoselection, a lot of bromo- and iodolactones were prepared as synthetic intermediates exploiting either the configuration of the double bond and the asymmetric induction by preexisting chirality centers in the starting structure [67-69]. Generally, these reactions display poor novelty, and the cyclization step's interest relies on the biological activity of the obtained haloderivatives and the final synthetic target. Lewis bases were found to be effective for stabilization of cationic species as haliranium ions [70] and when a catalytic amount of the Lewis base benzyl *trans*-cyclooctene **58** was added to *N*-bromoacetamide as halogen donor, the rate of bromocyclization of acids (*E*)-**56** strongly increased, leading with total regio-selection to δ-lactones **57**, exclusively, via a 6-*endo*-trig closure. On the contrary, under the same conditions, the acid (*Z*)-**59** provided a regioisomeric mixture of lactones **60** and **61**, although the addition of triethylamine in place of catalyst **55** led to the five-membered regioisomer **61**, exclusively via a 5-*exo*-trig closure [71].
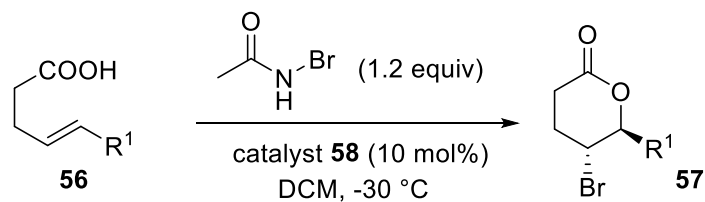
R¹ = 4-Br-C₆H₄, 87%; R¹ = 4-F-C₆H₄, 90%: R¹ = 2-naphthyl, 91%
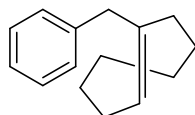

58
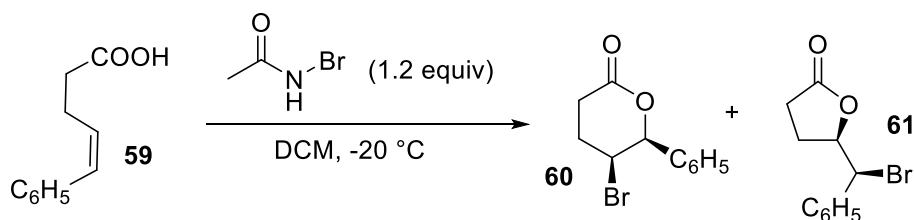
a. with catalyst **58** (10 mol %), 97%, 26:71
b. with Et₃N, 99%, >1:99

In addition, when the iodocyclization of (*E*)-alkenoic acid **62** mediated by NIS was carried out in the presence of Lewis bases **53, 65,** or **66,** the iodolactones **63** and **64** were isolated in very good yield with high regio- and total stereo selection, the regiochemistry being directed by electronic factors [70].
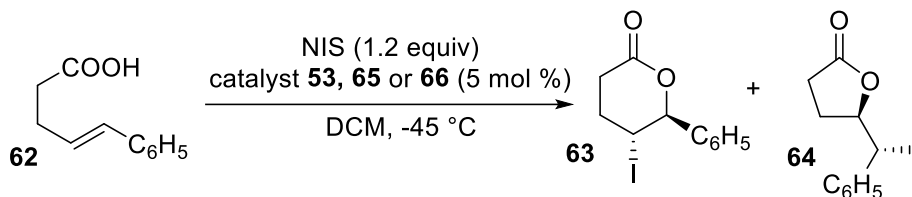
(C$_6$H$_5$)$_3$P=S, **53**, 92%, 85:15; (CH$_2$)$_4$S, **65**, 97%, 86:14; (C$_6$H$_5$)$_2$Se, **66**, 82%, 91:9

The cyclization of (*Z*)-alkenoic acids **67** mediated by NBS proceeded with total regio- and stereo-selection to give in moderate yield the corresponding bromolactones **68** in the presence of the Lewis base thiourea **69** [72].
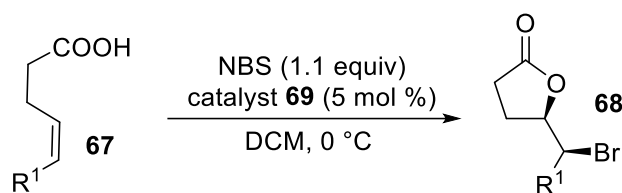
R^1 = C$_6$H$_5$, 63%; R^1 = 2-Br-C$_6$H$_4$, 58%; R^1 = 2-pyridyl, 68%;
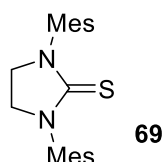
Moreover, when the Lewis base **73** was added to the reaction mixture in order to increase the rate of cyclization mediated by NBS, both the configuration and the substitution pattern of the double bond of the alkenoic acid strongly affected the regioselection of the ring closure. In fact, owing to the phenyl group effect, the (*E*)-alkenoic acid **70a** gave preferentially the lactone **71a** via 6-*endo* ring closure. Still, changing the phenyl with a methyl group, as in **70b**, the five-membered lactone **72b** was the major product owing to a diminished electronic effect. On the other hand, the (*Z*)-alkenoic acid **59** provided the five-membered ring lactone **61** as a major product since electronic factors were overwhelmed by steric factors [56].
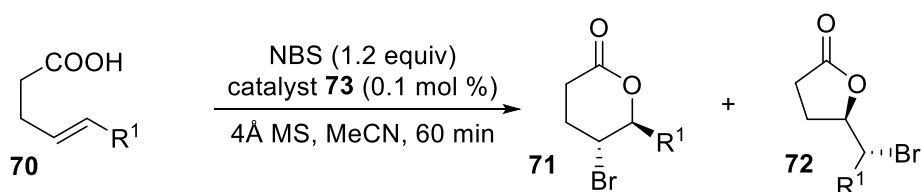
a. R^1 = C$_6$H$_5$, -30 °C, 94%, 95:5 d.r.
b. R^1 = CH$_3$, rt, 92%, 11:89 d.r.

73
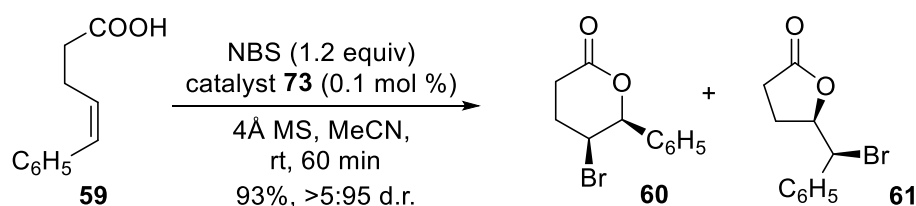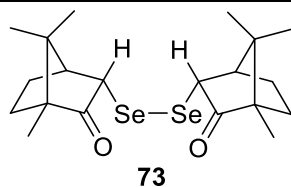
Also, the selenium derivative **76** allowed a strong increase in the reaction rate of the bromocyclization of alkenoic acids **74** mediated by bromine, to provide diastereomeric mixtures of lactones **75** in good yield but with poor stereoselection, whereas alkenoic acids **77** gave the corresponding lactones **78** in good yield with moderate to excellent stereoselection [73].
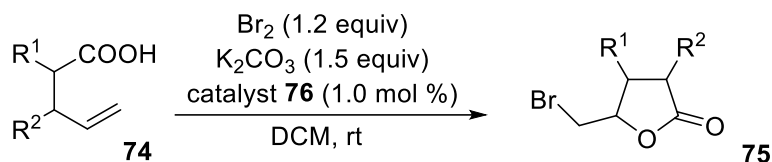
R^1 = H, R^2 = CH_3, 92%, 70:30 d.r.; R^1 = CH_3, R^2 = H, 88%, 68:32 d.r.
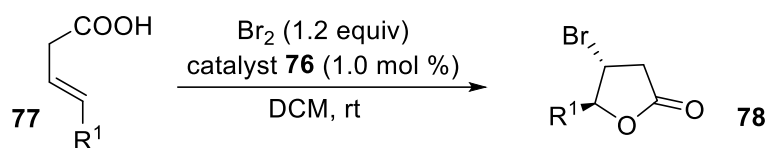
R^1 = CH_3, 72%, 85:15 d.r.; R^1 = C_6H_5, 95%, single diastereomer

76
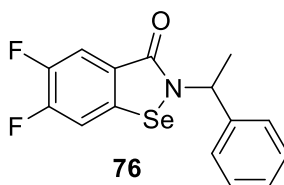
When hexafluoroisopropanol (HFIP) was added to the reaction mixture in order to activate NBS, (*E*)-alkenoic acids **79** afforded in good yield bromolactones **80** at increased reaction rates with total regio- and stereoselection, *via 5-endo* or *6-endo*-trig mode depending on the chain length, and DFT investigation of the reaction mechanism was carried out [74].

NBS (1.2 equiv)
A: DCM:HFIP 5:1, -40 °C
B: toluene:HFIP 5:1, 0 °C
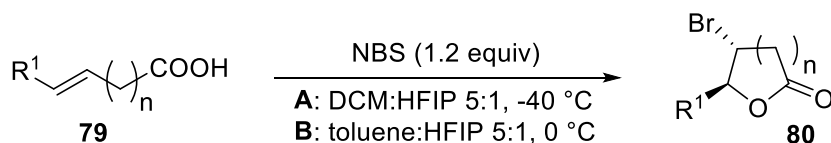
n = 1, R^1 = C_6H_5, **A**, 86%; n = 1, R^1 = n-C_4H_9, **B**, 71%; n = 2, R^1 = C_6H_5, **A**, 86%

A methyl group in the α position with respect to the double bond exerted a moderate 1,2-asymmetric induction when the unsaturated acids **81** were cyclized with NBS to give regioselectively bromolactones **82** and **83**, in the presence of a catalytic amount of acetic acid [75].

NBS (2.0 equiv)
CH_3COOH (2 mol%)
THF, rt
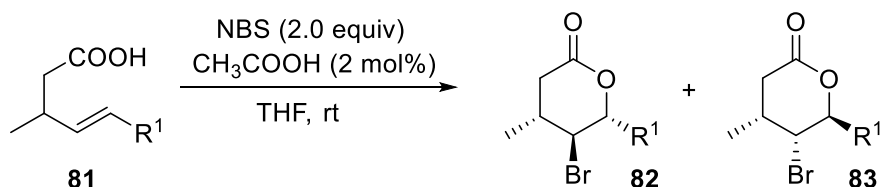
R^1 = C_6H_5, X = Br, 72%, 78:22: R^1 = 4-F-C_6H_4, 78%, 76:24 d.r.

However, starting from the acyclic alkenoic acid **84** bearing an aryl group in the α-position with respect to the double bond, mixtures of halolactones **85**-**87** were obtained in moderate yield and low regio- and stereoselection, depending on the halenium ion source [76].
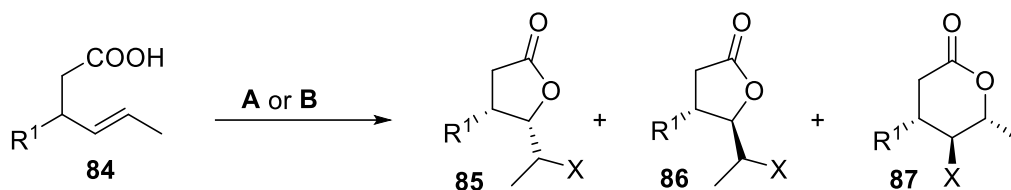
A: I_2, KI, $NaHCO_3$: X = I, R^1 = C_6H_5, 43:33:24; R^1 = n-C_3H_7-C_6H_4, 57:29:14
B: NBS, THF, AcOH: X = Br, R^1 = C_6H_5, 24:17:59; R^1 = n-C_3H_7-C_6H_4, 25:24:51

On the other hand, the enantiomerically enriched acid **88** afforded the corresponding iodolactones **89** and **90** with excellent regio- and stereoselection, leading preferentially to a 5-membered ring, and the regioisomeric ratio strongly relied upon the cyclization method [77].
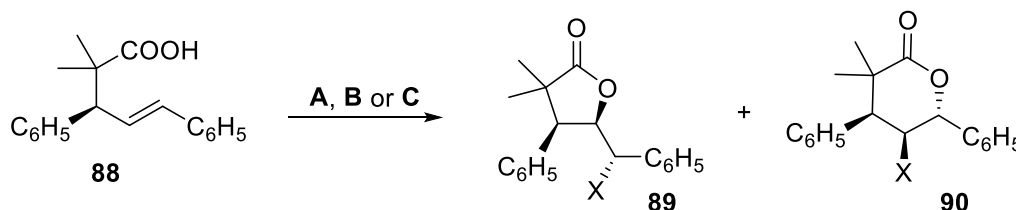
A: I_2, KI, $NaHCO_3$, MeCN, rt, X = I, 76%, 99:1
B: NBS (1.5 equiv), $NaHCO_3$, DCM, rt, X = Br, 74%, 90:10
C: Br_2, MeCN, X = Br, 71%, 50:50

In addition, starting from acid **91**, bearing a methyl group α to the double bond, under different conditions, the six-membered ring lactones **92** and **93** were exclusively isolated in moderate to low yield and with low to moderate stereoselection [78].
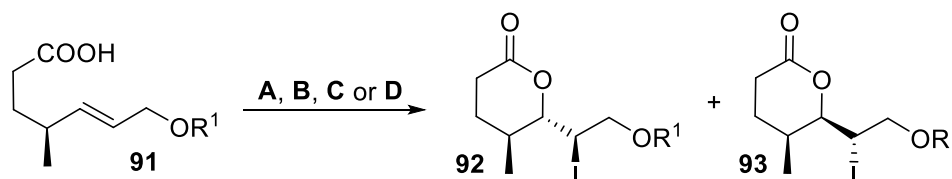
A: I_2 (3 equiv), MeCN, 0 °C, R^1 = Bn, 44%, 75:25 d.r.
B: I_2 (3 equiv), $NaHCO_3$, MeCN, 0 °C, R^1 = Bn, 23%, 29:71 d.r.
C: I_2 (1.2 equiv), MeCN, 0 °C, R^1 = 4-Br-Bn, 22%, 87:13 d.r.
D: IBr (1.2 equiv), MeCN, 0 °C, R^1 = 4-Br-Bn, 74%, 86:14 d.r.

Within the preparation of a bicyclic peptidomimetic, the cyclization of the chiral diacid **94** proceeded with total regio- and stereoselection to give the lactone **95,** and the formation of a five-membered ring was preferred with respect to the six-membered one [79].
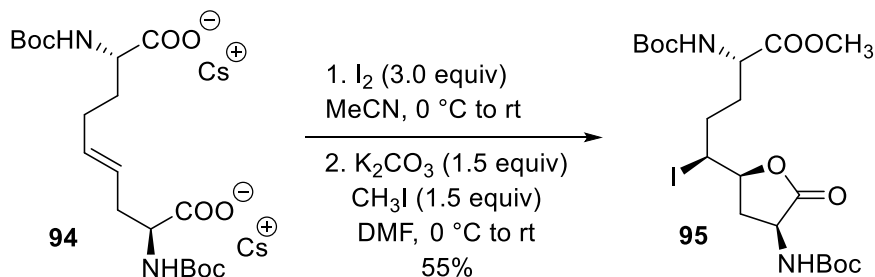
On the contrary, the reaction of diester **96**, carried out with iodine in a basic medium, provided a diastereomeric mixture of the *N*-Boc pyrrolidines **97** together with a diastereomeric mixture of lactams **98** [79].
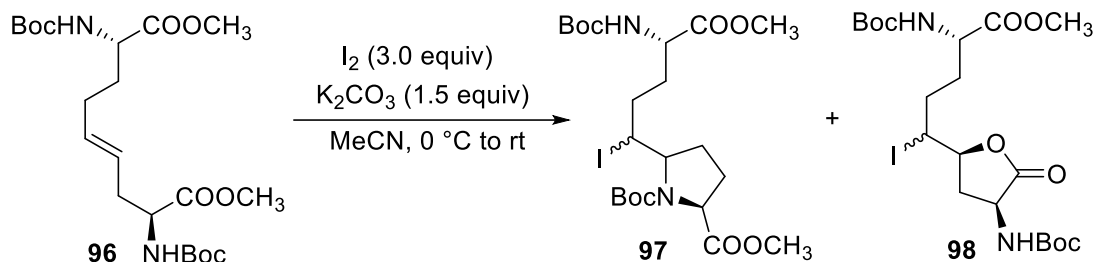
The cyclization of carboxylate **99**, carried out with iodine, afforded the iodomethyl lactone **100** with yields referred to as good, although the values were not reported, and the stereoselection changed on changing the reaction solvent [80].

a. THF: 80:20 d.r.; **b**. MeCN: 94:6 d.r.;
c. MeCN:H_2O 8:1: 96:4 d.r.
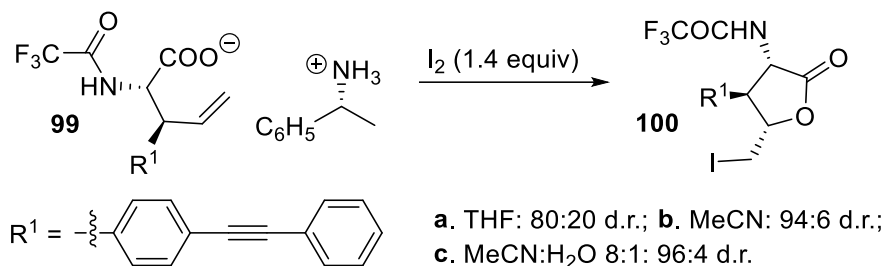
Starting from the enantiomerically pure unsaturated acid **101**, the spirolactone **102** was obtained in very good yield, and the configuration of the chirality center remained unaffected [81].
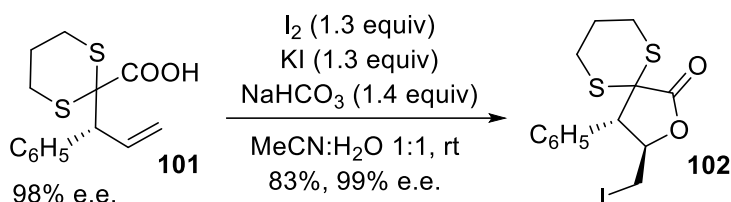
Furthermore, when the cyclization of (*E*)-alkenoic acids **103** was carried out in the presence of TFA, the six-membered bromolactones **104** were isolated with nearly total regio- and stereoselection with respect to five-membered derivatives **105** [82].

R^1 = 4-F-C_6H_4, 98%, >99:1; R^1 = H, 99%, >99:1; R^1 = 4-CH_3-C_6H_4, 98%, >99:1
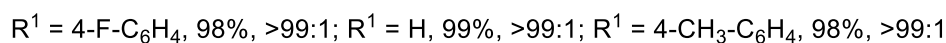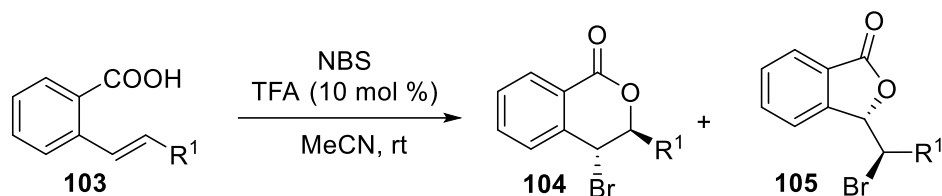
With the aim to easily prepare iodolactones from the unsaturated acids **106** and **108**, where an (*E*)-double bond was conjugated with an electron-withdrawing ester group, the carboxy group was first converted into a carboxylate anion. Then, the corresponding seven-membered lactones **107** and **109** were obtained in high yield with high regioselection via a 7-*exo*-closure, the eight-membered lactones arising from an 8-*endo*-mode closure being largely minor components of the reaction product [83].

R^1 = CH_3CH_2, R^2 = R^3 = H, 81%, >95:5 *exo:endo*;
R^1 = CH_3, R^2 = 2-CH_3, R^3 = 3-CH_3, 75%, >95:5 *exo:endo*;
R^1 = CH_3, R^2 = 4-F, R^3 = 3-CH_3, 82%, >95:5 *exo:endo*
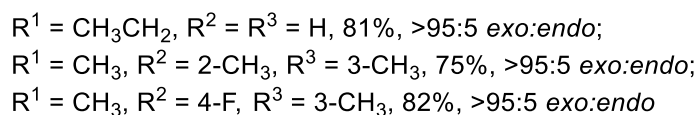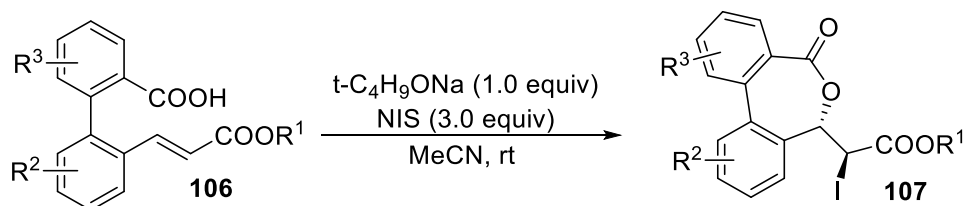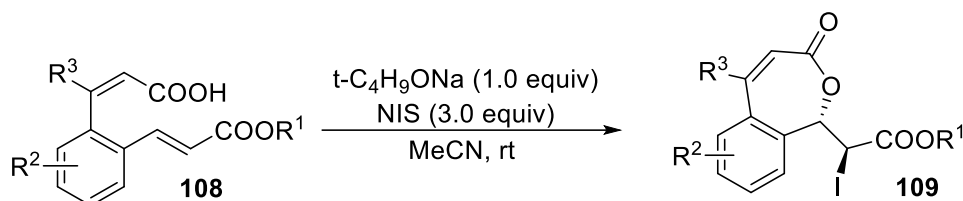
R^1 = CH$_3$, R^2 = H, R^3 = C$_6$H$_5$, 78%, >95:5 *exo:endo*;
R^1 = t-C$_4$H$_9$, R^2 = H, R^3 = C$_6$H$_5$, 93%, >95:5 *exo:endo*;
R^1 = CH$_3$, R^2 = 3-Cl, R^3 = 4-Cl-C$_6$H$_4$, 96%, >95:5 *exo:endo*

Exploiting internal asymmetric induction, the racemic cyclic alkenoic acid **110** gave the corresponding bicyclic lactone **111** with nearly total stereoselection [84-87].
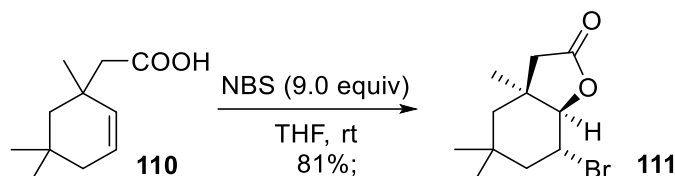
Accordingly, enantiomerically pure starting acid **112** gave lactones **113a** and **113b** in good yield with very high stereoselection, again exploiting double 1,2-asymmetric induction [88].
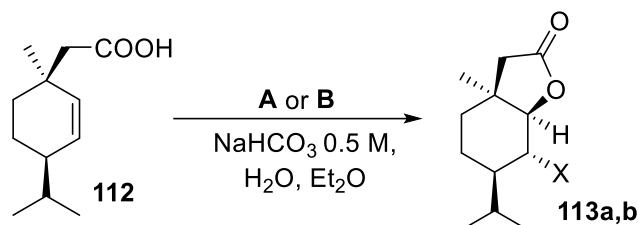
A: Br$_2$ (2.0 equiv), 0 °C to rt; **a.** X = Br, 83%, 97% e.e.;
B: I$_2$ (2.0 equiv), KI (6.0 equiv), 40 °C; **b.** X = I, 92%, 97% e.e.

Furthermore, within the total synthesis of Sorangicin A, the cyclization of acid **114**, where the carboxy group was tethered on a six-membered ring with a double bond in the 3 position, proceeded with 1,3-asymmetric induction to give the corresponding iodolactone **115** in good yield and total *anti*-stereoselection, irrespective of the configuration of the carbon atom bearing the allyl group [89-91].
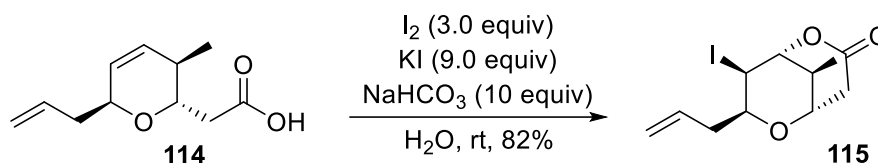
In analogy, the structure of the acid **116** directed the formation of the halolactones **117a,b** with total regio- and stereoselection [92].
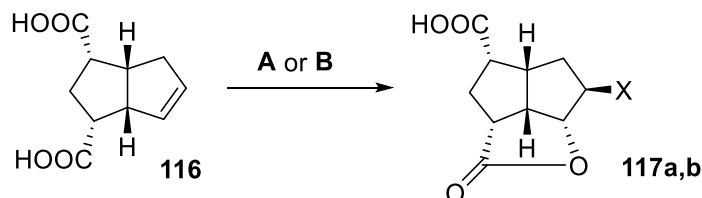
A: I$_2$ (2 equiv), NaHCO$_3$ (6 equiv), DCM, rt; **a.** X = I, 89%
B: NBS (1.5 equiv), acetone:water 10:1, rt; **b.** X = Br, 75%

Furthermore, the cyclization of acid **118** proceeded with 1,4-asymmetric induction, leading to the seven-membered lactone **119** [93].

$R^1 = CH_2CH(CH_3)_2$, R^2 = 2-naphthyl, R^3 = 4-$(CH_3)_2CH$-C_6H_4
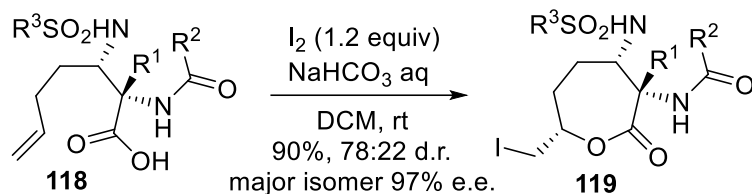
Accordingly, the cyclization of the racemic unsaturated acids **120** proceeded with total regio- and stereoselection, to give the macrolactones **121** in low to moderate yield [94].

R^1 = H, R^2 = CH_3, R^3 = Ts, 22%; R^1 = CH_3, R^2 = H, R^3 = Ns, 66%;
R^1 = H, R^2 = CH_3, R^3 = Ns, 56%
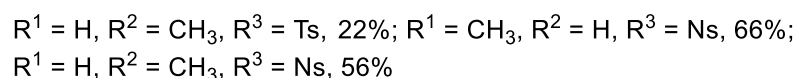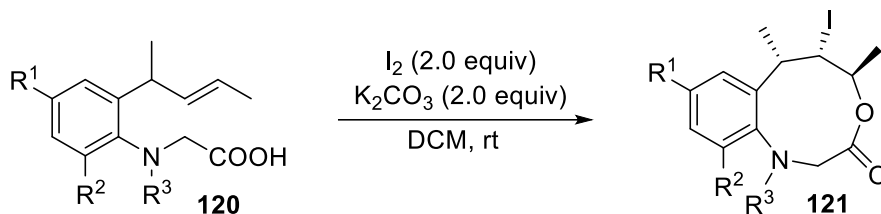
Eventually, when diesters **122** were treated with NBS, the reaction proceeded in good yield and high stereoselection leading to bromolactones **123** and **124**, the 1,3-*syn*-isomer **123** being largely the major component of the reaction mixture [95-96].

R^1 = 4-CH_3O-C_6H_4, 72%, 10:1 d.r.; R^1 = 4-Cl-C_6H_4, 81%, >20:1 d.r.;
R^1 = 4-CF_3-C_6H_4, 84%, >20:1 d.r.; R^1 = 3-CH_3O-C_6H_4, 85%, 10:1 d.r.
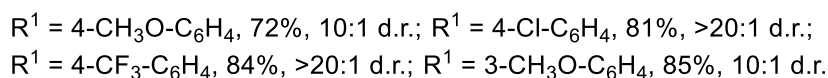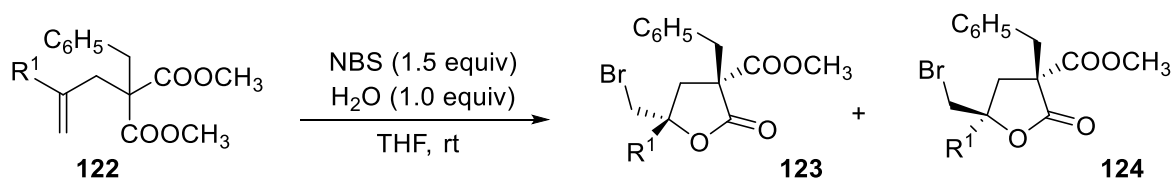
On the contrary, stereoselection was low and relied on the Lewis base added when the cyclization of cyclopropyl diesters **125** exploited NBS as bromenium source. In fact, in the presence of triphenylphosphine sulfide **53,** the major products were the 1,3-*anti*-isomers **126**, whereas the *syn*-ones **127** were prevalent when diphenyl selenide **66** was added to the reaction mixture [97].

catalyst = Ph_3P=S, **53**: R^1 = C_6H_5, 92%, 69:31 d.r.; R^1 = 4-CH_3-C_6H_4, 93%, 70:30 d.r.;
R^1 = 4-Cl-C_6H_4, 86%, 66:33 d.r.
catalyst = Ph_2Se, **66**: R^1 = C_6H_5, 92%, 28:72 d.r.; R^1 = 4-CH_3-C_6H_4, 88%, 32:68 d.r.;
R^1 = 4-Cl-C_6H_4, 59%, 36:64 d.r.
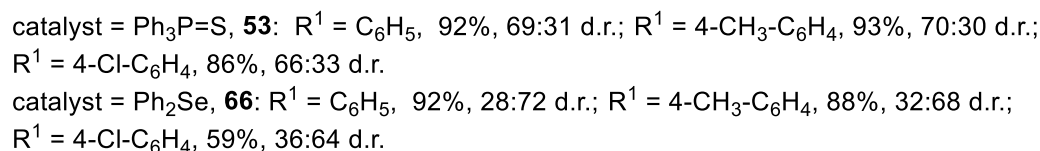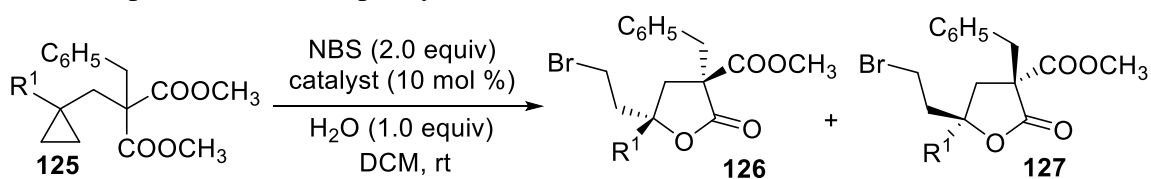
Moreover, when the oxidation of bromide ion was performed by using Oxone® [98-99] starting from the acids **128**, the corresponding diastereomeric γ-bromolactones **129** and **130** were prepared in excellent yield but with low 1,3-*cis*-stereoselection, and the process did not produce any organic wastes harmful for the environment [100-101].

128 → KBr (1.5 equiv), Oxone® (1.2 equiv), AcOEt, -10 °C → **129** + **130**
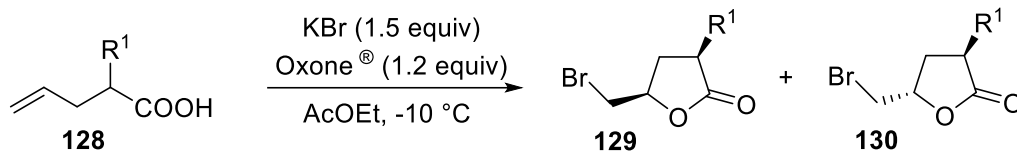
R^1 = (CH$_3$)$_2$CH, 98%, 81:19 *cis:trans*; R^1 = n-C$_8$H$_{17}$, 99%, 77:23 *cis:trans*;
R^1 = C$_6$H$_5$, 92%, 77:23 *cis:trans*; R^1 = 4-CH$_3$-C$_6$H$_4$, 92%, 77:23 *cis:trans*

According to the same procedure, the acid **131** afforded the corresponding bromoderivative **132** in good yield and nearly total stereoselection [101].

131 → KBr (1.5 equiv), Oxone® (1.2 equiv), AcOEt, rt → **132**
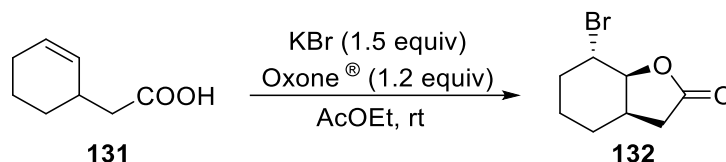
The cyclization of δ-pentenoic acids **133**, carried out with NBS, was efficiently catalyzed by 2-azaadamantane *N*-oxyl (AZADO) **135** to give six-membered lactones **134** in good yield and moderate to good 1,4-asymmetric induction. The catalytic effect was ascribed to a starting redox reaction where the catalyst **135** was converted into an oxoammonium ion able to increase the electrophilicity of the bromine atom of NBS [102].

133 → NBS (1.2 equiv), catalyst **135** (5 mol%), DCM, rt → **134**
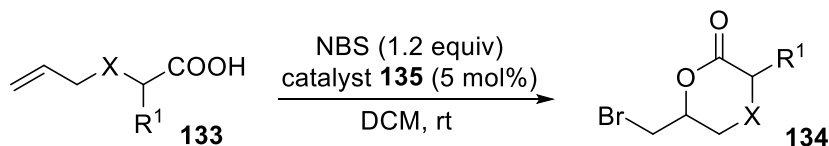
R^1 = CH$_3$, X = CH$_2$, 91%, 67:33 d.r.; R^1 = CH$_3$, X = NTs, >99%, 80:20 d.r.;
R^1 = C$_6$H$_5$, X = O, 68%, 65:35 d.r.; R^1 = CH$_2$C$_6$H$_5$, X = NTs, 99%, 91:9 d.r.

135
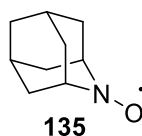
The bromolactonization of carboxylic acids **136** and **138**, displaying respectively an (*E*)- or (*Z*)-enyne functionality, was carried out with NBS, and the corresponding allenyl bromoderivatives **137** and **139** were isolated in good yield and with high stereoselection, the configuration of the allene relieing on the configuration of the starting double bond [103].

136 → NBS (1.2 equiv), DABCO (2 mol %), CHCl$_3$, rt → **137**
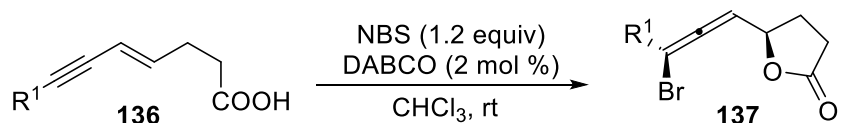
R^1 = n-C$_6$H$_{11}$, 90%, >20:1 d.r.; R^1 = t-C$_4$H$_9$, 83%, 10:1 d.r.

138 → NBS (1.2 equiv), DABCO (2 mol %), CHCl$_3$, rt → **139**
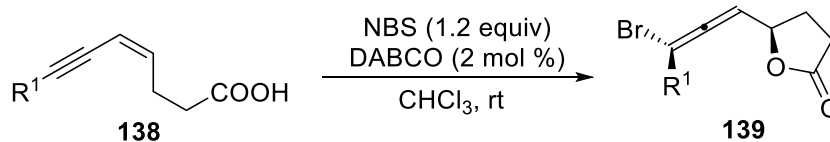
R^1 = n-C$_6$H$_{11}$, 87%, >20:1 d.r.; R^1 = C$_6$H$_5$(CH$_2$)$_3$, 80%, >20:1 d.r.

Eventually, iodolactonization was carried out starting from an atropoisomeric mixture of acids *syn*-**140** and *anti*-**141** afforded in low yield the eight-membered lactones **142** and **143**, respectively [104].

140   **141**

I₂, K₂CO₃
DCM, rt
27%

I₂, K₂CO₃
DCM, rt
32%

142   **143**
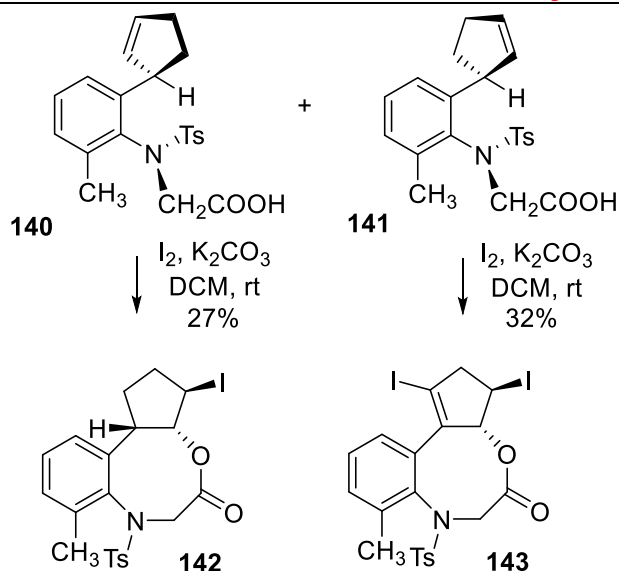
2.1.1.3. With external asymmetric induction.

A lot of syntheses of useful building blocks and biologically active molecules exploited halolactonization, and over the past decades a number of methods were used to construct enantiopure lactones. Despite the successful entries in some reports, many other cases returned with low enantioselectivities and the use of a prochiral alkenoic acid and an achiral halenium source coupled with a substoichiometric amount of chiral catalyst in the asymmetric halolactonization remains a challenge. However, beginning from 2010, intense research efforts led to the development of enantioselective halocyclization reactions exploiting organocatalysts [105].

(DHQD)₂PHAL, **144**

(DHQ)₂PHAL, **145**

(DHQD)₂Pyr, **146**
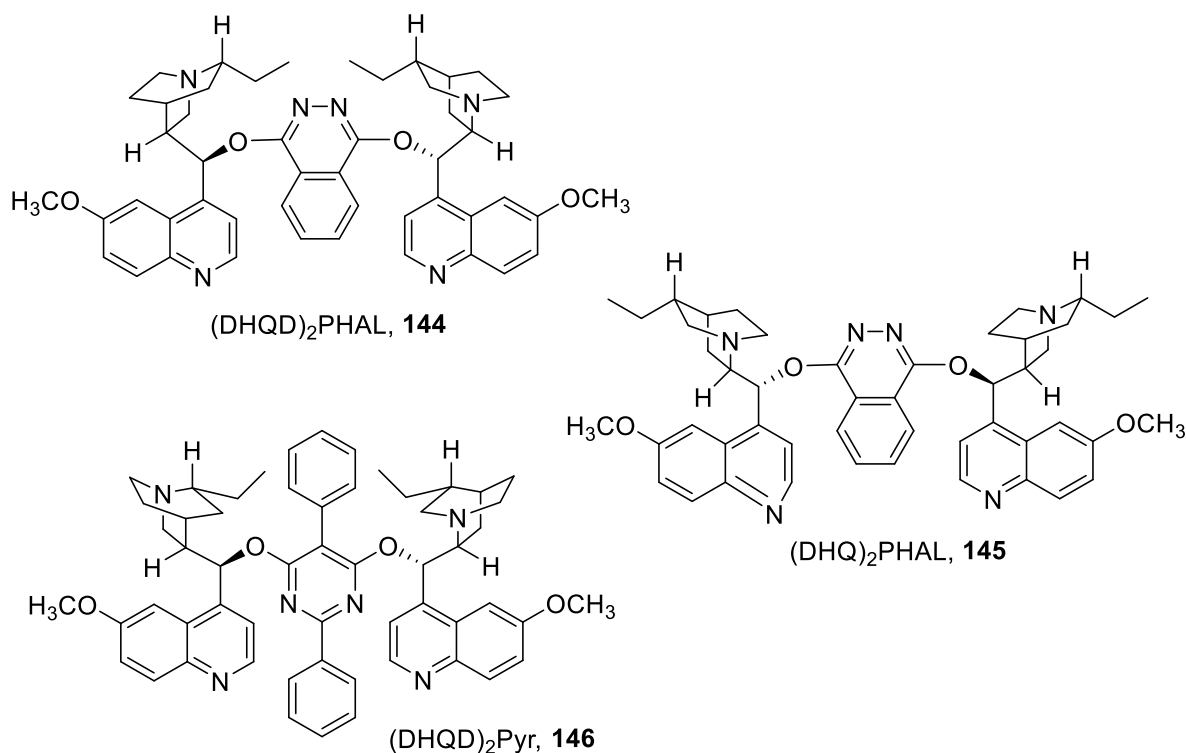
At first, Cinchona alkaloid derivatives did not lead to the discovery of asymmetric halocyclization reactions that take place with sufficiently high levels of enantioselection, but eventually, these alkaloids served as privileged catalysts for a number of processes. Highly effective reactions promoted by bis-Cinchona alkaloids, such as (DHQD)2PHAL, 144, (DHQ)2PHAL, 145, and (DHQD)2PYR, 146, in contrast to those induced by their monomeric counterparts, were reported

in many investigations [106]. Thus, the development of the enantioselective catalytic halolactonization is near to the progress of the corresponding non-enantioselective version since suitable catalytic systems that allow the effective transfer of the chiral information were identified, although the enantiomerically enriched haliranium-olefin intermediate could undergo racemization through a rapid olefin-olefin halogen exchange [28, 39, 69, 107-123].

2.1.1.3.1. Exploiting *Cinchona* alkaloids-derived catalysts.

By using the difunctional catalyst **149**, carboxylic acids **147** and **150**, bearing a (*Z*)-1,3-enyne functionality, were converted in good yield by NBS into the corresponding chiral allene derivatives **148** and **151**, respectively, and the 1,4-*syn*-bromolactonization proceeded with high enantioselection. A model for this enantioselective process was proposed, involving both activation of NBS by hydrogen bond with the urea functionality of the catalyst and deprotonation of the carboxylic acid by the quinuclidine nitrogen [124-126].

X = O, R^1 = H, 71%, 90% e.e.; X = O, R^1 = TES, 87%, 88% e.e.;
X = NTs, R^1 = H, 62%, 93% e.e.

R^1 = H, R^2 = Cl, 72%, 98% e.e.; R^1 = H, R^2 = CF$_3$, 74%, 99% e.e.;
R^1 = NO$_2$, R^2 = H, 80%, 97% e.e.
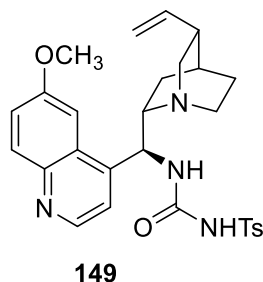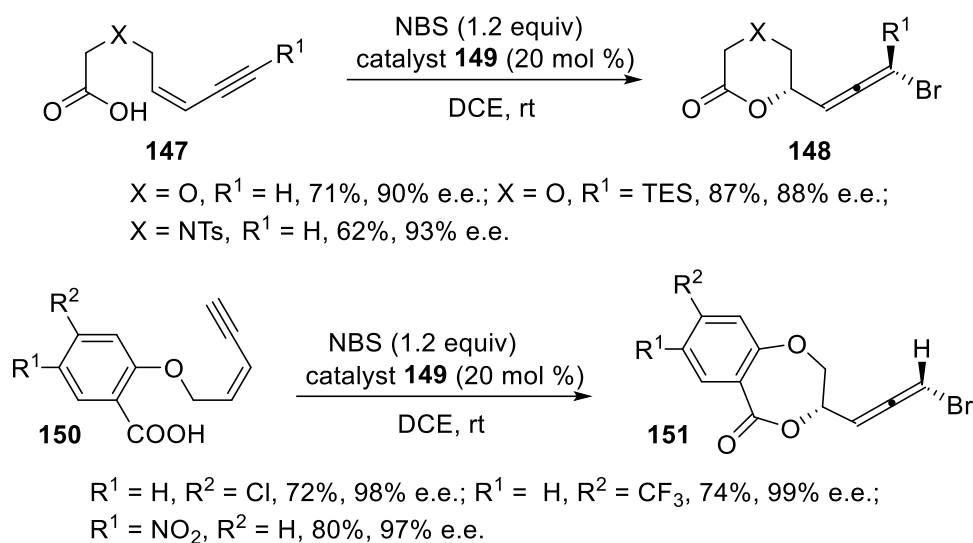
Bromolactonization of alkenoic acids **152**, carried out with NBS, proceeded in excellent yield in a stereodivergent mode using as chiral catalysts quinine-derived benzamides bearing three methoxy substituents in different regioisomeric positions, together with substituents at the quinoline moiety displaying different steric requirements. Thus, catalyst **154** allowed the prepare of the (*S*)-lactones **153** with excellent stereoselection, whereas the same reaction was carried out in the presence of catalyst **155** afforded very high stereoselection of the enantiomeric (*R*)-lactones, *ent*-**153**. Thus, the differences in steric and electronic properties of the substituents of the aromatic rings changed the reaction outcome, as evidenced by DFT calculations carried out in order to elucidate the origin of the different asymmetric behavior for both catalysts [127-128].

NBS (1.3 equiv)
catalyst **154** (5 mol %)
toluene:*m*-xylene 2:1
-60 °C

153

$R^1 = C_6H_5$, 94%, 91% e.e.;
$R^1 = $ 1-naphthyl, 99%, 91% e.e.;
$R^1 = $ cyclohexyl, 95%, 86% e.e.

NBS (1.3 equiv)
catalyst **155** (5 mol %)
toluene:*m*-xylene 2:1
-60 °C

ent-**153**

$R^1 = C_6H_5$, 99%, 98% e.e.;
$R^1 = $ 1-naphthyl, 99%, 92% e.e.;
$R^1 = $ cyclohexyl, 99%, 92% e.e.

154 $R^1 = C_6H_5$, $R^2 = CH_2$-t-C_4H_9

155 $R^1 = $ 9-anthracenyl, $R^2 = CH_3$
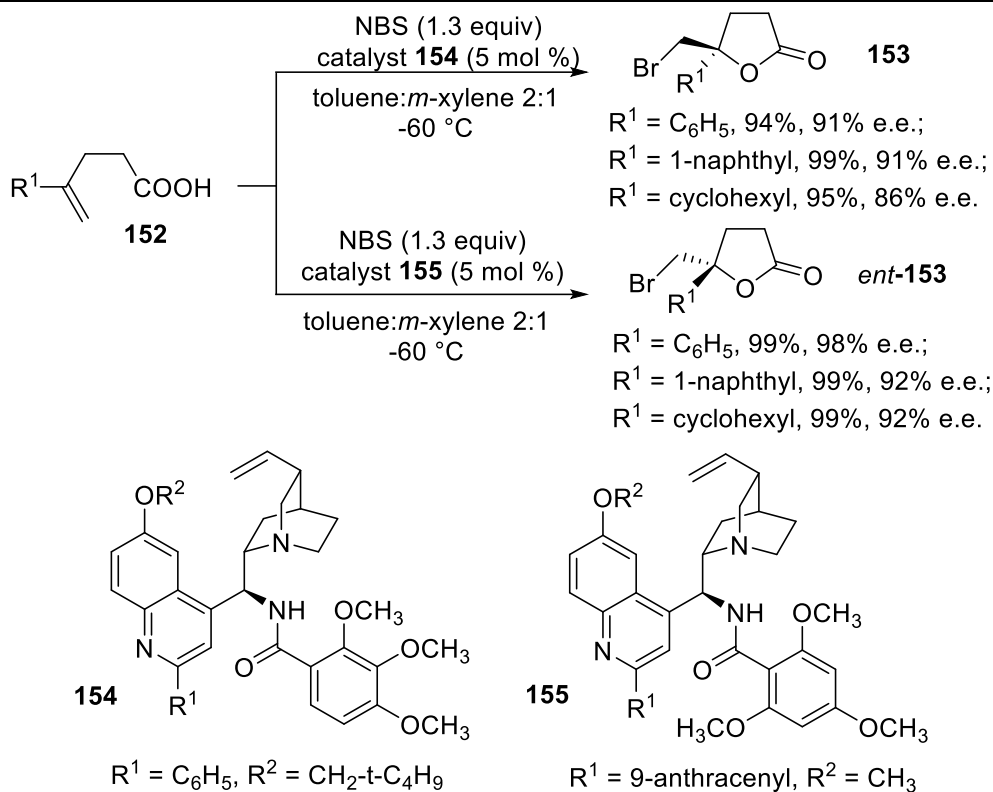
Whereas urea catalysts generally required electron-deficient substituents to enhance the hydrogen bond strength with the halogen donor [107], an electron-rich urea moiety was needed to obtain high enantioselection in bromolactonization of acids **156**, where the double bond is deactivated by conjugation with a carbonyl group. In fact, the reaction carried out in the presence of catalyst **158** afforded excellent yield and high enantioselection bromolactones **157**, whereas enantioselection was low using catalysts where the urea-aromatic substituent was not substituted by electron-releasing groups [129].

NBS (1.3 equiv)
catalyst **158** (15 mol %)
toluene, 15 °C

157

a. $R^1 = C_6H_5$, 96%, 80% e.e.; **b.** $R^1 = $ 2-naphthyl, 99%, 84% e.e.;
c. $R^1 = $ 4-CH_3-C_6H_4, 99%, 80% e.e.; **d.** $R^1 = $ 4-CH_3O-C_6H_4, 98%, 88% e.e.

158
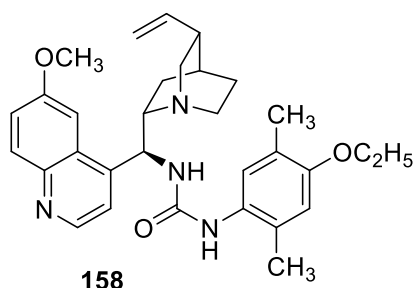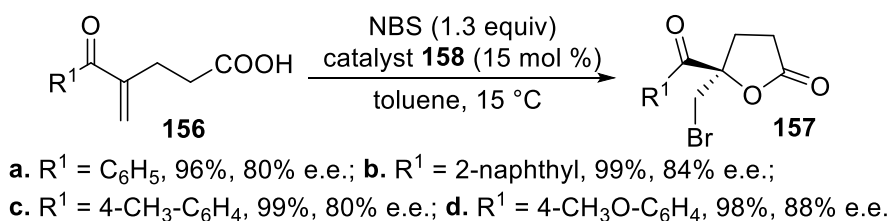
Moreover, the reaction of acid **156d**, carried out under the same conditions, but using the pseudoenantiomeric catalyst **159**, proceeded with excellent yield and high enantioselection leading to bromolactone *ent*-**157d** [129].

NBS (1.3 equiv)
catalyst **159** (15 mol %)
toluene, 15 °C

ent-**157d**

$R^1 = $ 4-CH_3O-C_6H_4, 97%, 86% e.e.

159
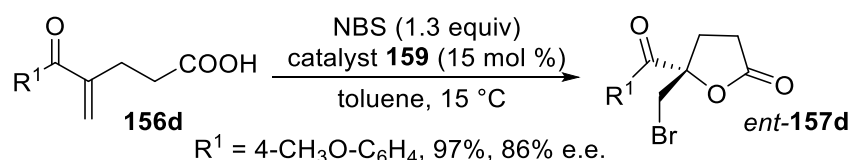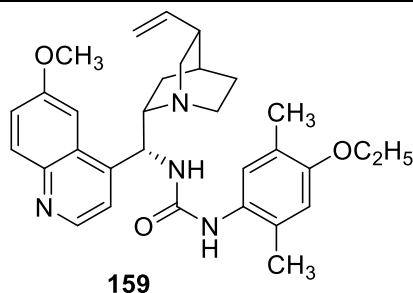
Another bromocyclization involving a double bond conjugated with a carbonyl group exploited the catalyst **162**, where an aryl group bearing electron-releasing substituents was placed on the urea functionality. Thus, the reaction of acids **160**, mediated by NBS, provided the six-membered lactones **161** with excellent yields but only moderate enantioselection [130].
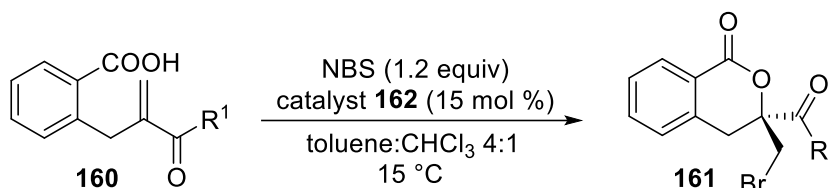
$R^1 = C_6H_5$, 98%, 70% e.e.; $R^1 = 2\text{-}CH_3\text{-}C_6H_4$, 99%, 78% e.e.; $R^1 = 4\text{-}CH_3O\text{-}C_6H_4$, 99%, 72% e.e.

162
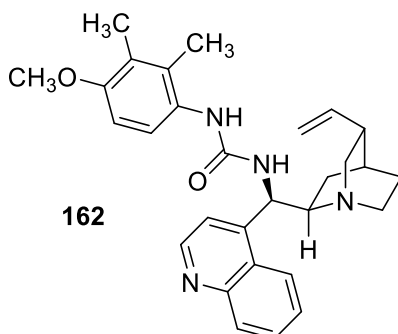
Besides ureas, chiral thiocarbamates derived from quinidine were employed in bromolactonization reactions mediated by NBS. For this purpose, a weak hydrogen bonding from NH able to coordinate the carbonyl group of succinimide, coupled with the addition of a weak acid as nosylamide, increased the bromine electrophilicity, whereas the tertiary nitrogen made the carboxy group deprotonation. Thus, exploiting the catalyst **165**, the bromocyclization of the alkenoic acids **163** provided the corresponding five-membered lactones **164** in excellent yield with very high enantioselection, and total regioselection was due to electronic factors [131].
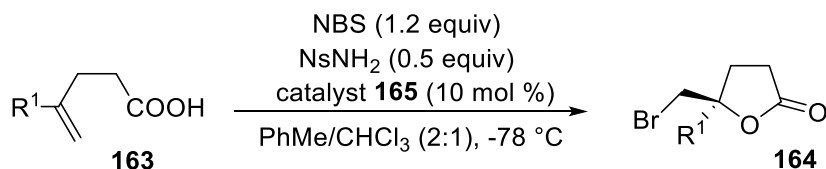
$R^1 = 2\text{-naphthyl}$, 98%, 90% e.e.; $R^1 = 4\text{-F-}C_6H_4$, 93%, 91% e.e.; $R^1 = t\text{-}C_4H_9$, 97%, 93% e.e.

165
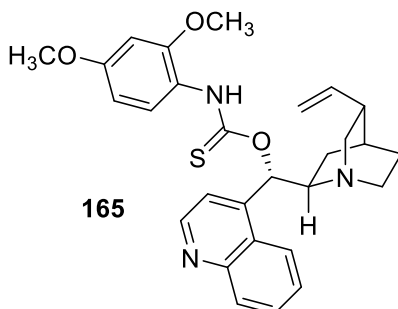
Also, the cyclization of (*E*)-alkenoic acids **166** was carried out with NBS in the presence of catalyst **165**, and six-membered lactones **167** were obtained in moderate to good yield and enantioselection but with total regioselection [132].
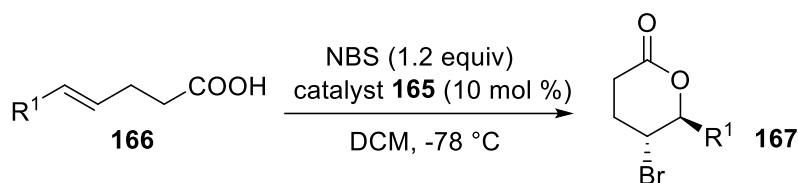
R^1 = C_6H_5, 99%, 91% e.e.; R^1 = 4-CH_3-C_6H_4, 99%, 94% e.e.; R^1 = 2-CH_3-C_6H_4, 70%, 64% e.e.

On the other hand, when the novel thiocarbamate **170** derived from quinidine was employed as the catalyst, the (*Z*)-alkenoic acids **168** provided the corresponding five-membered lactones **169** in excellent yield and enantioselection, through a cyclization proceeding in a 5-*exo*-mode mediated by NBS. The total regioselection of the process strongly relied upon the configuration of the starting double bond [133].
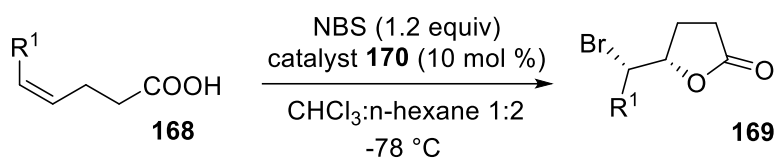
R^1 = C_6H_5, 77%, 93% e.e.; R^1 = 4-CH_3-C_6H_4, 94%, 98% e.e.; R^1 = 4-F-C_6H_4, 83%, 93% e.e.
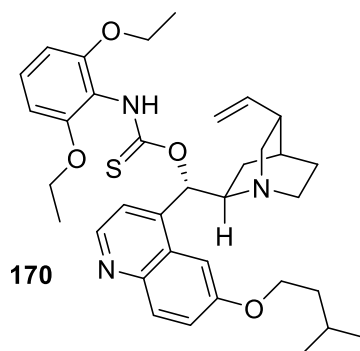
On the other hand, when the unsaturated carboxylic acids **171** having a conjugate double bond underwent cyclization mediated by NBS in the presence of thiocarbamate **174**, the cyclization reaction proceeded in good yield but affording mixtures of six-membered **172** or five-membered products **173** with low or moderate regioselection, depending on electronic factors, and only a few six-membered lactones were obtained with good enantioselection [134].
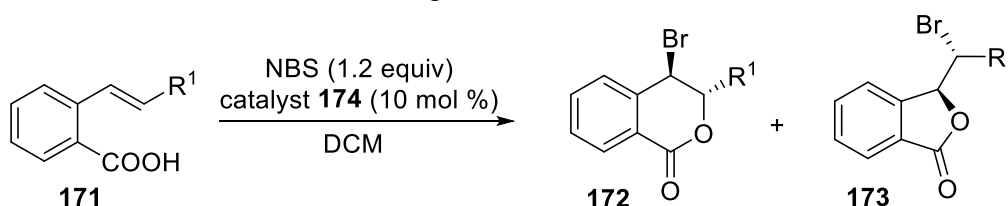
R^1 = 3-Cl-C_6H_4, -60 °C, 89% [60% (e.e. 96%), 40% (e.e. 41%)];
R^1 = C_6H_5, -78 °C, 96% [85% (e.e. 92%), 15% (e.e. 16%)];
R^1 = n-C_3H_7, -78 °C, 95% [12% (e.e. 53%), 88% (e.e. 12%)]

174
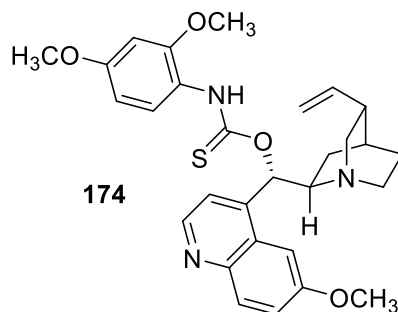
The bromolactonization of unsaturated acids **175**, carried out with NBS in the presence of benzoic acid, proceeded in a *5-exo* mode using catalyst **177**, to provide the corresponding lactones **176** in good yield and total regioselection, driven by electronic factors, whereas enantioselection was low [135].

NBS (1.5 equiv)
catalyst **177** (10 mol %)
C_6H_5COOH (20 mol %)
$CHCl_3$:toluene 1:2, -20 °C

175   **176**
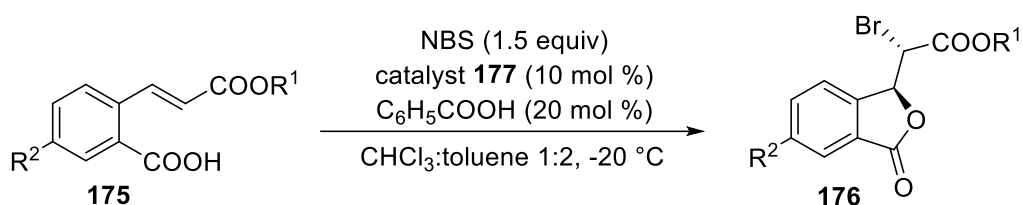
$R^1 = C_2H_5$, $R^2 = H$, 89%, 43% e.e.; $R^1 = t$-Bu, $R^2 = H$, 86%, 53% e.e.;
$R^1 = C_2H_5$, $R^2 = NO_2$, 98%, 49% e.e.

177
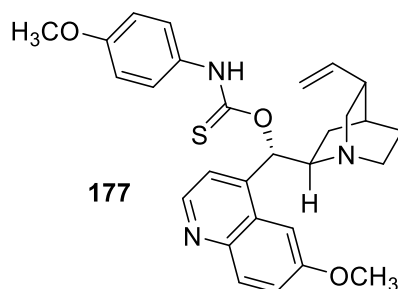
Eventually, the quinidine-derived carbamate **181**, displaying unsubstituted aromatic rings with respect to the previously reported catalysts, was employed for the bromolactonisation of alkenoic acids **178** and the reaction, mediated by NBS, proceeded with excellent yields and total regioselection trough a *5-endo*-mode cyclization driven by electronic factors. However, the enantioselection was low, so the corresponding butenolides **180**, arising from the elimination of bromine from lactones **179**, were obtained with low stereoselection [136].

NBS (1.2 equiv)
catalyst **181** (10 mol %)
$CHCl_3$:hexane 1:1, -78 °C

178   **179**   **180**
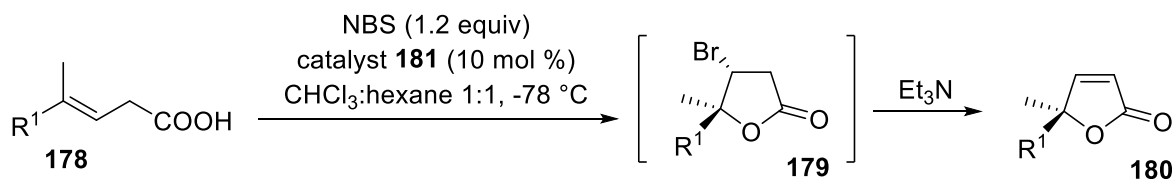
$R^1 = C_6H_5$, 98%, 52% e.e.; $R^1 = $ 2-naphthyl, 99%, 58% e.e;
$R^1 = $ 4-Br-C_6H_4, 98%, 56% e.e.

181
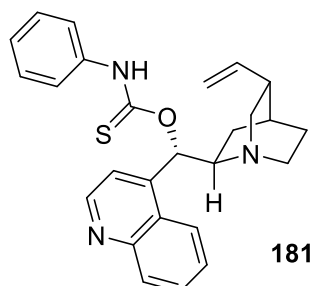
Besides the monomeric quinine and quinidine derivatives above reported, pseudoenantiomeric bis alkaloid compounds (DHQD)₂PHAL **144** and (DHQ)₂PHAL **145**, [137-140], containing the dimeric structure of dihydroquinidine and dihydroquinine, respectively, were effective catalysts to promote the halolactonisation in a highly enantioselective manner providing good asymmetric induction. Thus, desymmetrization of cyclohexadienes **182** by bromolactonization was carried out in excellent to moderate yield, but always with very high enantioselection, using NBS and (DHQD)₂PHAL **144** as the catalyst, leading to four-membered bromolactones **183** and the yield seemed to depend on the bulkiness of the substituent near to the double bond. When the pseudo enantiomeric catalyst (DHQ)₂PHAL **145** was used under the same reaction conditions, the corresponding enantiomers *ent*-**183** were isolated with a similar enantiomeric excess. Good yields and high enantioselection were also observed when five-membered bromolactones **185** were synthesized starting from acids **184** [141].
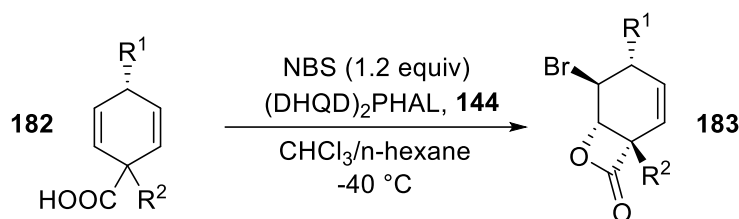
R^1 = H, R^2 = CH$_2$OTIPS, catalyst **144**, 3 mol %, 99%, 90% e.e.
R^1 = CH$_3$, R^2 = CH$_2$OTBDPS, catalyst **144**, 3 mol %, 89%, 81% e.e.
R^1 = OMOM, R^2 = CH$_2$OTBDPS, catalyst **144**, 20 mol %, 46%, 87% e.e.
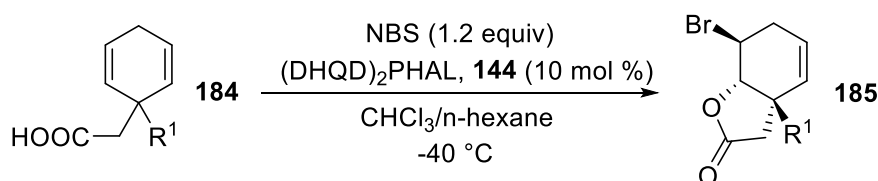
R^1 = COOt-Bu, 70%, 92% e.e. R^1 = CH$_2$OTBDPS, 90%, 92% e.e.

The desymmetrization of alkenoic acid **186** by bromolactonization was carried out in moderate yield, but with good enantioselection, by using NBS and catalyst (DHQD)₂Pyr **146**, to give bromolactone **187** and ester **188** after treatment of the reaction mixture with CH₂N₂ [141].

55%, 78% e.e.

39%, 92% e.e.
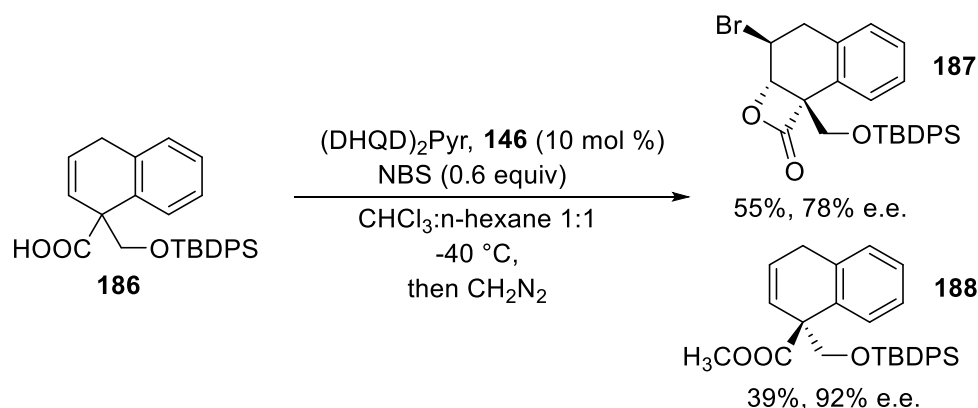
Starting from the unsaturated acids **189**, the bromocyclization carried out with NBS in the presence of (DHQD)₂PHAL **144**, with acidic catalysis by benzoic acid, afforded with excellent yield and enantioselection the corresponding α-methylene-butyrolactones **190**, that were evaluated for their cytotoxic activity [142-143].
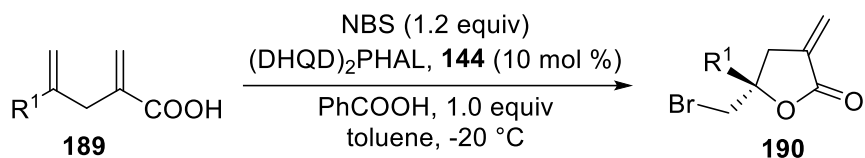
R^1 = C$_6$H$_5$, 99%, 84% e.e.; R^1 = 2-naphthyl, 98%, 92% e.e.; R^1 = 4-CH$_3$-C$_6$H$_4$, 98%, 92% e.e.

In the event, the cyclization of acids **191** mediated by NBS occurred even in the absence of benzoic acid, providing the corresponding α-methylene-δ-lactones **192** in excellent yield and enantioselection [142].
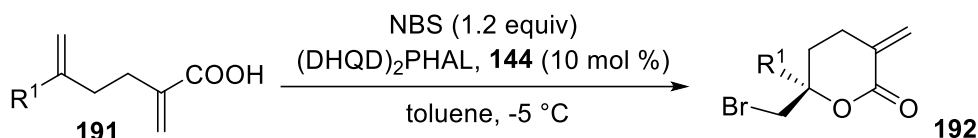
R^1 = C$_6$H$_5$, 98%, 94% e.e.; R^1 = 2-naphthyl, 96%, 90% e.e.; R^1 = 4-CH$_3$-C$_6$H$_4$, 98%, 94% e.e.

The bromocyclization of alkenoic acids **193** was again performed with NBS, and benzoic acid was added in order to activate the bromenium source. Thus, using (DHQD)$_2$PHAL **144** as a chiral catalyst, the corresponding bromolactones **194** were obtained in excellent yield but sometimes with low enantioselection, confirming that the enantioselection strongly relies on the substitution pattern of the double bond [144].
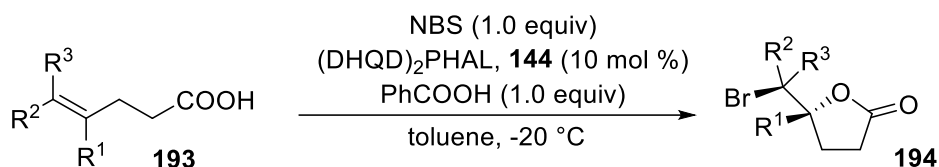
R^1 = C$_6$H$_5$, R^2 = R^3 = H, 95%, 82% e.e.; R^1 = C$_6$H$_5$, R^2 = allyl, R^3 = CH$_3$, 93%, 72% e.e.;
R^1 = R^2 = R^3 = H, 98%, 36% e.e.; R^1 = C$_6$H$_5$, R^2 = R^3 = CH$_3$, 95%, 38% e.e.

The bromolactonization of allenoic acids **195** induced by NBS in the presence of (DHQD)$_2$PHAL **144** proceeded with moderate yield and low enantioselection to give the corresponding lactones **196** [145].
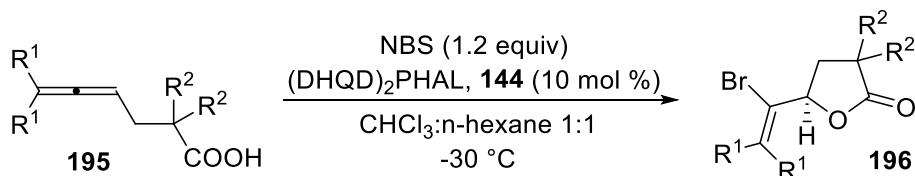
R^1...R^1 = -(CH$_2$)$_5$-, R^2 = H, 65%, 44% e.e.; R^1 = CH$_3$, R^2 = H, 58%, 20% e.e.;
R^1 = H, R^2 = C$_6$H$_5$, 86%, 50% e.e.; R^1...R^1 = -(CH$_2$)$_5$-, R^2 = C$_6$H$_5$, 72%, 50% e.e.

Starting from the unsaturated acids **197**, seven-membered ring azalactones **198** were prepared in excellent yield and enantioselection by cyclization mediated by NBS proceeding in a 7-*exo*-mode in the presence of the (DHQ)$_2$PHAL **145**. A reversal of enantioselection was observed when, under the same reaction conditions, the pseudoenantiomeric catalyst (DHQD)$_2$PHAL **144** was used so that, starting from the alkenoic acid **199**, both halolactones **200** and *ent*-**200** were available in excellent yield and enantioselection [146].
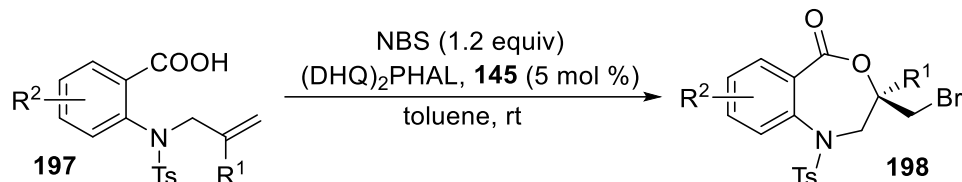
R^1 = R^2 = H, 97%, 99% e.e.; R^1 = 4-CH$_3$-C$_6$H$_4$, R^2 = H, 97%, > 99.5 e.e.;
R^1 = C$_6$H$_5$, R^2 = 4-OCH$_3$, 98%, > 99.5 e.e.; R^1 = C$_6$H$_5$, R^2 = 4-F, 99%, 99% e.e.
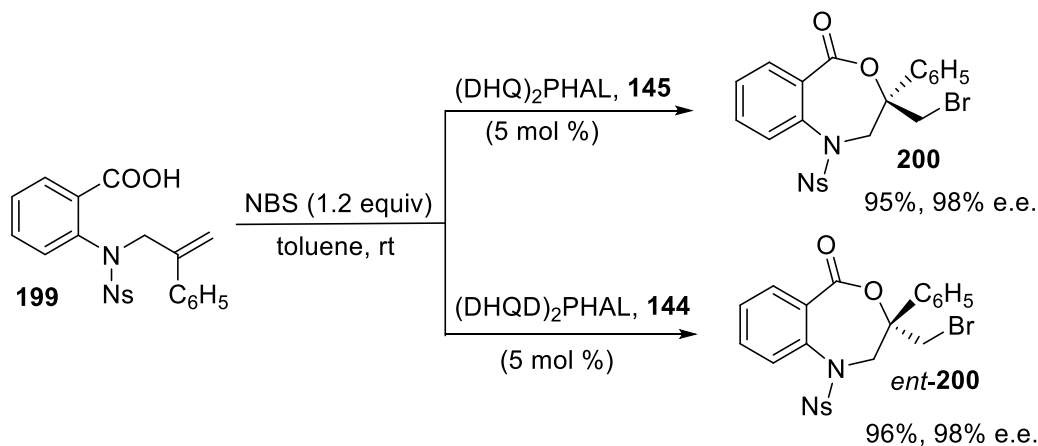
In order to prepare bromolactones in a highly enantioselective manner, the novel C_2-symmetric sulfur-based chiral catalyst **203** was prepared starting from quinine. The reaction of alkenoic acids **201** was performed with NBS to provide the corresponding lactones **202** in good yield but with moderate enantioselection [147].
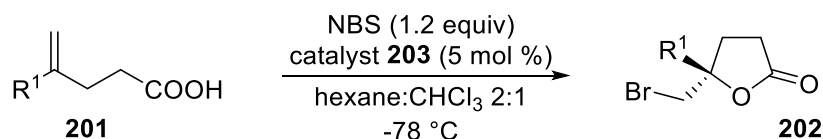
R^1 = C$_6$H$_5$, 97%, 83% e.e.; R^1 = 4-CH$_3$-C$_6$H$_4$, 98%, 82% e.e.;
R^1 = 4-CH$_3$O-C$_6$H$_4$, 95%, 66% e.e.; R^1 = 4-F-C$_6$H$_4$, 86%, 64% e.e.
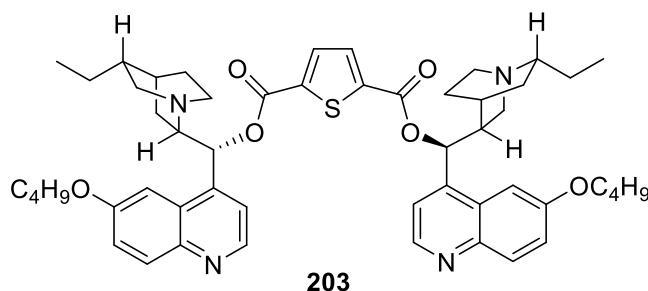
It is worth mentioning that in further development, the novel dinuclear catalyst **206** was prepared to start from L-proline, directed towards the bromolactonization of substrates **204** since low enantioselection was observed when the reaction of these compounds was carried out in the presence of a catalyst (DHQD)$_2$PHAL **144**. Thus, mediated by NBS, the cyclization exploiting the catalyst **206** proceeded in high yield and excellent enantioselection to afford α-methylene spirolactones **205** [148].
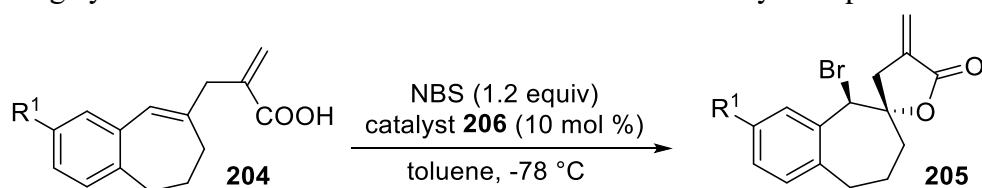
R^1 = H, 99%, d.r. >99:1, 96% e.e.; R^1 = Cl, 96%, d.r. 90:10, 97% e.e.;
R^1 = Br, 97%, d.r. >99:1, 94% e.e.
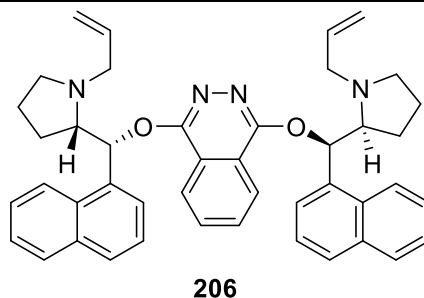
206

Eventually, the bromolactonization of alkenoic acids **207** was carried out with NBS in the presence of catalyst **209** and the corresponding six-membered lactones **208** were recovered in excellent yield. The reaction proceeded with total regioselection, driven by electronic factors, whereas the stereoselection was invariably low [149].
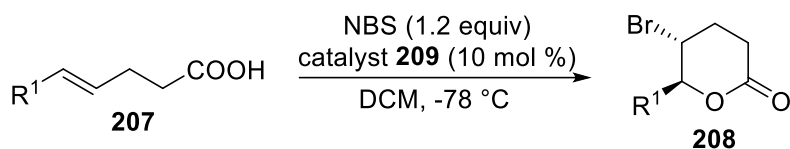
R^1 = C_6H_5, 94%, 47% e.e.; R^1 = 4-F-C_6H_4, 94%, 40% e.e.;
R^1 = 4-Cl-C_6H_4, 87%, 41% e.e.; R^1 = 4-Br-C_6H_4, 92%, 42% e.e.
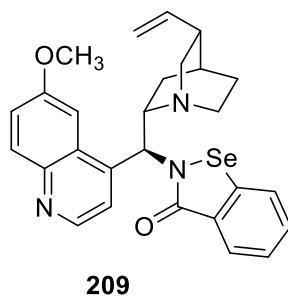
209

2.1.1.3.2. Exploiting BINAP-derived catalysts.

A Lewis base can mediate a proton transfer and/or stabilize an intermediate haliranium ion, whereas a halenium ion source can be activated by a Lewis or Brønsted acid [70] so that these catalytic elements were incorporated on BINAP-derived catalysts in which bulky groups at the 3- and/or 3′-position of binaphthyl were highly effective to increase the stereoselection. Thus, using the first-generation catalyst **212**, containing both an amidine moiety and a phenolic hydroxy group, together with a 3-phenyl substituent, (*Z*)-alkenoic acids **210** underwent regioselective bromolactonization via a 5-*exo*-mode closure, providing five-membered lactones **211** in good yield, total regioselection, and high enantioselection [150]. In addition, under the same reaction conditions, (*E*)-alkenoic acids **213**, according to a 6-*endo*-mode closure, afforded six-membered bromolactones **214** in good yield, total regioselection, and high enantioselection [150], and 2,4,4,6-tetrabromocyclohexa-2,5-dienone (TBCO) was more effective than NBS and DBDMH, previously reported as superior sources of bromenium ion. Eventually, high enantioselection was observed for the cyclization of 4-substituted pentenoic acids **215** to the corresponding γ-lactones **216** [125],[133].

$R^1 = C_2H_5$, 90%, 70% e.e.; $R^1 = (CH_3)_2CH$, 94%, 94% e.e.

$R^1 = C_6H_5$, 94%, 96% e.e.; R^1 = 1-naphthyl, 97%, 92% e.e.

$R^1 = C_6H_5$, 99%, 72% e.e.; $R^1 = 4\text{-}CN\text{-}C_6H_4$, 92%, 92% e.e.

212
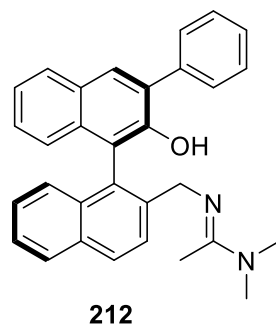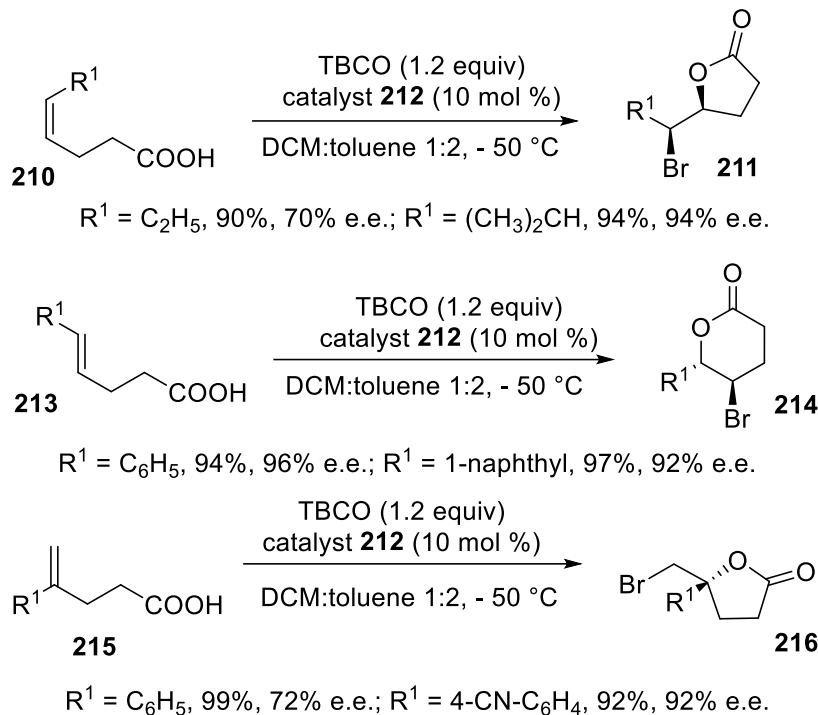
The iodolactonization of alkenoic acids where the double bond was substituted by alkyl groups was scarcely reported and invariably occurred with moderate enantioselection [151-152]. However, by using NIS together with catalyst **219**, which differs from **212** only by a bromine substituent, (*Z*)-alkenoic acids **217** afforded excellent yield and enantioselection of the corresponding iodolactones **218** where two chirality centers were introduced at once. The configuration of the double bond was determinant for the cyclization since (*E*)-alkenoic acids **220**, under the same reaction conditions, provided the iodolactones **221** in good yield but with very low enantioselection [153-154].

n = 1, $R^1 = (CH_3)_2CH$, 93%, 95% e.e.; n = 1, $R^1 = t\text{-}C_4H_9$, 99%, 94% e.e.;
n = 2, $R^1 = C_6H_5$, 89%, 98% e.e.; n = 2, $R^1 = t\text{-}C_4H_9$, 98%, 96% e.e.

$R^1 = (CH_3)_2CH$, 78%, 34% e.e.; $R^1 = 4\text{-}CN\text{-}C_6H_4$, 94%, 16% e.e.

219
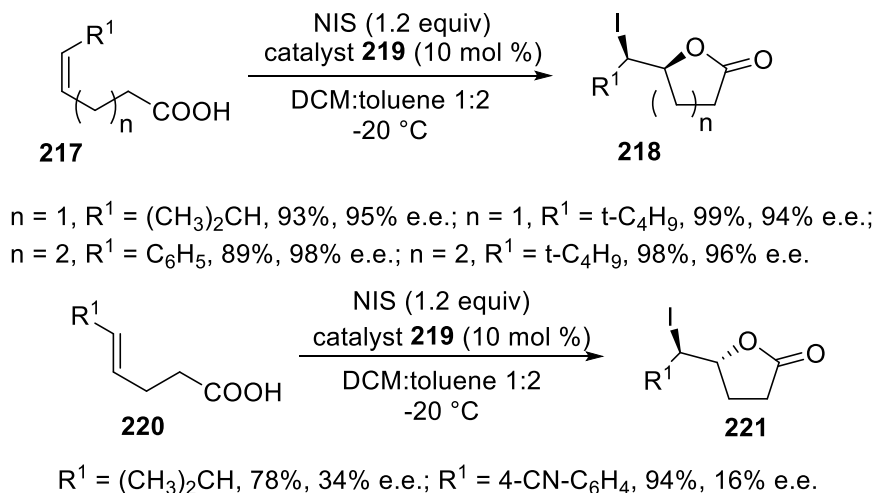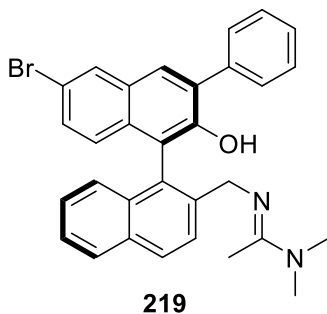
Within a total synthesis of (+)-Disparlure, using NIS in the presence of a catalytic amount of iodine, *ent*-**219** catalyzed in good yield and excellent enantioselection the cyclization of (*Z*)-alkenoic acid **222** to the corresponding iodolactone **223**, having the opposite configuration at the chirality centers with respect to iodolactones **218** [155].
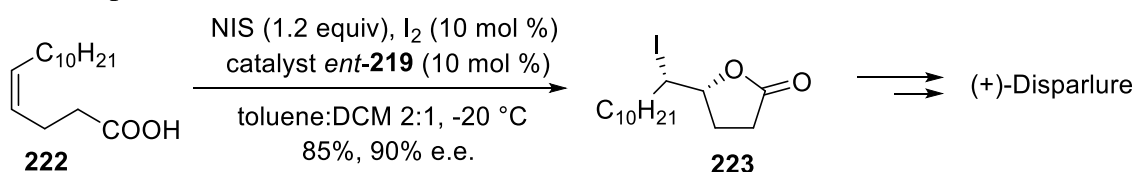
Both catalysts **219** and *ent*-**219** were also effective for the desymmetrization of *bis*-unsaturated acid **224**, which proceeded with moderate enantioselection to give the β-lactone **225** [150] or its enantiomer *ent*-**225**, respectively [156].
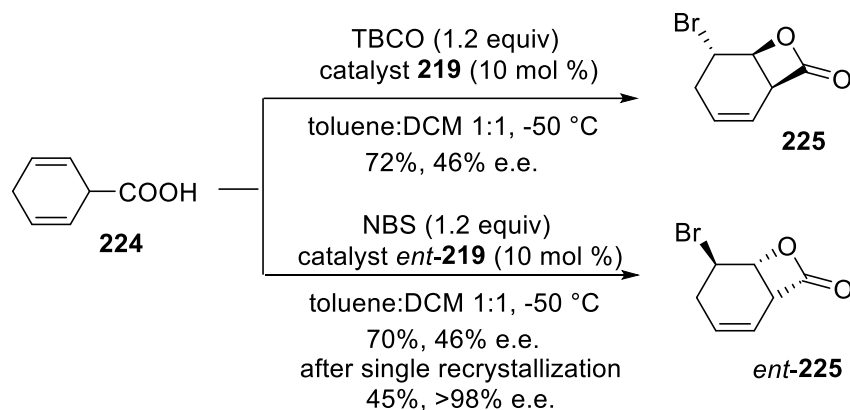
The bromolactonization of 4-aryl-4-pentenoic acids **226** mediated by TBCO was carried out in the presence of the catalyst **228** to give the corresponding bromolactones **227** in excellent yield and enantioselection. The length of the chain was critical since the cyclization of hexenoic acid proceeded with low enantioselection. Probably, alkenoic acids **226** formed a carboxylate with palladium, with simultaneous coordination of TBCO, leading to a chiral environment for the transfer of bromenium ion [157].
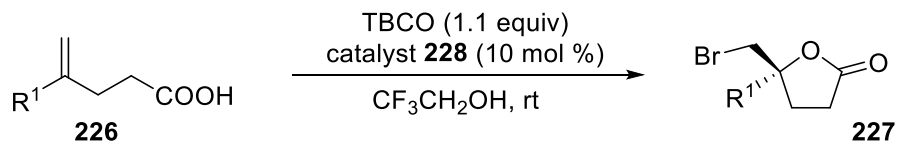
$R^1 = C_6H_5$, 98%, 75% e.e.; $R^1 = 4\text{-}CH_3\text{-}C_6H_4$, 97%, 85% e.e.; $R^1 = 4\text{-}CH_3O\text{-}C_6H_4$, 99%, 97% e.e.
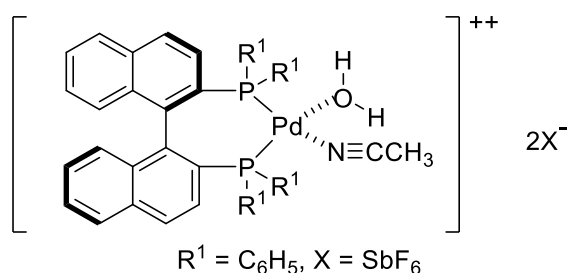
228

The chiral Lewis base **231** was employed together with *N*-chlorophthalimide (NCP) and iodine in the iodolactonization of 4-aryl pentenoic acids **229**, to give in excellent yield and enantioselection of the corresponding iodolactones **230** when the double bond was substituted with either electron-releasing or electron-withdrawing aryl groups. NCP promoted the reaction by acting both as an activating agent for iodine and as an oxidizing agent of the formed iodide, but when the double bond was substituted by the simple phenyl group, the cyclization proceeded with very low enantioselection [158].
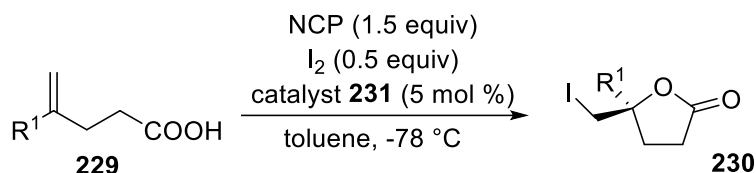
R^1 = 4-F-C$_6$H$_4$, 95%, 93% e.e.; R^1 = 4-Cl-C$_6$H$_4$, 92%, 94% e.e.;
R^1 = 4-CH$_3$C$_6$H$_4$CH$_2$, 90%, 92% e.e.; R^1 = C$_6$H$_5$, 72%, 10% e.e.

R^1 = (CH$_3$)$_2$CHCH$_2$
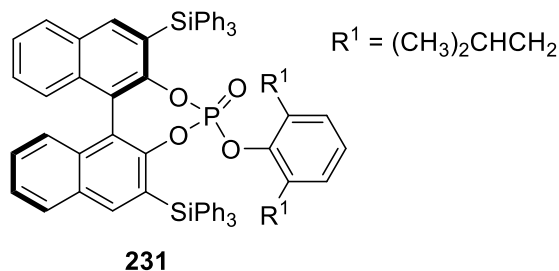
231

The cyclization of 5-aryl-5-hexenoic acids **232** was also performed with NIS and a catalytic amount of iodine using the trinuclear zinc complex **235** obtained from ligand **234** by the addition of three equivalents of Zn(OAc)$_2$, and the reaction allowed to prepare of the corresponding iodomethyl lactones **233** in excellent yield and enantioselection [159]. In this process, the starting alkenoic acids were converted to zinc carboxylates, whereas the *N*-iodosuccinimide (NIS) was activated, exploiting a hydrogen bonding with the diamine unit of the chiral ligand. In addition, iodine interaction with NIS led to a halogen bonding network, and the catalyst activated both the carboxylic group and the alkene moiety. In the event, using the NIS-I$_2$ complex, iodine was regenerated so that the actual iodination reagent was I$_2$ and not NIS [160].
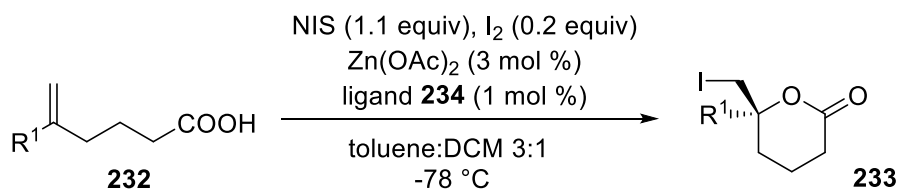
R^1 = C$_6$H$_5$, >99%, 99.5% e.e.; R^1 = 4-Br-C$_6$H$_5$, >99%, 99.8% e.e.; R^1 = 4-Cl-C$_6$H$_4$, >99%, 99.8% e.e.

234   **tri-Zn, 235**
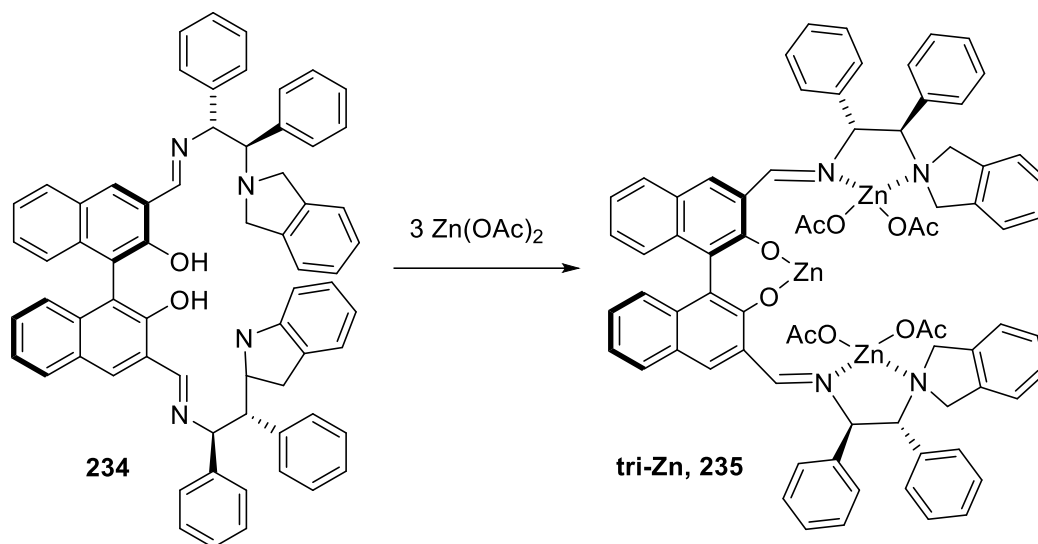
The chiral complex **235** was also useful for desymmetrization of carboxylic acids **236**, and the corresponding iodolactones **237** were isolated in excellent yield and very high enantioselection [160].

NIS (1.1 equiv), I$_2$ (0.2 equiv)
Zn(OAc)$_2$ (15 mol %)
ligand **234** (5 mol %)
toluene:DCM 3:1
-78 °C

236   **237**
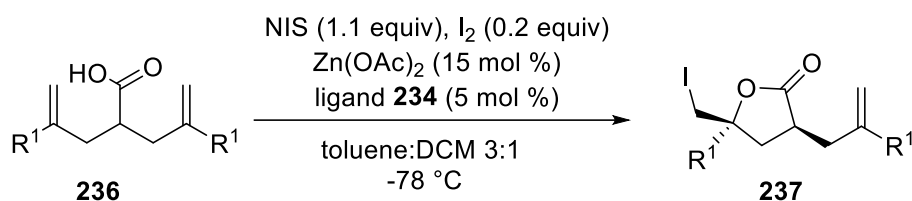
R^1 = C$_6$H$_5$, 94%, d.r. 99:1, 94% e.e.; R^1 = 3-CF$_3$-C$_6$H$_4$, 93%, d.r. 99:1, 98% e.e.;
R^1 = 2-naphthyl, 80%, d.r. 99:1, 92% e.e.; R^1 = 3-CH$_3$O-C$_6$H$_4$, 99%, d.r. 99:1, 96% e.e.

This catalyst was also prepared in the polymeric form Poly-Zn2b **241**, exploiting the polymeric ligand **240**, and under these conditions, the cyclization of alkenoic acids **238**, mediated by NIS and iodine, afforded the corresponding 5-iodomethyl lactones **239** in excellent yield and high enantioselection, whereas the catalyst could be used again efficiently [161].

NIS (1.1 equiv)
I$_2$ (0.2 equiv)
Poly-**Zn2b, 241** (2 mol %)
toluene:DCM 3:1
-78 °C

238   **239**
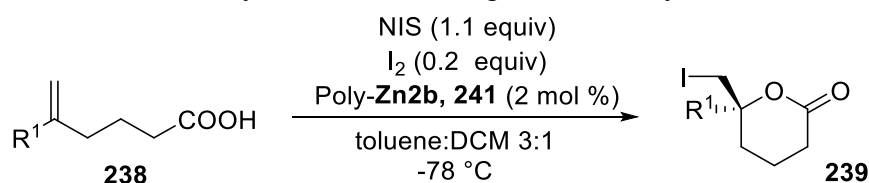
R^1 = C$_6$H$_5$, >99%, 96% e.e.; R^1 = 4-CH$_3$-C$_6$H$_4$, >99%, 91% e.e.;
R^1 = 4-Cl-C$_6$H$_4$, >99%, 97% e.e.; R^1 = cyclohexyl, >99%, 95% e.e.

240
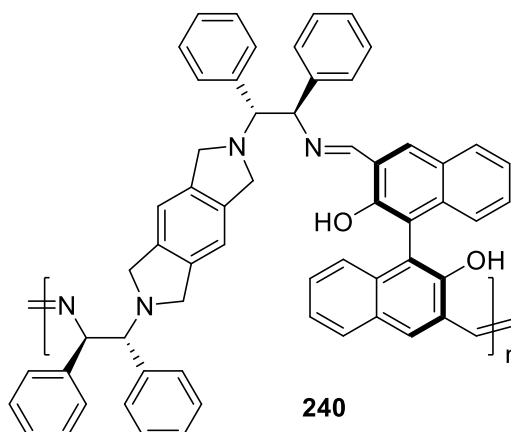
Acids **242**, containing a trisubstituted double bond, underwent bromocyclization mediated by NBS in the presence of the catalyst **244** containing a chiral pyridyl phosphoramide, to afford excellent yield, total regioselection and good enantioselection of the corresponding γ-lactones **243**, bearing two contiguous stereocenters, whereas total regioselection arising from cyclization proceeding in a 5-*exo*-mode was driven by electronic factors [162].
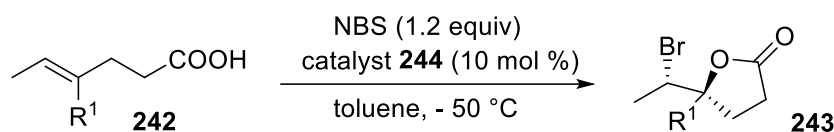
R^1 = C$_6$H$_5$, 95% (*E:Z* 4:96), 92% e.e.; R^1 = 4-Cl-C$_6$H$_4$, 97% (*E:Z* 9:91), 95% e.e.;
R^1 = 4-CH$_3$-C$_6$H$_4$ (*E:Z* 7:93), 91%, 92% e.e.

244
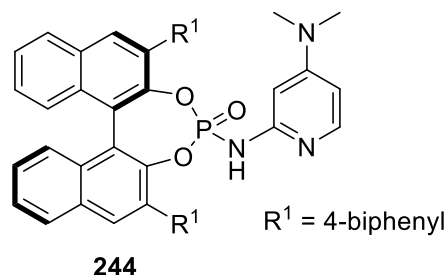
Moreover, under the same conditions, *via* a 6-*endo*-mode cyclization, the alkenoic acids **245** provided the δ-lactones **246** in excellent yield and enantioselection, the regioselection being again driven by electronic factors. The reaction mechanism probably involved the coordination of the alkenoic acid to the dimethylaminopyridyl group, together with the interaction of phosphoramide with NBS, leading to a chiral environment [162].
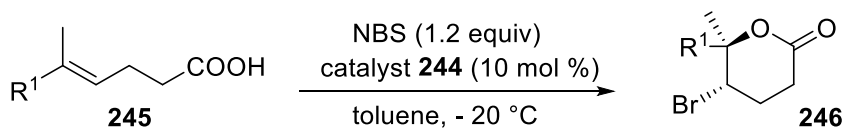
R^1 = C$_6$H$_5$, 85%, 95% e.e.; R^1 = 4-Cl-C$_6$H$_4$, 100%, 96% e.e.; R^1 = 4-CH$_3$-C$_6$H$_4$, 83%, 98% e.e.

The chiral bifunctional catalyst **249**, containing both urea and a dialkyl sulfide tethered on the 1,1'-*bi*-2-naphthyl (BINAP) structure, was effective in bromocyclization of unsaturated acids **247**. The reaction, mediated by NBS, allowed preparing of the corresponding δ-lactones **248** in high yield, with total regioselection and high enantioselection. The roles of both the sulfide group stabilizing the bromenium ion and the urea moiety as coordinating of NBS were clarified based on the results of experimental and theoretical investigations [163].
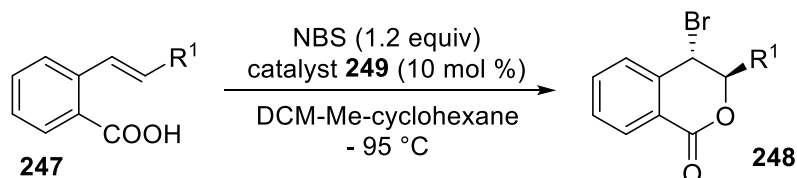
R^1 = C$_6$H$_5$, 94%, 83% e.e.; R^1 = 4-F-C$_6$H$_4$, 89%, 83% e.e.; R^1 = 4-CH$_3$O-C$_6$H$_4$, 87%, 81% e.e.

249
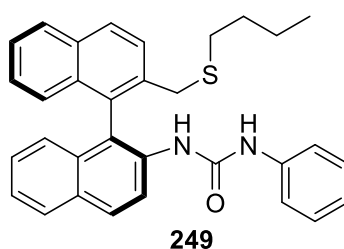
The bromolactonization of stilbene-type carboxylic acids **250**, bearing an electron-withdrawing group, was carried out using the chiral bifunctional sulfide catalyst **253** with a slightly modified structure with respect to **249**. The reaction, mediated by dibromoisocyanuric acid (DBI), proceeded with high regioselection, due to electronic factors to give the corresponding γ-lactones **251** in good yield but with moderate enantioselection, together with traces of δ-lactones **252** [164].
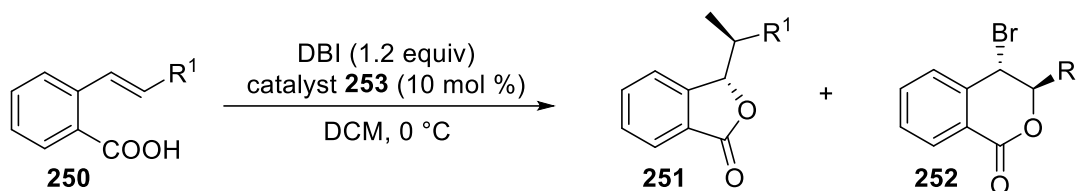
R^1 = 4-CF_3-C_6H_4, **251a:252a** 18:1, **251a** 92%, 64% e.e.;
R^1 = 4-CN-C_6H_4, **251b:252b** 24:1, **251b** 83%, 56% e.e.;
R^1 = 4-NO_2-C_6H_4, **251c:252c** >50:1, **251c** 96%, 62% e.e.
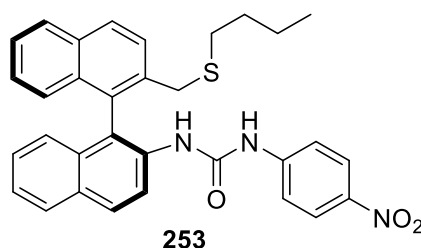
The difunctional catalyst **256**, again arising from 1,1'-*bi*-2-naphthyl structure (BINAP), was prepared and employed in regioselective bromolactonization of alkenoic acids **254** mediated by *N*-bromophthalimide (NBPhth), and the five-membered bromolactones **255** were isolated in excellent yield and good enantioselection [165].
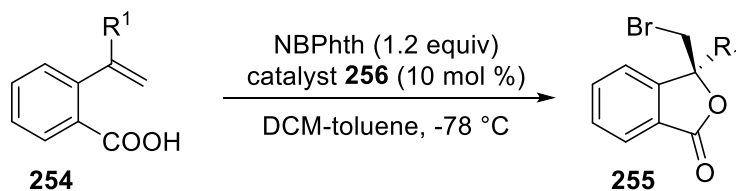
R^1 = C_6H_5, 99%, 92% e.e.; R^1 = 4-Cl-C_6H_4, 98%, 82% e.e.; R^1 = 4-CH_3-C_6H_4, 97%, 80% e.e.
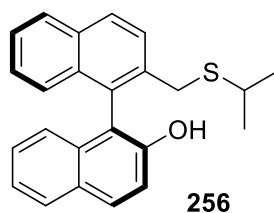
The bromolactonization of alkenoic acids **257** mediated by dibromohydantoin (DBH) was carried out also in the presence of the chiral bifunctional selenide catalyst **259**, and the corresponding γ-lactones **258** were isolated in good yield and moderate enantioselection [166].
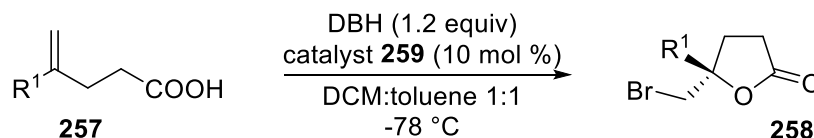
R^1 = C_6H_5, 85%, 82% e.e.; R^1 = 4-F-C_6H_4, 99%, 78% e.e.;
R^1 = 4-CH_3-C_6H_4, 87%, 70% e.e.; R^1 = 3-F-C_6H_4, 90%, 70% e.e.

259

$R^1 = 3,5\text{-}(C_6H_5)_2\text{-}C_6H_3$
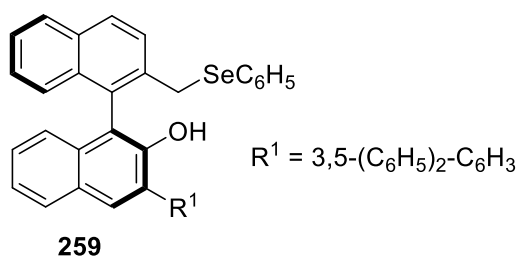
The alkenoic acids **260** underwent cyclization mediated by TBCO in the presence of the difunctional catalyst **262**, containing a sulfide group in place of the selenide group in catalyst **259**, and bromolactones **261** were isolated in excellent yield and higher enantioselection in comparison with catalyst **259** [167].
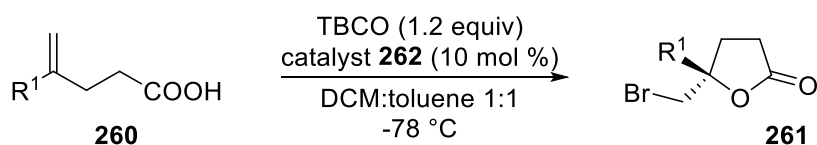
$R^1 = C_6H_5$, 99%, 94% e.e.; $R^1 = 4\text{-}Cl\text{-}C_6H_4$, 85%, 93% e.e.;
$R^1 = 4\text{-}CF_3O\text{-}C_6H_4$, 91%, 95% e.e.; $R^1 = 3\text{-}CH_3S\text{-}C_6H_4$, 97%, 92% e.e.

262
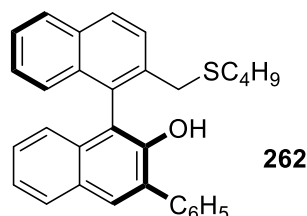
Catalyst **262** was also very effective for the desymmetrization of α,α-diallyl carboxylic acid **263**, and the reaction carried out with *N*-bromophthalimide (NBPhth) afforded the corresponding bromolactone **264** in excellent yield and high enantioselection [168].

99%, d.r. >20:1, e.e. 88%
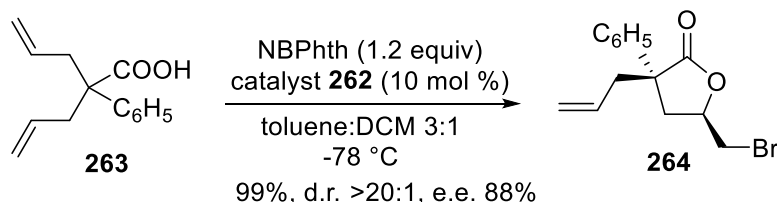
2.1.1.3.3. Exploiting catalysts generating double H-bonding

The difunctional catalyst 265 containing a urea moiety useful for hydrogen bonding was effective for the asymmetric iodolactonization reaction mediated by N-iodo-4-fluorophthalimide in the presence of iodine. In fact, starting from the alkenoic acids 215 and 266, either γ-lactones 216 and δ-lactones 267 were obtained in good yield and good to excellent enantioselection. Still, the chirality center was formed with the opposite configuration in five-membered rings with respect to the six-membered ones [151].
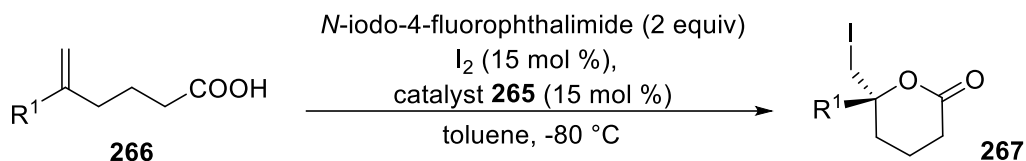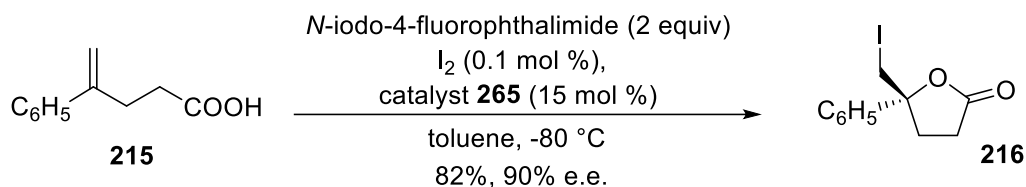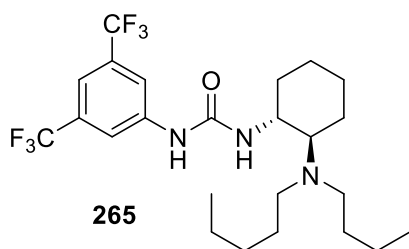
In place of urea, the squaramide moiety was chosen in order to exploit the H-bonding system [169]. Thus, the iodolactonization of alkenoic acids 266 was carried out with NIS and a small amount of iodine acting as Lewis base in the presence of the squaramide catalyst 268, and the reaction proceeded with excellent yields and stereoselection, providing δ-lactones 267 with the same configuration as 265. However, when the double bond was substituted by an electron-rich aromatic ring and/or by an alkyl group, the stereoselection was poor, and similar results were observed when γ-lactones were prepared under the same reaction conditions [170].
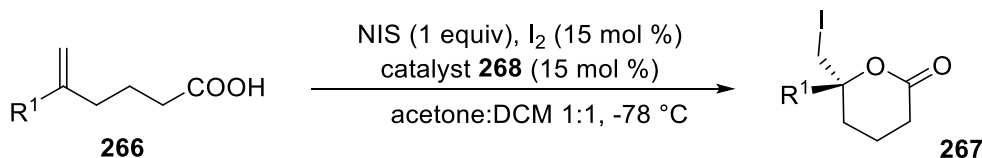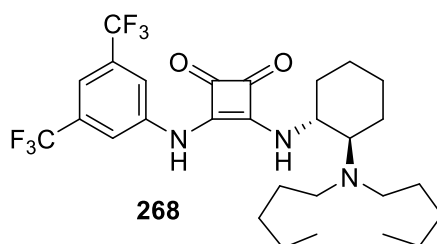
Even the allenoic acids 269 underwent cyclization using the same reaction conditions, but the corresponding δ-lactones 270 were isolated in very low yields and moderate to low enantioselection [171].
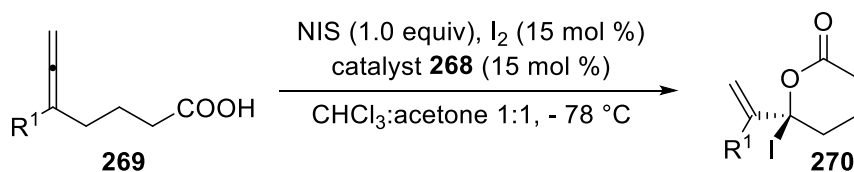
Moreover, starting from the alkenoic acids 271, bromolactones 272 were isolated in good yield and excellent enantioselection when the cyclization was carried out using N-bromophthalimide and catalyst 273, which had nitro groups in place of trifluoromethyl groups of catalyst 268 [172-173].
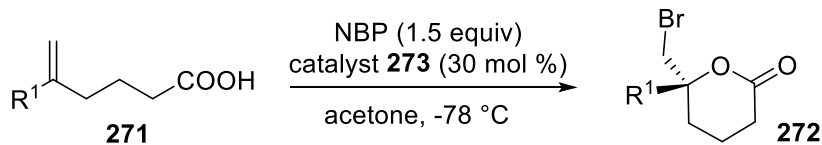
R^1 = C$_6$H$_5$, 88%. e.e. 80%; R^1 = 2-naphthyl, 94%, e.e. 92%; R^1 = 3-FC$_6$H$_4$, 91%, e.e. 91%; R^1 = cyclohexyl, 95%, e.e. 21%
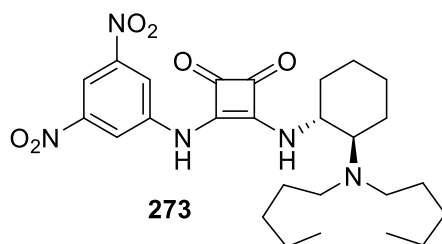
2.1.1.3.4. Exploiting C$_3$-symmetric catalysts.

An enantioselective bromolactonization was carried out in the presence of the C3-symmetric chiral trisimidazoline 276. In this case, the alkenoic acids 274 could form an ion pair with a basic sp2 nitrogen atom. In contrast, the carbonyl group could be activated by a hydrogen bond, eventually generating a chiral environment in which one of the two bromiranium ions reacted preferentially to give bromolactones 275. The reaction proceeded with excellent yields and high enantioselection [174].
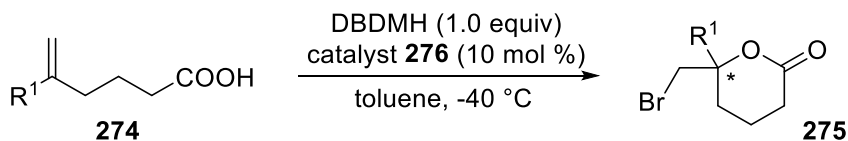
R^1 = C$_6$H$_5$, 99%, 91% e.e.; R^1 = 4-CH$_3$-C$_6$H$_4$, 96%, 90% e.e.; R^1 = 4-Br-C$_6$H$_4$, 93%, 89% e.e.
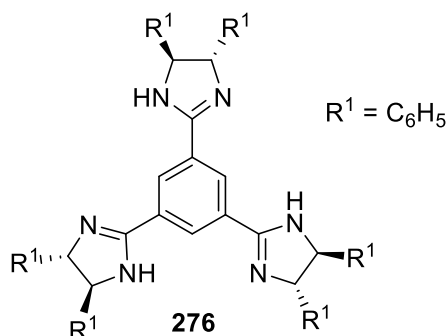
Under the same conditions, besides acids 274, displaying a terminal double bond, alkenoic acids 277 with a trisubstituted double bond were also converted into the corresponding bromolactones 278 in very good yield, but excellent enantioselection was observed only when the R1 substituent was an aromatic group. According to the same procedure, also spirolactones 280 were prepared in good yield and enantioselection starting from acids 279 [175].

277 → **278**
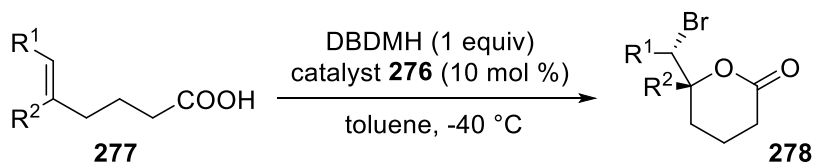
$R^1 = C_2H_5$, $R^2 = C_6H_5$, 92%, 88% e.e.; $R^1 = $ n-C_4H_9, $R^2 = $ 4-Cl-C_6H_4, 99%, 90% e.e.;
$R^1 = C_2H_5$, $R^2 = $ 2-naphthyl, 93%, 78% e.e.; $R^1 = C_2H_5$, $R^2 = C_2H_5$, 97%, 62% e.e.

279 → **280**
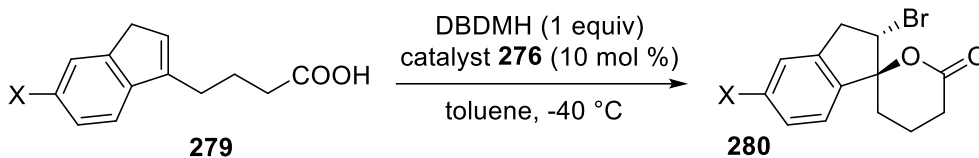
X = H, 86%, 89% e.e.; X = Cl, 91%, 82% e.e.

On the other hand, the iodolactonization of allenoic acids 281 was carried out with iodine, and the slightly modified catalyst 283 was used together with 2,6-di-tert-butylpyridine (DTBP), which allowed removing of the hydroiodic acid arising from the reaction, and iodolactones 282 were isolated in good yield and moderate to high enantioselection [176].

281 → **282**
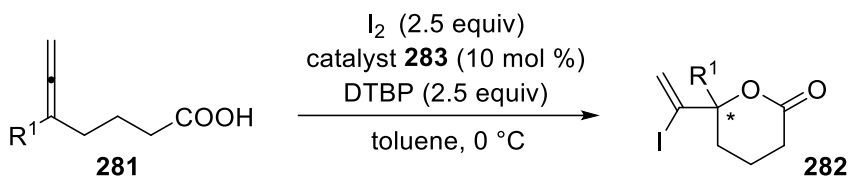
$R^1 = C_6H_5$, 83%, 66% e.e.; $R^1 = $ 4-t-Bu-C_6H_4, 89%, 82% e.e.; $R^1 = $ 4-TMS-C_6H_4, 78%, 80% e.e.

$R^1 = $ 2,3-$(CH_3)_2$-C_6H_3

283
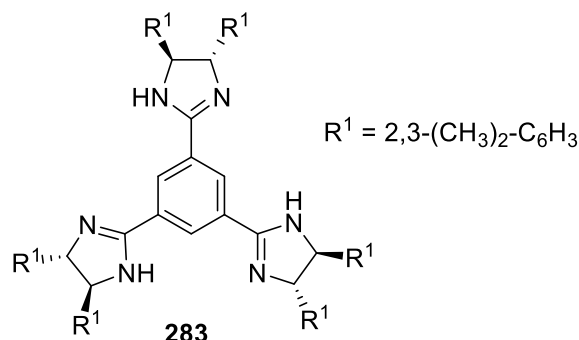
The resolution of alkenoic acids 284, bearing a substituent at C-3, was carried out by bromolactonization mediated by dibromodimethylhydantoin (DBDMH) and catalyst 287, having a slightly modified structure with respect to both catalysts 276 and 283, was effective in generating either bromolactones 285 or acids 286 in moderate to high enantioselection. However, the configurations were not assigned [177].

284 → **285** + **286**
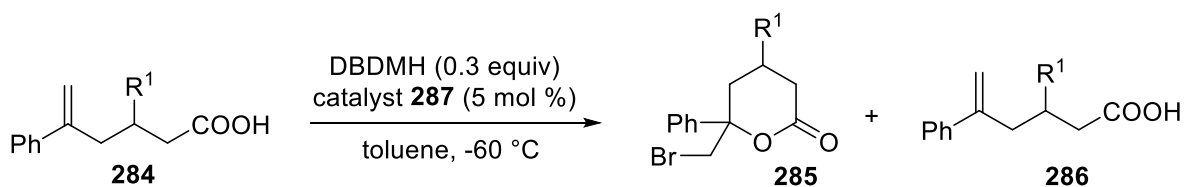
$R^1 = C_6H_5$, **285a**, 43%, 84% e.e., **286a**, 50%, 62% e.e.;
$R^1 = $ 4-Cl-C_6H_4, **285b**, 43%, 85% e.e., **286b**, 49%, 66% e.e.;
$R^1 = $ 4-Br-C_6H_4, **285c**, 43%, 61% e.e., **286c**, 49%, 47% e.e.;
$R^1 = CH_3$, **285d**, 56%, 65% e.e., **286d**, 34%, 94% e.e.

287
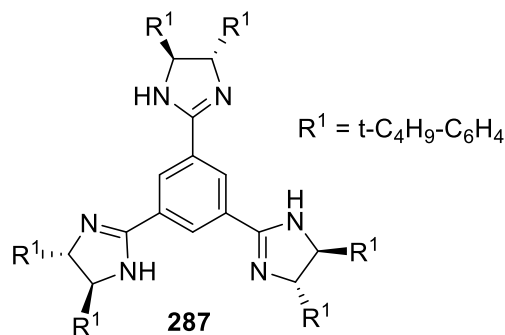
Eventually, the desymmetrization of dicarboxylic acids **288** was performed by bromolactonization reaction induced by DBDMH, carried out in the presence of trisimidazoline **276**. After treatment of the reaction products with trimethylsilyldiazomethane, esters **289** were isolated in excellent yield and moderate to high optical purity [178].
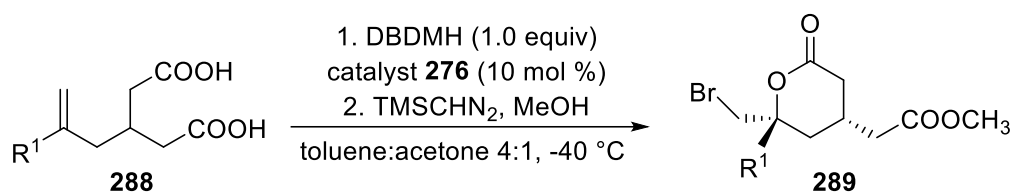
R^1 = C$_6$H$_5$, 98% (>20:1), 82% e.e.; R^1 = 2-naphthyl, 97% (>20:1), 82% e.e.;
R^1 = 3-CH$_3$O-C$_6$H$_4$, 98% (>20:1), 82% e.e.; R^1 = 4-F-C$_6$H$_4$, 99% (>20:1), 67% e.e.

2.1.1.3.5. Exploiting miscellaneous catalysts.

Many oligopeptides containing an iodo-aryl amide were treated with NBS with the aim of generating chiral bromenium sources as bromoiodinanes **293**, but only the amide of iodo-aryl tripeptide **292** reacting with NBS allowed to convert the unsaturated acid **290** into bromolactone **291** in quantitative yield, although with very low enantioselection [179-180].
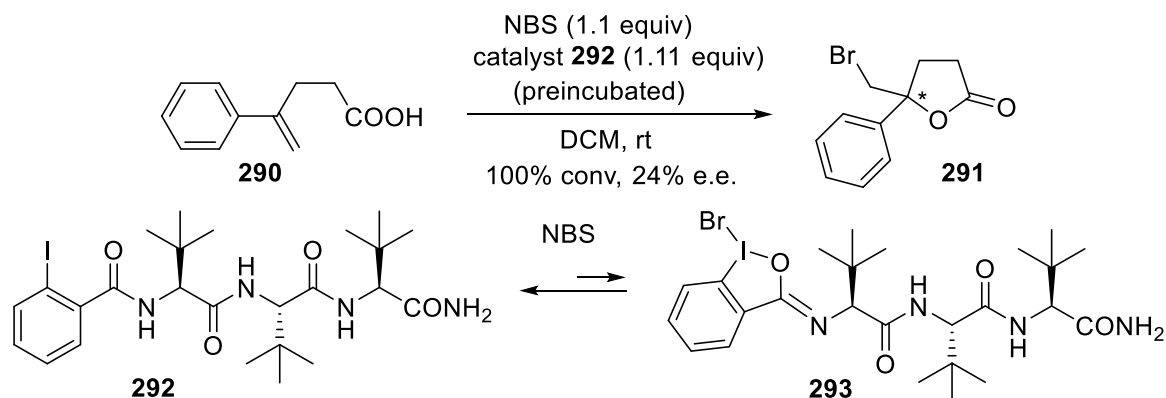
The Cinchona alkaloid-derived catalysts containing an O-alkyl thiocarbamate were effective in enantioselective bromocyclization reactions in which the bromine atom was activated by interaction with the Lewis basic sulfur atom of the catalyst. However, although the pseudo-enantiomeric pairs of Cinchona alkaloids were available, the corresponding enantiomeric products were not formed with the same enantioselection. Thus, the novel L-proline-derived catalyst **296**, containing an S-alkyl thiocarbamate moiety, was prepared and used for bromolactonization of acids **294** induced by N-bromophthalimide (NBPhth), providing the corresponding lactones **295** in excellent yield and high enantioselection [181].
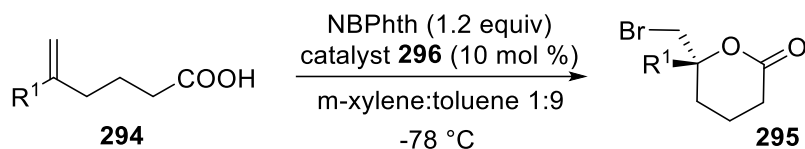
R^1 = C$_6$H$_5$, 97%, 92% e.e.; R^1 = 4-CH$_3$-C$_6$H$_4$, 95%, 90% e.e.; R^1 = 4-F-C$_6$H$_4$, 99%, 91% e.e.

296
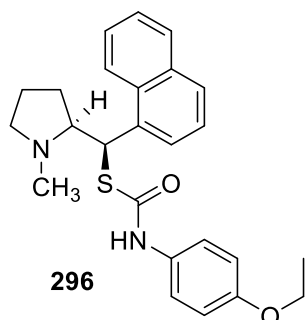
On the other hand, when the cyclization of alkenoic acids 297 was carried out under the same conditions but in the presence of catalyst 299, the five-membered lactones 298, displaying the opposite configuration at the chirality center with respect to 295, were isolated in good yield and high enantioselection [182].
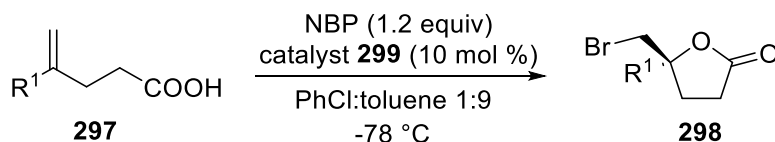
R^1 = 1-naphthyl, 99%, 91% e.e.; R^1 = 4-CH$_3$-C$_6$H$_4$, 93%, 82% e.e.; R^1 = 4-F-C$_6$H$_4$, 96%, 84% e.e.

299
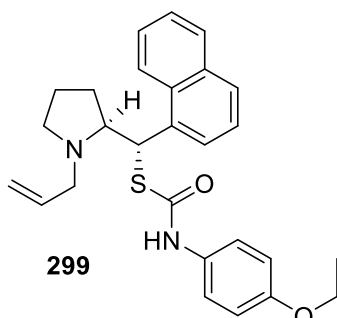
The chiral bis(amidine) (BAM)-protic acid complex 302 was employed as a bifunctional catalyst in iodolactonization of acids 300 mediated by NIS. The reaction proceeded with excellent yields and enantioselection, to afford δ-lactones 301 [152].
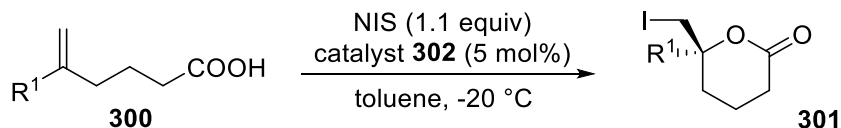
R^1 = C$_6$H$_5$, 95%, 97% e.e.; R^1 = 4-CH$_3$C$_6$H$_4$, 97%, 96% e.e.; R^1 = n-Bu, 95%, 89% e.e.

StilPBAM · HNTf$_2$ **302**
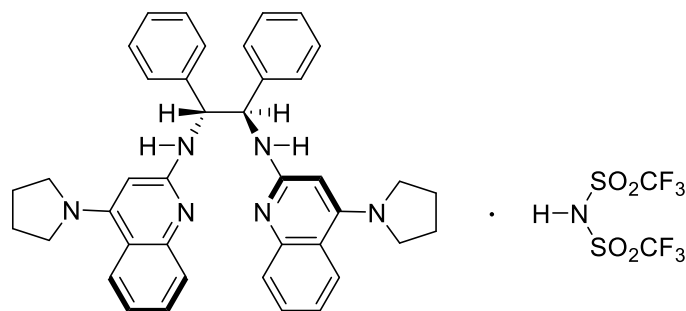
The chiral bis(imidazolidine)pyridine (PyBidine) ligand 305, in the presence of nickel acetate, was an effective catalyst for the iodolactonization of alkenoic acids 303 mediated by NIS in the presence of a catalytic amount of iodine. The reaction, proceeding through the formation of intermediate Ni-carboxylates, complexed with PyBidine that gives the chiral environment, provided the corresponding lactones 304 in moderate to good yield and enantioselection, with the opposite configuration with respect to catalyst 302 [182].
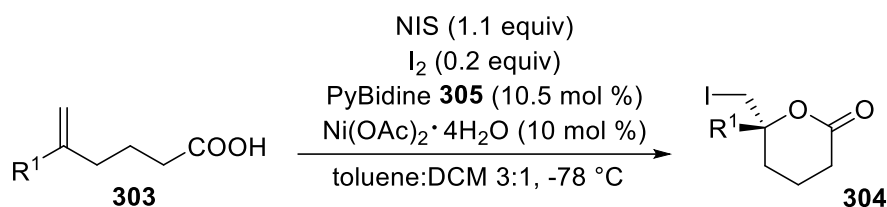
$R^1 = C_6H_5$, 85%, 78% e.e.; $R^1 = 4\text{-}F\text{-}C_6H_4$, 67%, 75% e.e.;
$R^1 = 4\text{-}CH_3\text{-}C_6H_4$, 95%, 89% e.e.; $R^1 = $ 2-naphthyl, 45%, 75% e.e.

PyBidine 305
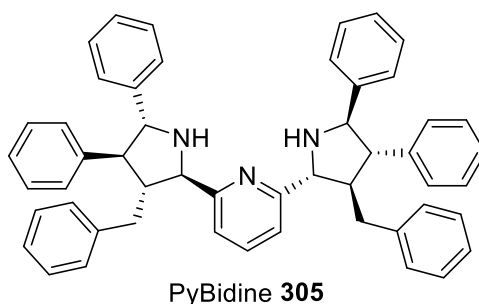
Cyclopentenyl carboxylic acids 306 underwent enantioselective desymmetrization by iodolactonization in the presence of the chiral Brønsted base 308 through a substrate-catalyst complex. The reaction, mediated by N-iodophthalimide (NIPhth), led to the corresponding bridged bicyclic lactones 307 in good yield and high enantioselection [183].
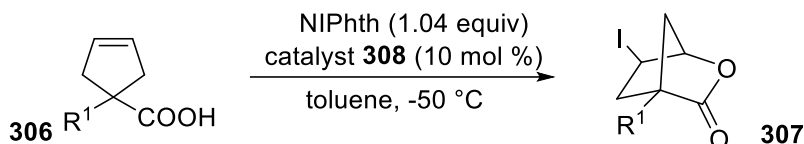
$R^1 = C_6H_5$, 87%, 93% e.e.; $R^1 = $ 2-naphthyl, 78%, 90% e.e.; $R^1 = (CH_3)_2CH$, 74%, 87% e.e.

308
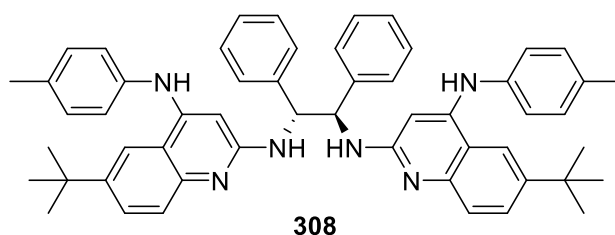
The iodolactonization of 5-aryl-5-hexenoic acids 300 induced by NIS provided six-membered iodolactones 301 in good yield with moderate to good enantioselection when the dinuclear zinc complex 309 was added to the reaction mixture. However, cyclization proceeded with low enantioselection when the double bond was substituted by either electron-rich aromatic or alkyl groups [184].
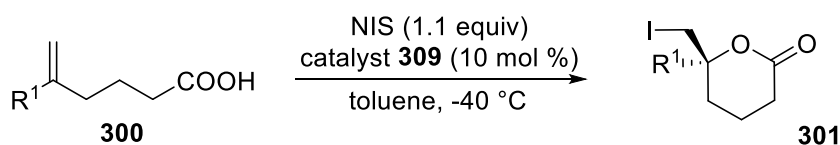
$R^1 = C_6H_5$, 70%, 82% e.e.; $R^1 = 4\text{-}CH_3\text{-}C_6H_4$, 87%, 62% e.e.; $R^1 = 4\text{-}Cl\text{-}C_6H_4$, 82%, 70% e.e.

309
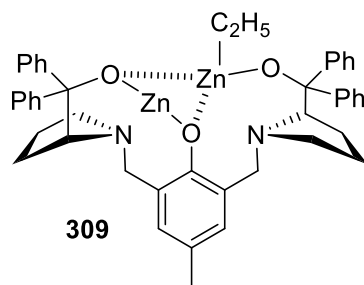
Eventually, exploiting Flavin-dependent Halogenases (FDHs), engineered to catalyze site-selective aromatic halogenation, bromolactones 311 were obtained from alkenoic acids 310 with high enantioselection. This goal was reached by characterizing and mitigating the release of HOBr from the FDH active site using a combination of reaction optimization and protein engineering [185]. In fact, these enzymes catalytically activate a halogen source in a chiral environment, avoiding halenium ion transfer between olefins, which leads to racemization [186].
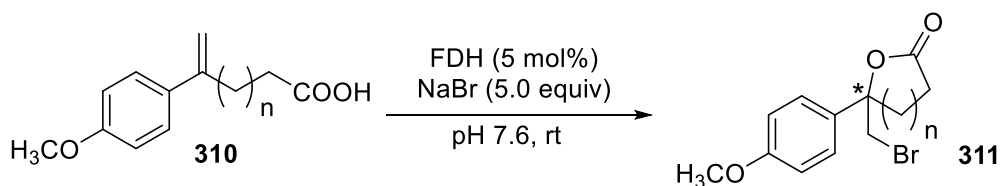
n = 1, FDH = (V+S), 91%, e.r. 96:4; n = 2, FDH = (4PL+E461G), 82%, 91:9 e.r.

2.1.2. Chlorolactones from carboxylic acids and esters.

Fluorine is not an effective bridging atom, and the rare cyclizations induced by fluorine or fluorine-containing reagents suggest the formation of a carbenium ion intermediate. On the other hand, chlorine, owing to its smaller size and lesser polarizability with respect to bromine and iodine, is not highly able to maintain bridging for an alkene [1],[4],[187]. Thus, bromiranium and iodiranium intermediates generally gave anti-addition at a higher degree with respect to chlorination, and chlorine-induced cyclizations can be accompanied by other reactions that are indicative of carbenium ion intermediates [188]. Recently, a role was suggested for the nucleophile in activating alkenes, specifically in chlorolactonization reactions [189]. Moreover, in some cases, a concerted mechanism was effective in these reactions, whereas in other cases, the formation of a carbocation intermediate seemed to be favored [189-190].

2.1.2.1. Without asymmetric induction.

A lot of reagents were employed in order to prepare chlorolactones, starting from unsaturated acids, esters, and amides. Thus, chloramine T in the presence of InCl$_3$ was effective in converting acids 312 into the corresponding chlorolactones 313 in good yield but without any stereoselection [191].
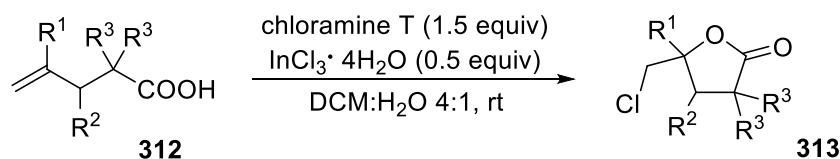
R^1 = R^2 = R^3 = H, 64%; R^1 = R^3 = H, R^2 = CH$_3$, 67%. d.r. 55:45;
R^1 = R^2 = H, R^3 = CH$_3$, 96%; R^1 = C$_6$H$_5$, R^2 = R^3 = H, 57%

2.1.2.2. With internal asymmetric induction.

A very fast and clean chlorolactonization reaction of acid 314 exploited 1,3-dichlorodimethylhydantoin (DCDMH) as chlorenium ion source and quinuclidine as a Lewis base. The stereochemistry of lactone 315, isolated in excellent yield, was assigned from the configuration of the starting double bond [192].
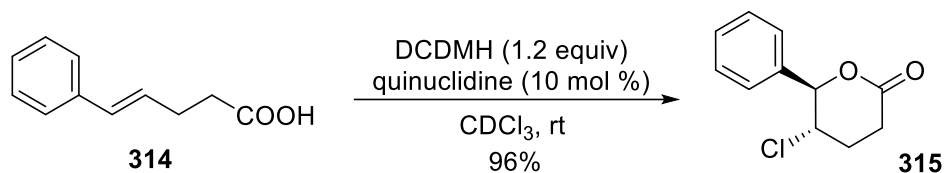
However, when the ammonium carboxylate 316 underwent cyclization with DCDMH in the presence of quinuclidine, a regioisomeric mixture of 315 and 317 was obtained since the Brønsted base quinuclidine transferred the chlorenium ion to both carbons of the double bond, irrespective of electronic factors [192].
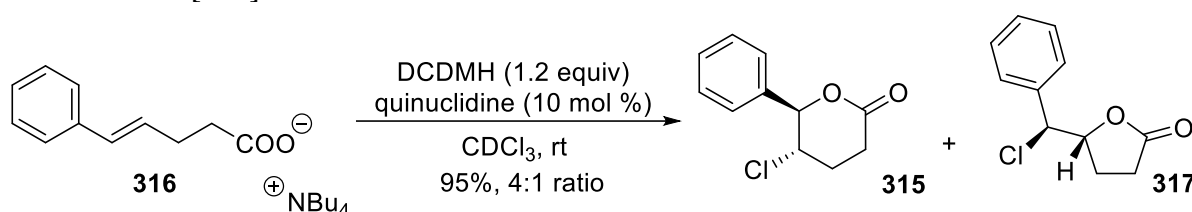
On the contrary, only five-membered chlorolactones 319 were obtained in good yield and total regioselection when acids 318 were treated with DCDMH and DABCO as a Brønsted base [192].

R^1 = 2-Cl-C_6H_4, 73%; R^1 = 3-CH_3-C_6H_4, 84%; R^1 = C_6H_5, 81%
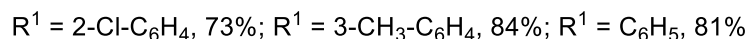
Furthermore, using $PhICl_2$ in the absence of a Lewis base, esters 320 gave the corresponding six-membered lactones 321 in moderate to good yield with total regio- and stereoselection [193].

R^1 = C_6H_5, R^2 = H, 90%; R^1 = C_6H_5, R^2 = 3-CH_3, 65%;
R^1 = 3-Cl-C_6H_4, R^2 = H, 88%; R^1 = $(CH_3)_2CH$, R^2 = H, 60%
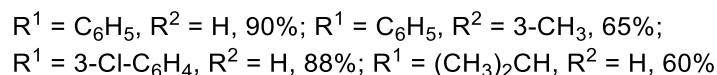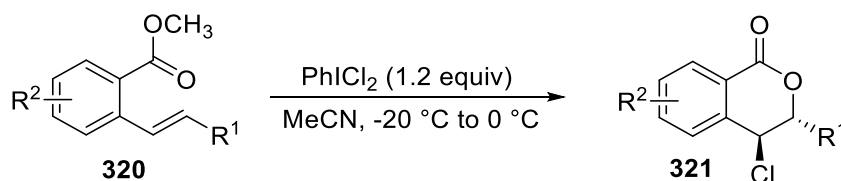
Eventually, the chiral ester 322 underwent cyclization mediated by N-chlorosuccinimide (NCS) to give chlorolactone 323 a good yield and excellent stereoselection [92].
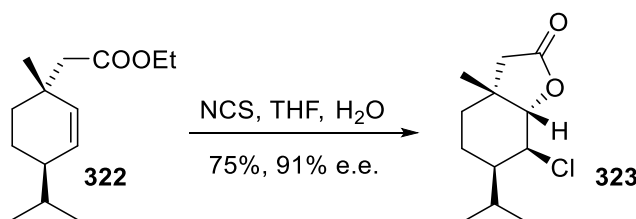
2.1.2.3. With external asymmetric induction exploiting *Cinchona* alkaloids derived catalysts.

The chlorolactonization of 4-substituted 4-pentenoic acids 324 was carried out with dichlorodimethylhydantoin (DCDMH) in the presence of catalyst 144, and the corresponding chlorolactones 325 were isolated in good yield but with very low e.e. [125]. The enantioselection of the process significantly increased using the modified catalyst 326, where a linker was introduced for the tosyl-urea group, and the double bond was converted into an ethyl group. The reaction was solvent-dependent since a toluene-chloroform mixture was compulsory for obtaining high enantioselection, but catalyst 326 promoted the enantioselective chlorolactonization of 4-arylpent-4-enoic acids exclusively [125].
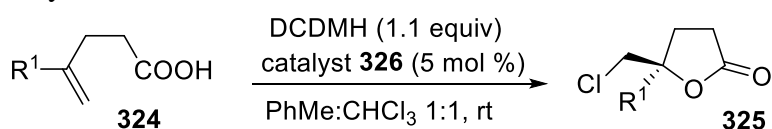
R^1 = C$_6$H$_5$, 92%, 91% e.e.; R^1 = 4-FC$_6$H$_4$, 99%, 87% e.e.; R^1 = 4-Br-C$_6$H$_4$, 95%, 80% e.e.
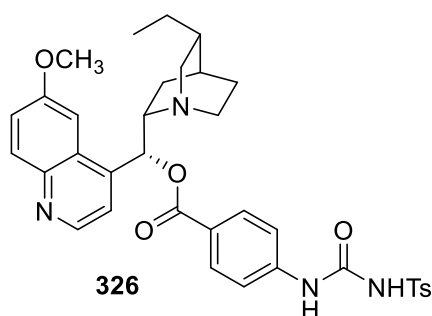
The 4-substituted 4-pentenoic acids 327 were converted into five-membered chlorolactones 328 using as chlorenium source 1,3-dichloro-5,5-diphenylhydantoin (DCDPH), activated by benzoic acid in the presence of (DHQD)2PHAL, 144, but when the double bond was substituted by an alkyl group, the chlorolactones were isolated in low yield and stereoselection. On the contrary, when the substituent was an aryl group, the reaction proceeded with good yield and high enantioselection, so the aryl group was supposed to direct stereoselection owing to a better interaction with the catalyst [194].
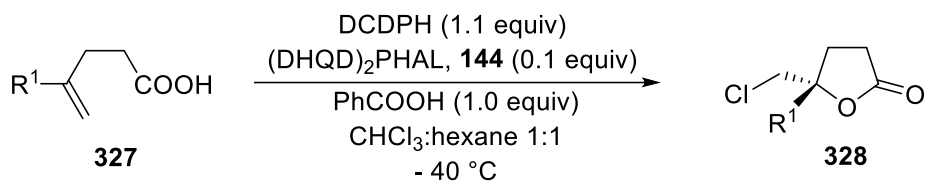
R^1 = C$_6$H$_5$, 86%, 89% e.e.; R^1 = 4-CH$_3$-C$_6$H$_4$, 86%, 80% e.e.;
R^1 = 4-F-C$_6$H$_4$, 81%, 89% e.e.; R^1 = cyclohexyl, 55%, 43% e.e.

A mechanistic investigation carried out using deuterium-labeled substrates allowed to establish that chlorolactonization of 329 to 330 occurred predominantly as a syn addition of both chlorenium ion and the nucleophile across the double bond, without the formation of a bridged chloriranium ion as an intermediate. The catalyst independently controlled the formation steps of the two new bonds. It was responsible not only for determining which olefin face is attacked by the chlorenium ion but also for guiding the final enantioselective cyclization so that the reaction proceeded via an open tertiary carbocation intermediate, which then underwent ring closure under the stereocontrol of the catalyst. This hypothesis was further supported by the results of the cyclization of ester 331, where interactions by hydrogen bonding with the chiral amine catalyst are missing, leading to the chlorolactone ent-330 with the opposite configuration [192-193],[195].
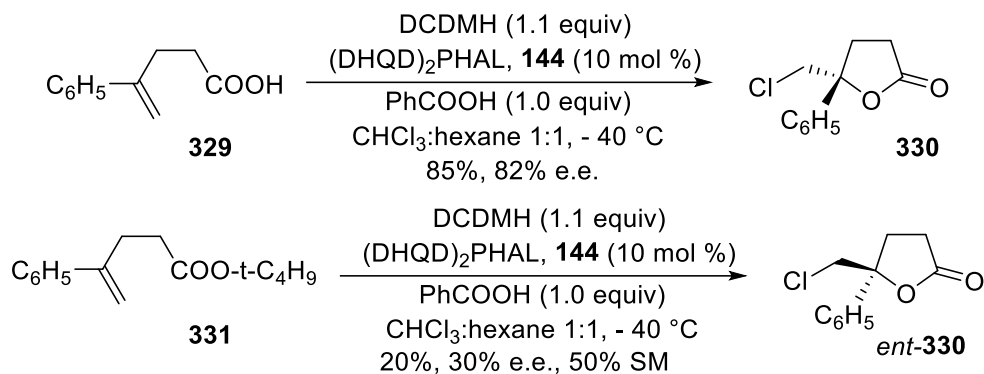
The stereochemical outcome of this chlorolactonization was further investigated, and chiral hydantoins (S)-334, (R)-335, (S)-336, and (R)-337 were used, together with catalysts 144 and 145 in order to ascertain the best match/mismatch conditions. Starting from the alkenoic acid 332, in the presence of benzoic acid, chlorolactone (R)-333 was obtained in the best yield and, e.e. by using (DHQD)2PHAL 144 coupled with hydantoin (S)-334. In contrast, the enantiomeric chlorolactone ent-333, having the opposite configuration, obtained a similar yield and enantioselection using (DHQ)2PHAL 145 and hydantoin (R)-337 [196-197].
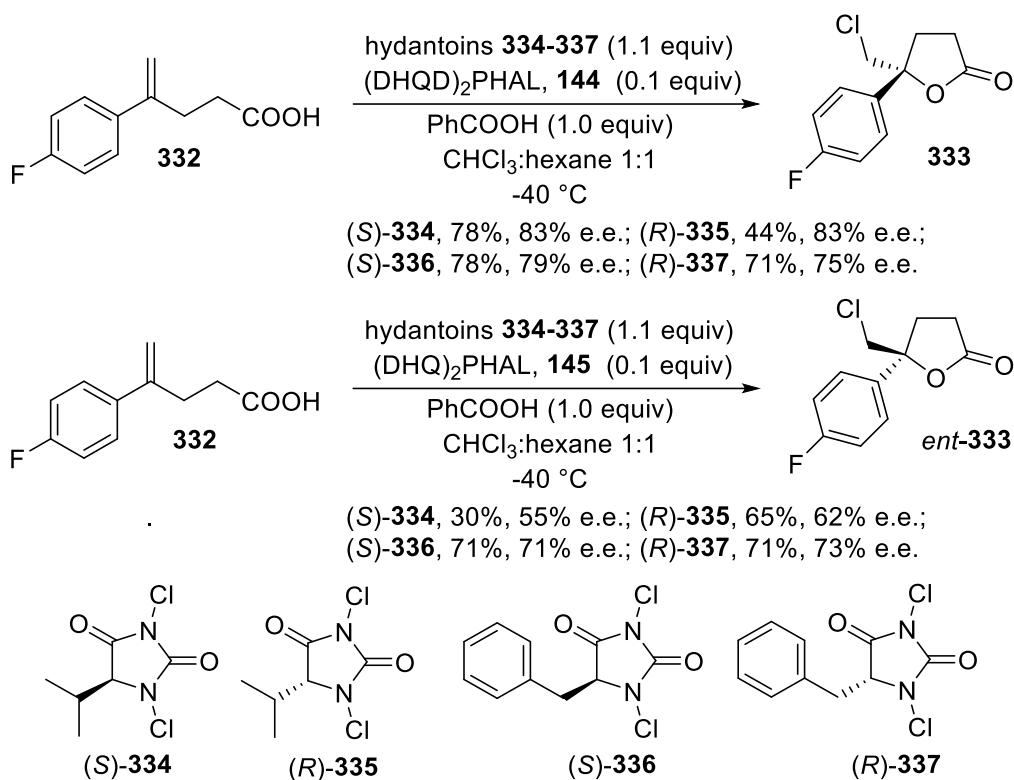
Thus, the enantioselective chlorolactonization of 332 was successfully optimized and applied to deeply evaluate the features at the basis of the enantioselective (DHQD)2PHAL 144 catalyzed halofunctionalization of olefins. In order to design simplified organocatalysts, the mechanistic investigation also gave indications about both the optimal range of alkene halenium affinity (HalA) values needed to favor concerted reactions and the requisites for obtaining relative and absolute stereochemistry. Moreover, when the cyclization of acid 338 was induced by 1,3-dichloro-5,5-dimethyl-hydantoin (DCDMH), the corresponding chlorolactone 339 was isolated in lower yield but with better enantioselection in comparison with cyclization induced by NBS [143].
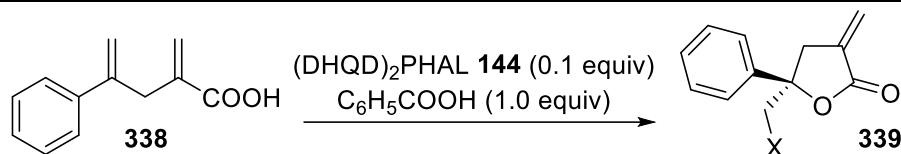
X = Br: NBS (1.2 equiv), toluene, -20 °C, 99%, 84% e.e.
X = Cl: DCDMH (1.2 equiv), CHCl$_3$/hexane, -20 °C, 88%, 92% e.e.

Moreover, novel pseudoenantiomeric catalysts (ECin)2PHAL 342 and (Cin)2PHAL 343, prepared from epi-cinchonin and cinchonin, respectively, were used for chlorocyclization of unsaturated acid 340 induced by dichlorodimethylhydantoin (DCDMH). The reaction proceeded through an 8-endo-mode driven by electronic factors, and both the enantiomeric eight-membered ring azalactone 341 and ent-341 were obtained in excellent yield and high enantioselection [146].

(ECin)$_2$PHAL, 342   (Cin)$_2$PHAL, 343
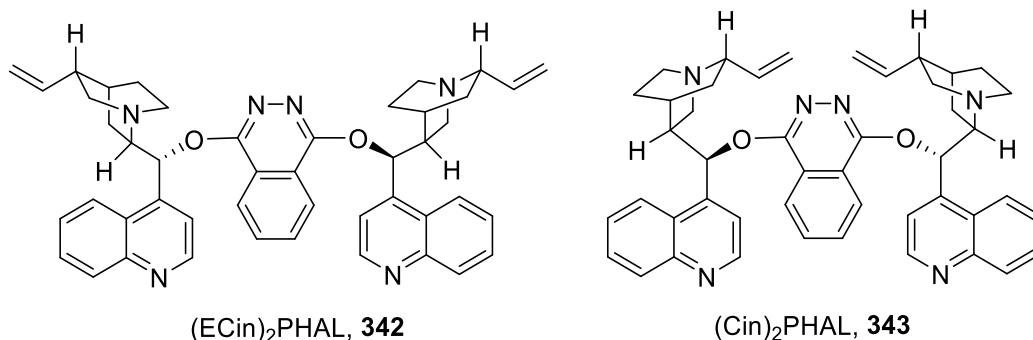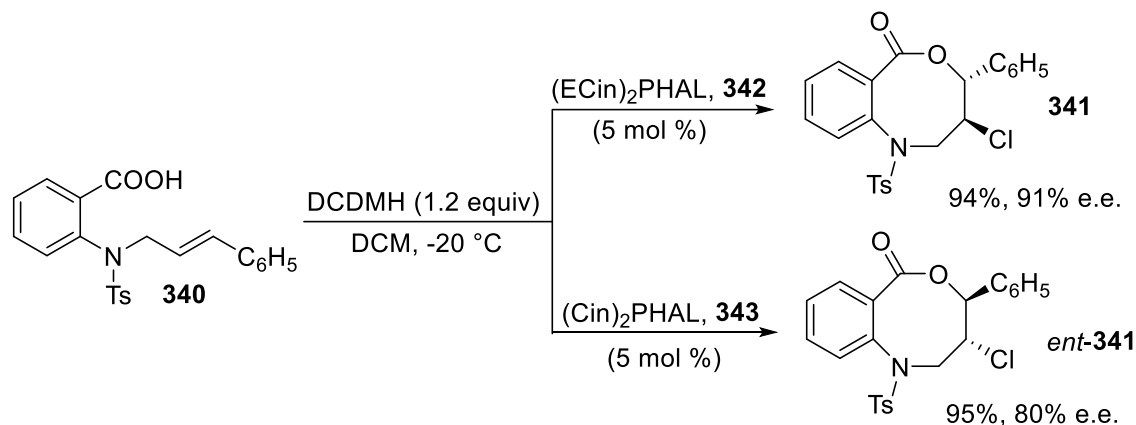
The C3-symmetrical catalyst 347, containing both the cinchonine and the squaramide moieties, was used for the chlorolactonization of acids 344 induced by DCDMH in the presence of an excess nosylamide. The corresponding chlorolactones 345 or 346 were isolated in very good yield, and regioselection was driven by electronic factors. The cyclization proceeded with high enantioselection, and the catalyst could be recovered and used again [198].
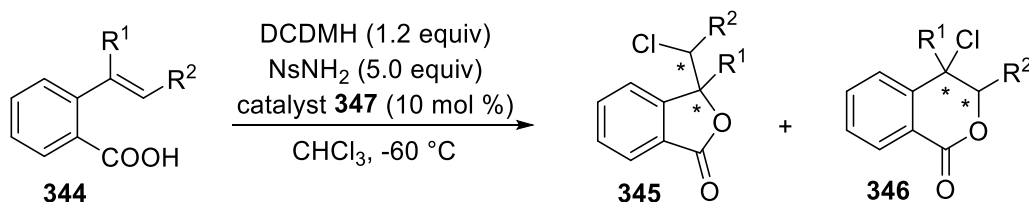
R^1 = CH$_3$, R^2 = H, 93% (>99:1), 83% e.e.; R^1 = H, R^2 = CH$_3$, 94% (1:99), 95% e.e.;
R^1 = 4-Cl-C$_6$H$_4$, R^2 = H, 93% (99:1), 82% e.e.; R^1 = C$_6$H$_5$, R^2 = CH$_3$, 92% (1:99), 80% e.e.

347
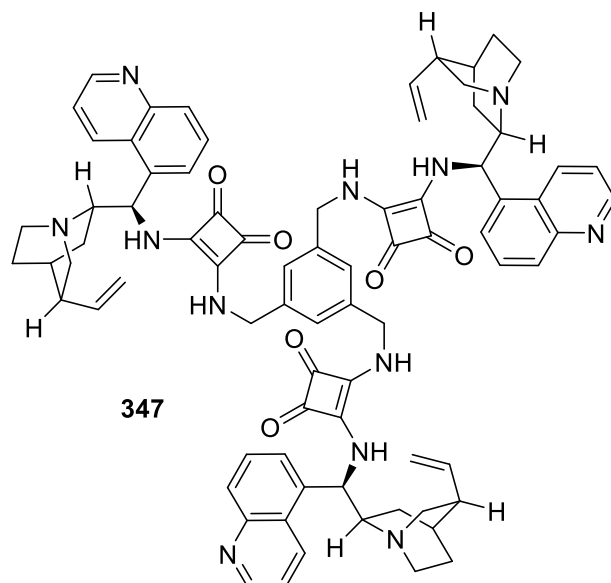
2.1.3. Iminolactones from amides of alkenoic acids.

2.1.3.1. Without asymmetric induction.

The amides 348, bearing an allenyl group, underwent cyclization mediated by NIS to provide the intermediate iminolactones 349 that, by aromatization followed by further reaction with NIS, led to substituted diiodofurans 350 in good yield [199].

$R^1 = CH_3$, $R^2 = R^3 = C_6H_5$, 78%; $R^1 = n\text{-}C_4H_9$, $R^2 = R^3 = C_6H_5$, 70%;
$R^1 = CH_3$, $R^2 = 4\text{-}CH_3\text{-}C_6H_4$, $R^3 = C_6H_5$, 71%
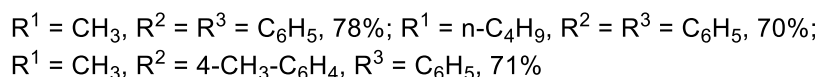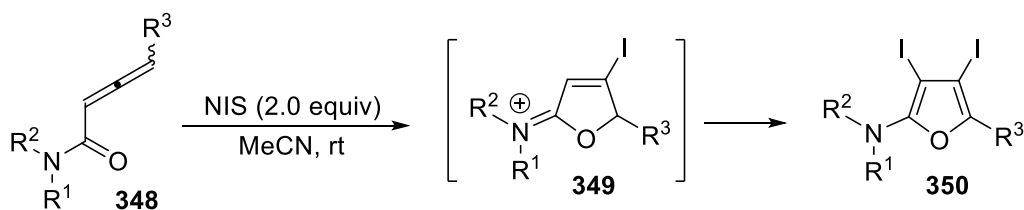
2.1.3.2. With internal asymmetric induction.

Besides carboxylic and carboxylate groups, the amido group can undergo cyclization mediated by haliranium ions. When an electron-withdrawing group on the nitrogen atom was missing, the attack occurred via the nucleophilic carbonyl oxygen, leading first to an iminolactone that, in the presence of water, could undergo hydrolysis to the corresponding lactone. Thus, the stereoselective cyclization in the absence of water of the chiral amide 351 led to the corresponding iminolactone 352 in excellent yield [200-201].
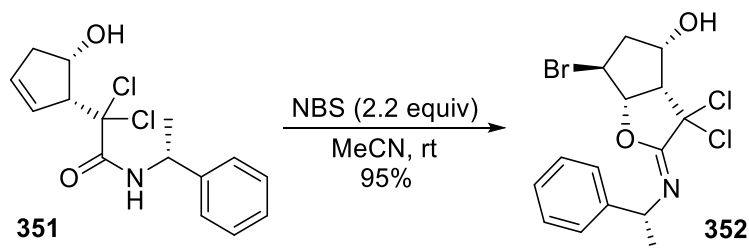
On changing the cyclization conditions, a reversal of stereoselection was observed for the cyclization of malonamides 353 bearing an allyl group at C-2. In fact, the reaction carried out with NBS led preferentially to the 1,3-cis-disubstituted diastereomer 354, whereas electrochemically

generated bromine as the bromiranium source afforded the 1,3-trans-disubstituted diastereomer 355 as the major product [202].
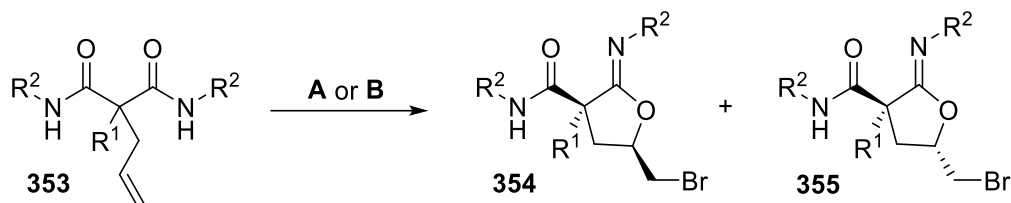
A: NBS (2 equiv), toluene, rt
B: Et$_4$NBr (2 equiv), Zn(OTf)$_2$ (10 mol %), 2,2'-bipyridine (10 mol %), DCM, rt, beaker-type undivided cell, Pt plate electrode, 1.0 x 2.0 cm2, 20 mA, 4F/mol.

R^1 = C$_2$H$_5$, R^2 = C$_6$H$_5$, **A**: 98%, 95:5 d.r.; **B**: 73%, 0.1:99.9 d.r
R^1 = R^2 = C$_6$H$_5$, **A**: 98%, 94:7 d.r.; **B**: 82%, 12:88 d.r.
R^1 = CH$_3$, R^2 = 4-CH$_3$O-C$_6$H$_4$, **A**: 97%, 95:5 d.r.; **B**: 97%, 1:99 d.r.

In addition, when PhICl$_2$ was used to generate a chloriranium ion, the amides 356 afforded regio- and stereosectively the corresponding iminolactones 357 [195].
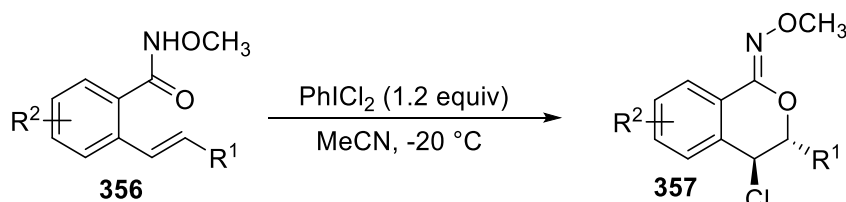
R^1 = C$_6$H$_5$, R^2 = H, 89%; R^1 = C$_6$H$_5$, R^2 = 4-CF$_3$, 81%;
R^1 = 3-Cl-C$_6$H$_4$, R^2 = H, 75%; R^1 = 2-naphthyl, R^2 = H, 84%

However, when the cyclization occurred in the presence of water and with the Oxone®/KBr system to generate the bromiranium ion, the imino intermediate underwent cleavage, and starting from amides 358, the corresponding disubstituted lactones 359 and 360 were isolated with moderate to good stereoselection, the major product being the 1,3-trans-disubstituted diastereomer 359 [100].
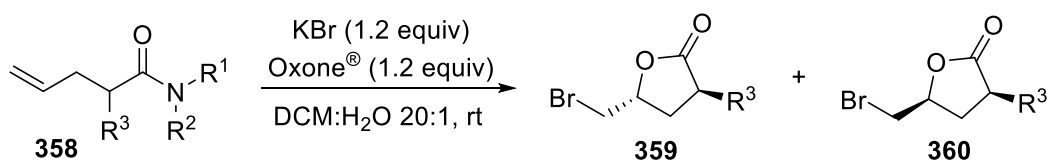
R^1 = R^2 = C$_6$H$_5$CH$_2$, R^3 = CH$_3$, 78%, 83:17 d.r.; R^1 = R^3 = CH$_3$, R^2 = OCH$_3$, 74%, 90:10 d.r.;
R^1 = R^2 = CH$_3$, R^3 =(CH$_3$)$_2$CH, 87%, 86:14 d.r.; R^1 = R^2 = CH$_3$, R^3 = n-C$_8$H$_{17}$, 90%, 88:12 d.r.;
R^1 = R^2 = CH$_3$, R^3 = cyclohexyl, 81%, 93:7 d.r.; R^1 = R^2 = CH$_3$, R^3 = C$_6$H$_5$CH$_2$, 91%, 94:6 d.r.

A regiodivergent functionalization reaction was reported for the amide 361, proceeding via an intermediate iminolactone. In fact, in sunlight and at room temperature, the six-membered ring 362 was favored. On the contrary, when the reaction was carried out in the dark and at a higher temperature, the major product was the five-membered ring 363. In both cases, the hydroxy functionality was introduced by displacement of iodide by the water present in the reaction medium [203].
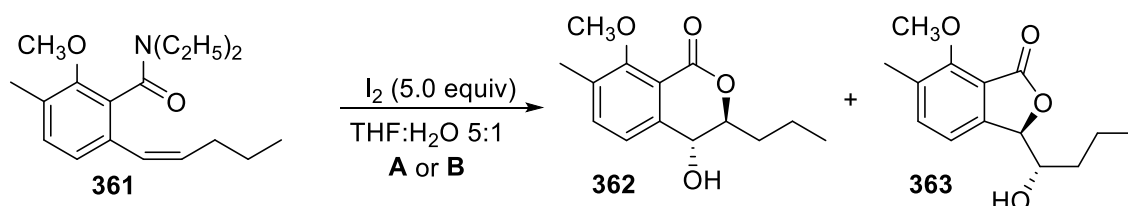
A: sunlight, rt, 75%, 55:45, d.r. >95:5; **B**: dark, 65 °C, 72%, 6:94, d.r >95:5

Unsaturated diastereomeric tertiary amides 364 and 367, bearing a chiral group on the nitrogen atom, underwent iodine-mediated cyclization in an aqueous solvent, leading in moderate to good yield but with low stereoselection to diastereomeric mixtures of lactones 365, 366 and 368, 369, respectively [204].
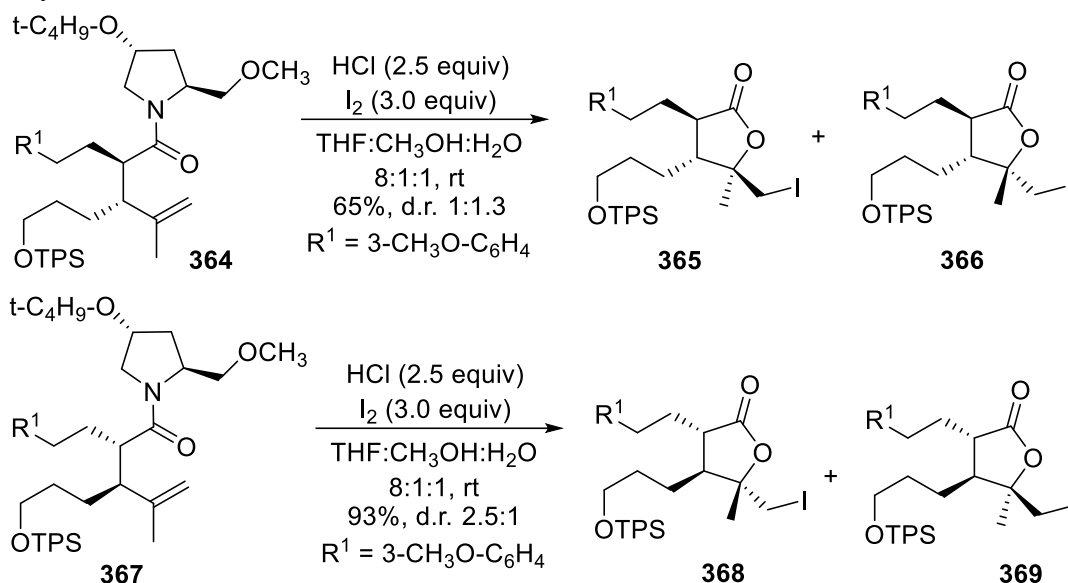
In a similar approach, the amide 370 afforded a mixture of lactones 371 with total regioselection, but stereoselection was practically missing [205].
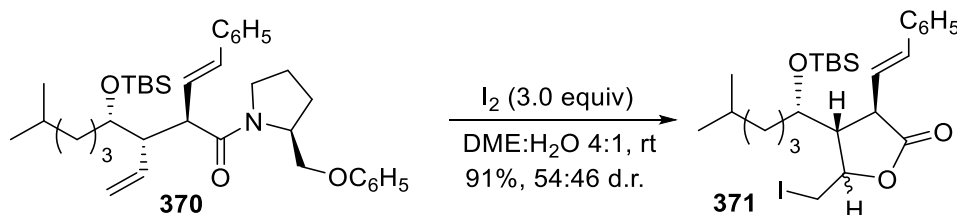
2.1.3.3. With external asymmetric induction.

In the presence of ligand 374 and copper(I) acetate, N-tosyl amides 372 underwent cyclization mediated by NIS, used together with catalytic iodine employed as activating reagent. However, whereas N-tosyl amides generally react intramolecularly, leading to a new C-N bond, in this case, a new C-O bond was exclusively formed via a 6-exo-mode, leading to excellent yield and good enantioselection to iminolactones 373 [206].

$R^1 = C_6H_5$, 98%, 93% e.e.; $R^1 = 4$-F-C_6H_4, 90%, 90% e.e.;
$R^1 = CH_3$, 80%, 87% e.e.; $R^1 = $ cyclohexyl, 99%, 91% e.e.
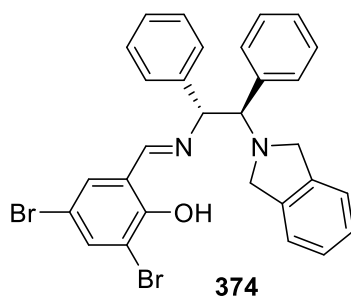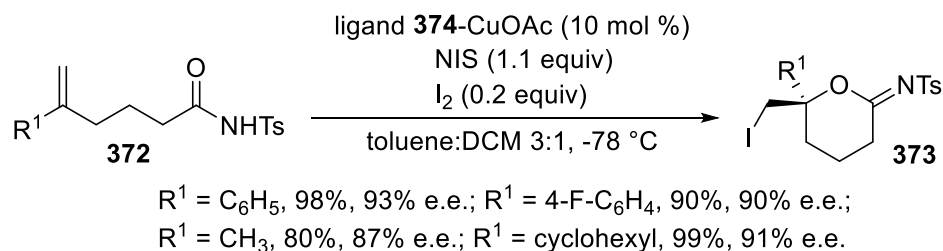
2.1.4. 4,5-Dihydro-1,3-oxazoles and 5,6-dihydro-4*H*-1,3-oxazines from *N*-alkenyl amides.

2.1.4.1. Without asymmetric induction.

N-alkenyl amides were converted into the corresponding 1,3-dihydrooxazoles or 1,3-dihydrooxazines by halocyclization exploiting the carbonyl oxygen as a nucleophile. Thus, amides 375 gave the corresponding 1,3-dihydrooxazoles 376 in good yield, and the iodide anion was converted in situ into iodine by I2O5, according to a novel environmentally friendly methodology for generating the intermediate iodiranium ion [207].

R^1 = C$_6$H$_5$, 94%; R^1 = 4-F-C$_6$H$_4$, 91%; R^1 = cyclohexyl, 81%
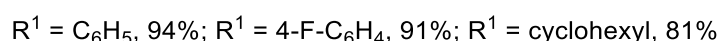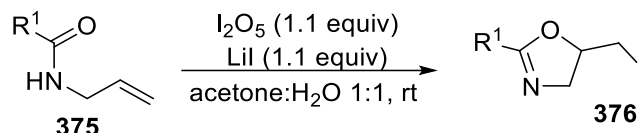
The environmentally friendly umpolung of the bromide ion was obtained also by reaction with Oxone®, and amides 377 were efficiently converted into the corresponding 4,5-dihydro-1,3-oxazoles 378 [101].

R^1 = 4-CH$_3$O-C$_6$H$_4$, R^2 = C$_6$H$_5$, 94%; R^1 = 2-Br-C$_6$H$_4$, R^2 = C$_6$H$_5$, 93%;
R^1 = C$_6$H$_5$, R^2 = 4-Cl-C$_6$H$_4$, 92%; R^1 = C$_6$H$_5$, R^2 = n-C$_6$H$_{13}$, 98%
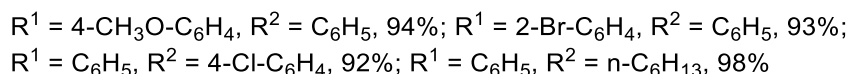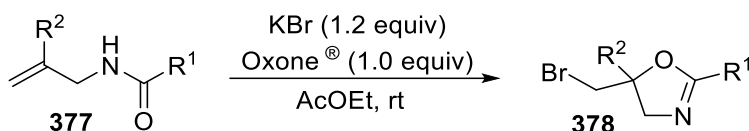
Moreover, in analogy with homohalocyclization of acids bearing a cyclopropyl group [62], amides 379 reacted with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH), and the corresponding dihydro-1,3-oxazoles 380 were isolated in excellent yield, but the Lewis basic sulfide 53 was required for cyclization. In analogy, amides 381 gave in moderate to good yield the trans-disubstituted 5,6-dihydro-4H-1,3-oxazines 382, exclusively, probably via an intermediate analog of bromiranium ion [208].

R^1 = 4-t-C$_4$H$_9$-C$_6$H$_4$, R^2 = C$_6$H$_5$, 97%; R^1 = 4-CH$_3$O-C$_6$H$_4$, R^2 = C$_6$H$_5$, 87%;
R^1 = 4-NO$_2$-C$_6$H$_4$, R^2 = C$_6$H$_5$, 95%; R^1 = C$_6$H$_5$, R^2 = 4-Cl-C$_6$H$_4$, 95%

R^1 = 4-t-C$_4$H$_9$-C$_6$H$_4$, R^2 = C$_6$H$_5$, 71%; R^1 = C$_6$H$_5$, R^2 = 4-Cl-C$_6$H$_4$, 62%;
R^1 = 4-Br-C$_6$H$_4$, R^2 = C$_6$H$_5$, 77%; R^1 = 4-t-C$_4$H$_9$-C$_6$H$_4$, R^2 = 4-CH$_3$O-C$_6$H$_4$, 82%;
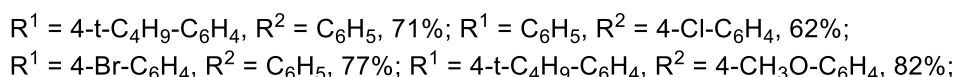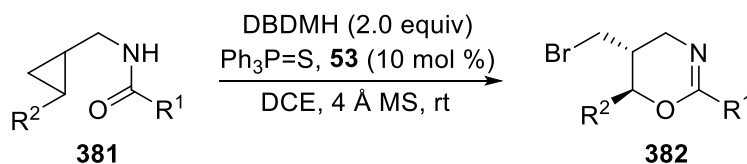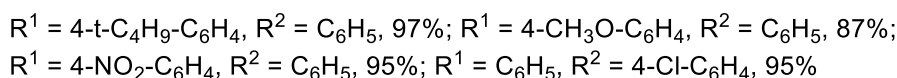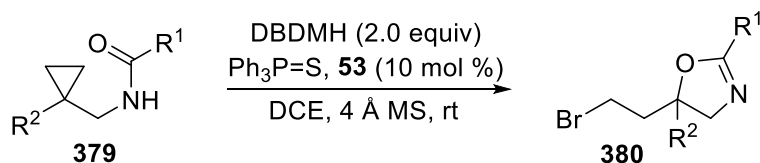
Eventually, the 5,6-dihydro-4H-1,3-oxazines 384 were isolated in moderate yield without any stereoselection when the amides 383 underwent cyclization mediated by NBS and (diacetoxyiodo)benzene (PIDA), followed by eventual bromoazidation of the conjugate double bond [209].
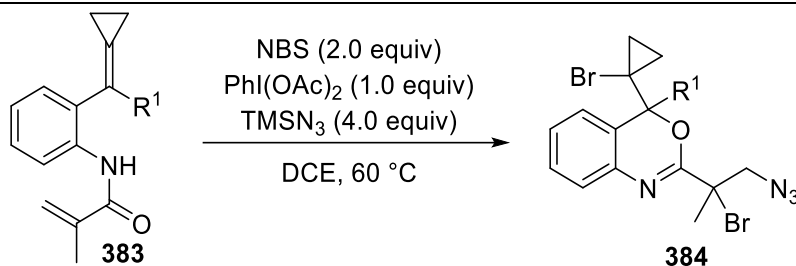
R^1 = C$_6$H$_5$, 78%, d.r. 1:1.4; R^1 = 4-Cl-C$_6$H$_4$, 70%, d.r. 1:1.1;
R^1 = 4-Br-C$_6$H$_4$, 75%. d.r. 1:1.2

2.1.4.2. With external asymmetric induction.

The bromocyclization of N-alkenyl amides 385 was carried out in the presence of the catalyst 387, containing two phosphine groups, leading to 4,5-dihydro-1,3-oxazoles 386 in good yield and high enantioselection [210-211]. In a further development, the catalyst structure was modified, introducing a phosphine oxide moiety, 388, and the same amides 385 were converted into the corresponding heterocyclic derivatives 386 in good yield but with better stereoselection, even using a minor amount of the catalyst [212-213].
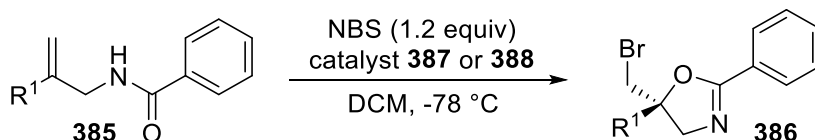
catalyst 387 (10 mol%): R^1 = C$_6$H$_5$, 99%, 99% e.e.; R^1 = 4-CH$_3$-C$_6$H$_4$, 91%, 95% e.e.;
R^1 = 4-NC-C$_6$H$_4$, 95%, 98% e.e.
catalyst 388 (1 mol%): R^1 = C$_6$H$_5$, 99%, 98% e.e.; R^1 = 4-CH$_3$-C$_6$H$_4$, 91%, 97% e.e.;
R^1 = 4-NC-C$_6$H$_4$, 90%, >99.5% e.e.
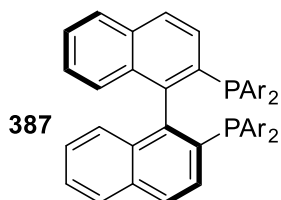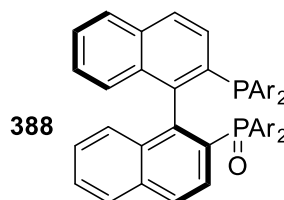
Ar = 3,5-(t-Bu)$_2$-4-CH$_3$O-C$_6$H$_2$ Ar = 3,5-(t-Bu)$_2$-4-CH$_3$O-C$_6$H$_2$

Moreover, the reaction of amides 389 performed with dichlorodimethylhydantoin (DCDMH) in the presence of (DHQD)2PHAL 144 led to the corresponding 5,6-dihydro-4H-1,3-oxazines 390 in moderate yield but with high enantioselection, together with products 391, arising from the simple electrophilic addition to the double bond [214].

R^1 = OCH$_3$, 94% e.e.
R^1 = NO$_2$, 92% e.e.
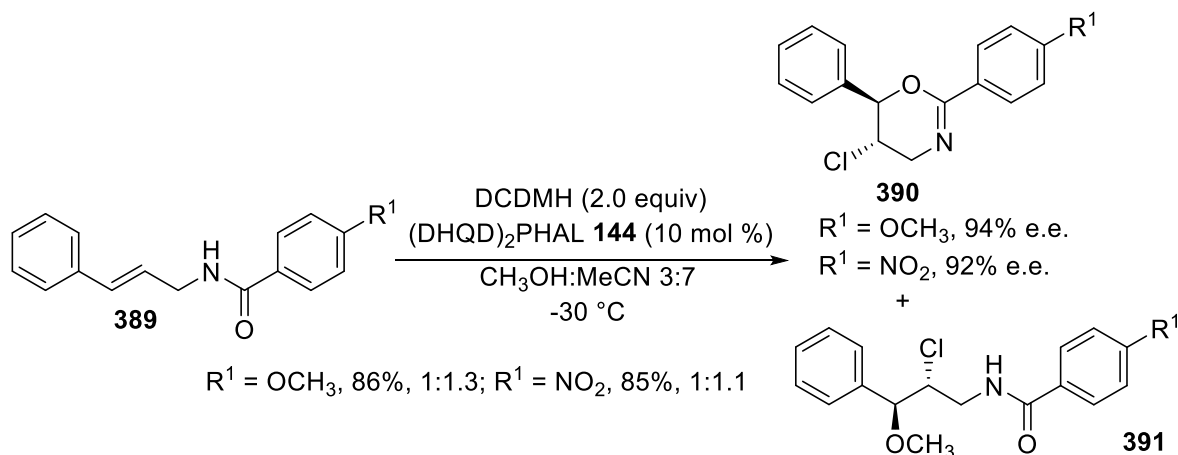
R^1 = OCH$_3$, 86%, 1:1.3; R^1 = NO$_2$, 85%, 1:1.1

When the cyclization of γ,δ-unsaturated amides 392 was carried out using the catalyst (DHQD)2PHAL 144 in the presence of about half equivalent of N-chloropyrrolidin-2-one (NCP) as chlorenium source, a kinetic resolution took place, providing a mixture of diastereomeric 5,6-dihydro-4H-1,3-oxazines 393 and 394 in high e.e., where 393 was the major component, together with enantiomeric amides (S)-392 isolated in high e.e. [215].
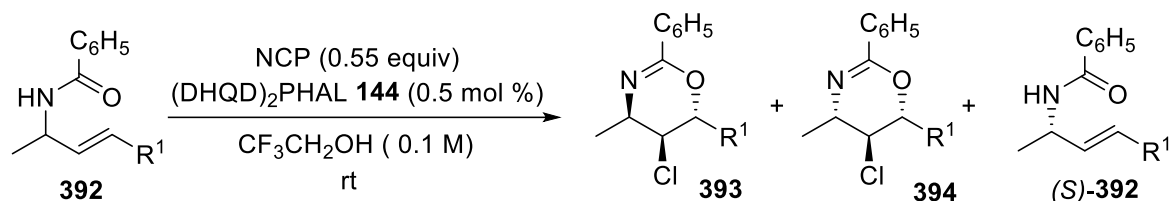
$R^1 = C_6H_5$, 55% (393+394), 95:5 e.r. (393), 97:3 d.r. (393:394), 98.5:1.5 e.r. (392);
$R^1 = 4\text{-Cl-}C_6H_4$, 54% (393+394), 95.5:4.5 e.r. (393), 96:4 d.r. (393:394), 99.5:0.5 e.r. (392);
$R^1 = 4\text{-F-}C_6H_4$, 46% (393+394), 95:5 e.r. (393), 93.5:6.5 d.r. (393:394), 99:1 e.r. (392)

When o-anilidostyrenes 395 were treated with a chiral anion phase-transfer system using cation 397, derived from DABCO, together with the highly lipophilic phosphoric acid 398 having 6,6′-TIPS substituents, the corresponding 4H-3,1-benzoxazines 396 were isolated in moderate to good yield but with excellent enantioselection [216].
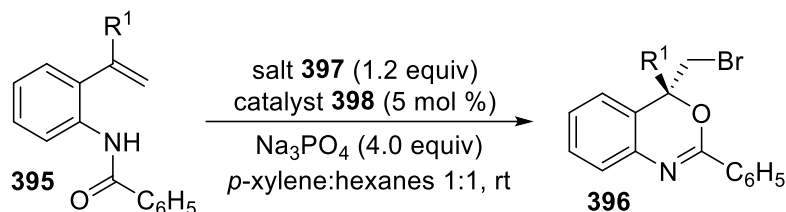
$R^1 = CH_3$, 82%, 94% e.e.; $R^1 = (CH_3)_2CH$, 94%, 99% e.e.;
$R^1 = (CH_2)_3OTBS$, 85%, 99% e.e.; $R^1 = (CH_2)_3N(CH_3)_2$, 67%, 91% e.e.

$R^1 = 2,4,6\text{-}[(CH_3)_2CH]_3\text{-}C_6H_2$
$R^2 = [(CH_3)_2CH]_3Si$
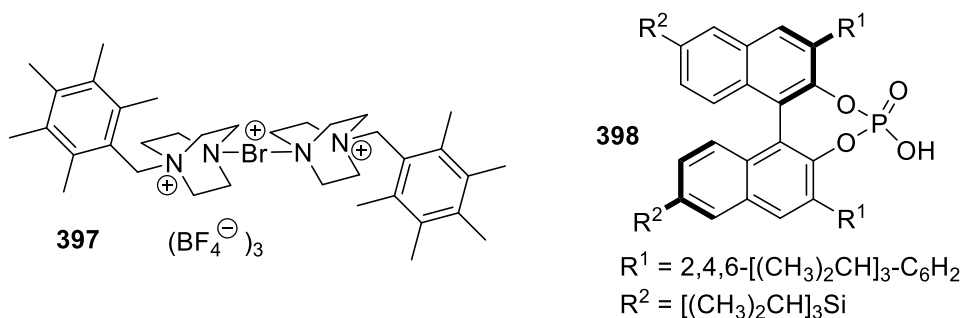
On the contrary, the cyclization of o-anilidostyrenes 399, carried out with dichlorodimethylhydantoin (DCDMH) in the presence of catalyst 401, afforded good yield and high enantioselection chloromethyl 4H-1,3-benzoxazines 400, displaying the opposite chirality at C-4, with respect to compounds 396 [217].
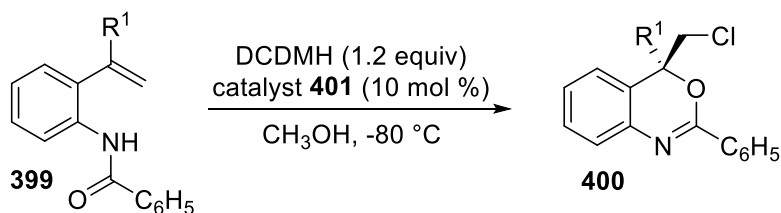
$R^1 = C_6H_5$, 84%, 92% e.e.; $R^1 = 3\text{-CH}_3O\text{-}C_6H_4$, 93%, 90% e.e.;
$R^1 = 3\text{-CF}_3\text{-}C_6H_4$, 88%, 87% e.e.; $R^1 = n\text{-}C_4H_9$, 96%, 49% e.e.

401

$R^1 = 2\text{-}CH_3\text{-}C_6H_4$
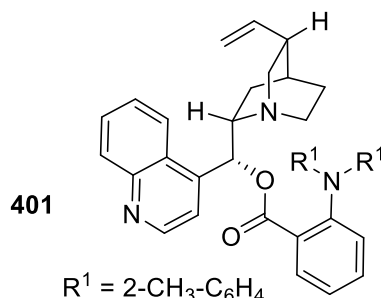
The haliranium ion intermediate can display very unstable chirality, and a rapid olefin-to-olefin transfer process exists between the enantiomerically enriched haliranium ion and electron-rich indole substrates. However, the cyclization of amides 402 tethered on an indolic structure was carried out with dichlorodimethylhydantoin (DCDMH) in the presence of catalyst (DHQD)2PHAL 144 to give the tricyclic 5,6-dihydro-4H-1,3-oxazines 403 in good yield and excellent enantioselection, according to a 6-endo-trig mode closure [218].
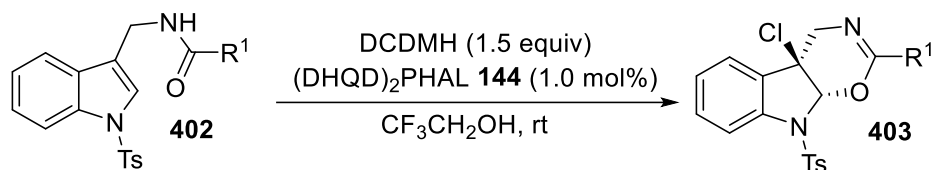
$R^1 = 3\text{-}CH_3\text{-}C_6H_4$, 93%, >99% e.e.; $R^1 = 4\text{-}CH_3\text{-}C_6H_4$, 89%, >99% e.e.;
$R^1 = 4\text{-}Cl\text{-}C_6H_4$, 91%, >99% e.e.; $R^1 = 2\text{-naphthyl}$, 98%, >99% e.e.

Catalyst (DHQD)2PHAL 144 was also highly effective for the cyclization of compounds 404 mediated by dichlorodiphenylhydantoin (DCDPH), and the spiroindoline derivatives 405 were isolated in good yield and excellent stereoselection [219].
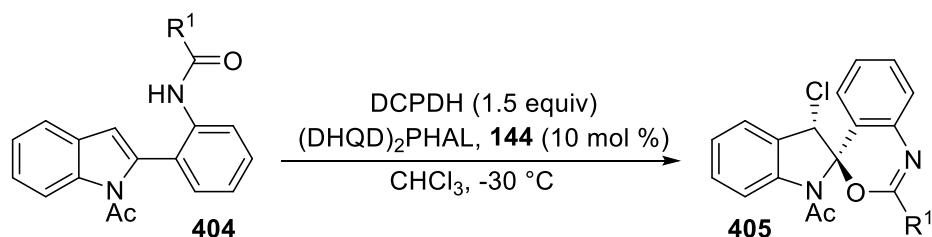
$R^1 = C_6H_5$, 85%, 95% e.e.; $R^1 = 3\text{-}CH_3\text{-}C_6H_4$, 80%, 95% e.e.;
$R^1 = 4\text{-}CH_3\text{-}C_6H_4$, 87%, 95% e.e.; $R^1 = 4\text{-}CH_3O\text{-}C_6H_4$, 82%, 91% e.e.

In the presence of the same catalyst 144, amides 406 underwent cyclization mediated by N-chlorophthalimide (NCP), and dearomatizazion of benzofurans provided spiro 4,5-dihydro-1,3-oxazoles 407 in good yield and excellent stereoselection [220].
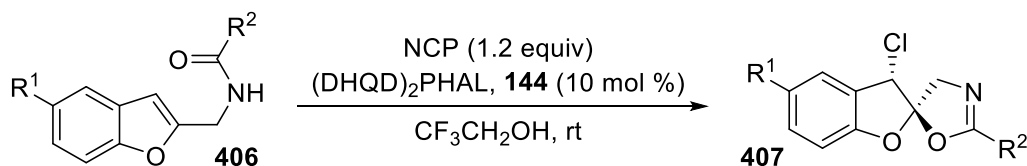
$R^1 = H$, $R^2 = C_6H_5$, 99%, 99% e.e.; $R^1 = H$, $R^2 = 4\text{-}CH_3O\text{-}C_6H_4$, 76%, 99% e.e.;
$R^1 = Cl$, $R^2 = C_6H_5$, 99%, 99% e.e.; $R^1 = R^2 = C_6H_5$, 90%, 99% e.e.

The cyclization of simple unsaturated arylamides 408 and 410 was carried out also by using Chloramine-T·3H$_2$O (TsNNACl . 3H$_2$O) in the presence of catalyst 144, exploiting fluorinated solvents with the aim to increase the reaction rate. The corresponding 4,5-dihydro-1,3-oxazoles 409 and 5,6-dihydro-4H-1,3-oxazines 411, arising from 5-exo-trig and 6-endo-trig closures, respectively, were obtained in good yield and high enantioselection [221].
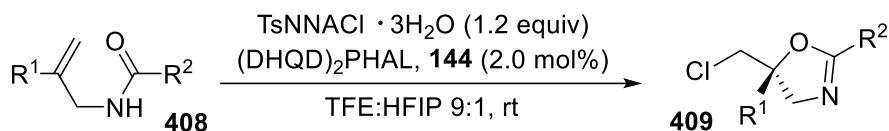
R^1 = R^2 = C$_6$H$_5$, 85%, 92% e.e.; R^1 = R^2 = 4-Br-C$_6$H$_4$, 87%, 90% e.e.;
R^1 = 4-Cl-C$_6$H$_4$, R^2 = 4-Br-C$_6$H$_4$, 86%, 92% e.e.
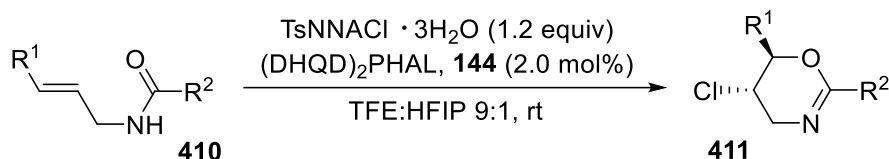
R^1 = C$_6$H$_5$, R^2 = 4-CH$_3$O-C$_6$H$_4$, 93%, >99% e.e.; R^1 = R^2 = 4-Br-C$_6$H$_4$, 95%, 91% e.e.;
R^1 = 2-CH$_3$-C$_6$H$_4$, R^2 = 4-Br-C$_6$H$_4$, 95%, 91% e.e.

Using again catalyst 144 together with dichlorodiphenylhydantoin (DCDPH) as a source of chlorenium ions, amides 412 were converted into the corresponding 4,5-dihydro-1,3-oxazoles 413 in good yield with high regio- and enantioselection, and the 5-exo-trig closure was directed by electronic factors [222].
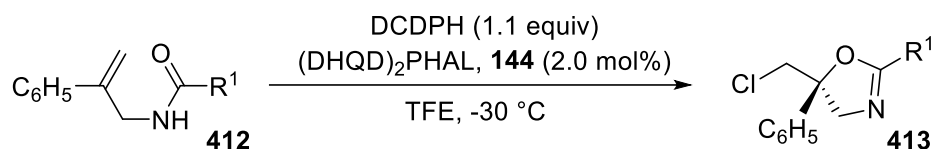
R^1 = C$_6$H$_5$, 96%, 90% e.e.; R^1 = 4-NO$_2$-C$_6$H$_4$, 97%, 93% e.e.;
R^1 = 4-CH$_3$O-C$_6$H$_4$, 90%, 93% e.e.

Eventually, the bromocyclization of bis-allylic amides 414 was carried out with NBS in the presence of the chiral phosphine oxide 388 as a Lewis base, and the desymmetrization was highly effective, leading to the 4,5-dihydro-1,3-oxazoles 415 in high yield and good enantioselection [223]. Furthermore, within a synthetic approach to the antiviral Nelfinavir, catalyst 387, bearing two phosphine functional groups, was employed in minor amount for the same process, and both yields and enantioselection for the desymmetrization of amide 414c to 1,3-oxazole 415c were slightly better [224].
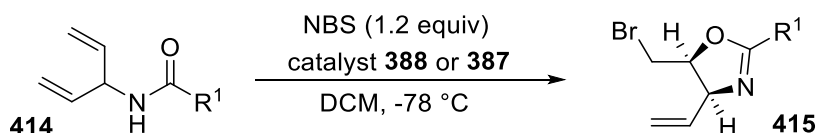
catalyst 388 (10 mol %) a. R^1 = 3-Br-C$_6$H$_4$, 87%, *cis:trans* 92:8, (*cis*): 90% e.e.;
catalyst 388 (10 mol %) b. R^1 = 4-Br-C$_6$H$_4$, 87%, *cis:trans* 93:7, (*cis*): 92% e.e.;
catalyst 388 (10 mol %) c. R^1 = 4-CH$_3$O-C$_6$H$_4$, 89%, *cis:trans* 93:7, (*cis*): 94% e.e.;
catalyst 387 (5 mol %) c. R^1 = 4-CH$_3$O-C$_6$H$_4$, 95%, *cis:trans* 93:7, (*cis*): 95% e.e.

2.1.5. 1,3-Oxazolidin-2-ones, 1,3-oxazin-2-ones, 1,3-dioxolan-2-ones and 1,3-dioxan-2-ones from alkenyl carbamates and carbonates.

In the halocyclization of unsaturated substrates having ambident nucleophiles, such as carbamates, ureas, or amides, usually, O-cyclized products were preferred over N-cyclized products, in agreement with the hard and soft (Lewis) acids and bases (HSAB) theory [225-226] since oxygen, being more electronegative than nitrogen atom, prefer to attack the haliranium ion that is characterized as a hard electrophile. Thus, in order to obtain N-cyclized products, the pKa values of NH groups were lowered with the help of N-substitution, as it occurred in N-tosylcarbamates and N-tosylamides [227].

2.1.5.1. Without asymmetric induction.

Unsaturated carbamates underwent cyclization mediated by haliranium ions to give oxazolidin-2-ones or oxazin-2-ones. Thus, in the presence of ICl, the N-t-Boc derivatives 416 gave the corresponding 5-iodomethyl oxazolidin-2-ones 417 in good yield [228].

R^1 = 4-CH$_3$-C$_6$H$_4$, 85%; R^1 = C$_6$H$_5$, 80%; R^1 = 3-CH$_3$-C$_6$H$_4$, 92%
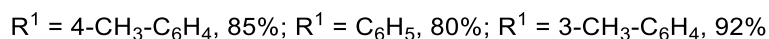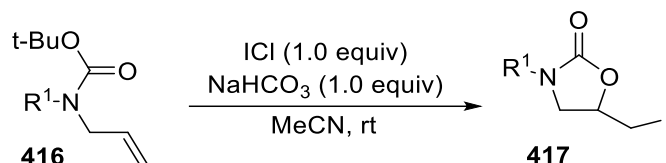
In analogy, imides 418 underwent iodocyclization mediated by ICl to give in good yield the corresponding oxazolidin-2,4-diones 419 [228].

R^1 = 4-CH$_3$O-C$_6$H$_4$, 89%; R^1 = C$_6$H$_5$, 86%; R^1 = C$_6$H$_5$CH$_2$, 91%
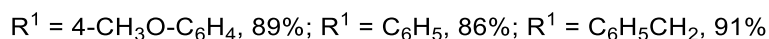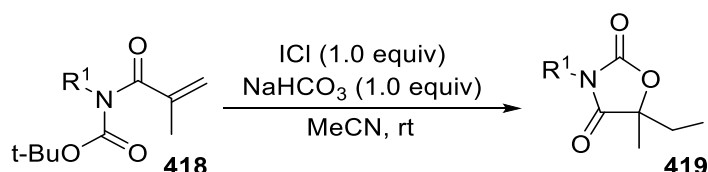
Oxazolidin-2-ones 421 were obtained in good yield when atmospheric carbon dioxide was fixed by allylic amines 420 [229], followed by cyclization mediated by t-butyl hypoiodite [230].

R^1 = R^2 = H, 91%; R^1 = H, R^2 = n-C$_3$H$_7$, 81%; R^1 = C$_6$H$_5$CH$_2$, R^2 = H, 87%
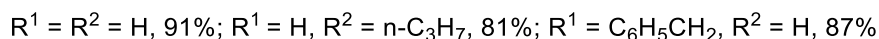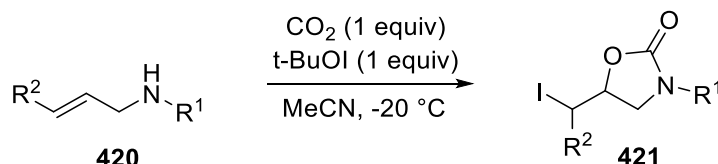
Good results were also observed when allylic amines 422 fixed carbon dioxide in the presence of Ag nanoparticles decorating nanoporous covalent organic frameworks (Ag@TpPa-1 and Ag@TpTta), and subsequent cyclization induced by NIS gave the N-unprotected oxazolidin-2-ones 423 [231].

R^1 = R^2 = R^3 = H, 96%; R^1 = R^2 = H, R^3 = CH$_3$, 72%, R^1 = R^2 = CH$_3$, R^3 = H, 78%
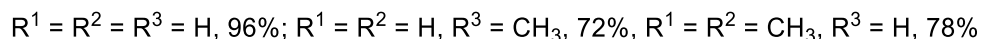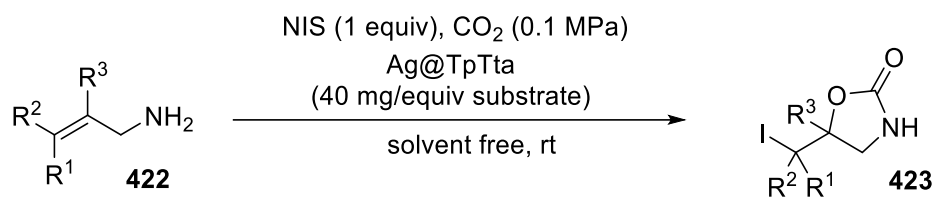
2.1.5.2. With internal asymmetric induction.

In 1981, the work of Cardillo demonstrated the utility of the cyclization of allylic and homoallylic carbonates, which allowed the introduction of one or two chirality centers starting from a preexisting one [26-27],[232]. Others recently built upon these studies, exploiting the cyclization of t-Boc derivatives 424 and 426, and polyfunctionalized sequences 425 and epoxy alcohols 427 were respectively prepared, which are useful intermediates within the synthesis of bioactive compounds [233-234].
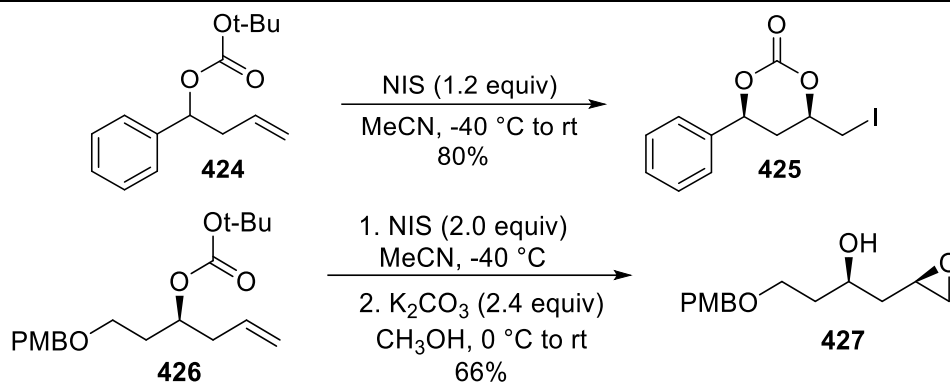
The cyclization of t-Boc derivatives 428 proceeded with excellent regio- and stereoselection, to give 429 with preferential functionalization of the chain double bond with respect to the ring double bond, probably in order to avoid the strain arising from two fused cycles [89-90],[235].
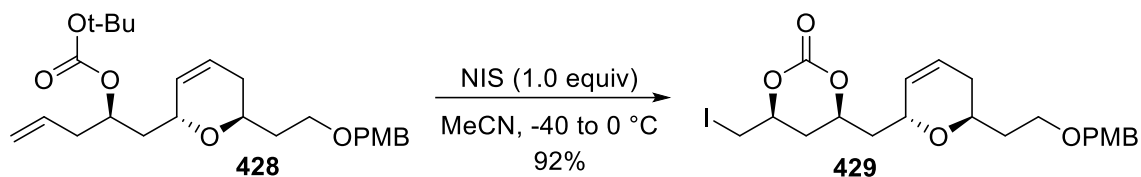
In addition, either the t-Boc geranyl 430a and the corresponding t-butylcarbamate 430b were treated with NIS in the presence of morpholine-HFIP (hexafluoroisopropanol) salt, leading to the corresponding bicyclic derivative 431 in good yield and high stereoselection through the formation of a new C-C bond [236].
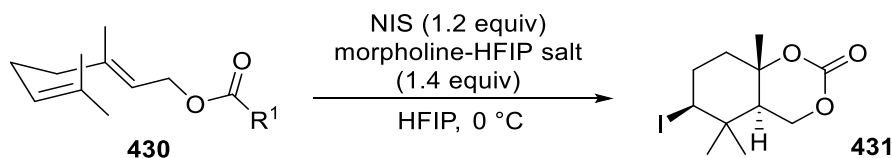
a. R[1] = Ot-Bu, 87%, d.r. >95:5; **b.** R[1] = NHt-Bu, 72%, d.r. >95:5

According to a similar procedure, the cyclization of t-Boc farnesyl 432, carried out using bromodiethylsulfonium bromopentachloroantimonate (BDSB), provided the tricyclic derivative 433 in low yield but with good stereoselection through the formation of two C-C bonds [237].
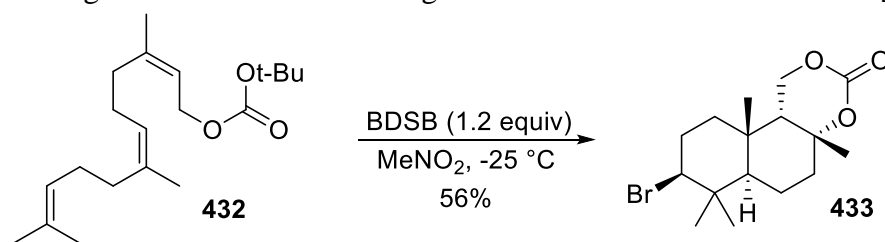
When two identical t-butoxycarbonylamino groups were present on the molecular backbone, as it occurred in compound 434, the angular strain biased the reaction to proceed in moderate yield but with high regioselection through a 6-endo mode. The major product was the 1,3-oxazin-2-one 435 arising from an attack of an oxygen atom to the intermediate iodiranium ion [238].
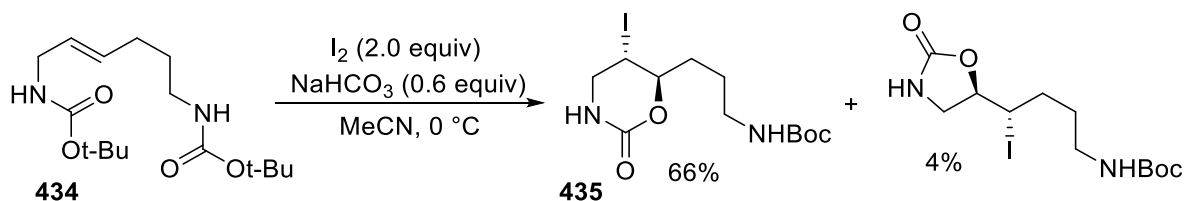
Moreover, within a synthesis of D-Vinecisamine and its epimers, the chiral acyclic carbamates 436 and 438 on treating with iodine afforded in good yield and high stereoselection the oxazolidin-2-ones 437 and 439, respectively [239].
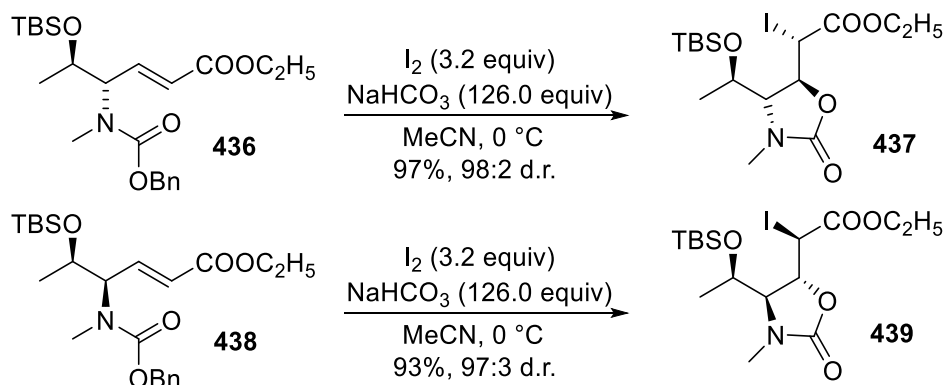
Eventually, a procedure closely related to the "phosphate extension" [27] and "emiacetal extension" [240] was devised starting from allylic silanol substrates 440. According to a 6-endo-trig cyclization, the substrates were converted in moderate to good yield, but with total regio- and stereoselection, into the corresponding six-membered 5-iodo-4-methyl-1,3,2-dioxasilinanes 441. These products were ascertained to be both kinetically and thermodynamically preferred based on DFT calculations and were suitable for further transformations, such as deiodination and conversion into azides and epoxides [241].
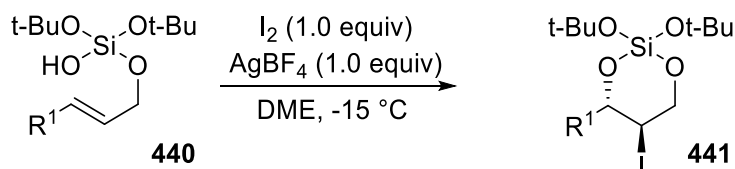
R^1 = $(CH_3)_2CHCH_2CH_2$, 89%; R^1 = cyclohexyl, 70%;
R^1 = 4-tetrahydropyranyl, 75%; R^1 = $C_6H_5CH_2CH_2$, 77%

2.1.5.3. With external asymmetric induction.

The cyclization of alkenols 442 mediated by NIS was performed with carbon dioxide in the presence of catalyst MeO-StilPBAM. HNTf2 444, and the corresponding 4-iodomethyl 1,3-dioxanones 443 were isolated in excellent yield and high enantioselection [242].
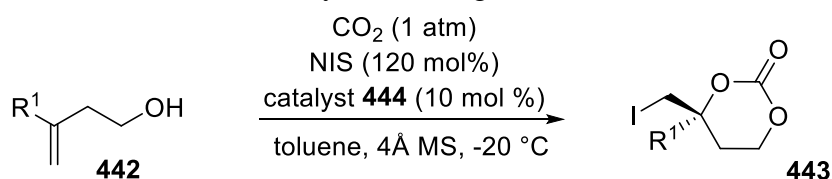
R^1 = C_6H_5, 95%, 91% e.e.; R^1 = 3-CH_3O-C_6H_4, 97%, 90% e.e.;
R^1 = 2-naphthyl, 88%, 90% e.e.; R^1 = 3-CH_3-C_6H_4, 96%, 93% e.e.

MeO-StilPBAM · HNTf$_2$, 444
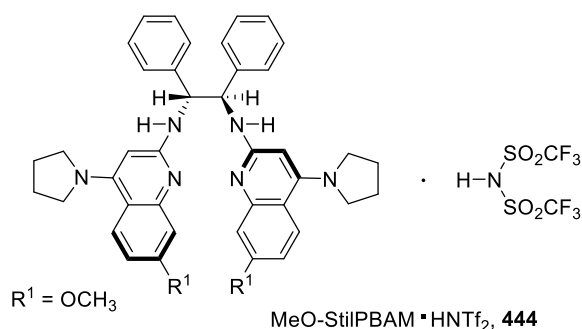
Moreover, oxazolidin-2-ones 446 and ent-446 were obtained in a stereo divergent mode by cyclization of allylic carbamates 445. The reaction exploited dichlorodimethylhydantoin (DCDMH) as a source of chlorenium ions and was carried out in the presence of a catalyst (DQHD)2PHAL 144. The configuration of the final product strongly relied on the solvent employed since in propanol, the enantiomers 446 were isolated in excellent yield as the major products, whereas an equimolar mixture of chloroform and hexanes allowed obtaining the opposite enantiomers ent-446, again in excellent yield, and enantioselection [243].
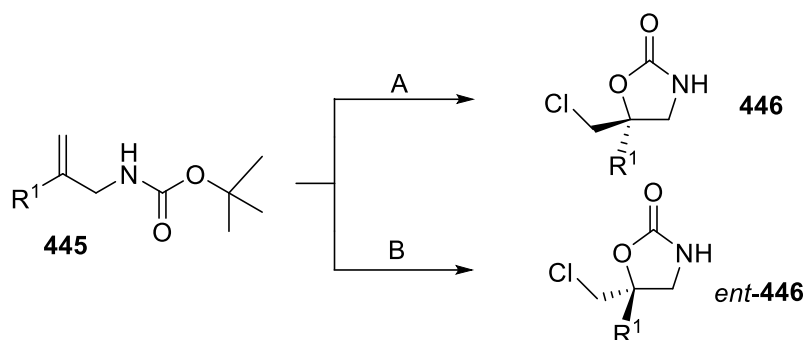
A: DCDMH (1.3 equiv), (DHQD)$_2$PHAL **144** (1 mol %), C$_6$H$_5$COOH (0.5 equiv), CH$_3$CH$_2$CH$_2$OH, -30 °C: R^1 = C$_6$H$_5$, 87%, 80% e.e.; R^1 = 4-F-C$_6$H$_4$, 92%, 87% e.e.; R^1 = 4-Cl-C$_6$H$_4$, 98%, 92% e.e.
B: DCDMH (1.3 equiv), (DHQD)$_2$PHAL **144** (20 mol %), CHCl$_3$/hexanes 1:1, 0 °C
R^1 = C$_6$H$_5$, 87%, 80% e.e.; R^1 = 4-F-C$_6$H$_4$, 92%, 87% e.e.; R^1 = 4-Cl-C$_6$H$_4$, 98%, 92% e.e.

An asymmetric chlorocyclization reaction, performed again with dichlorodimethylhydantoin (DCDMH) in the presence of catalyst 401, allowed to prepare chiral 4-chloromethyl-1,4-dihydro-1,3-benzoxazin-2-one derivatives 448 in good yield and high enantioselection starting from 2-vinyl phenylcarbamates 447 [244].
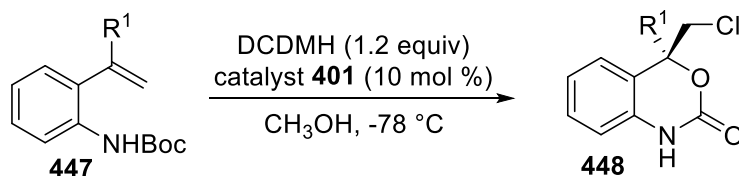
R^1 = C$_6$H$_5$, 86%, 90% e.e.; R^1 = 3-CH$_3$O-C$_6$H$_4$, 88%, 91% e.e.;
R^1 = 3-CF$_3$-C$_6$H$_4$, 71%, 94% e.e.; R^1 = n-C$_4$H$_9$, 92%, 66% e.e.

1,3-Oxazin-2-ones 451 were also obtained in good yield and high enantioselection from carbamates generated in situ by treating unsaturated amines 449 with CO2. The 6-exo-trig cyclization was mediated by NIS in the presence of the bifunctional organocatalyst 444, which stabilized the carbamic acid intermediate 450 and activated it towards the final enantioselective carbon-oxygen bond formation [245].
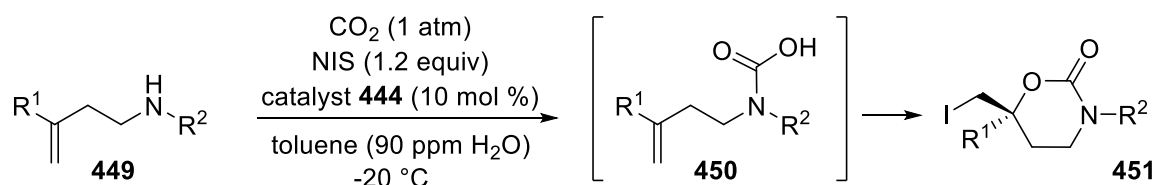
R^1 = C$_6$H$_5$, R^2 = C$_6$H$_5$CH$_2$, 75%, 89% e.e.; R^1 = C$_6$H$_5$, R^2 = 3-CH$_3$O-C$_6$H$_4$CH$_2$, 85%, 90% e.e.;
R^1 = 2-naphthyl, R^2 = C$_6$H$_5$CH$_2$, 72%, 93% e.e.; R^1 = 4-F-C$_6$H$_4$, R^2 = C$_6$H$_5$CH$_2$, 77%, 94% e.e.

In analogy with N-tosyl amides 372 [208], the oxygen atom of the carbonyl group of N-tosylcarbamates 452 attacked a chloriranium ion leading to N-tosyl-1,3-dioxolan-2-imines 453 and

the reaction, mediated by dichlorodimethylhydantoin (DCDMH) in the presence of catalyst **454**, proceeded in moderate to good yield and excellent stereoselection [246].
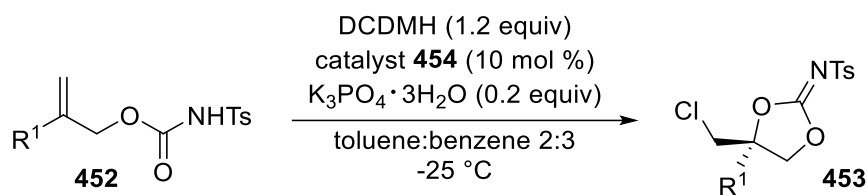
R^1 = C$_6$H$_5$, 88%, 91% e.e.; R^1 = 4-F-C$_6$H$_4$, 68%, 91% e.e.;
R^1 = 4-CH$_3$-C$_6$H$_4$, 62%, 79% e.e.; R^1 = CH$_3$, 85%, 88% e.e.

454
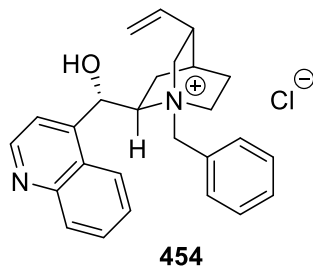
2.1.6. Polycyclic compounds from heterocycles.

Many cyclization reactions exploited the oxygen of a carbonyl group embedded in a heterocyclic ring for an attack on a haliranium ion arising from simple allyl or homoallyl moieties tethered on a heterocyclic ring [247]. However, it is worth mentioning that these processes have low novelty and occur directed by trivial electronic factors, so they deserve interest only for the unusual heterocyclic structures formed. Thus, the bicyclic 1-allyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid alkylamides **455** reacted with bromine to afford the tricyclic 2-bromomethyl-5-oxo-1,2-dihydro-5H-oxazolo[3,2-a]quinoline-4-carboxylic acid amides **456** in excellent yield [248-250].
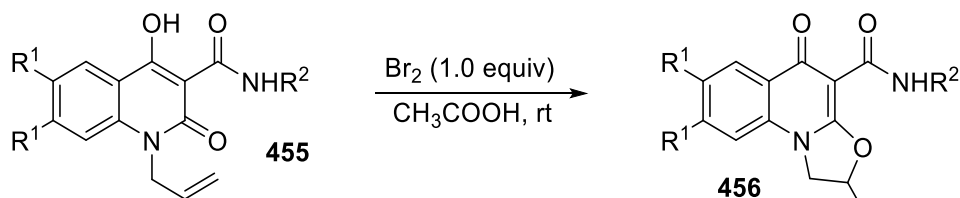
R^1 = H, R^2 = [pyrazinyl], 74%; R^1 = OCH$_3$, R^2 = (CH$_3$)$_2$CH, 72%;

R^1 = OCH$_3$, R^2 = C$_6$H$_5$CH$_2$, 95%; R^1 = OCH$_3$, R^2 =4-Cl-C$_6$H$_4$CH$_2$, 96%

Good results were also observed when the similar 1-allyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid pyridin-4-ylmethylenehydrazide **457** underwent cyclization mediated by bromine leading to 2-bromomethyl-5-oxo-1,2-dihydro-5H-oxazolo[3,2-a]quinoline-4-carboxylic acid pyridin-4-yl-methylenehydrazide **458** in good yield [251].
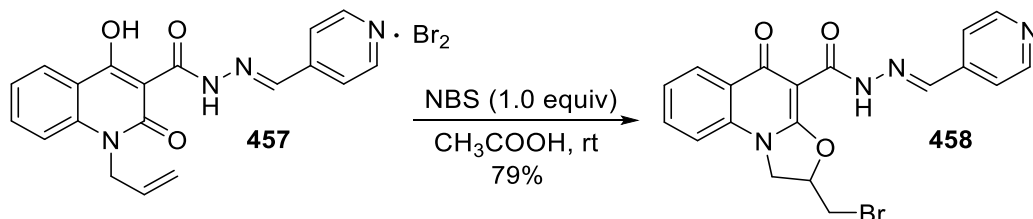
Electronic factors directed the 5-exo-mode cyclization of bicyclic 4-methyl-(3-methylbut-2-enyl)quinolin-2(1H)-one **459**, providing the tricyclic 2-(1-iodo-1-methylethyl)-5-methyl-1,2-dihydro[1,3]oxazolo[3,2-a]quinolinium triiodide **460** in high yield [252].

459 → **460**

I₂ (2.0 equiv)
CH₃COOH, rt
81%
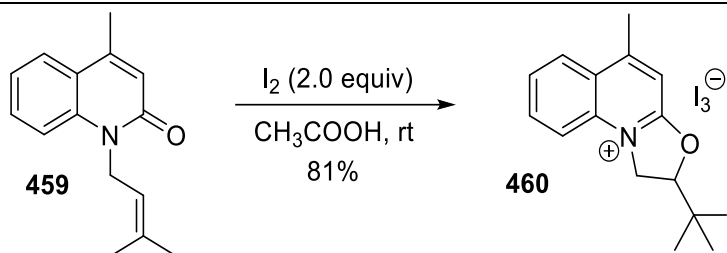
Again, electronic factors directed the 5-exo-mode cyclization of 1-allyl-5-nitropyridones 461 with bromine to give in moderate yield the bicyclic 2-bromomethyl-6-nitro-2,3-dihydrooxoazolo[3,2-a]pyridinium bromides 462 [253].

461 → **462**

Br₂ (2.0 equiv)
DCM, 0 °C

R^1 = H, 38%; R^1 = CH₃, 51%
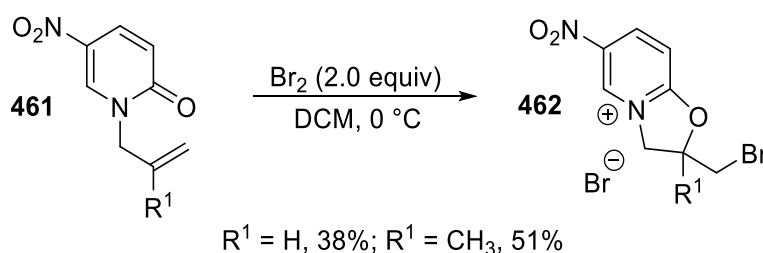
The same behavior was observed when 4-methyl-1-(2-methylprop-2-en-1-yl)quinolin-2(1H)-one 463 was treated with excess iodine leading to 2-iodomethyl-2,5-dimethyl-1,2-dihydro[1,3]oxazolo [3,2-a]-quinolinium triiodide 464 in good yield [254].

463 → **464**

I₂ (2.0 equiv)
CHCl₃, rt
88%
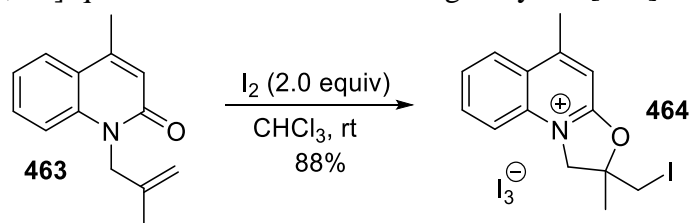
In analogy, 2-iodomethyl-5-methyl-2,3-dihydrooxazolo-8H-[3,2-b]pyrimidinium triiodide 466 was obtained in moderate yield by iodine-induced 5-exo-trig iodocyclization of 1-(N-allyl)-6-methylpyrimidine-2,4-dione 465, whereas the formation of the six-membered ring in 2-phenyl-3-iodo-6-methyl-2,3-dihydrooxazine-9H-[3,2-b]pyrimidinium triiodide 468 starting from 1-(N-cinnamyl)-6-methylpyrimidine-2,4-dione 467 was due to a 6-endo closure directed by electronic factors, owing to the presence of the phenyl group [255].

465 → **466**

I₂ (2.0 equiv)
C₂H₅OH, 0-5 °C
39.5%

467 → **468**

I₂ (2.0 equiv)
C₂H₅OH, 0-5 °C
59%
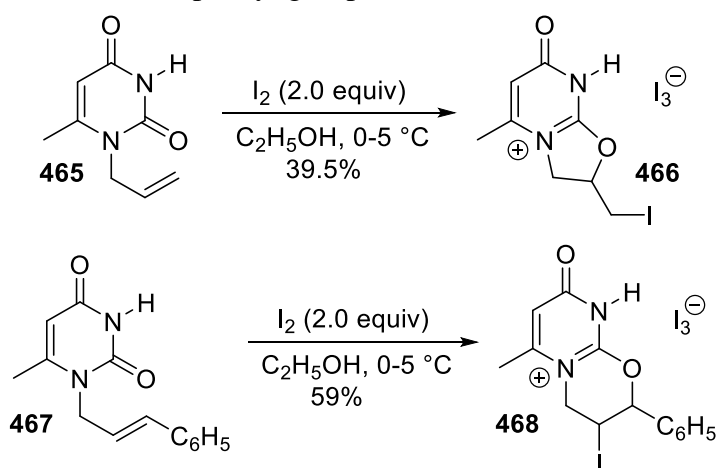
Again, the tricyclic 2-iodomethyl-7-methyl-1,2-dihydro[1,3]oxazolo-[3,2-a] quinolinium triiodides 470 were prepared in very good yield by iodocyclization starting from the 1-allyl-6-methylquinolin-2(1H)-ones 469 [256].

$R^1 = CH_3$, $R^2 = H$, 94%; $R^1 = H$, $R^2 = CH_3$, 85%
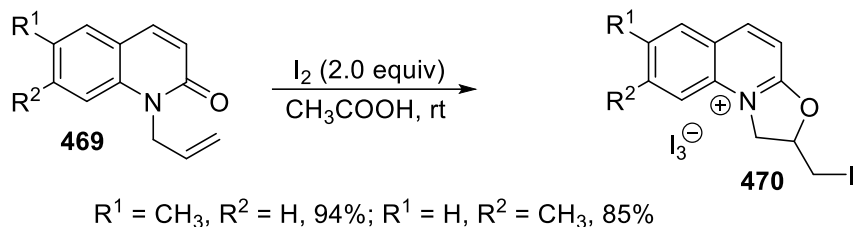
A further example of cyclization involving a similar heterocyclic core disclosed the novel compound 8-cyano-2-iodomethyl-5,7-dimethyl-2,3-dihydro[1,3]-oxazolo[3,2-a] pyridinium triiodide 472 starting from 4,6-dimethyl-2-oxo-1-(prop-2-en-1-yl)-1,2-dihydropyridine-3-carbonitrile 471 [257].
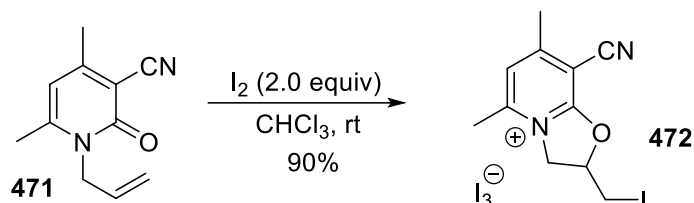
Moreover, when a homoallyl group was present, 2-(iodomethyl)-3,4-dihydro-2H-pyrido-[2,1-b]-[1,3]oxazinium triiodides 474 containing a six-membered ring were recovered in moderate yield starting from 1-(but-3-en-1-yl)pyridin-2(1H)-ones 473 by cyclization proceeding in a 6-exo-mode [258].

$R^1 = H$, 61%; $R^1 = NO_2$, 62%
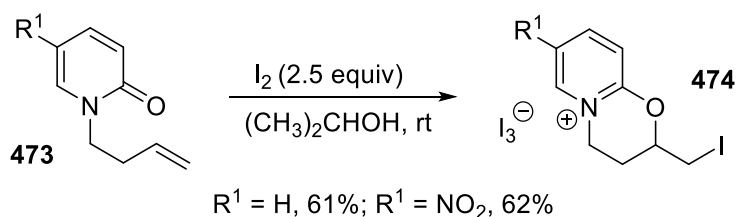
The allyl group was also bonded to a carbon atom of the heterocyclic ring, and in this case the bicyclic 2-(benzylsulfanyl)-6-(iodomethyl)-4-methyl-5,6-dihydrofuro[2,3-d] pyrimidine 476 was obtained in only moderate yield starting from 2-benzylsulfanyl-6-methyl-5-(prop-2-en-1-yl)-pyrimidin-4(3H)-one 475 [259].
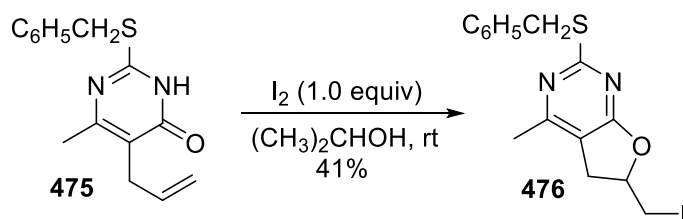
Eventually, the cyclization of 4-hydroxy-2-pyridone 477, mediated by iodine, afforded the tricyclic product 478 exclusively, whereas, in the presence of a base, the regioisomeric compound 479 was obtained in good yield [260].
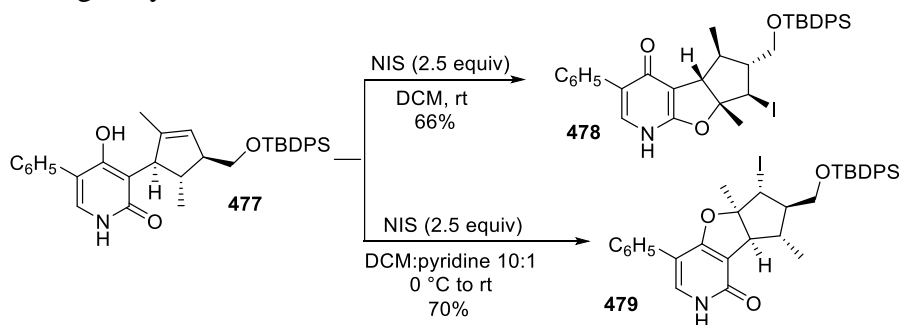
2.1.7. Oxiranes, oxetanes, tetrahydrofurans, tetrahydropyrans and larger ring ethers from unsaturated alcohols and ethers.

The hydroxy functionality of appropriate alkenols could attack haliranium ions intermediates generated from the double bond, and cyclization led to oxiranes, oxetanes, tetrahydrofurans, tetrahydropyrans, and larger ring ethers, generally within the synthesis of polyfunctionalized bioactive or natural products [26, 69, 261-265].

2.1.7.1. Synthesis of oxiranes from allylic alcohol with external asymmetric induction.

In the presence of catalyst 482, where a chiral phosphate anion displays a DABCO-derived quaternary ammonium counterion, the allylic alcohols 480 underwent cyclization mediated by NIS to give in excellent yield and stereoselection of the corresponding oxiranes 481 through an unusual 3-exo-trig mode [266].

R^1 = H, 87%, 95.5 e.e.; R^1 = 4-CH$_3$, 94%, 96% e.e.; R^1 = 4-Cl, 92%, 98% e.e.

R^1 = 2,4,6-(i-C$_3$H$_7$)$_3$-C$_6$H$_2$ R^2 = 4-C$_6$H$_{13}$OC$_6$H$_4$
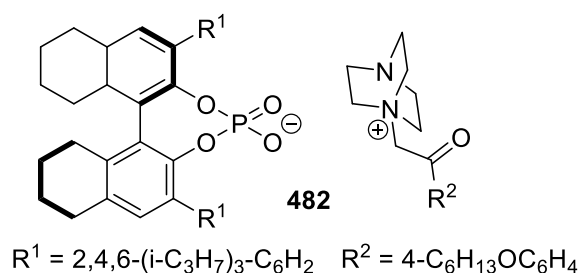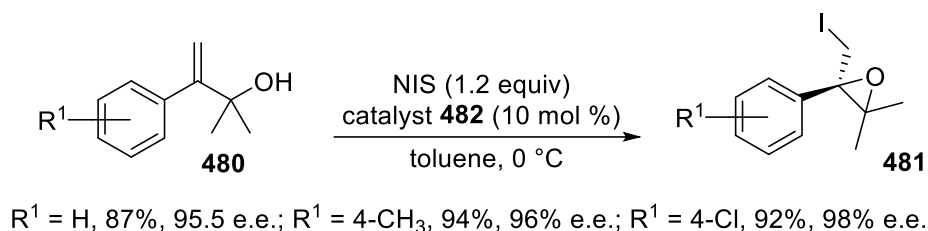
2.1.7.2. Synthesis of oxetanes from homoallylic alcohols without asymmetric induction.

By reaction with excess iodine in a basic medium, the alkenol 483 afforded the bicyclic oxetane 484 in low yield [267].
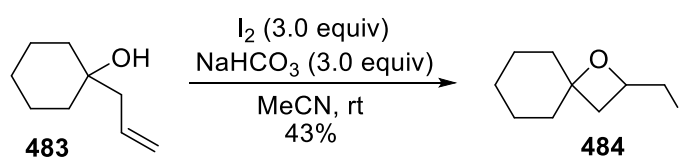
However, when cyclization of tertiary alkenols 485 was carried out in methanol using [hydroxy(tosyloxy)iodo]-benzene (HTIB) together with a catalytic amount of iodine, tetrahydrofurans 488 were isolated in moderate yield from the bicyclic onium ion intermediate 487, arising from the first formed oxetane 486 [267].

$R^1...R^2$ = (CH$_2$)$_5$, 64%; $R^1...R^2$ = (CH$_2$)$_{11}$, 55%;
R^1 = R^2 = n-C$_4$H$_9$, 47%; R^1 = C$_6$H$_5$, R^2 = CH$_3$, 43%
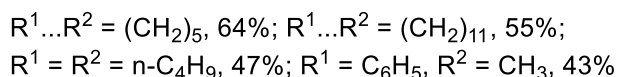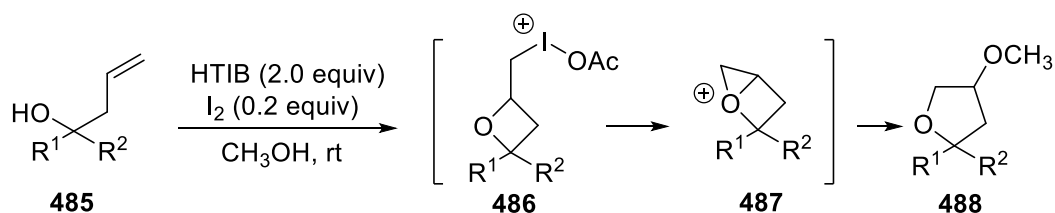
2.1.7.3. Synthesis of tetrahydrofurans and analogs from unsaturated alcohols and ethers.

2.1.7.3.1. Without asymmetric induction.

2-Oxabicyclo[2.1.1]hexanes 490, useful as constrained mimetics for the benzene ring, were obtained in good yield by reaction of alkenols 489 with NIS in methyl t-butyl ether (MTBE)-water mixtures [268].

R^1 = H, 78%; R^1 = CH_2CH_3, 90%; R^1 = $CH_2C_6H_5$, 95%; R^1 = $COOC_2H_5$, 80%
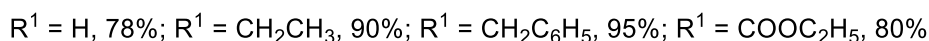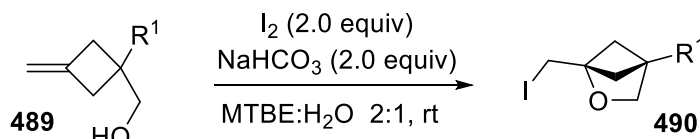
The cyclization of alkenols 491 was carried out with NBS in the presence of the Lewis base 493, to give a good yield to the corresponding tetrahydrofurans 492 [75].

R^1 = C_6H_5, 94%; R^1 = 4-CH_3O-C_6H_4, 91%; R^1= 4-Cl-C_6H_4, 82%
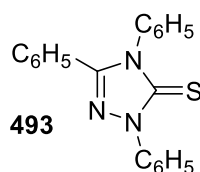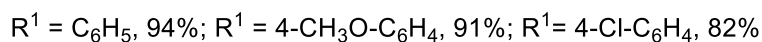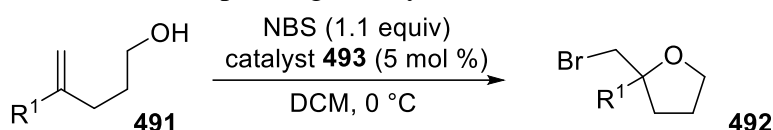
In a novel synthetic approach, the cyclization of alkenols 494 to tetrahydrofurans 495 was efficiently carried out using mechanical force under solvent and catalyst-free conditions [53].

R^1 = 4-CH_3-C_6H_4, 99%; R^1 = 4-CH_3O-C_6H_4, 76%;
R^1 = 4-CF_3-C_6H_4, 98%; R^1 = 4-F-C_6H_4, 93%
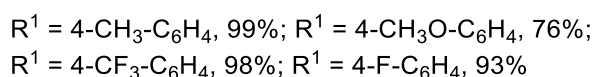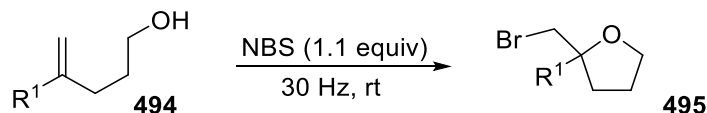
Linear alkenols 496 were also converted in good yield into the corresponding monosubstituted tetrahydrofurans 497 by chemoenzymatic cyclization when halide ions were oxidized to hypohalites by vanadium-dependent chloroperoxidase from Curvularia inaequalis (CiVCPO) [269].

n = 1, X = Cl, 78%; n = 1, X = Br, 81%; n = 2, X = Cl, 77%; n = 2, X = Br, 77%
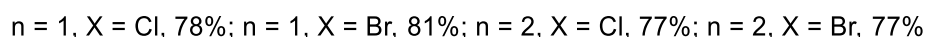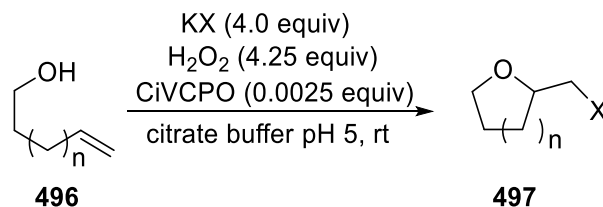
The halocyclization of allenic alcohols was carried out with bromine generated by oxidation of bromide anion exploiting the chloroperoxidase of Caldariomyces fumago, and both dihydrofurans 499 or dihydropyrans 501 were obtained in moderate to good yield starting from 498 or 500, respectively [270].

NaBr (3.0 equiv)
D-glucose (2.0 equiv)
glucose oxidase (*A. niger*) 50 U
chloroperoxidase (*C. fumago*) 200 U

air, citrate buffer pH 4.5
Brij 35 (1.0 equiv), hexane, rt

498 → **499**

$R^1 = R^2 = CH_3$, $R^3 = C_6H_5$, 93%; $R^1 = R^2 = CH_3$, $R^3 = n\text{-}C_7H_{15}$, 81%

NaBr (3.0 equiv)
D-glucose (2.0 equiv)
glucose oxidase (*A. niger*) 50 U
chloroperoxidase (*C. fumago*) 200 U

air, citrate buffer pH 4.5
Brij 35 (1.0 equiv), hexane, rt
46%

500 → **501**
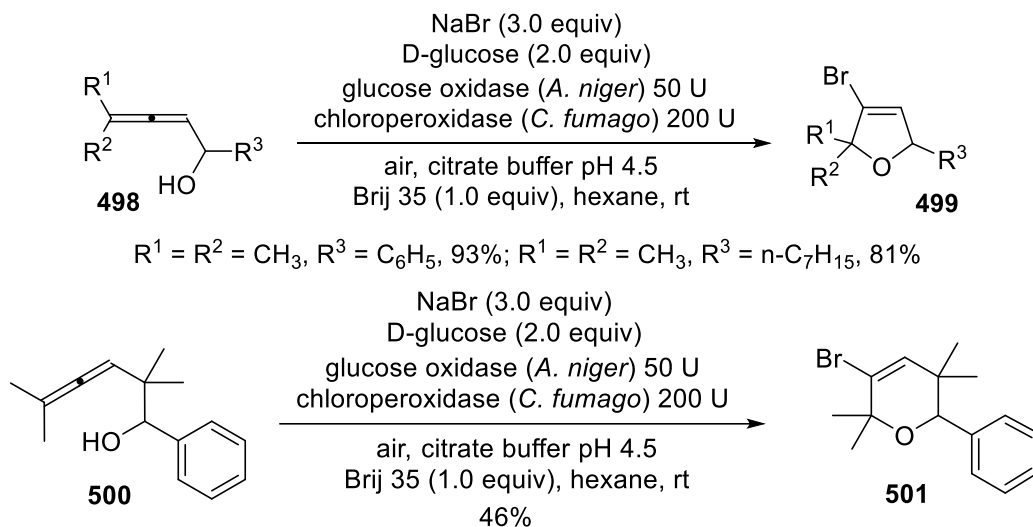
The allenyl alcohol **502**, by reaction with NBS in the presence of catalytic AuCl₃, gave the spirobicyclic lactam **503** a very good yield, the bromine atom being eventually transferred by the catalyst to the aromatic ring [271].

NBS (1.3 equiv)
AuCl₃ (5 mol %)

DCM, rt
93%

502 → **503**
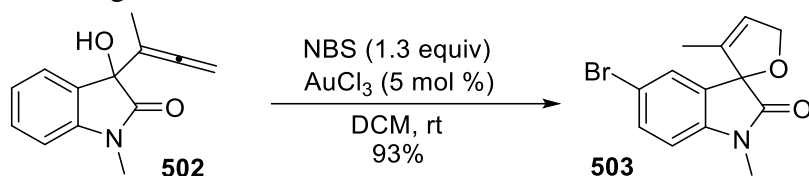
Alkynyl diols **504** in the presence of excess iodine afforded diiododihydrofurans **507** in good yield. The reaction proceeded through the addition of an iodide anion to a first formed allenyl cation **505**, leading to intermediate **506**, followed by an eventual 5-endo attack of the hydroxy functionality to a subsequently formed iodiranium ion [272-274].

I₂ (3.0 equiv)
DCM, rt

504 → **505** → **506** → **507**

$R^1 = H$, $R^2 = 4\text{-}CH_3O\text{-}C_6H_4$, 99%; $R^1 = H$, $R^2 = 4\text{-}Br\text{-}C_6H_4$, 85%;
$R^1 = C_6H_5$, $R^2 = CH_3$, 93%; $R^1...R^2 = \text{-}(CH_2)_4\text{-}$, 92%
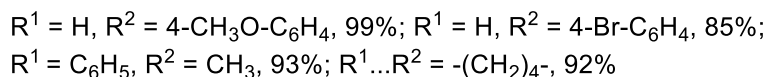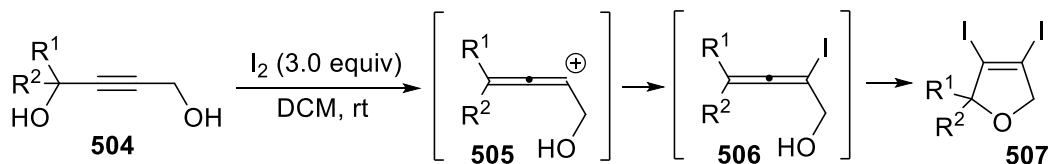
Similarly, compounds **508** generated allenyl cations that evolved to enolethers **509**, eventually converted in very good yield into the diiodofurans **510**, again according to a 5-endo-mode cyclization [275].

I₂ (3.0 equiv)
CH₃OH, rt

508 → **509** → **510**

$R^1 = C_6H_5$, $R^2 = 4\text{-}Cl\text{-}C_6H_4$, 91%; $R^1 = n\text{-}C_5H_{11}$, $R^2 = C_6H_5$, 89%;
$R^1 = n\text{-}C_5H_{11}$, $R^2 = 4\text{-}Cl\text{-}C_6H_4$, 88%; $R^1 = H$, $R^2 = C_6H_5$, 85%
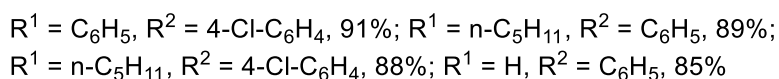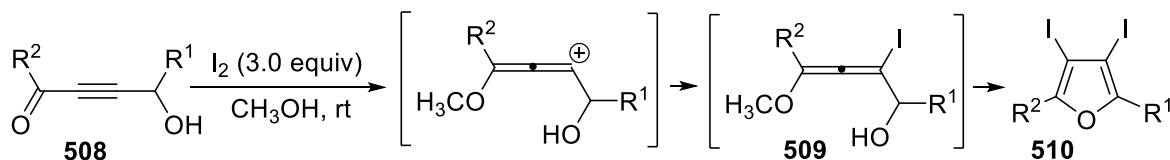
Exploiting another 5-endo-mode cyclization, the α-trifluoromethylallenyl phosphonates **511**, in the presence of iodine, provided in good yield the corresponding trifluoromethyl oxaphospholenes **512** with total regioselection [276].
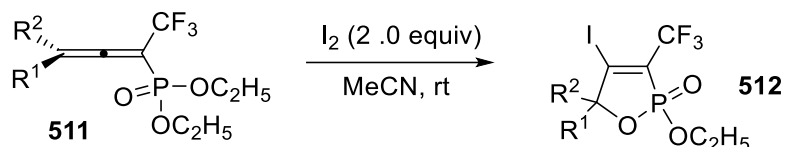
$R^1 = R^2 = C_2H_5$, 92%; $R^1 = R^2 = CH_3$, 83%; $R^1...R^2 = -(CH_2)_5-$, 82%

2.1.7.3.2. With internal asymmetric induction.

Bromofuranoindolines **514** were obtained with total regio- and stereoselection when bromine was generated by electrochemical oxidation, starting from indoles **513** [277].
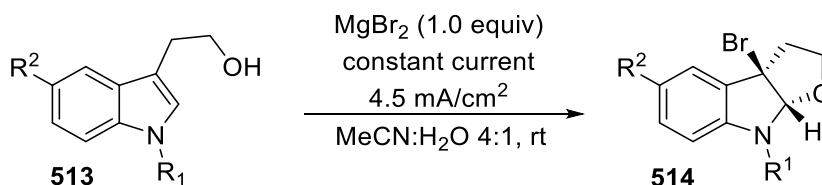
R^1 = Boc, R^2 = H, 75%; R^1 = Ts, R^2 = H, 90%;
R^1 = Ts, R^2 = Cl, 62%; R^1 = Ts, R^2 = OCH$_3$, 73%

Again, indoles **515** underwent cyclization mediated by halogens generated by the oxidation of halides with Oxone®, and halofuranoindolines **516** were isolated in good yield [278].
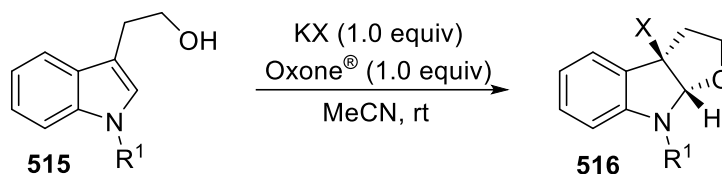
X = Br, R^1 = Boc, 92%; X = Br, R^1 = Ts, 91%; X = Cl, R^1 = Ts, 78%; X = Cl, R^1 = Boc, 80%

The halocyclization could be stereoselective when substituents were present on the alkenol chain [261],[263]. In fact, the reaction of alkenols **517** mediated by NBS proceeded with total stereoselection, leading to *cis*-2,4-disubstituted tetrahydrofurans **518**, and the cyclization rate strongly increased when catalyst **519** was added to the reaction mixture [279].
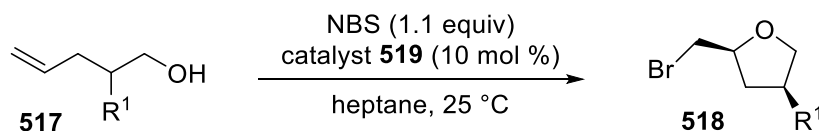
$R^1 = C_6H_5$, 74% (without catalyst 15%); $R^1 = CH_2OH$, 95% (without catalyst 36%)
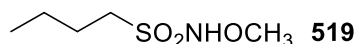
In addition, when magnesium alkoxides **520** underwent cyclization mediated by C$_6$H$_5$I(OAc)$_2$, that oxidized the bromide anion to bromine, the corresponding *trans*-2,5-disubstituted tetrahydrofurans **521** (n = 1) were isolated in moderate yield and low stereoselection, whereas with a longer chain (n = 2) the *cis*-2,6-tetrahydropyran **522** was the major product [280].

n = 1. R^1 = C$_6$H$_5$, 60%, *trans:cis* 2.3:1;
R^1 = 4-Cl-C$_6$H$_4$, 44%, *trans:cis* 4.1:1;
R^1 = 4-CH$_3$O-C$_6$H$_4$, 91%, *trans:cis* 2.8:1;
n = 2. R^1 = C$_6$H$_5$, 42%, *trans:cis* 1:7
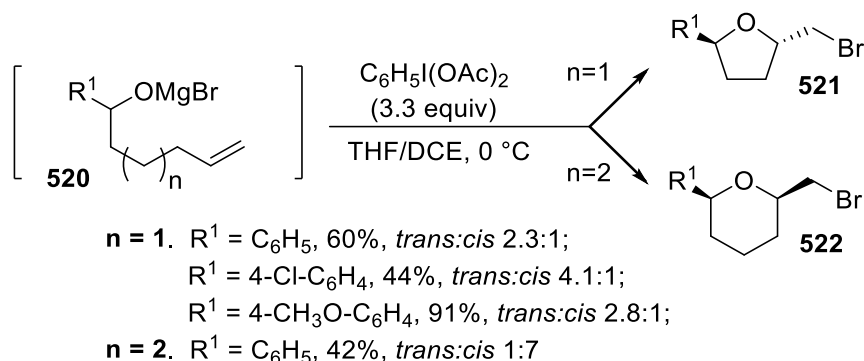
Very low stereoselection was also observed when compound **523** underwent cyclization with NIS, leading to a nearly equimolecular mixture of disubstituted tetrahydrofurans, 2,5-*trans*-**524,** and 2,5-*cis*-**525** [281].
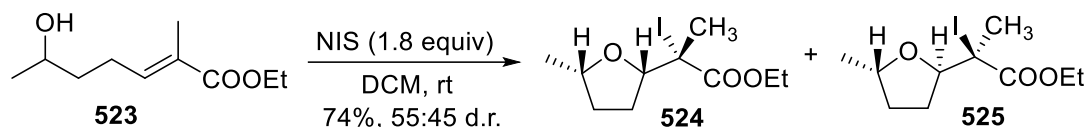
Again, enantiomeric nitroalkenols **526**, prepared to exploit a highly enantioselective Henry reaction, afforded a mixture of 2,5-disubstituted tetrahydrofurans **527** and **528** in very good yield but with very low stereoselection [282].
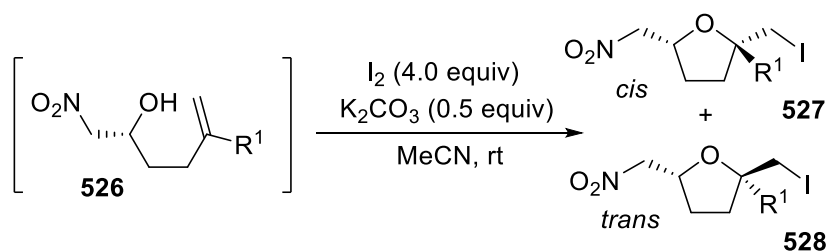
R^1 = C$_6$H$_5$, 88%, *cis:trans* 42:58, *cis* 90% e.e; *trans* 88% e.e.;
R^1 = 2-F-C$_6$H$_4$, 87%, *cis:trans* 40:60, *cis* 94% e.e., *trans* 94% e.e.;
R^1 = 4-CH$_3$-C$_6$H$_4$, 97%, *cis:trans* 48:52 *cis* 93% e.e., *trans* 87% e.e.

Moreover, the enantiomerically pure chiral unsaturated diol **529** underwent cyclization mediated by iodine in a basic medium to give in good yield and with moderate asymmetric induction, a diastereomeric mixture of trisubstituted tetrahydrofurans **530** and **531** [283].
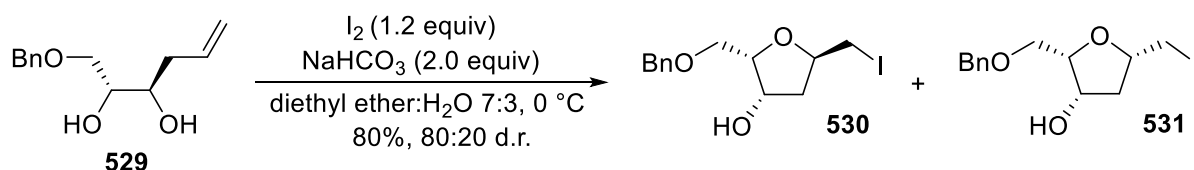
Better results were observed when, according to a 5-*endo*-mode cyclization directed by electronic factors, the enantiomerically pure alkenol **532** afforded the polysubstituted tetrahydrofuran **533** in very good yield and excellent stereoselection, with retention of configuration at the preexisting chirality centers [284].
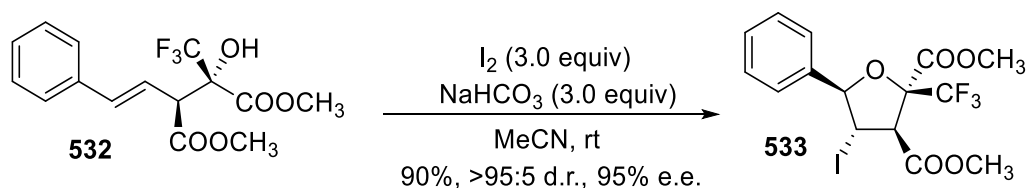
Moreover, starting from **534**, the alkoxy group at C-4 strongly influenced the 5-*endo*-trig cyclization, and the 2,5-*trans*-tetrahydrofurans **535** were exclusively isolated in high yield from the reaction mixture [285].
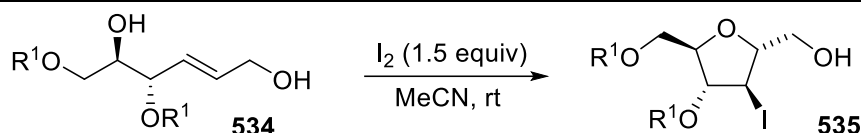
R^1 = CH$_3$, 88%; R^1 = Bn, 84%

Accordingly, the alkenol **536a**, displaying the opposite configuration at C-4 with respect to **534**, gave a good yield to the 2,5-*cis*-tetrahydrofuran **537**, owing to the directing effect exerted by the secondary methoxy group. On the contrary, in compound **536b,** displaying the same configuration at chirality centers but having benzyloxy groups in place of methoxy groups, the oxygen of the terminal benzyloxy group was the preferred nucleophile, and the cyclization proceeded with moderate stereoselection to give in low yield, after HOI elimination, a diastereomeric mixture of 2-vinyl tetrahydrofurans **538** and **539** [286].
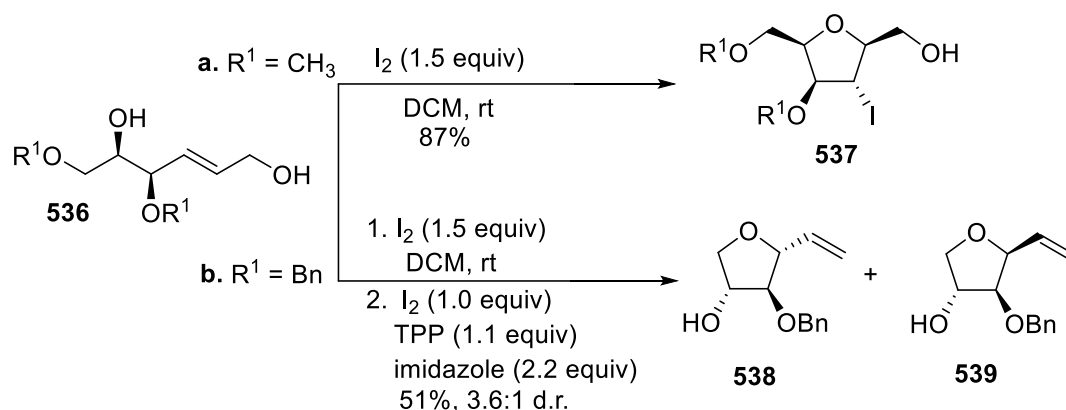
The cyclization of alkenol **540** proceeded with low stereoselection, the 2,5-*trans*-disubstituted tetrahydrofuran **541** being the major component of the reaction mixture. On the contrary, under the same conditions, the dichlorobenzyl (DCB) ether **543** gave in high yield the 2,5-*cis*-disubstituted derivative **544**, exclusively due to a double 1,2-*trans*-disposition of substituents at the transition state [286].
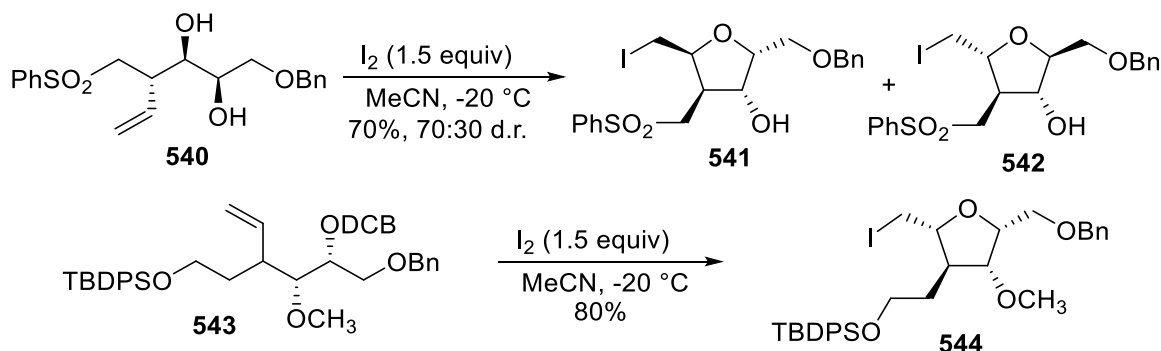
In analogy, when alkenols **545** underwent cyclization, a transient TMS-ether was created at the hydroxy functionality to give in high yield and good stereoselection of the corresponding 2,5-*cis*-disubstituted tetrahydrofurans **546**, owing to a double 1,2-*trans*-disposition of substituents occurring at the transition state [287].
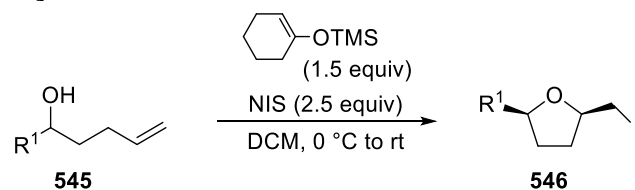
R^1 = CH$_3$, 82%, 6:1 d.r.; R^1 = (CH$_3$)$_2$CH, 85%, 15:1 d.r.;
R^1 = (CH$_2$)$_4$OTBS, 82%, 11:1 d.r.; R^1 = (CH$_2$)$_4$OBn, 85%, 12:1 d.r.

Exploiting the same trick, *bis*-tetrahydrofuran **548** displaying 2,5-*cis*-configuration was obtained in high yield and stereoselection starting from diol **547** [288].

cis/threo/cis, 83%, 90:10 d.r.
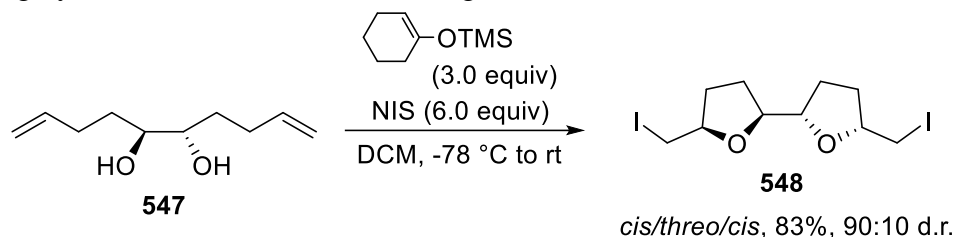
On the contrary, the totally stereoselective iodocyclization of compound **549**, performed in a basic medium to provide the trisubstituted tetrahydrofuran **550**, was ascribed to a 1,2-*cis*-directing effect due to the interaction of the oxygen of the hydroxy group with the intermediate iodiranium ion [289-291].
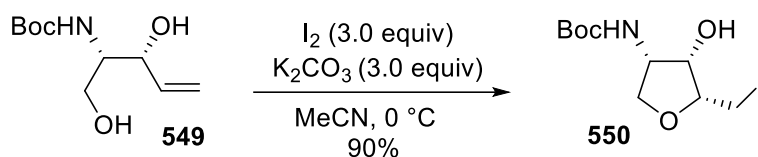
Again, the same effect of a vicinal hydroxy group led to total stereoselection to the trisubstituted tetrahydrofuran **552**, starting from the enantiomerically pure diol **551** [292].
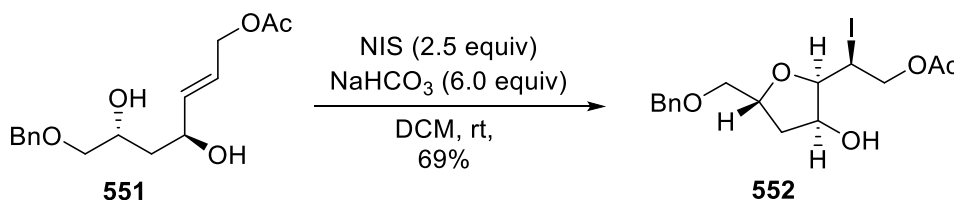
In analogy, the cyclization of substituted alkenol **553** gave a mixture of tetrahydrofurans **554** and **555** in good yield and moderate diastereoselection by using equimolar amounts of NIS and iodine; this latter employed as Lewis base to increase the cyclization rate [293].
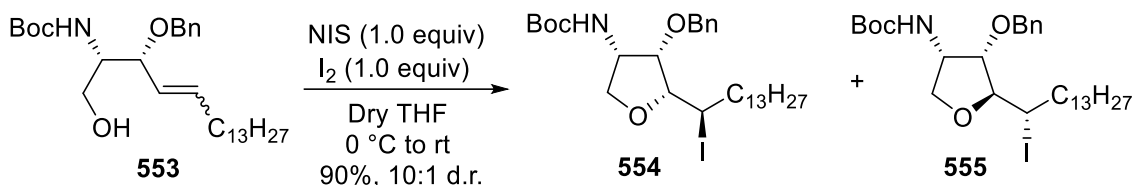
The reaction of compound **556**, carried out with iodine in a basic medium, led to a moderate yield of a nearly equimolar regioisomeric mixture of tetrahydrofurans **557** and **558**. However, tetrahydrofuran **557**, arising from a 5-*endo*-mode cyclization, was isolated as an equimolar diastereomeric mixture, whereas product **558**, which formed by ring closure proceeding with total stereoselection in a 5-*exo*-mode, was isolated as a single diastereomer [205].
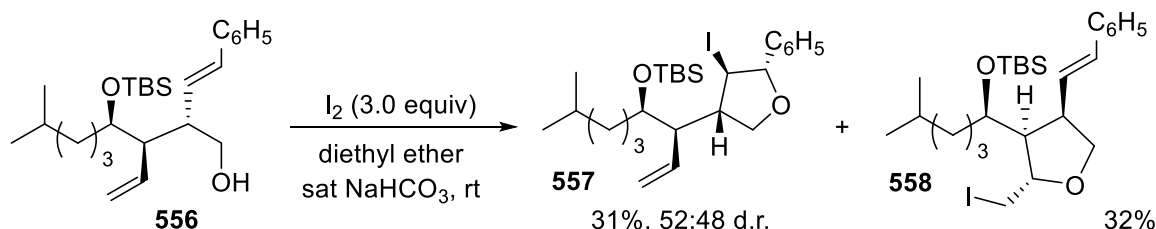
Starting from the chiral substrates **559** and **561**, the corresponding 1,3-disubstituted tetrahydrofurans **560** and **562** were respectively obtained with total stereoselection. However, when a substituent at C-5 was missing, as it occurred in **559**, having a hydroxymethyl group, the substitution pattern for bulky substituents was 2,4-*trans*. On the contrary, a substituent at C-5 biased the

cyclization outcome to give the 2,5-*trans* isomer **562** (or 2,4-*cis*), irrespective of the substituent at C-4 [294].

R^1 = R^2 = H, 90%; R^1 = CH$_3$, R^2 = H, 92%; R^1 = H, R^2 = CH$_3$, 95%

R^1 = R^2 = H, 90%; R^1 = CH$_3$, R^2 = H, 79%; R^1 = H, R^2 = CH$_3$, 83%
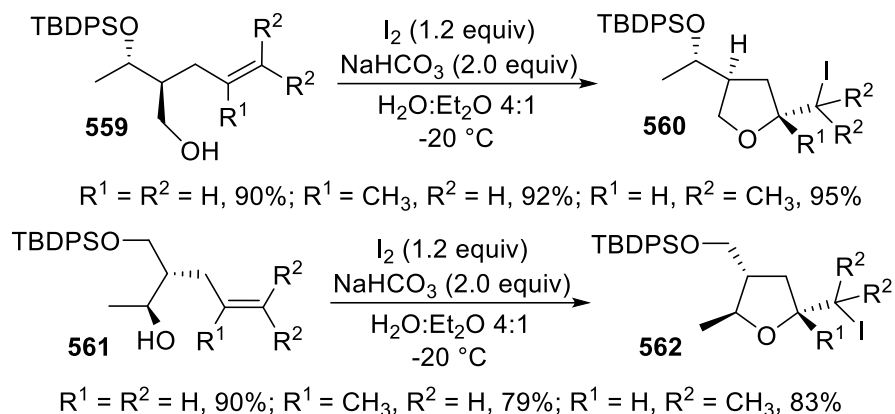
In addition, 2,7-disubstituted fused-*bis*-tetrahydrofurans **564**-**566** were obtained by cyclization of compounds **563a,b**, and the product ratio strongly relied on the starting functionalization pattern. In fact, *bis*-hydroxy pattern preferentially led to *trans*-substitution, whereas *bis*-ether groups mainly led to *cis*-substitution [295].
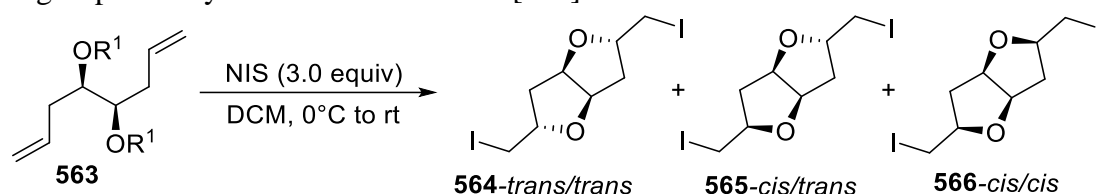
a. R^1 = H, 73%, 7:4:0 d.r.; **b.** R^1 = TMS, 100%, 0:2:1 d.r.

Moreover, besides the oxygenated functionalities present on the chain, the configuration of the double bonds in the substrates strongly determined the stereochemical outcome of the reaction. In fact, diol **567** having *Z*-double bonds led to *trans/trans* fused-*bis*-tetrahydrofuran **568**, exclusively, by a matching effect. On the contrary, diether **569**, having *E*-double bonds, provided only *cis/cis* fused *bis*-tetrahydrofuran **570** [295].
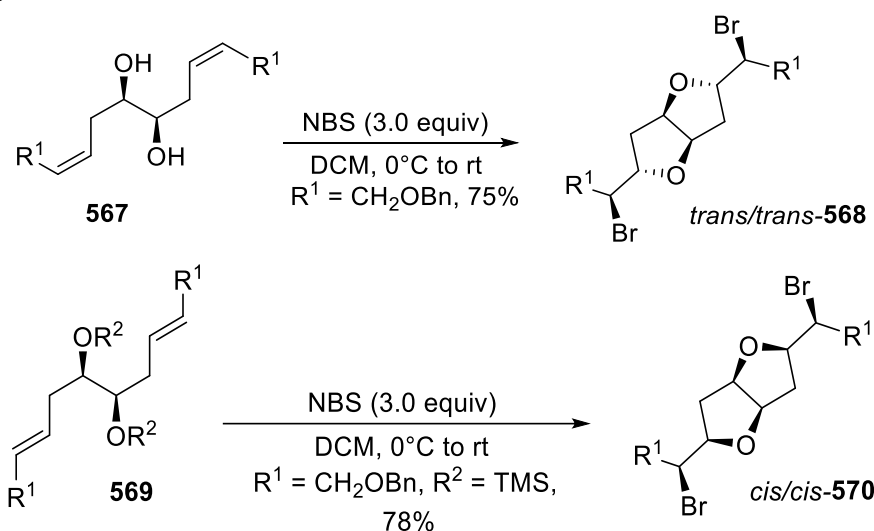
Thus, diol **571**, containing both (*Z*)-double bonds and enyne functionalities, underwent double cyclization induced by 2,4,4,6-tetrabromocyclohexa-2,5-dienone (TBCO) to give in good yield and moderate stereoselection a mixture of *trans,trans*-diastereomers **572** and **573** bearing a chiral allene group [295].

R^1 = CH$_2$CH$_2$OTBDPS
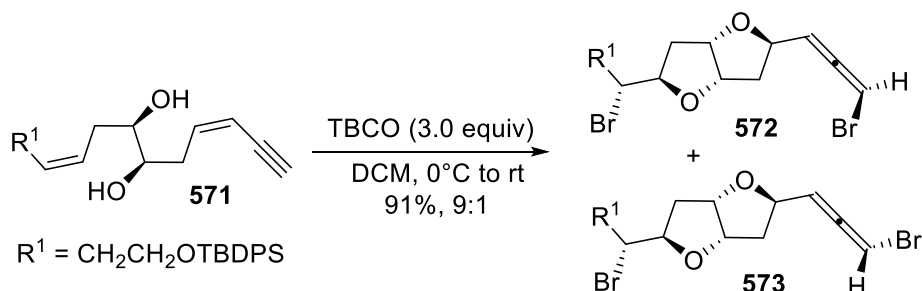
Tetrahydrofurans fused with other heterocyclic rings were obtained by halocyclization, and high asymmetric induction arose from the preexisting chirality centers. In addition, the regioselection of cyclization of compound **574** strongly relied on the solvent employed. In fact, when DCM or MeCN were used, tetrahydrofuran **575** was isolated in low yield as the major product with total stereoselection, according to a 5-*exo*-mode closure. On the contrary, when MeNO$_2$ was employed as the solvent, a nearly equimolar mixture of regioisomers **575** and **576** was obtained, arising from a 5-*exo* and a 6-*endo*-mode, respectively, but always with total stereoselection [296].

	575	**576**
DCM, -78 °C to 0 °C,	36%	7%
MeCN, -23 °C to 0 °C,	44%	4%
MeNO$_2$, 0 °C,	20%	25%
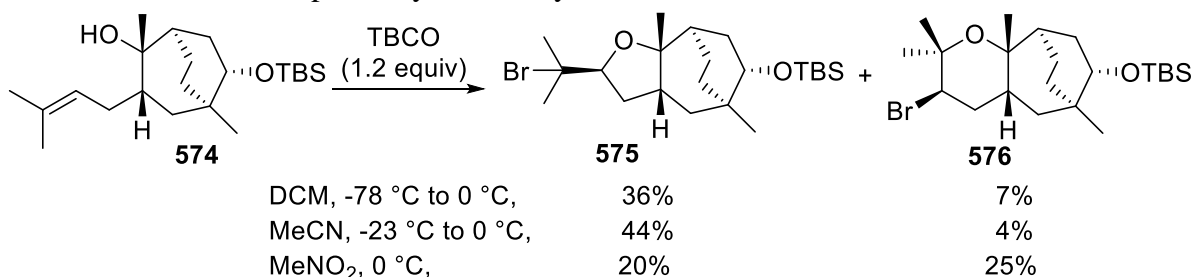
Moreover, starting from 3-hydroxy-γ-lactones **577**, mixtures of bicyclic derivatives **578** and **579** were obtained in good yield and high stereoselection by a 5-*endo* cyclization [297].

R^1 = n-C$_5$H$_{11}$, 73%, 93:7 d.r.
R^1 = n-C$_3$H$_7$, 89%, 93:7 d.r
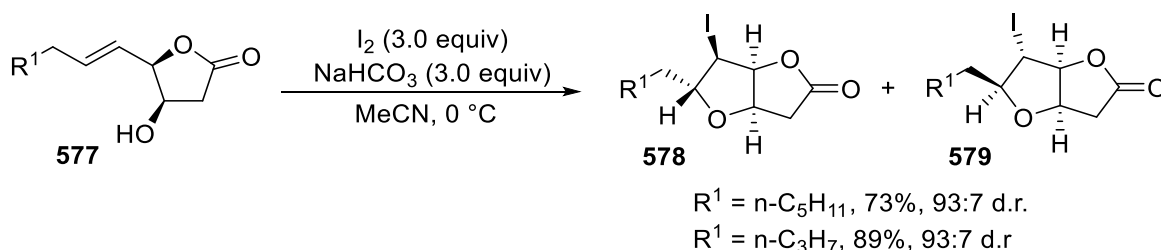
Again, when compound **580** underwent cyclization to give the bicyclic compound **581** in good yield and total stereoselection *via* a debenzylative chloroetherification mediated by *N*-chlorosuccinimide, the stereochemical outcome of the reaction was directed by the chirality centers present in the structure [298].
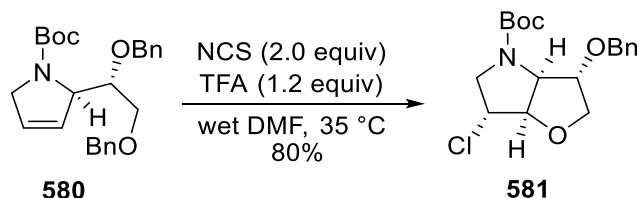
A preexisting cyclic structure displaying chirality centers biased the nucleophile attack to haliranium ion to give a sole product also in the case of compounds **582** and **584**. Thus, the bicyclic compound **583** was exclusively isolated in good yield starting from **582** via a 5-*endo*-mode cyclization [299], whereas **585** was obtained from **584** according to a 5-*exo*-mode reaction [300].
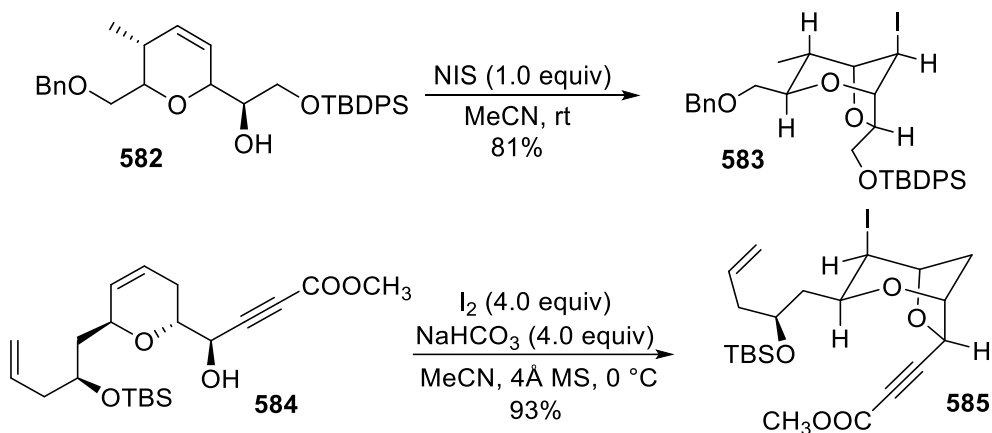
Furthermore, starting from compound **586**, the bicyclic compound **587** was exclusively isolated when the cyclization was carried out with iodine [301].
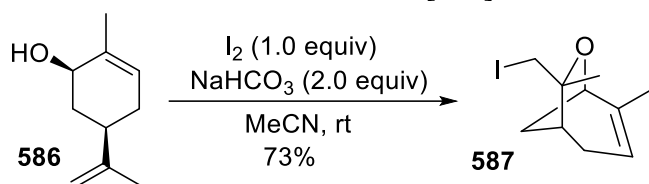
As a further example, the tricyclic unsaturated alcohol **588** was converted into the tetracyclic product **589**, exclusively [302].
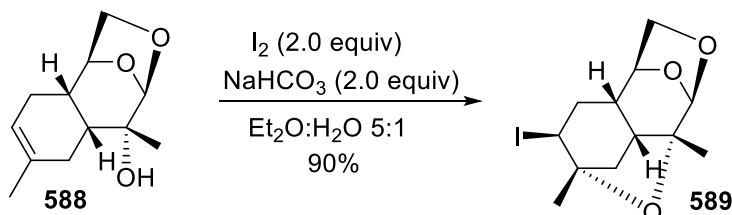
Within a synthesis of bromofucins, bromocyclization of unsaturated ether **590**, mediated by excess NBS**,** gave with total stereoselection compound **591**, displaying tetrahydrofuran fused with a large ring ether [303].
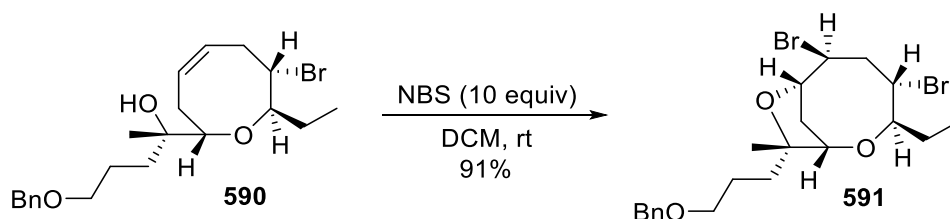
Eventually, the reaction of geraniol **592**, carried out with NBS or NIS in the presence of morpholine-HFIP salt, provided moderate to good yield for both derivatives, **593a** and **593b,** with high diastereoselection [236].
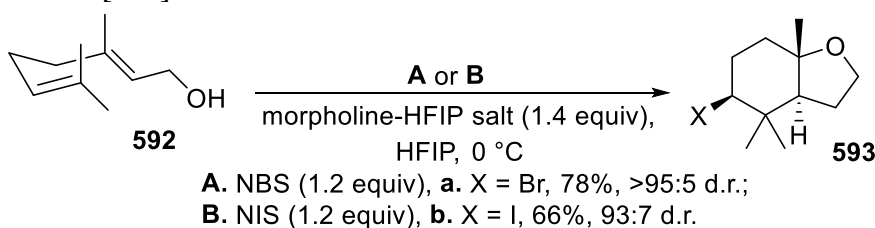
Moreover, chiral oxa-spirocyclic indanones **594** gave tetracyclic compounds **595** in moderate to good yield and good stereoselection via a 5-*endo*-trig cyclization directed by electronic factors [304].

R^1 = C$_6$H$_5$, 71%, 91:9 d.r.; R^1 = 2-Cl-C$_6$H$_4$, 69%, 92:8 d.r.;
R^1 = 4-i-Pr, 65%, 90:10 d.r.; R^1 = 2-thienyl, 61%, 92:8 d.r.
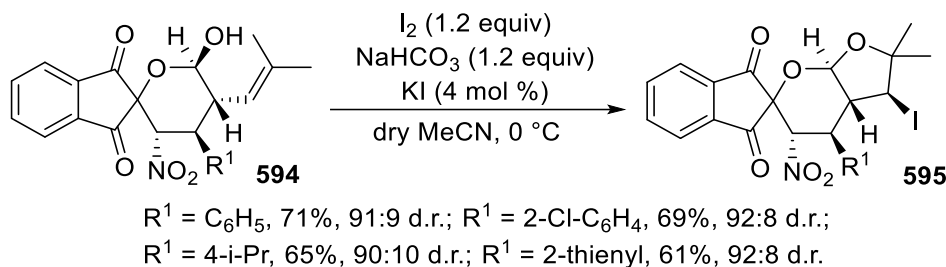
Again, through a cyclization proceeding in a 5-*endo*-mode, both diastereomeric spiro butenolides **597** and **598** were obtained from **596** in good yield but with low 1,3-stereoselection [305].
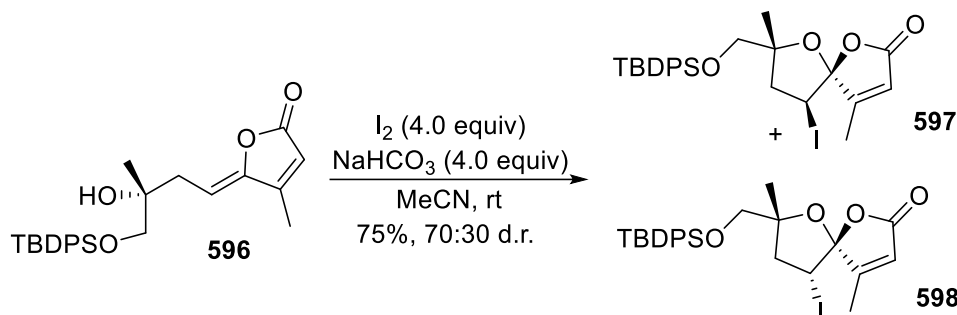
However, under the same conditions, butenolide **599** was converted into the spiro butenolide **600** in moderate yield but with total stereoselection, probably exploiting the directing effect of the hydroxy group lieing α to the double bond [306].
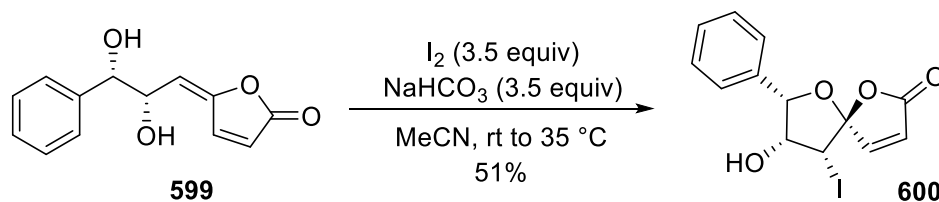
In place of double bonds, cyclopropanes were also effective for the generation of haliranium ions, leading to substituted tetrahydrofurans by the attack of a nucleophilic hydroxy group. Thus, cyclopropylmethanols **601** underwent first a Brønsted acid-catalyzed formation of homoallylic alcohols by ring-opening with water, followed by halocyclization providing in good yield tetrahydrofurans **602** as the sole products [307].

R^1 = C$_6$H$_5$, R^2 = 1-naphthyl, 80%; R^1 = n-C$_5$H$_{11}$, R^2 = C$_6$H$_5$, 88%;

R^1 = 4-Cl-C$_6$H$_4$, R^2 = (thienyl alkyne), 96%; R^1 = t-C$_4$H$_9$, R^2 = C$_6$H$_5$, 83%;
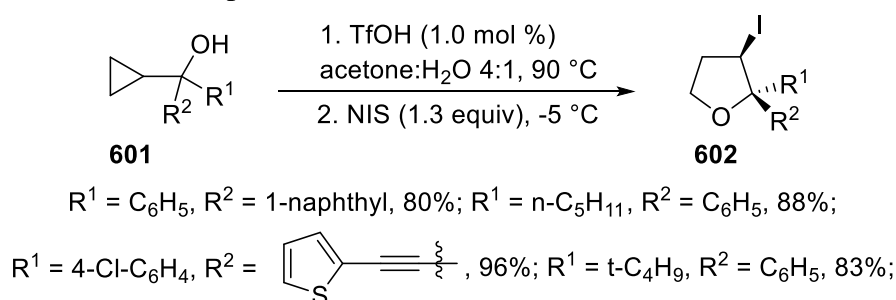
Moreover, starting from cyclopropyl derivatives **603**, cyclization induced by 1,3-DBDMH led to the corresponding tetrahydrofurans **604** in good yield, whereas starting from compounds **605**, bearing a substituent on the chain, trisubstituted tetrahydrofurans **606** were obtained in moderate to good yield, but with good 1,2-*trans* stereoselection [62].

R^1 = C$_6$H$_5$, 76%; R^1 = 4-t-C$_4$H$_9$-C$_6$H$_4$, 96%;
R^1 = 4-CH$_3$O-C$_6$H$_4$, 98%; R^1 = 4-CH$_3$-C$_6$H$_4$, 92%
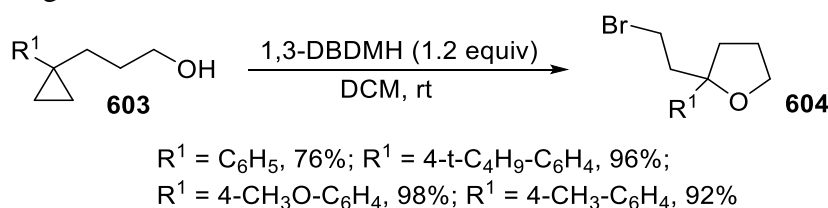
R^1 = C$_6$H$_5$, 63%, 91:9 d.r.; R^1 = CH$_3$, 96%, 95:5 d.r.; R^1 = CH$_2$CH$_3$, 55%, 84:16 d.r.

2.1.7.3.3. With external asymmetric induction.

As it occurred for the halolactonization reaction, also the haloetherification reaction was carried out in the presence of appropriate catalysts in order to generate chirality centers with high enantioselection, as required within the synthesis of bioactive natural products. Thus, many catalysts were employed, although their number was largely smaller than those used for the halolactonization reaction. Thus, homoallylic alcohols 607 underwent cyclization proceeding in a 5-endo-mode to give tetrahydrofurans 608 in good yield and excellent enantioselection, when the reaction was promoted by N-chlorosuccinimide (NCS) in the presence of catalyst 609, although a double bond substituted by an aryl group was needed for enantioselection [308].
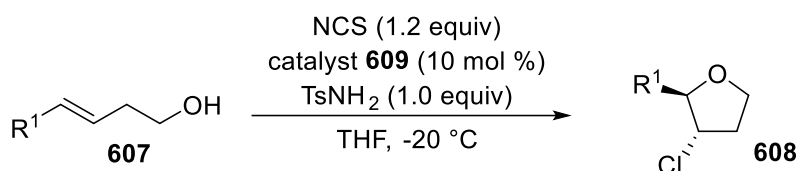
R^1 = 3-CH$_3$-C$_6$H$_4$, 81%, 92% e.e.; R^1 = C$_6$H$_5$, 85%, 95% e.e.;
R^1 = 4-Ch-C$_6$H$_4$, 80%, 96% e.e.; R^1 = cyclohexyl, 56%, 11% e.e.
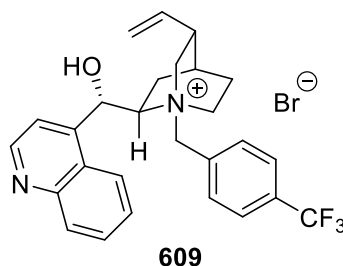
The chiral Bronsted acid TRIP 612 containing the phosphoric acid moiety was also effective for the cyclization of (Z)-alkenols 610 mediated by NBS, leading in good yield to the monosubstituted tetrahydrofurans 611 with moderate enantioselection when R1 = alkyl group [309]. However, when R1 was an aryl group, the addition of the Lewis base Ph3P=S 53, together with 612, was necessary in order to attain the same results with a minor amount of catalyst, exploiting the cooperative activation of NBS. In fact, the intermediate phosphate hypobromite was able to transfer the bromenium ion via a hydrogen-bonded transition state, providing a chiral bromiranium-phosphate ion pair [310-311].
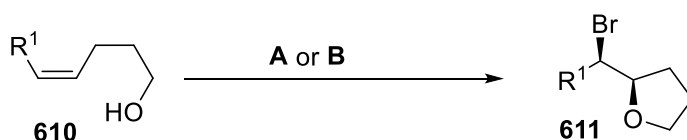
A. NBS (1.2 equiv), catalyst **612** (10 mol %), DCM, 0 °C
R^1 = n-C$_5$H$_{11}$, 95%, 75% e.e.; R^1 = CH$_2$CH$_3$, 96%, 81% e.e.; R^1 = t-C$_4$H$_9$, 86%, 75% e.e.
B. NBS (1.2 equiv), catalyst **612** (5 mol %), (C$_6$H$_5$)$_3$P=S **53** (5 mol %), toluene, 0 °C
R^1 = C$_6$H$_5$, 77%, 82% e.e.; R^1 = 2-naphthyl, 73%, 84% e.e.;
R^1 = 4-CH$_3$-C$_6$H$_4$, 64%, 88% e.e.; R^1 = 4-CF$_3$O-C$_6$H$_4$, 77%, 72% e.e.

TRIP, **612**   R^1 = CH(CH$_3$)$_2$
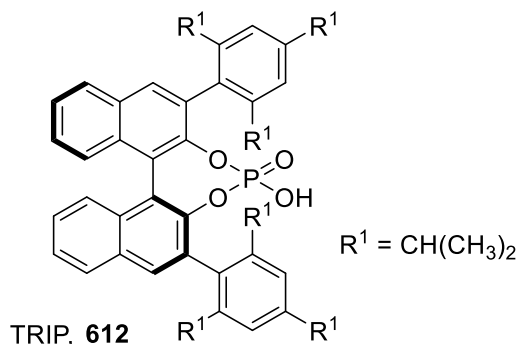
The cyclization of the alkenediol 613 was carried out using the enantiomerically pure N-iodolactam 615, but the corresponding tetrahydrofuran 614 was isolated as a racemic mixture. However, the addition of catalyst 616 to the reaction mixture allowed us to obtain the product with moderate enantioselection [312].
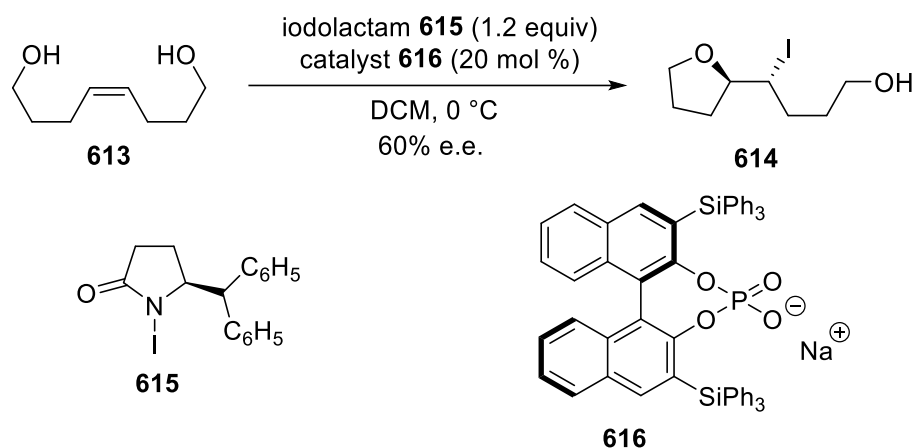
A similar reaction was carried out using both enantiomers of chiral bromolactam 618 together with catalyst TRIP, 612. The alkenediol 613 was converted into tetrahydrofuran 617 with comparable results exploiting both brominating reagents, so the stereoselection was ascribed to the initial formation of a complex between substrate and TRIP 612, whereas the process was irrespective of the chirality of the brominating reagent [312-313].
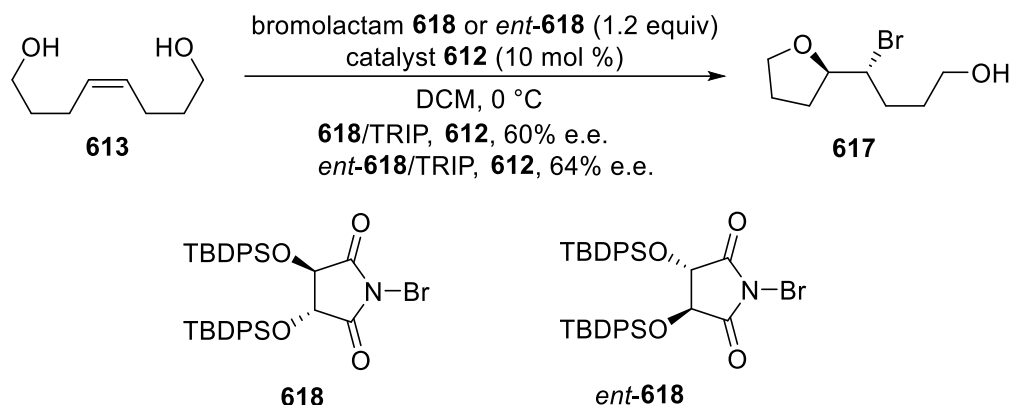
In addition, using both chloroacetic acid as Brønsted acid and the chiral Lewis base 621 [314-315], the cyclization of alkenol 619 mediated by NBS afforded tetrahydrofuran 620 in excellent yield, although with low enantioselection. On the contrary, when the base 622 was employed, the major product was the tetrahydrofuran 620, which displayed the opposite configuration, but absolute configurations were not assigned [186].

catalyst **621**: 100% conversion, e.r. 74:26, 48% e.e.;
catalyst **622**: 100% conversion, e.r. 21:79, 58% e.e.

$R^1 = CH_2CH_2OCH_3$, $R^2 = CH(CH_3)_2$

The indole derivatives 623 underwent cyclization to give 3-iodofuroindolines 624 with excellent yield and stereoselection on treatment with 1,3-diiododimethylhydantoin (DIDMH) in the presence of the anionic chiral Co(III) complex 625 [316].

R^1 = H, 98%, 95% e.e.; R^1 = CH_3, 97%, 90% e.e.; R^1 = Cl, 95%, 96% e.e.

Λ-(S,S)-**625**

R^1 = t-C_4H_9, R^2 = $(CH_3)_2CH$

In addition, 3-bromofuroindolines 627 were obtained in good yield and excellent enantioselection starting from indoles 626 by using catalyst TRIP 612 and the DABCO-derived brominating reagents 628 and 629 [317].

R^1 = Cbz, R^2 = H, 98%, 98% e.e.; R^1 = Boc, R^2 = 5-CH_3O, 94%, 98% e.e.;
R^1 = Boc, R^2 = 4-F, 90%, 97% e.e.; R^1 = Boc, R^2 = 6-Cl, 100%, 97% e.e.

628

629

The chlorocyclization of alcohol 630 was carried out using the catalyst 633 and the halogen donor 632, to give the bicyclic tetrahydrofuran 631 in high yield and good enantioselection, and similar results were observed when the reaction was carried out exploiting the catalyst ent-633 to provide the corresponding ent-631 [318].

reagent **632** (1.3 equiv)
catalyst **633** (10 mol %)
Na$_2$CO$_3$ (4.0 equiv)

PhF:n-heptane 1:1, -30 °C
71%, 84% e.e.

631

630

reagent **632** (1.3 equiv)
catalyst *ent*-**633** (10 mol %)
Na$_2$CO$_3$ (4.0 equiv)

PhF:n-heptane 1:1, -30 °C
79%, 86% e.e.

ent-**631**

632

633

R^1 = 2,4,6-(cyclohexyl)$_3$-C$_6$H$_2$
R^2 = n-C$_8$H$_{17}$
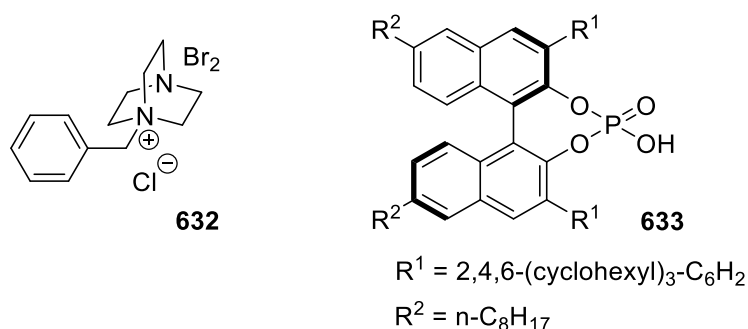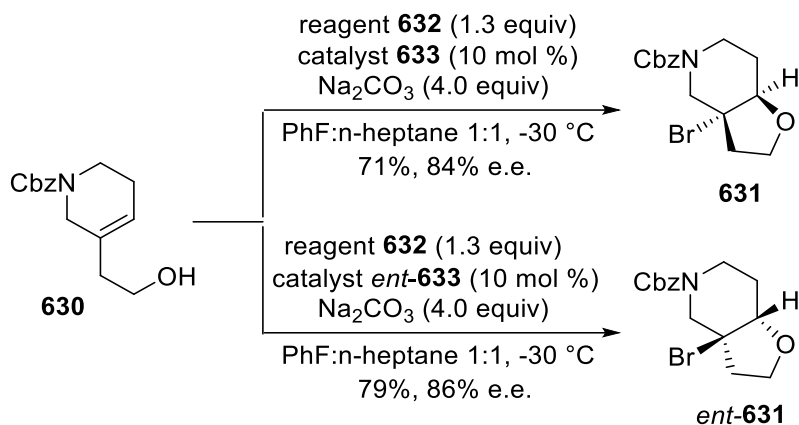
In addition, the cyclization of bicyclic alcohols 634, mediated by the chiral phosphoric acid derivative TRIP 612 coupled with the slightly modified halogen donor 636, proceeded with excellent enantioselection, to give the tricyclic tetrahydrofurans 635 in very good yield [319].

636 (1.5 equiv)
catalyst TRIP **612** (10 mol %)
Na$_2$CO$_3$ (4.0 equiv)

p-xylene, rt

634

635

n = 1, 96%, 96% e.e.; n = 2, 98%, 99% e.e.;

636
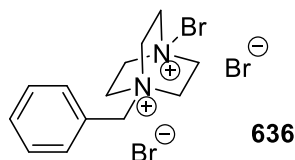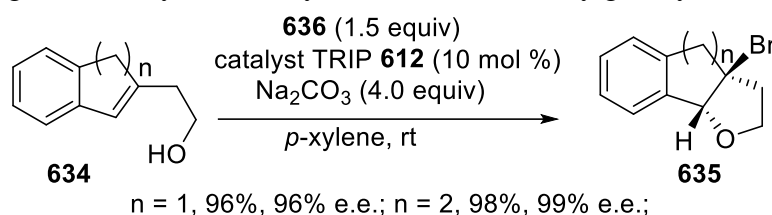
Catalyst 621 was highly effective in desymmetrization of alkenediols 637 that underwent cyclization mediated by NBS to give the trisubstituted tetrahydrofurans 638 in excellent yield, almost complete diastereoselection and very high enantioselection [320].
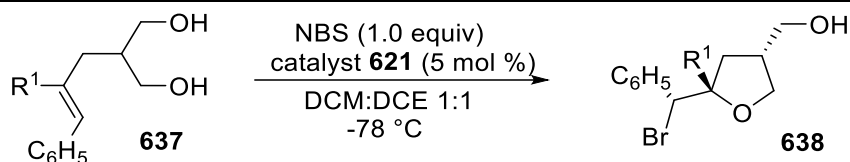
R^1 = C$_6$H$_5$, 99%, >99:1 d.r., 96.5:3.5 e.r.; R^1 = 4-C$_2$H$_5$-C$_6$H$_4$, 99%, > 99:1 d.r., 96:4 e.r.
R^1 = 4-F-C$_6$H$_4$, 92%, >99:1 d.r., 97.5:2.5 e.r.

The same catalyst 621 was also employed in the presence of metansulphonic acid, with similar results, for the desymmetrization of diol 639 to give the tetrahydrofuran 640 with good stereoselection [321].

80%, 92:8 d.r., 85.5:14.5 e.r.
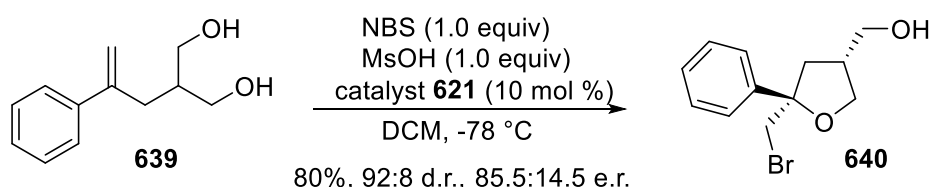
The desymmetrization of diols 641 exploited the bromocyclization mediated by N-bromopyrrolidin-2-one (NBP) in the presence of the chiral catalyst 643, and the major diastereomeric product 642 was isolated in excellent yield and good stereoselection [322].
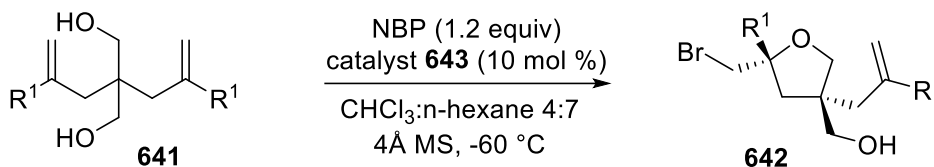
R^1 = C$_6$H$_5$, 93%, 84:16 d.r., 92% e.e.; R^1 = 2-CH$_3$-C$_6$H$_4$, 90%, 95:5 d.r., 92% e.e.;
R^1 = 4-CH$_3$-C$_6$H$_4$, 92%, 82:18 d.r., 90% e.e.; R^1 = 1-naphthyl, 96%, 95:5 d.r., 86% e.e.
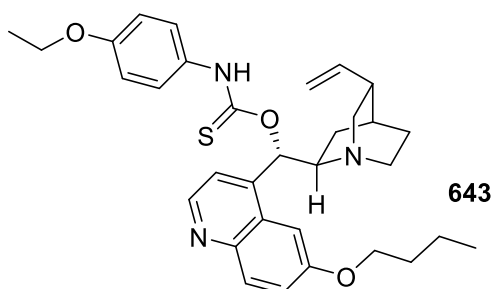
With the same catalyst 643, the desymmetrization of diol 644, displaying both a double and a triple bond, occurred with better enantioselection to give the chiral tetrahydrofuran 645, and this result was probably due to the higher molecular diversity with respect to 641 [320].

91%, 84:16 d.r., 99:1 e.r.
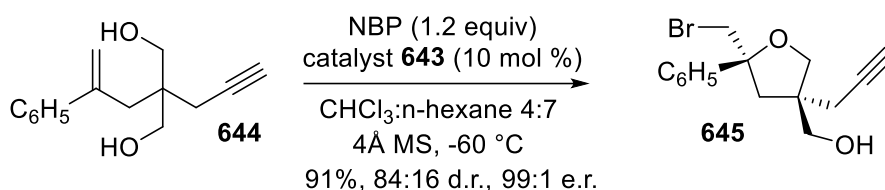
In addition, the desymmetrization of symmetric alkenediols 646, performed with NIS in the presence of the chiral sodium phosphate 648, proceeded with moderate enantioselection to give in moderate to good yield the chiral tetrahydrofurans 647 [323].
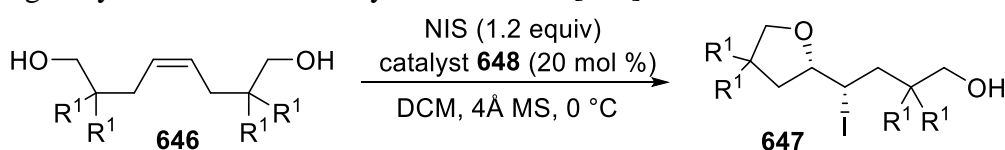
R^1 = H, 81%, 62% e.e.; R^1 = CH$_3$, 60%, 68% e.e.; R^1 = C$_6$H$_5$, 82%, 71% e.e.

648
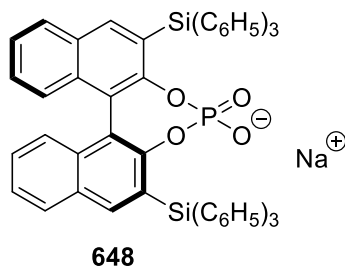
On the other hand, the cyclization of the same alkenediols 646, carried out with N-iodopyrrolidinone (NIPyr) in a basic medium in the presence of the catalyst ent-648, provided the enantiomeric tetrahydrofurans ent-647 in moderate to good yield but with slightly better enantioselection [324].

R^1 = H, 54%, 64% e.e.; R^1 = CH$_3$, 72%, 80% e.e.; R^1 = C$_6$H$_5$, 86%, 80% e.e.
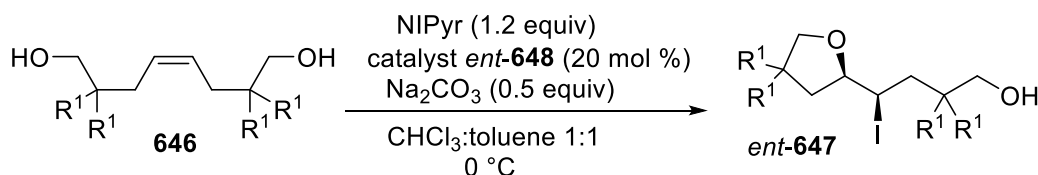
Another oxyfunctionalization of a double bond mediated by a haliranium ion allowed to prepare bicyclic derivatives exploiting the additional formation of carbon-carbon bonds. In fact, compound 650 was obtained in low yield but with excellent enantioselection, starting from the acyclic compound 649, using NBS together with catalyst 651 [325].

651 R^1 = 2,4,5-Cl$_3$-C$_6$H$_2$
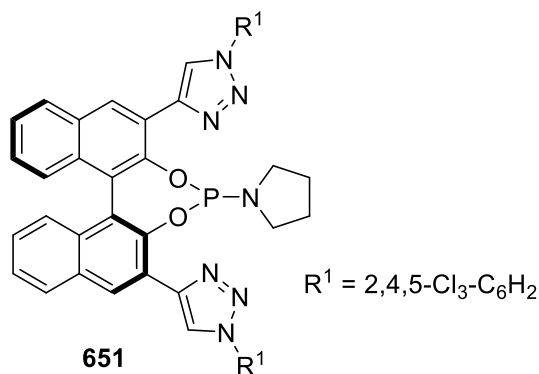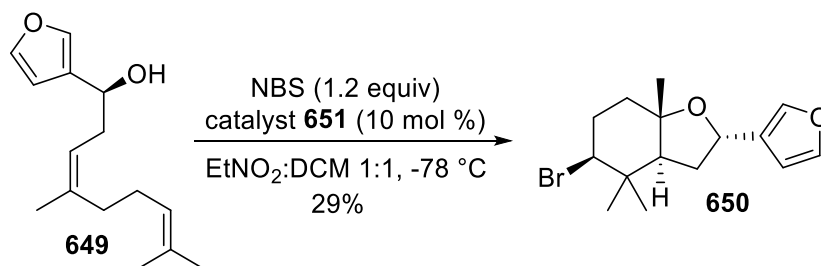
Intramolecular addition of phosphoramidic acids to double bonds exploiting an iodiranium ion allowed stereocontrol at both carbon and phosphorus chirality centers. Thus compound 652, in the presence of catalyst StilPBAM·HNTf2 302 acting as Brønsted acid, afforded the cyclic phosphoramidates 653 in good yield and stereoselection [326].
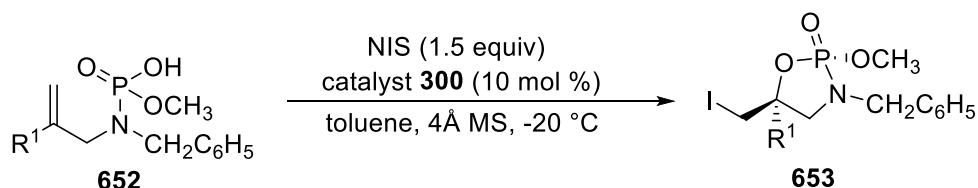
R^1 = 4-CH$_3$O-C$_6$H$_4$, 83%, 18:1 d.r., 94% e.e.; R^1 = 4-Cl-C$_6$H$_4$, 74%, >20:1 d.r., 97% e.e.;
R^1 = 3-butenyl, 92%, >20:1 d.r., 98% e.e.; R^1 = CH$_3$, 91%, 8:1 d.r., 91% e.e.

Eventually, starting from silanols 654 containing a double bond, benzoxasiloles 655 were isolated in good yield with excellent stereoselection by using the chiral anionic phase-transfer catalyst 656, coupled with bromine/N-benzyl-DABCO complex 657. Using K2CO3 as the base gave the best outcome, but phenyl groups on silicon were compulsory since changing them with methyl or isopropyl groups caused a decreased stereoselection [327].

R^1 = H, 87%, 95.5 e.e.; R^1 = 4-CH$_3$, 94%, 96% e.e.; R^1 = 4-Cl, 92%, 98% e.e.

R^1 = 2,4,6-(i-C$_3$H$_7$)$_3$-C$_6$H$_2$
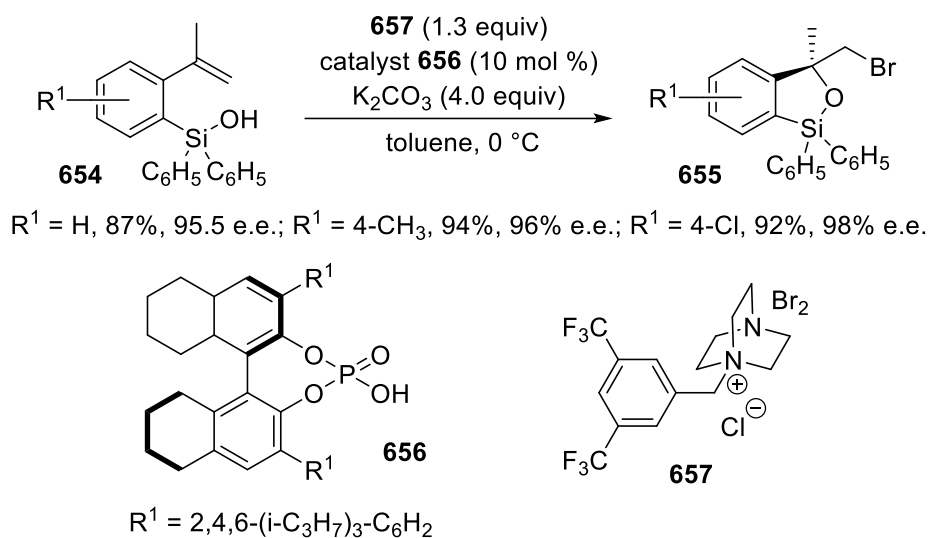
2.1.7.4. Synthesis of tetrahydropyrans and larger ring ethers from unsaturated alcohols and ethers.

2.1.7.4.1. Cyclization without asymmetric induction.

Unsaturated alcohols **658** gave the corresponding isochromans **659** in very good yield as racemic mixtures, and the cyclization was directed by electronic factors [328].

R^1 = H, R^2 = C$_6$H$_5$, 94%; R^1 = H, R^2 = CH$_3$, 80%; R^1 = OCH$_3$, R^2 = C$_6$H$_5$, 92%
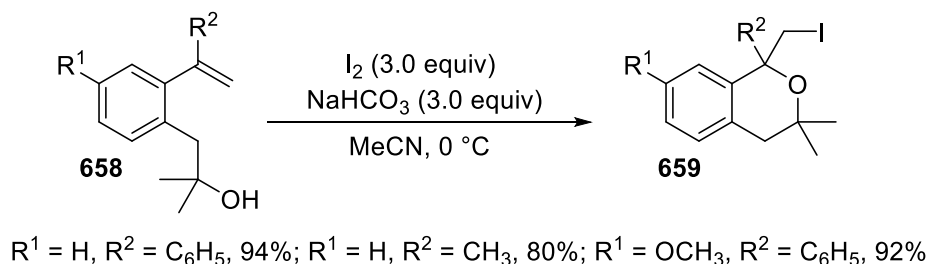
2.1.7.4.2. Cyclization with internal asymmetric induction.

The stereoselective cyclization of alkenols proceeding with internal asymmetric induction relied on either the configuration of the double bond or the presence of chirality centers tethered on the carbon chain. The presence of a Lewis base as Ph3P=S 53 allowed an increase in the cyclization rate of unsaturated alcohols carried out with NBS, but the process was not highly regioselective since the (E)-alkenol 660 afforded a regioisomeric mixture of 661 and 662, although electronic factors favored the 6-endo-mode formation of tetrahydropyran 661. Both cyclizations, however, were stereoselective, owing to the anti-addition to the (E)-double bond [70].

69%,
11:1 regioisomeric ratio
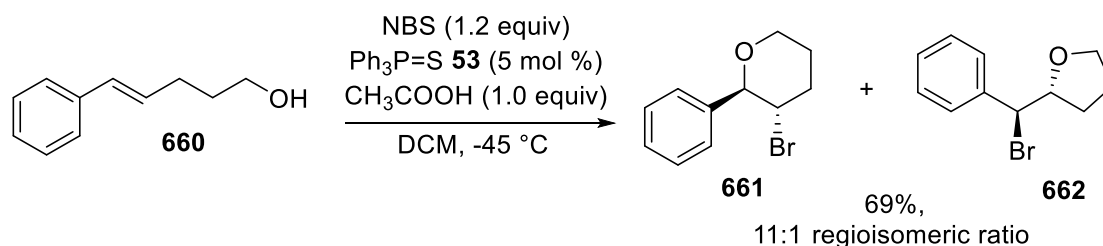
Tetrahydropyrans 664 were isolated with total regioselection and stereoselection in moderate to good yield starting from alkenols 663 using BDSB (bromodiethylsulfonium bromopentachloroantimonate), and the 6-endo-mode cyclization was directed again by electronic factors [329].

R^1 = CH$_2$CH=CH$_2$, 66%; R^1 = CH=CHCH$_3$, 57%; R^1 = C$_6$H$_5$, 75%
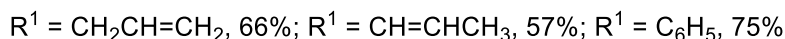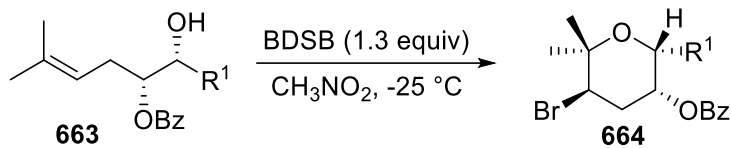
Polysubstituted dihydropyrans 666 were also obtained in good yield but with very low stereoselection, when secondary alkenols 665 were treated with iodine in the presence of FeCl3 [330].

R^1 = R^2 = C$_6$H$_5$, 90%, 60:40 *cis:trans*; R^1 = C$_6$H$_5$, R^2 = 4-Cl-C$_6$H$_4$, 92%, 60:40 *cis:trans*;
R^1 = n-C$_4$H$_9$, R^2 = 4-Cl-C$_6$H$_4$, 90%, 54:46 *cis:trans*
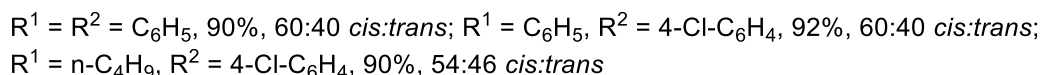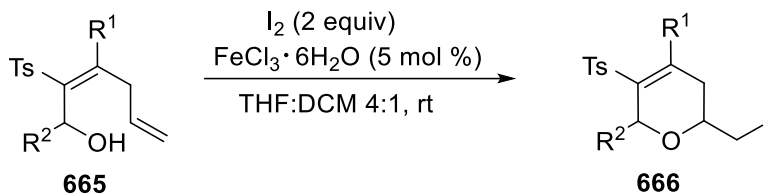
The cyclization of the chiral tosylamino derivatives 667, bearing a secondary hydroxy functionality, was carried out exploiting reagent 669, which generated halogens by oxidation of halide anions, and morpholine derivatives 668 were isolated in very good yield with good to excellent stereoselection [331].

X = Br, R^1 = 2-CH$_3$O-C$_6$H$_4$, 92%, 16:1 d.r.; X = Br, R^1 = 4-F-C$_6$H$_4$, 92%, 17:1 d.r.;
X = I, R^1 = 2-CH$_3$O-C$_6$H$_4$, 75%, 10:0.9 d.r.; X = I, R^1 = 4-CH$_3$O-C$_6$H$_4$, 82%, 10:1 d.r.
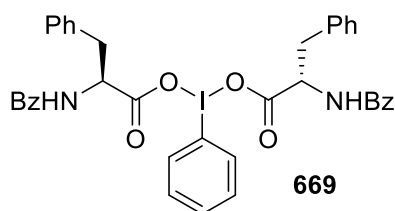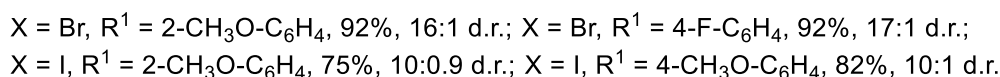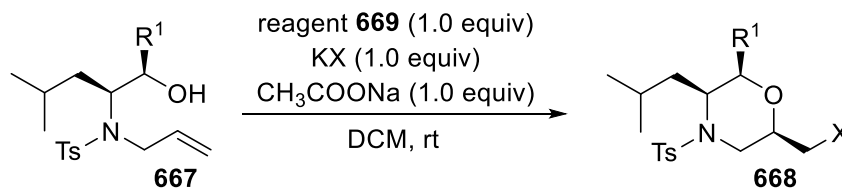
Mixtures of chiral diastereomers 670 and 671, intermediate to cyclooxygenase-2 inhibitors, led with total stereoselection to mixtures of substituted tetrahydropyrans 672 and 673 displaying the same ratios as the starting material, and the configuration of the quaternary center directed the cyclization outcome to generate 1,3-cis-isomers with respect to the hydroxy group [332].

R^1 = CH$_3$, 75%, 73:27 d.r.; R^1 = C$_6$H$_5$, 75%, 87:13 d.r.;
R^1 = 4-F-C$_6$H$_4$, 80%, 71:29 d.r.; R^1 = 4-Cl-C$_6$H$_4$, 80%, 80:20 d.r.
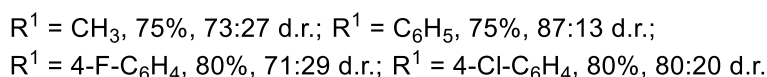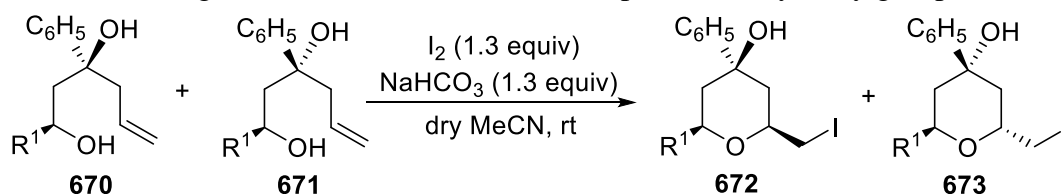
The cyclization of compounds 674 or 676, mediated by iodine and bis-(sym-collidine)2AgPF6, occurred in a 6-endo-mode, leading to the corresponding tetrahydropyrans 675 or 677 in moderate to good yield but with total stereoselection owing to the preexisting chirality centers [333].
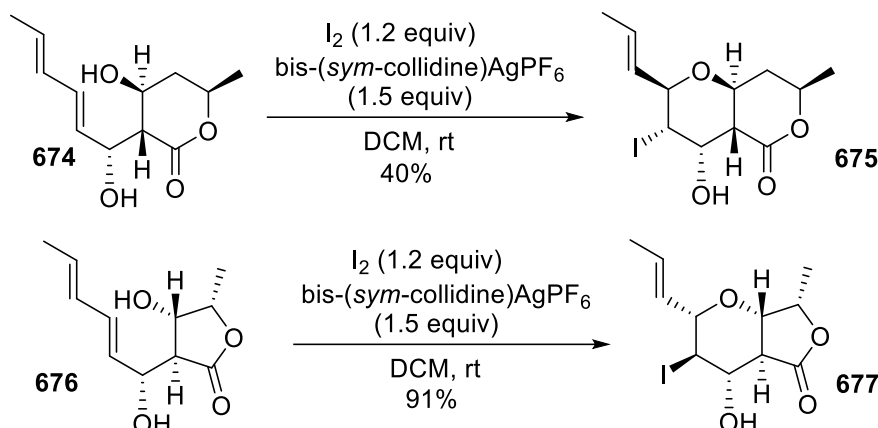
Moreover, by reaction of chiral ether 678 with NIS, the dioxane derivative 679 was obtained in good yield and total stereoselection [334].
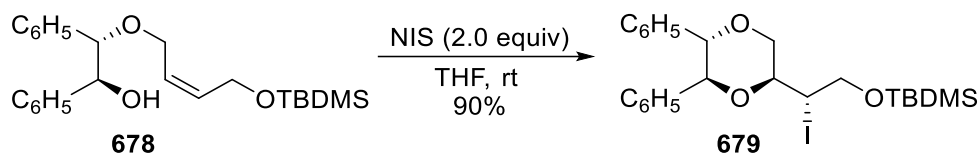
In addition, when chiral tosylamides 680 were treated with iodine, the corresponding 1,4-trans-disubstituted morpholine derivatives 681 were isolated in good yield with nearly total stereoselection [335].
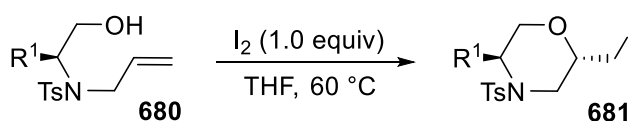
$R^1 = CH_3$, 74%, 99% d.e.; $R^1 = CH(CH_3)_2$, 73%, 99% d.e.

The bromocyclization of compound 682 to give the tricyclic derivatives 683 exploited the hydroxy group of an N-acyl hemiaminal as a nucleophile, and the regioselection of the process was directed by electronic factors. Diastereoselection arose from anti-addition to the (E)-double bond, but only moderate enantioselection was achieved when dimeric Cinchona alkaloid-derived catalysts 144 and 145 were added to the reaction. Concerning the regioselection of the process, it is worth nothing that the formation of a six-membered ring avoided the angular strain due to two fused five-membered rings, although the electron-withdrawing trifluoromethyl group was placed on the incipient cation [336].

$R^1 = C_6H_5$, 86%; $R^1 = CH_3$, 78%; $R^1 = CF_3$, 96%
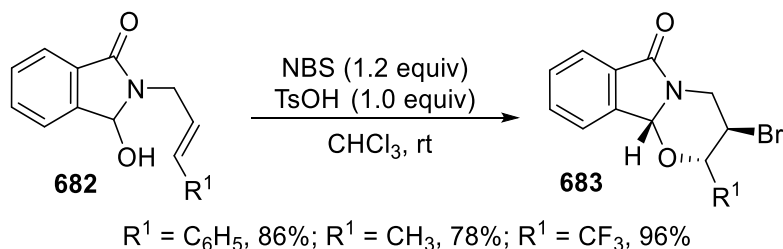
Oxocenes 685 and 687 were obtained in moderate yield starting from dienyl alcohols 684 and 686, respectively, the reaction proceeding through an unusual 8-endo-mode irrespective of the configuration of the double bond [337].
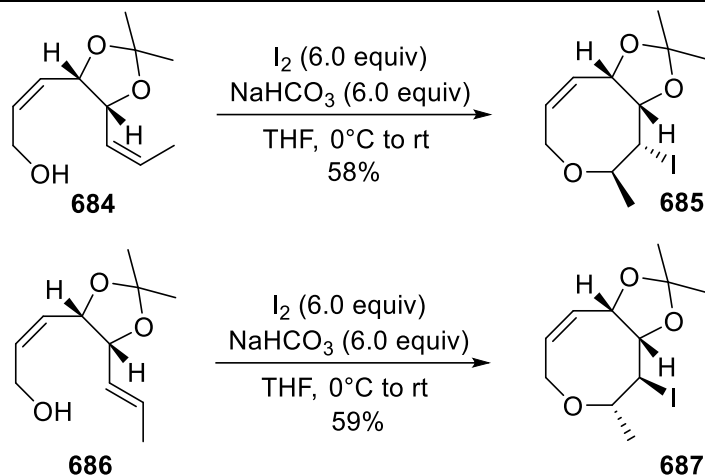
On the other hand, within a total synthesis of laurendecumallene, 8-membered cycles were produced through a ring-expanding bromocycloetherification, which was based on the formation of a bicyclic oxonium intermediate by attack of tetrahydrofuran oxygen onto a bromiranium ion, followed by a nucleophilic attack of a strategically placed Boc functionality to cleave the preexisting tetrahydrofuran ring. To this end, tetrahydrofuran 688 reacted with the novel reagent bromodiethylsulfonium bromopentachloroantimonate (BDSB) to give the oxocanes 689 and 690 in moderate yield but with good stereoselection [292].
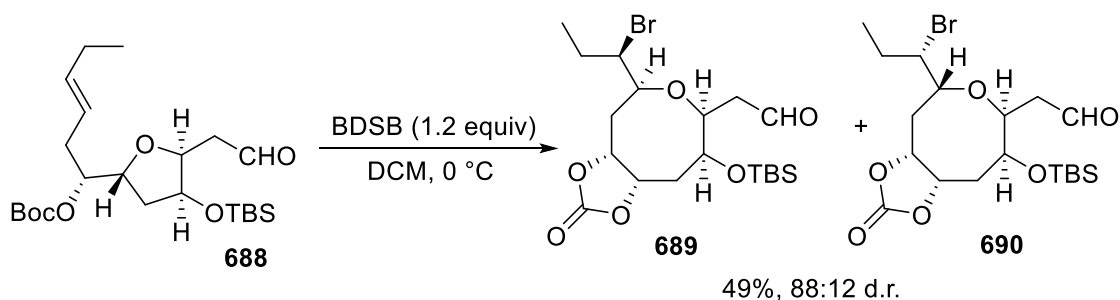
Eventually, within an approach to the bioactive alkaloid perophoramidine, compound 691 was treated with an excess NIS to give a moderate yield of the polycyclic derivative 692, where the formation of a tetrahydropyran ring was accompanied by an unexpected de-aromatization reaction [338].
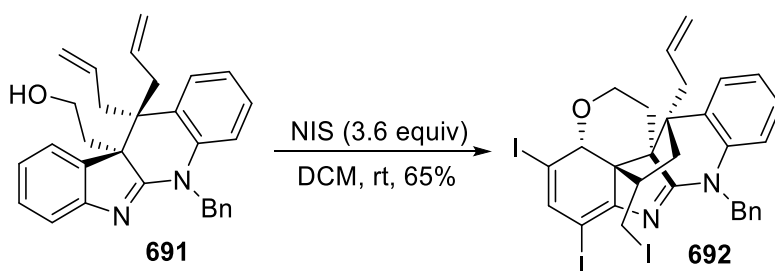
2.1.7.4.3. Cyclization with external asymmetric induction.

The intramolecular bromoetherification of enones **693** was carried out with BsN(CH$_3$)Br in the presence of the chiral ligand **695** and Fe(acac)$_3$, and the tetrahydropyrans **694** were obtained in very good yield with excellent diastereo- and enantioselection [339].

$R^1 = C_6H_5$, 97%, e.e. 96%, d.r. 96:4; $R^1 = 4\text{-}F\text{-}C_6H_4$, 98%, e.e. 97%, d.r. 99:1;
$R^1 = CH_3$, 68%, e.e. 93%, d.r. 94:6

$R^1 = 2,6\text{-}^iPr_2\text{-}C_6H_3$

695
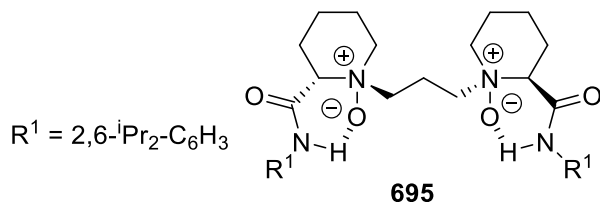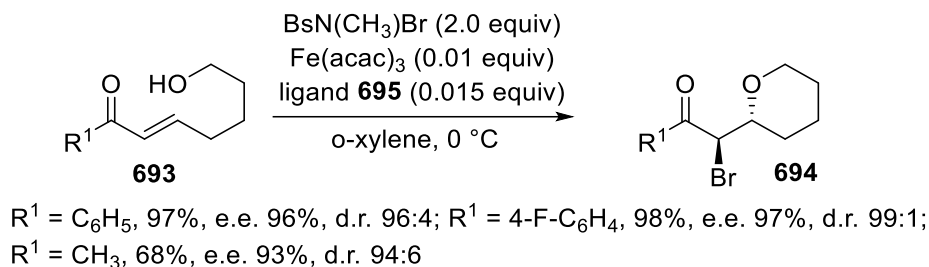
It is worth mentioning that oxepanes **698** were also easily obtained starting from enones **696**, with changed reaction conditions. However, although nearly equimolar diastereomeric mixtures **697** were initially obtained, the removal of bromine allowed the isolate chiral oxepanes **698** to have excellent enantioselection [339].

$R^1 = C_6H_5$, 86%, d.r. 57:43, e.e. 98% ; $R^1 = 4\text{-}F\text{-}C_6H_4$, 74%, d.r. 57:43, e.e. 97%;
$R^1 = 4\text{-}C_6H_5\text{-}C_6H_4$, 84%, d.r. 57:43, e.e. 99%,
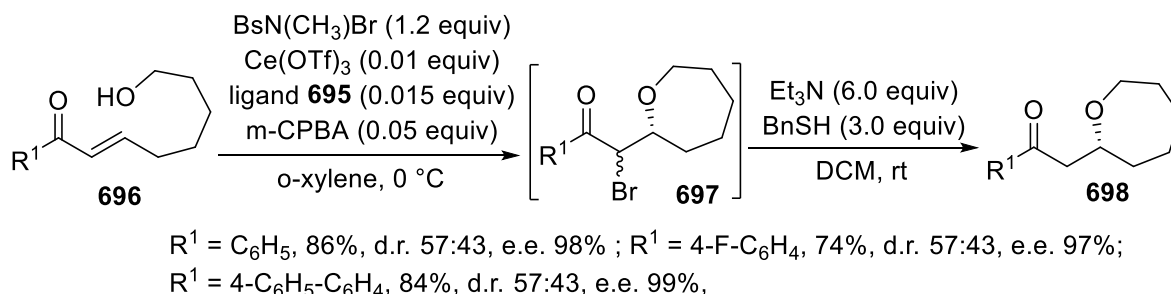
A similar reaction was carried out starting from phenol **699** but changing $BsN(CH_3)Br$ with $4\text{-}NsNCl_2$ in order to avoid bromination at the aromatic ring of tetrahydrobenzopyran **700**, which was isolated in good yield but moderate diastereoselection, although the major isomer was obtained with high enantioselection [339].
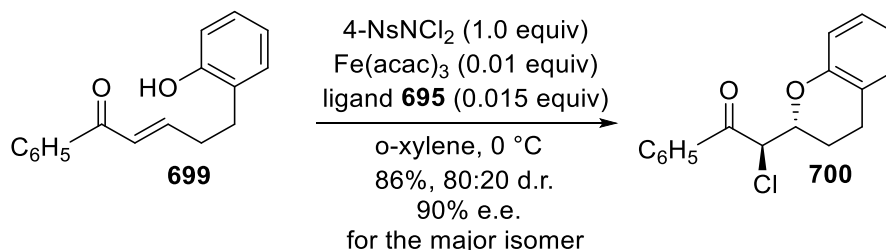
2.1.8. Dihydrobenzofurans from phenols.

Besides an alcoholic hydroxy group, a nucleophilic phenolic hydroxy group can attack a haliranium ion, leading to giving five-membered heterocyclic rings according to a 5-exo-mode cyclization. Thus, 2-(iodomethyl)dihydrobenzofurans 702 were obtained in very good yield and total regioselection by reaction of allylphenols 701 with iodine [340].

$R^1 = R^2 = CH_3$, $R^3 = H$, 89%; $R^1 = R^3 = CH_3$, $R^2 = H$, 93%;
$R^1 = H$, $R^2 = R^3 = CH_3$, 91%;
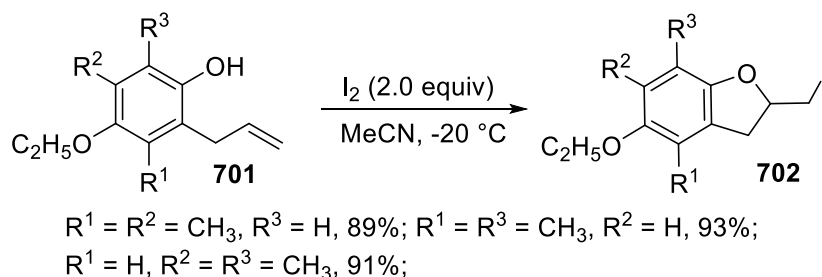
Whereas NBS alone was ineffective for the cyclization of o-allylphenols, the reaction of compounds 703, carried out with NBS in the presence of a catalytic amount of DBU and acetic acid, proceeded in good yield to give 2-(bromomethyl)dihydrobenzofurans 704 with contemporary bromination at the aromatic ring, the active brominating agent is believed to be acetyl hypobromite generated in situ [341].
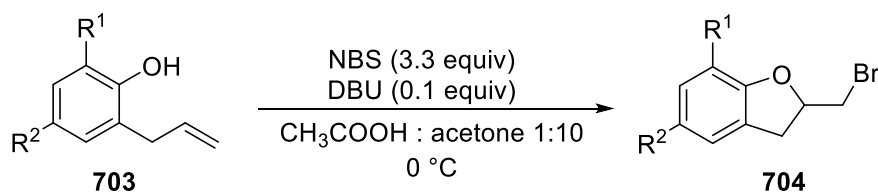
Substrate: R^1 = R^2 = H, Product: R^1 = R^2 = Br, 79%;
Substrate: R^1 = H, R^2 = t-C_4H_9, Product: R^1 = Br, R^2 = t-C_4H_9, 83%;
Substrate: R^1 = CH_3, R^2 = H, Product: R^1 = CH_3, R^2 = Br, 82%

A HBr-mediated tandem allylation/iodocyclization sequence carried out in air allowed to prepare of the 2-(iodomethyl)dihydrobenzofuran 705 starting from 2-naphthol, the iodine required for cyclization arising from oxidation of the iodide anion formed during the allylation [342].
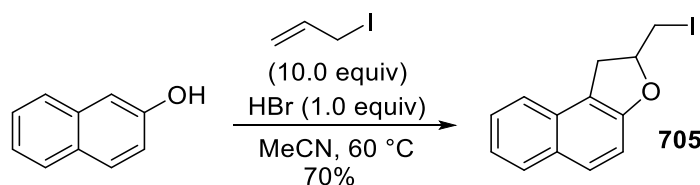
Under electrochemical conditions, the iodide anion was oxidized to iodine in order to convert phenols 706 into the cyclic compounds 707 in good yield [343].
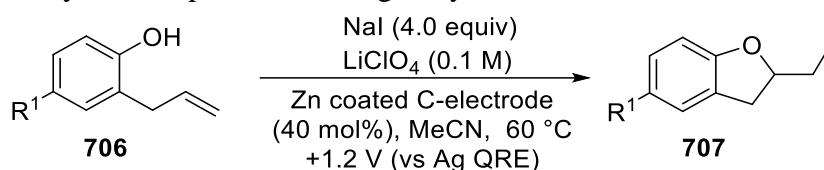
R^1 = H, 99%; R^1 = CH_3, 93%; R^1 = Br, 83%; R^1 = Cl, 81%

With the aim to avoid the use of organic solvents, the iodocyclization of liquid 2-allylphenols 708 was carried out in the water to give the corresponding cyclic derivatives 709 in very high yield, but lower yields were observed when NaHCO3 was added [344].
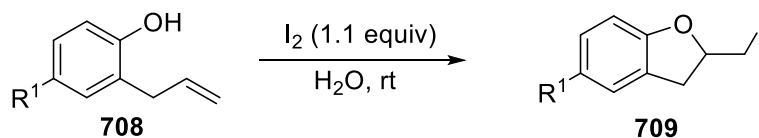
R^1 = H, 87%; R^1 = OCH_3, 90%; R^1 = CH_3, 73%

The cyclization of phenol 710 was promoted also by NIS, to give the corresponding 2-iodomethyl-2,3-dihydrobenzofuran 711 in good yield [345].
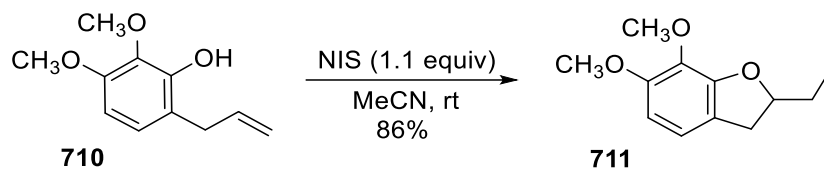
It is worth mentioning that iodine in aqueous micelles (CTAB) was effective in cyclizing allylphenols 712 to the corresponding cyclic derivatives 713 in good yield [346].
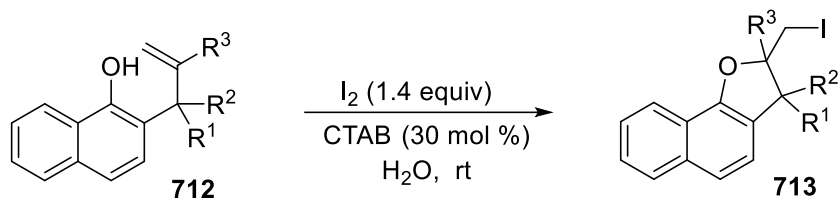
R^1 = R^2 = R^3 = H, 88%; R^1 = R^2 = H, R^3 = CH$_3$, 84%; R^1 = CH$_3$, R^2 = R^3 = H, 83%

Eventually, on treatment with iodine using DMSO in order to avoid solubility problems, 2-allyl-3-hydroxynaphthalene-1,4-dione 714 afforded tricyclic compound 715 in high yield and total regioselection exploiting the tautomerism of the structure [347].
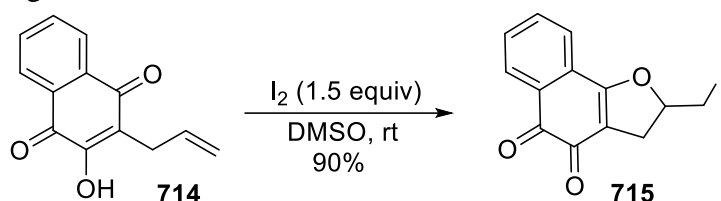
2.1.9. Chromanes from o-alkenylphenols.

2.1.9.1. Without asymmetric induction.

Starting from phenol 716, bearing an unsaturated substituent at the 2-position, the chromane 717 was obtained in good yield and total regioselection using bromodiethylsulfonium bromopentachloroantimonate (Et2SBr . SbCl5Br, BDSB) as a source of the intermediate bromiranium ion [348].
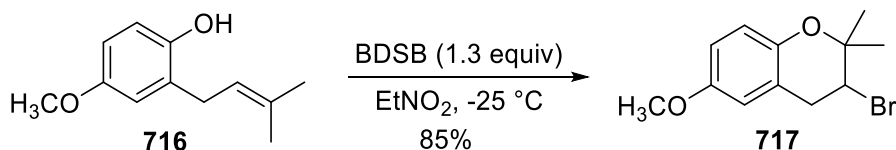
2.1.9.2. With internal asymmetric induction.

The cyclization of phenol 718 was carried out with NBS in the presence of the morpholine-HFIP salt, and the cyclization afforded the tricyclic compound 719 in good yield and high stereoselection [236, 349].
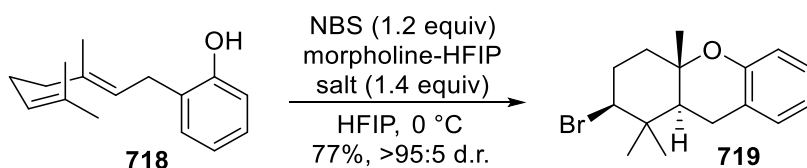
In addition, using bromodiethylsulfonium bromopentachloroantimonate (BDSB), the cyclization of the MOM-ether 720 afforded the corresponding tricyclic derivative 721 in good yield and total stereoselection [236].
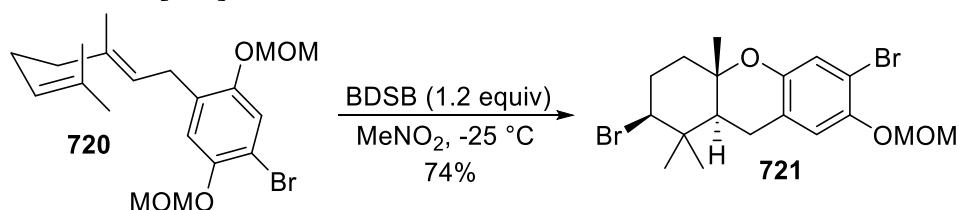
2.1.9.3. With external asymmetric induction.

When the chiral amidophosphate catalyst 724 coupled with a halo-Lewis acid such as N-chlorosuccinimide (NCS) was employed for the cyclization, chromanes 723 and 726 were obtained in good yield and excellent stereoselection starting from 722 and 725, respectively, through a reactive species where iodine was directly bonded to the catalyst [350-351].
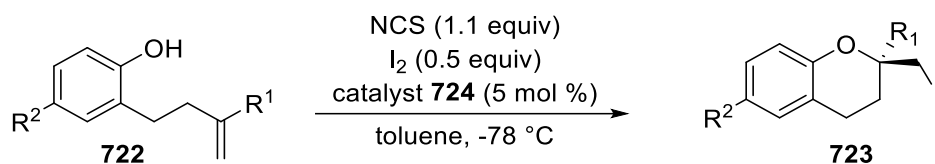
$R^1 = CH_3$, $R^2 = H$, 97%, 95% e.e.; $R^1 = n\text{-}C_7H_{15}$, $R^2 = H$, 99%, 98% e.e.;
$R^1 = R^2 = CH_3$, 93%, 94% e.e.; $R^1 = CH_3$, $R^2 = OCH_3$, 95%, 96% e.e.
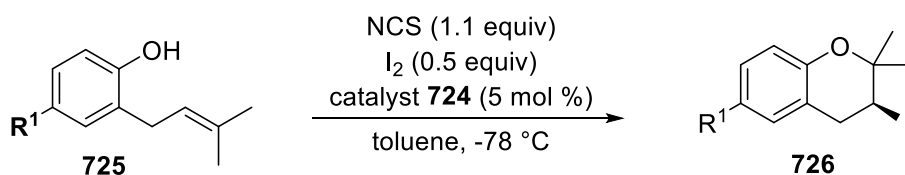
$R^1 = H$, 92%, 96% e.e.; $R^1 = Cl$, 88%, 94% e.e.; $R^1 = OCH_3$, 97%, 96% e.e.
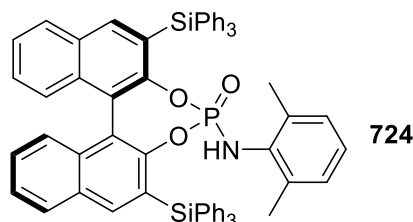
However, the bromocyclization of 2-geranylphenol 727 was carried out with N-bromophthalimide (NBPhth) in the presence of the chiral phosphite-urea bifunctional catalyst 729, but tricyclic tetrahydropyrans 728 were recovered in very low yields and enantioselection [352].

$R^1 = CF_3$, 23%, e.e. 29%;
$R^1 = CH_3$, 16%, e.e. 19%;
$R^1 = Br$, 18%, e.e. 21%

$R^1 = CF_3$, 60%, e.e. 66%;
$R^1 = CH_3$, 56%, e.e. 67%;
$R^1 = Br$, 61%, e.e, 71%

$R^1 = 3,5\text{-}(SF_5)_2C_6H_3$
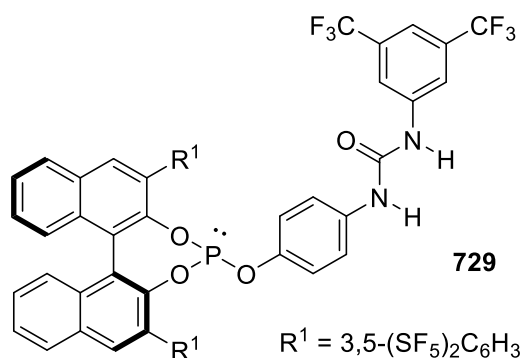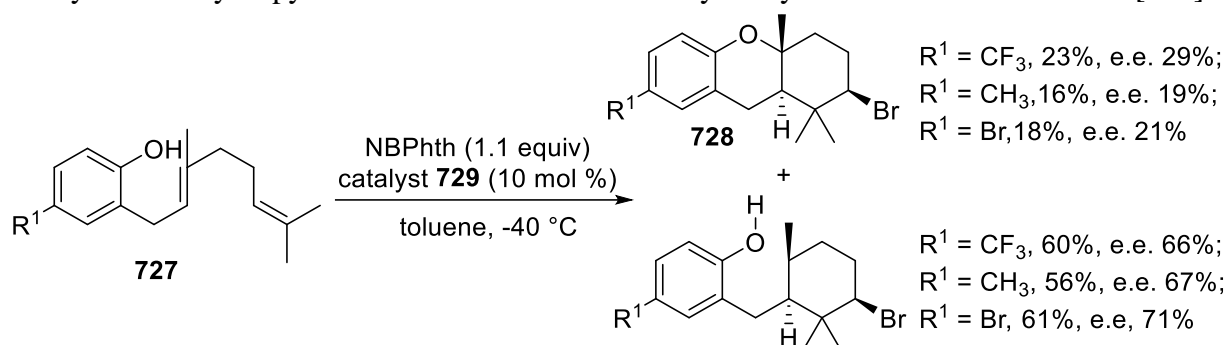
Eventually, within a total synthesis of Azamerone, the cyclization induced by t-butyl hypochlorite in the presence of ligand 732 allowed to prepare the chromane 731 in low yield but with good enantioselection exploiting the tautomerism of the structure of compound 730 [157, 353].
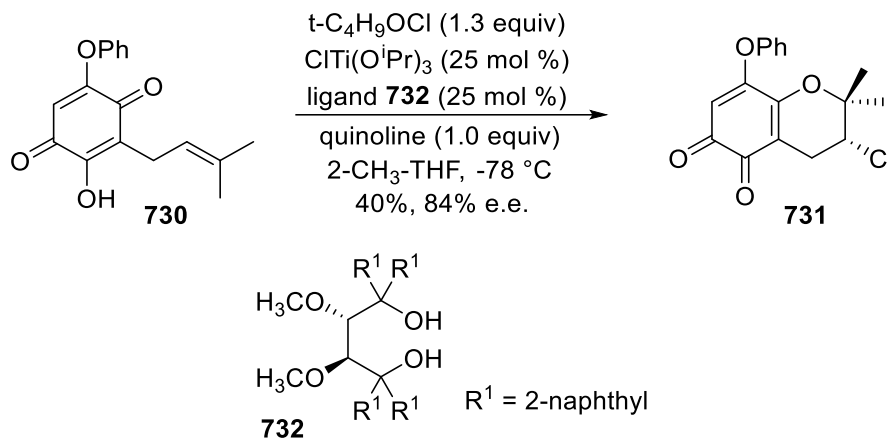
2.1.10. Chromenes from o-alkynyl phenols via allene intermediates.

Alkynyl phenols 733 reacted first with iodine, leading to the intermediate iodoallenyl phenols 734, and subsequent attack of the phenolic oxygen to haliranium ions in a 6-endo-trig mode gave diiodochromenes 735 in moderate to good yield [354].

$R^1 = R^2 = C_6H_5$, 98%; $R^1 = R^2 = 4$-CH_3-C_6H_4, 92%;
$R^1 = R^2 = 4$-Cl-C_6H_4, 89%; $R^1 = CH_3$, $R^2 = C_6H_5$, 52%
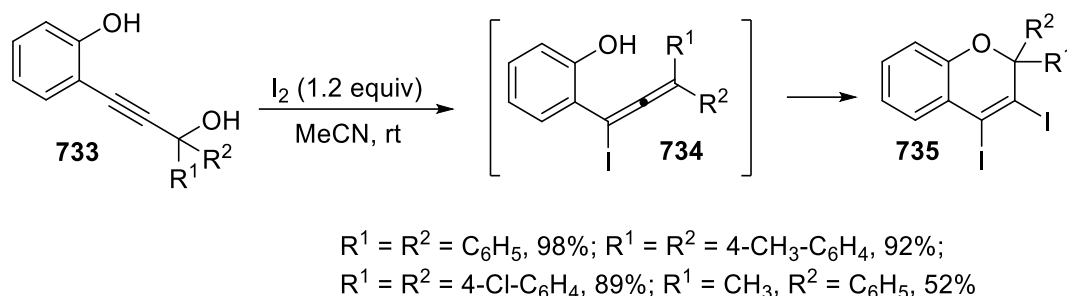
2.1.11. Tetrahydrofurans from chiral acetals and ketals with internal asymmetric induction.

An elegant regio- and stereoselective functionalization of a double bond was carried out by exploiting the attack of an ene ketal oxygen to a haliranium ion, directed by the chirality centers of the diol component of the ketal. This methodology, exploiting I(coll)2PF6 as iodenium donor, was employed for the enantioselective formation of bis-tetrahydrofurans trans/threo/cis 737 and cis/threo/cis 739 in good yield starting from the same diene diol, simply changing the ketal functionality of 736 for the acetal functionality in 738 [355].
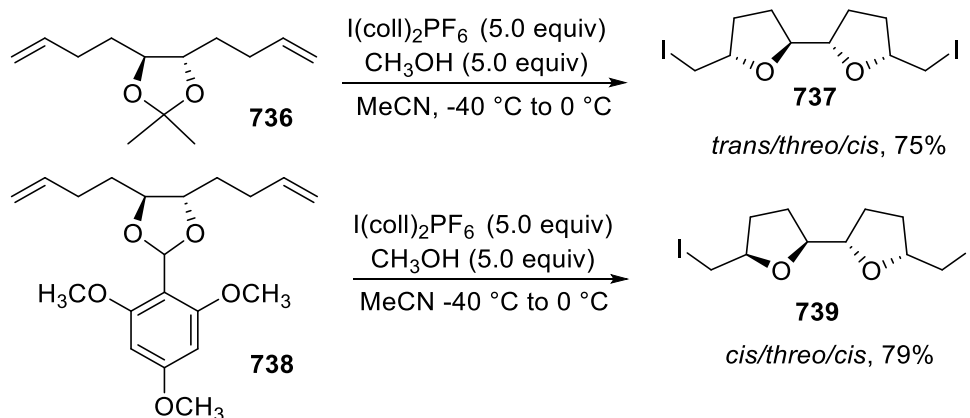
Again, through a regio- and stereoselective functionalization of a double bond leading to chiral tetrahydrofuran mediated by iodonium bis-(sym-collidine)2 perchlorate (IDCP), compounds 740 and 742 were converted in good yield and with total enantioselection into 741 and 743, respectively [356].
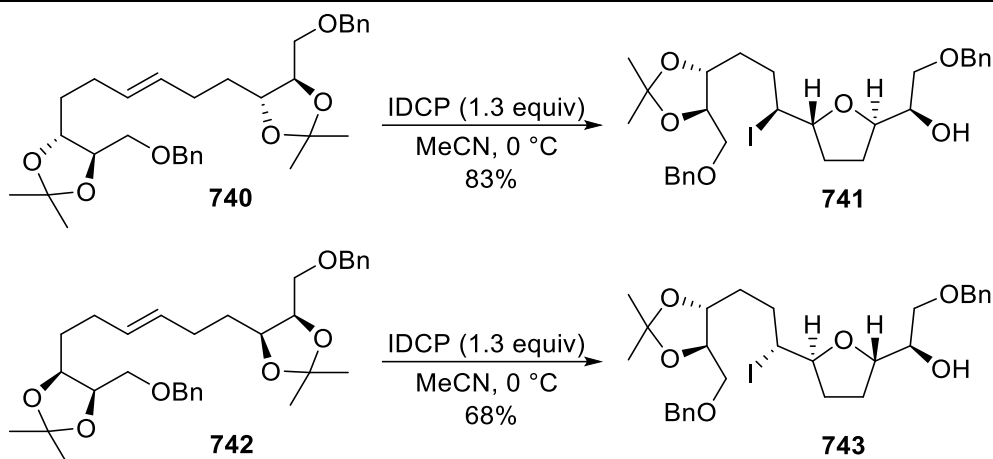
Good stereoselection was also observed when substrate 744 underwent cyclization with IDCP to afford tetrahydrofuran 745 as diastereomeric mixture, whereas changing the methoxycarbonyl group with a benzyl ether group in 746 allowed obtaining product 747 with total stereoselection [357].
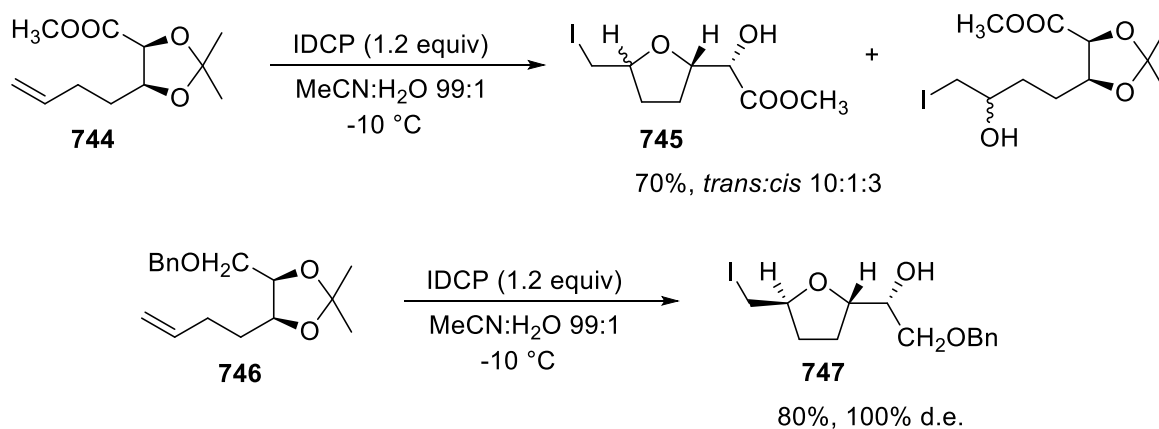
Eventually, compound 748 was converted into the eight-membered heterocycle spiro ketal 749 in moderate yield but with total stereoselection. On the other hand, when a carboxy group was present, as it occurred in compound 750, the spiro derivative 751 was obtained, containing a lactone moiety [355].
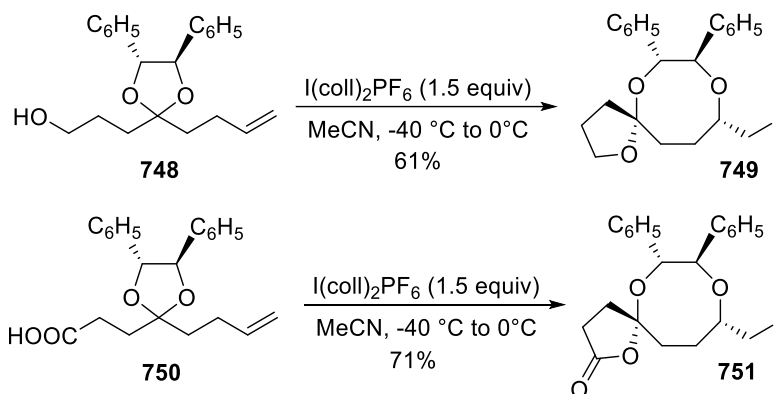
Moreover, the diene ketal 752 afforded the chiral spiroketal 753 in moderate yield but with total stereoselection, through the functionalization of both the double bonds [355].
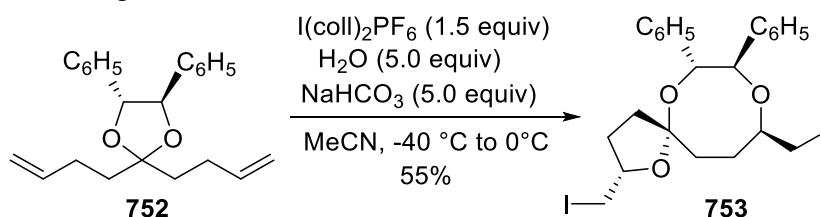
2.1.12. Dihydrofurans, furans and spiroketals from ketones.

2.1.12.1. Without asymmetric induction.

Under basic conditions, the oxygen atom of a ketone within a β-dicarbonyl structure was able to attack a haliranium ion arising from a double bond or an allene functionality [358-359]. Thus, when the diketone 754 was treated with NBS in the presence of the Lewis base 756, bromination at the α position did not occur, whereas dihydrofuran 755 was obtained by cyclization proceeding in a 5-exo-mode [360].
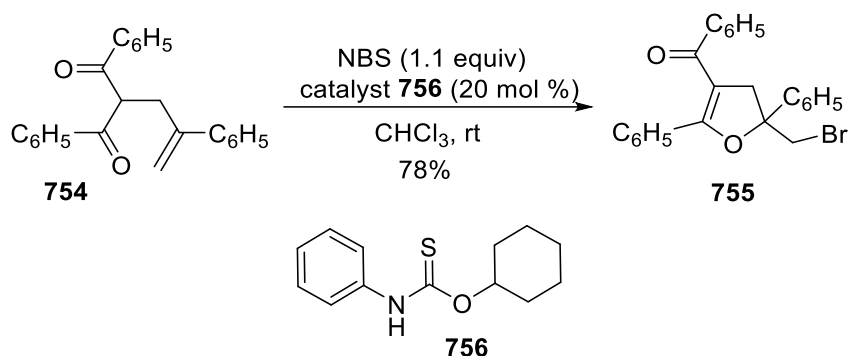
In addition, starting from 757, also dihydrofurans 758 were obtained in moderate to good yield according to a 5-exo mode cyclization [361].
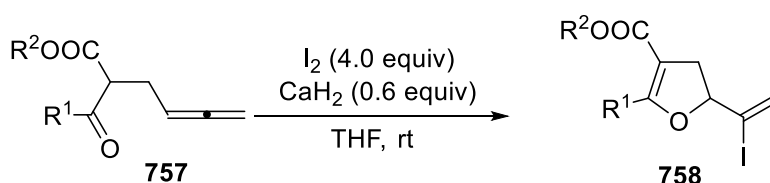
$R^1 = CH_3$, $R^2 = C_2H_5$, 74%; $R^1 = C_6H_5CH_2$, $R^2 = CH_3$, 61%; $R^1 = C_6H_5$, $R^2 = C_2H_5$, 83%

Moreover, in the absence of a base, the oxygen of ketone 759 was able to attack a double bond of an allene coordinated with Cu(II) arising from the reaction of Cu(I) with iodine. The cyclopropyl group was opened by the iodide anion to give furans 760 in moderate to good yield according to cyclization proceeding in a 5-endo-dig mode [362].
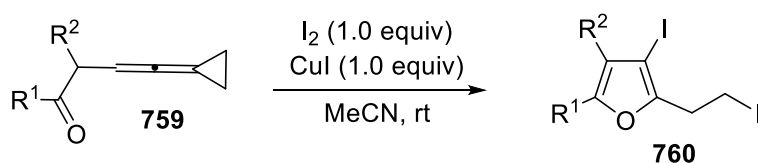
$R^1 = R^2 = C_6H_5$, 99%; $R^1 = $ 2-thienyl, $R^2 = C_6H_5$, 99%;
$R^1 = $ n-C_3H_7, $R^2 = C_6H_5$, 91%; $R^1 = C_6H_5$, $R^2 = $ 2-naphthyl, 61%

Eventually, exploiting the effect of the sulphonyl electron withdrawing group, ketones 761 were converted via a 5-endo-trig iodocyclization into the corresponding furans 762 in moderate to good yield, the cyclopropane ring being cleaved by a nucleophilic iodide anion [363].
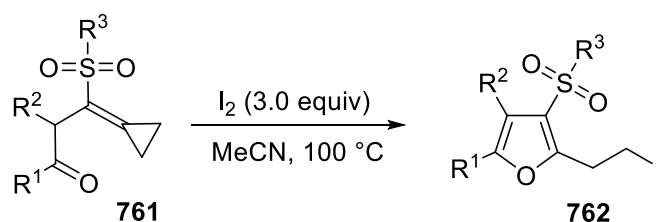
$R^1 = R^2 = R3 = C_6H_5$, 73%; $R^1 = R^2 = C_6H_5$, $R^3 = $ 4-CH_3-C_6H_4, 75%;
$R^1 = $ 2-thienyl, $R^2 = C_6H_5$, $R^3 = $ 4-CH_3-C6H4-SO_2, 42%

2.1.12.2. With internal asymmetric induction.

Bicyclic ketals were obtained by reaction of 2-allyl substituted β-dicarbonyl compounds in the presence of hydrogen peroxide. According to the proposed mechanism, the initial cyclization of **763** and **765** led to intermediate iodomethyl derivatives that underwent attack by peroxide ion to provide the bicyclic compounds **764** and **766** in moderate to good yield but with total stereoselection [364].
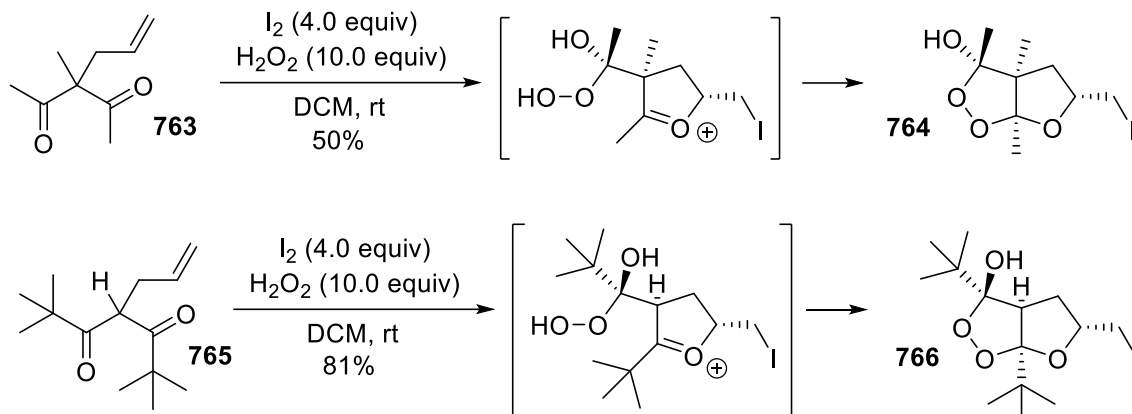
Exploiting the halenium affinity property (HalA), ketones **767** bearing a double bond underwent cyclization induced by bromenium ions to give bromine-containing spiroketals **768**. The reaction was carried out using a mixture of DCDMH and DBDMH in order to generate a more reactive source of bromenium ion and the stabilizing effect of the oxygen of THF on the carbonylic center to be determinant with respect to other protecting groups, allowing the reaction to proceed *via* the lower TS. Thus, the [6,6]-bromospiroketals **768** were isolated in very good yield and excellent diastereoselection, and the same result was observed for the cyclization of **769** leading to [6,5]-spiroketal **770** [365].

$R^1 = C_6H_5$, 99%, d.r. > 98:2; R^1 = 2-naphthyl, 93%, d.r. > 98:2;
$R^1 = 4\text{-}CH_3\text{-}C_6H_4$, 87%, d.r. > 98:2; $R^1 = 4\text{-}F\text{-}C_6H_4$, 84%, d.r. > 98:2
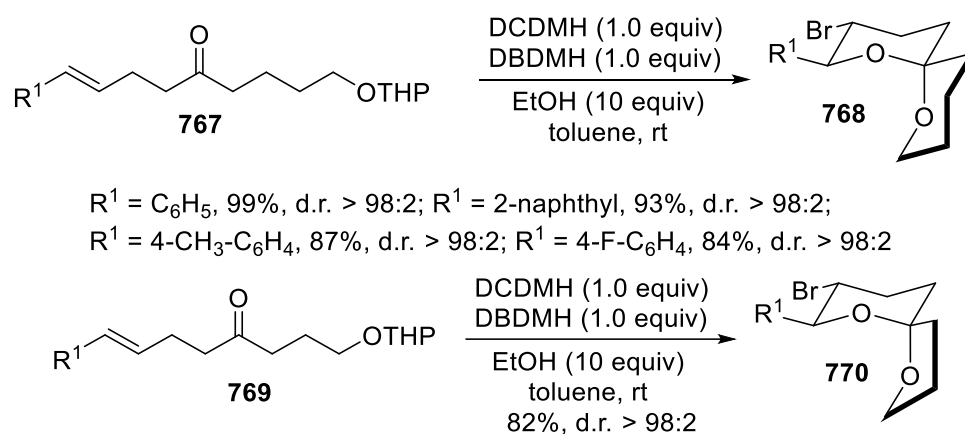
2.1.12.3. With external asymmetric induction.

Starting from diketones 771, the cyclization carried out with NBS in the presence of catalyst 773 provided the corresponding dihydrofurans 772 in excellent yield and good enantioselection. The bifunctional catalyst appeared to be responsible for the high reaction efficiency since the nitrogen of the quinuclidine moiety of the catalyst could deprotonate the 1,3-dicarbonyl unit, while the sulfur atom of the thiocarbamate acting as Lewis base was able to coordinate the attacking Br of NBS [360].
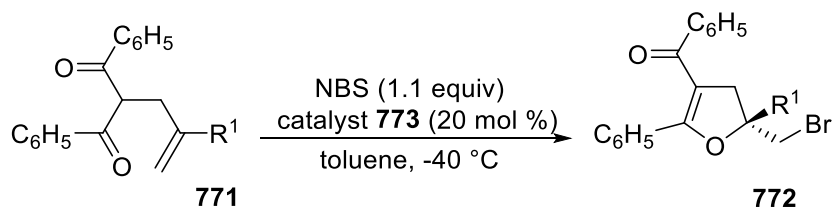
R^1 = 4-F-C$_6$H$_4$. 89%, 98% e.e.; R^1 = 2-naphthyl, 87%, 81% e.e.;
R^1 = t-C$_4$H$_9$, 86%, 92% e.e.; R^1 = (CH$_3$)$_2$CH, 87%, 90% e.e.
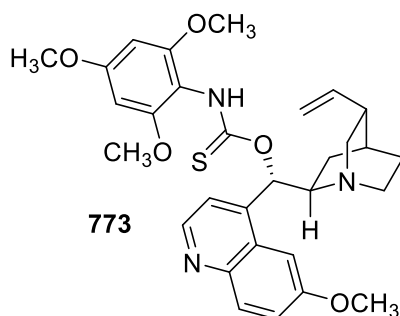
Moreover, exploiting domino halocyclization/spiroketalization, chiral spiroketals were prepared with high enantioselection. Different haloimides were used, but the best results were obtained with N-chlorosuccinimide (NCS) coupled with catalyst 776, and spiroketals 775 were isolated in high yield and excellent stereoselection starting from ketoacids 774 [366].
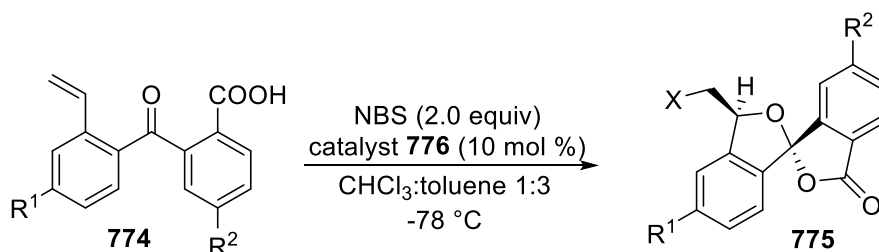
R^1 = R^2 = H, 91%, 96% e.e., d.r. >50:1; R^1 = H, R^2 = CH$_3$, 93%, 99% e.e., d.r. >50:1;
R^1 = R^2 = Cl, 75%, 99% e.e., d.r. 56:1; R^1 = Cl, R^2 = CH$_3$, 90%, 94% e.e., d.r. 45:1
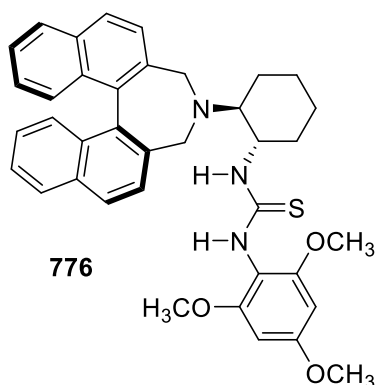
In addition, chloro-spiroketalization of acid 777, containing two carbonyl groups, proceeded with moderate yield but with high stereoselection, leading to the tricyclic spiroderivative 778. In this case, however, catalyst 779, coupled with dichlorodiphenylhydantoin (DCDPH), provided better results than catalyst 776 [366].
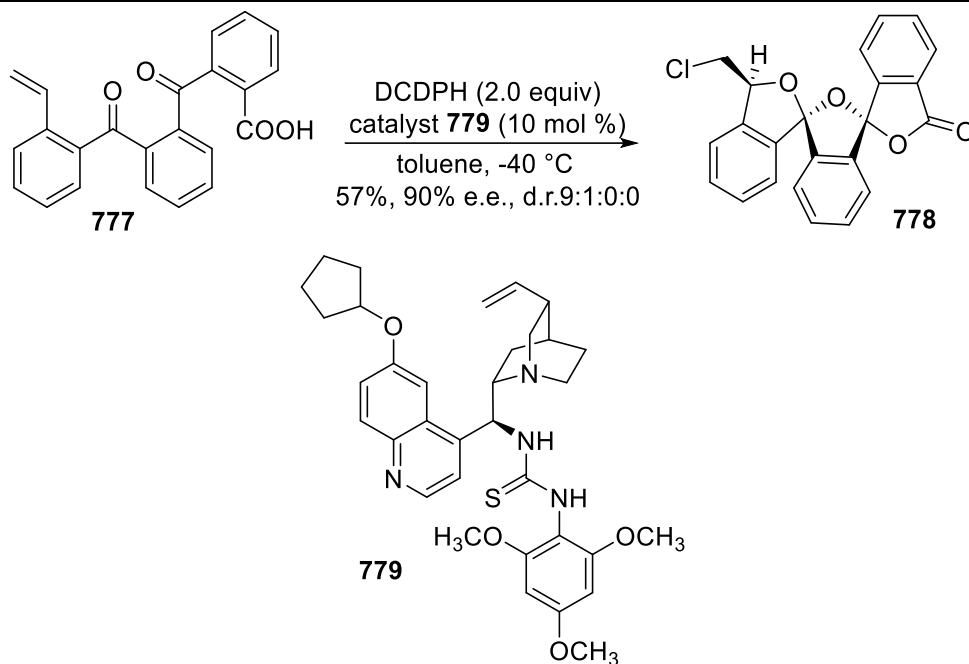
2.1.13. 1,2-Dihydro-1,3-oxazoles and 1,2-dihydro-4*H*-1,3-oxazines from oximes.

2.1.13.1. Without asymmetric induction.

Unsaturated oximes arising from non-conjugated ketones underwent intramolecular oxyfunctionalization mediated by a haliranium ion to give 1,2-dihydro-1,3-oxazoles. Thus, cyclization of β,γ-unsaturated oximes 780, performed with iodine and excess TBHP that oxidized iodide anion, gave dihydrooxazoles 781 in excellent yield with iodine atom economy and significant organic waste reduction [367-368].

$R^1 = C_6H_5$, $R^2 = H$, 80%; $R^1 = 4\text{-}NO_2\text{-}C_6H_4$, $R^2 = H$, 89%;
$R^1 = 4\text{-}CF_3\text{-}C_6H_4$, $R^2 = H$, 94%; $R^1 = C_6H_5$, $R^2 = CH_3$, 93%
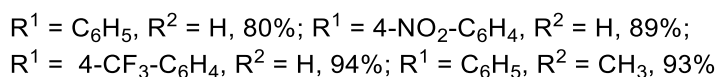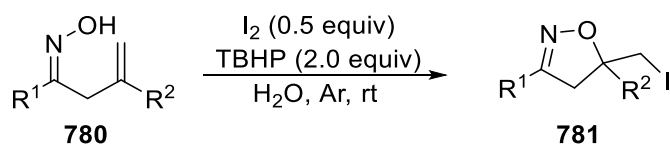
2.1.13.2. With external asymmetric induction.

The cyclization of β,γ-unsaturated oximes 782 and γ,δ-unsaturated oximes 785 was performed in the presence of the bifunctional dihydrocinchonidine-derived tertiary aminothiourea catalysts 784 and 787, using NIS in the presence of a catalytic amount of iodine. Both the corresponding 1,2-dihydro-1,3-oxazoles 783 [122] and 1,2-dihydro-4H-1,3-oxazines 786 [369] were recovered in excellent yield and high enantioselection, although catalyst 784, where a saturated alkyl chain is present, allowed slightly better results [370].

$R^1 = R^2 = C_6H_5$, 88%, 90% e.e.; $R^1 = C_6H_5$, $R^2 = 4\text{-}Cl\text{-}C_6H_4$, 88%, 94%e.e.;
$R^1 = R^2 = 4\text{-}Cl\text{-}C_6H_4$, 82%, 93% e.e.; $R^1 = $ cyclohexyl, $R^2 = CH_3$, 91%, 20% e.e.

R^1 = R^2 = C$_6$H$_5$, 99%, 94% e.e.; R^1 = 4-CH$_3$-C$_6$H$_4$, R^2 = C$_6$H$_5$, 90%, 90% e.e.;
R^1 = 3-F-C$_6$H$_4$, R^2 = C$_6$H$_5$, 97%, 90% e.e.

784, R^1 = CH$_2$CH$_3$
787, R^1 = CH=CH$_2$
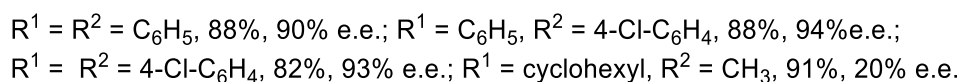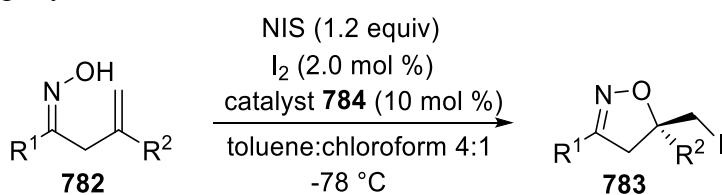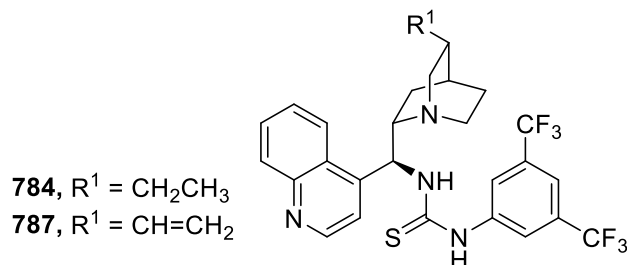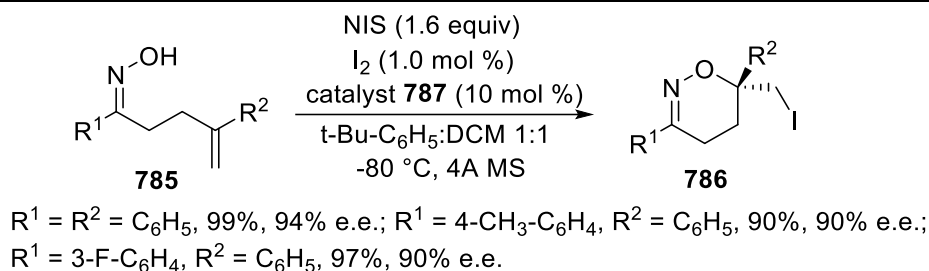
2.2. N-C(sp^3) bond formation by the attack of nitrogen nucleophiles.

The syntheses and structures of non-aromatic *N*-containing heterocycles remain fascinating because these compounds have a great richness of structural, physicochemical, and biological properties. Hence, the development of improved ways aimed at their preparation continues to be a challenging goal [264],[371-372]. Within this field, the intramolecular difunctionalization of unactivated alkenes, such as haloamination and haloamidation reactions, is a powerful tool to create molecular complexity by both building a new ring and installing halide functionalities, which are present in a number of bioactive molecules and can disclose the access to further derivatizations.

2.2.1. Non-aromatic heterocyclic amines from alkenylamines.

2.2.1.1. Synthesis of azetidines with internal asymmetric induction.

The haloaminocyclization was generally carried out with iodine in a basic medium, directed towards the preparation of cyclic amines [373]. Thus, whereas N-tosyl cinnamyl amines were already converted to substituted azetidines by a highly unfavorable 4-endo-process [373], homoallylamines 788 underwent a high regio- and stereoselective cyclization proceeding through a preferential 4-exo-mode to give azetidines 789 in good yield, the 1,3-cis-disubstituted stereoisomers being the main components of the reaction mixture [374-375].

R^1 = C$_6$H$_5$, R^2 = CH$_2$C$_6$H$_5$, >99%, >99:1; R^1 = t-C$_4$H$_9$, R^2 = C$_6$H$_5$, 99%, >99:1;
R^1 = 4-pyridyl, R^2 = CH$_2$C$_6$H$_5$, >99%, 6:1; R^1 = 3-furyl, R^2 = CH$_2$C$_6$H$_5$, >99%, >99:1
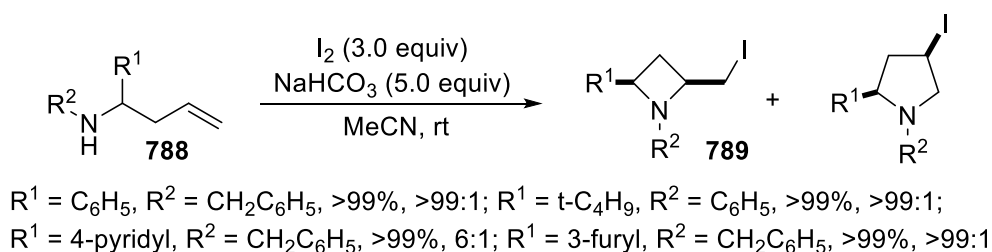
2.2.1.2. Synthesis of pyrrolidines without asymmetric induction.

The spiro derivative 791 was obtained in moderate yield starting from the unsaturated amine 790 by reaction with iodine in a basic medium proceeding in 5-endo mode [376].

790 + I$_2$ (1.2 equiv), NaHCO$_3$(aq) 15%, DCM, rt, 50% → **791**
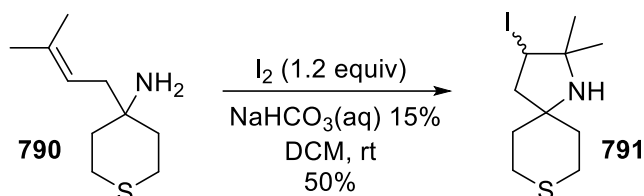
2.2.1.3. Synthesis of pyrrolidines with internal asymmetric induction.

The amine 792 underwent cyclization to provide the spiro derivative 793 with low stereoselection, but the reaction yield was not reported [377].

792 + I$_2$ (1.0 equiv), NaHCO$_3$, DCM, rt → **793**

R^1 = 4-CH$_3$O-C$_6$H$_4$; yield not reported, d.r. 2:1
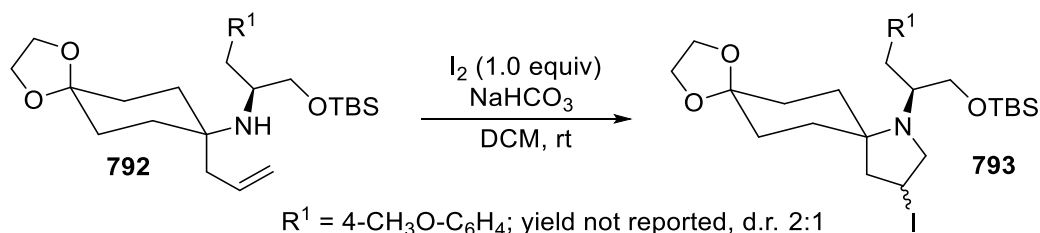
When the amino group and the double bond were tethered on a chiral cyclic structure, the functionalization proceeded with high stereoselection, to give a fused polycyclic structure. In fact, compound 794 led to the bicyclic derivatives 795 in excellent yield with total stereoselection, according to a 5-exo-mode cyclization directed by the phenyl substituent and biased by angular strain [378].

794 + I$_2$ (1.2 equiv), K$_2$CO$_3$, DCM, rt → **795**

R^1 = C$_6$H$_5$, 90%; R^1 = 4-CH$_3$-C$_6$H$_4$, 82%; R^1 = cyclohexyl, 90%
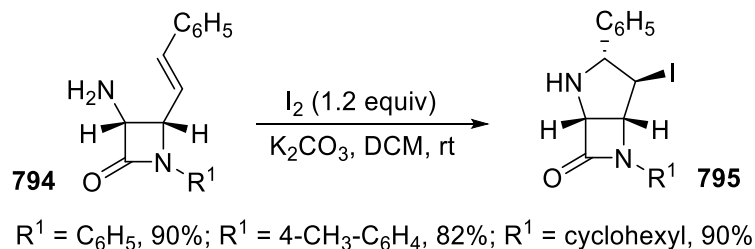
Moreover, starting from amines 796, a pyrrolidine ring was formed on the preexisting heterocyclic structure, and bicyclic derivatives 797 were isolated in good yield with total stereoselection [379]. The same result was observed when compound 798 underwent cyclization to give bicyclic derivatives 799 [380].

796 + I$_2$ (1.0 equiv), K$_2$CO$_3$ (5.0 equiv), DCM, rt → **797**

R^1 = R^2 = C$_6$H$_5$, 88%; R^1 = 4-Cl-C$_6$H$_4$, R^2 = C$_6$H$_5$, 90%;
R^1 = 4-CH$_3$-C$_6$H$_4$, R^2 = 4-Cl-C$_6$H$_4$, 87%; R^1 = C$_6$H$_5$, R^2 = 4-Cl-C$_6$H$_4$, 90%

798 + I$_2$ (1.0 equiv), K$_2$CO$_3$ (5.0 equiv), DCM, rt → **799**

R^1 = R^2 = C$_6$H$_5$, 74%; R^1 = C$_6$H$_5$, R^2 = 4-CH$_3$-C$_6$H$_4$, 67%;
R^1 = 4-CH$_3$O-C$_6$H$_4$, R^2 = 4-Cl-C$_6$H$_4$, 78%
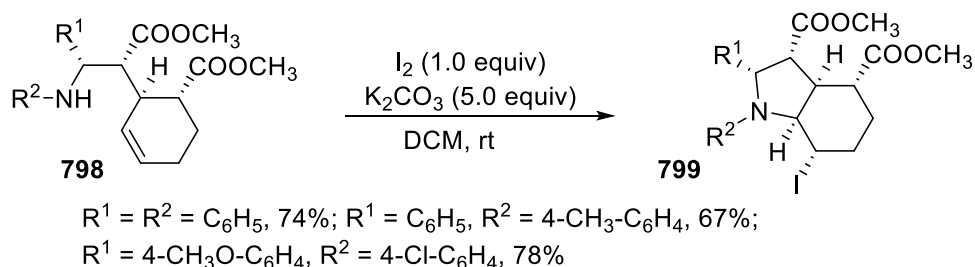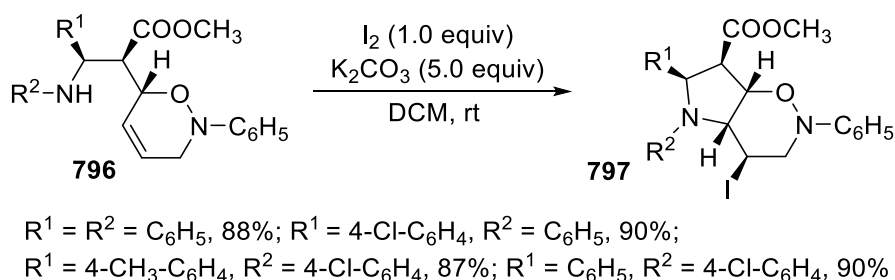
Again, the tricyclic products 801 containing a pyrrolidine ring were prepared in good yield and total stereoselection starting from amines 800 [381].

R^1 = 4-CH$_3$-C$_6$H$_4$, R^2 = C$_6$H$_5$, 74%; R^1 = R^2 = 4-CH$_3$-C$_6$H$_4$, 67%;
R^1 = 4-CH$_3$-C$_6$H$_4$, R^2 = 4-Cl-C$_6$H$_4$, 78%
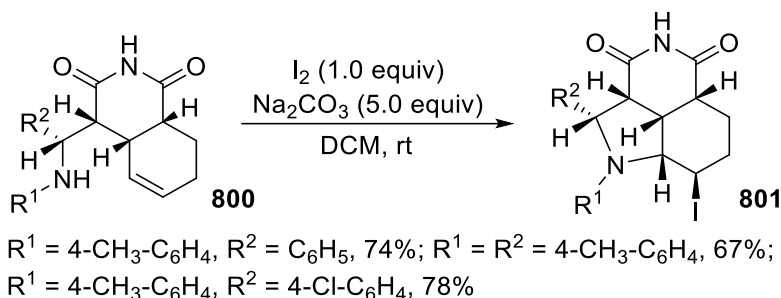
The aminoalkendiol 802 afforded the bicyclic compound 803 with total regio- and stereoselection exploiting a direct amination followed by insertion of a carbon dioxide molecule at nitrogen, with eventual substitution of the iodide functionality. According to the same methodology, the bicyclic compound 805 was exclusively isolated starting from the amino derivative 804 and in both cases, the cis-2,3-relationship at the pyrrolidine ring was directed by the preexistent hydroxy functionality [289, 382].
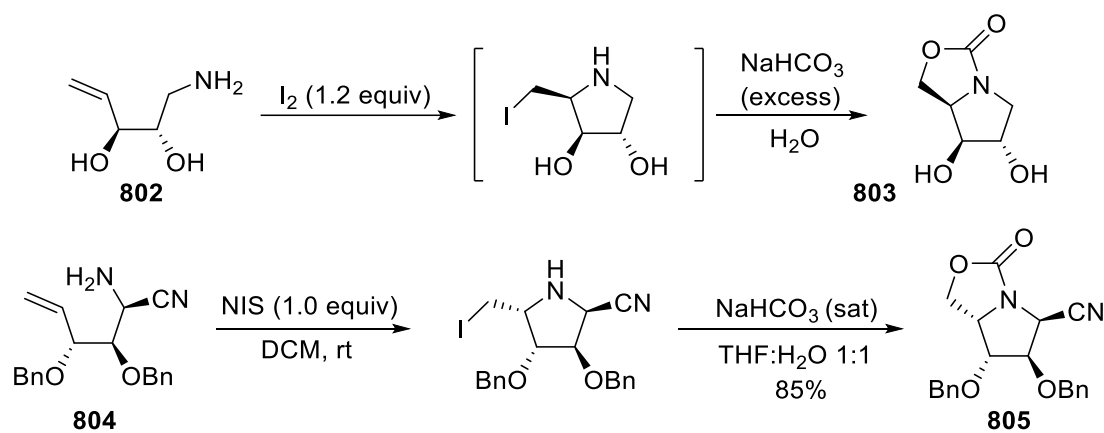
Aminoalkenes 806 and 809, displaying different configurations at the chirality centers, gave the corresponding bicyclic oxazolidin-2-ones 807,808 and 810,811, respectively, in good yield but with low stereoselection due to the 2,5-cis unfavorable configuration with respect to 2,5-trans-one. On the contrary, a single diastereomer, 813, was obtained starting from 812, although in moderate yield [289, 383].
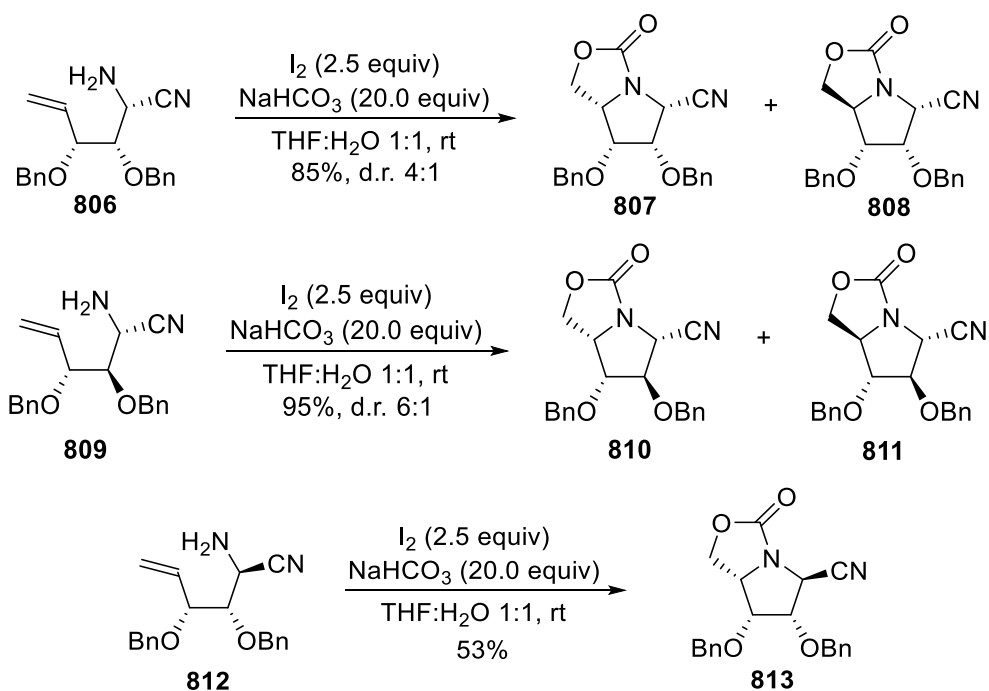
Eventually, by reaction with bromine in acetic acid, the bicyclic compounds 815 were obtained in moderate yield starting from aminopyridine derivatives 814, and the cyclization proceeded in a 5-exo-mode driven by electronic factors [384].

R^1 = H, 65%; R^1 = CH$_3$, 88%; R^1 = Br, 69%
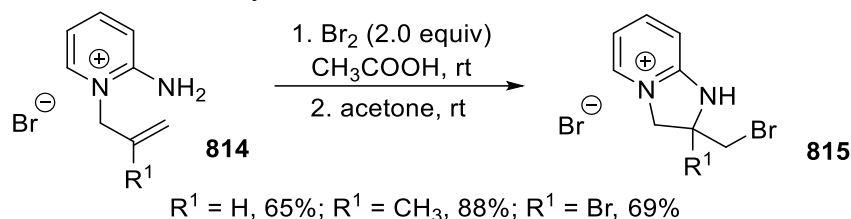
2.2.1.4. Synthesis of piperidines and larger cyclic amines without asymmetric induction.

The cyclization of unsaturated N-chloramines 816 involved first the conversion into N-iodoamines by exchange with catalytic iodide anion, followed by substitution leading to the intermediate aziridinium ions 817 [385]. Then, eventual nucleophilic attack by fluoride anion provided mixtures of piperidines 818 and pyrrolidines 819 in good yield but with moderate to low regioselection [386].

R^1 = t-C$_4$H$_9$, R^2 = CH$_3$, 82%, >15:1; R^1 = (CH$_3$)$_2$CHCH$_2$, R^2...R^2 = -(CH$_2$)$_5$-, 88%, 8:1;
R^1 = C$_6$H$_5$CH$_2$, R^2...R^2 = -(CH$_2$)$_2$-, 78%, 2.5:1; R^1 = C$_6$H$_5$CH$_2$, R^2 = H, 75%, 1:1
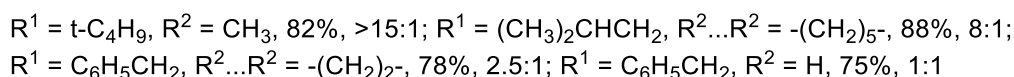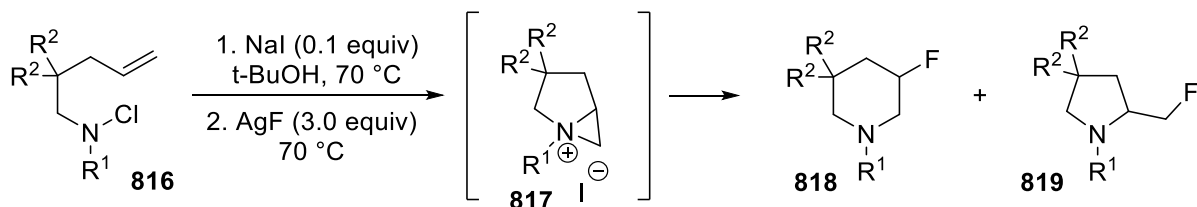
On the contrary, when N-iodoamine was generated with NIS starting from amines 820, the 3-fluoropiperidines 821 were exclusively obtained in good yield with total regioselection [386],[387].

R^1 = C$_6$H$_5$CH$_2$, R^2 = CH$_3$, R^3 = H, 74%; R^1 = (CH$_3$)$_2$CHCH$_2$, R^2 = R^3 = CH$_3$, 42%;
R^1 = (CH$_3$)$_2$CHCH$_2$, R^2...R^2 = -(CH$_2$)$_2$-, R^3 = H, 59%;
R^1 = (6-methoxy-1-naphthyl)-(CH$_2$)$_3$, R^2 = CH$_3$, R^3 = H, 80%
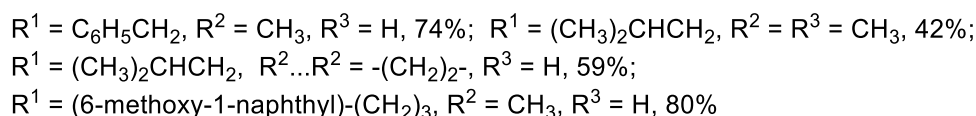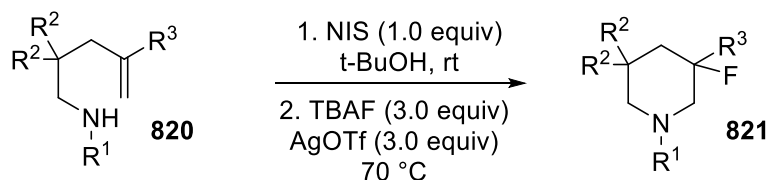
A similar procedure allowed to prepare of very good yield bromopiperidines 823 starting from alkenyl amines 822. In order to generate the intermediate iodiranium ion, a catalytic amount of iodine was employed that, after conversion into iodide anion within the process, was again oxidized by K2S2O8 [388].

R^1 = C$_6$H$_5$, R^2 = CH$_2$C$_6$H$_5$, 86%; R^1 = C$_6$H$_5$, R^2 = 4-CH$_3$-C$_6$H$_4$CH$_2$, 90%;
R^1 = C$_6$H$_5$, R^2 = 4-F-C$_6$H$_4$CH$_2$ 83%; R^1 = C$_6$H$_5$, R^2 = 4-NO$_2$-C$_6$H$_4$CH$_2$ 83%
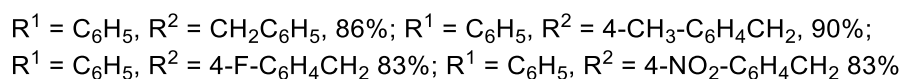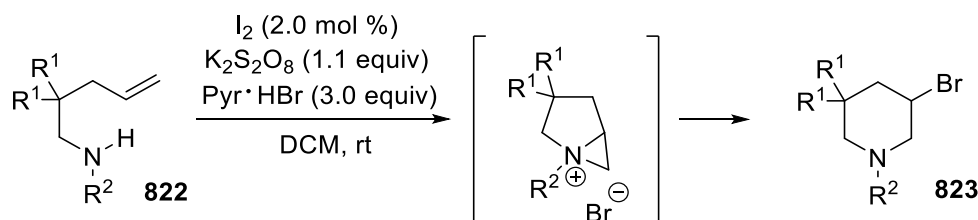
Eventually, the cyclization of aniline derivatives 824, proceeding via an unusual 7-exo-trig mode, afforded in good yield the tricyclic compounds 825, containing a seven-membered heterocyclic ring [389].

R^1 = H, 84%; R^1 = OCH$_3$, 80%
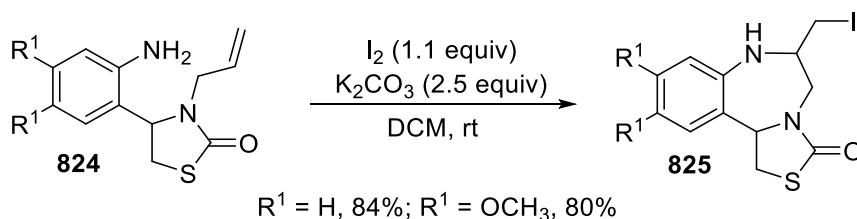
2.2.1.5. Synthesis of piperidines and piperazines with internal asymmetric induction.

The cyclization of 1-phenylpent-4-en-1-amines 826 carried out with NIS provided exclusively the corresponding trans-5-iodo-2-phenylpiperidines 827 in good yield and NMR analysis allowed to ascertain that cyclization proceeding in a 6-endo mode was thermodynamically favored, whereas the 5-exo-trig mode leading to the formation of pyrrolidines was kinetically favored [390].

R^1 = CH$_3$, 75%; R^1 = C$_2$H$_5$, 70%; R^1 = C$_6$H$_5$CH$_2$, 79%
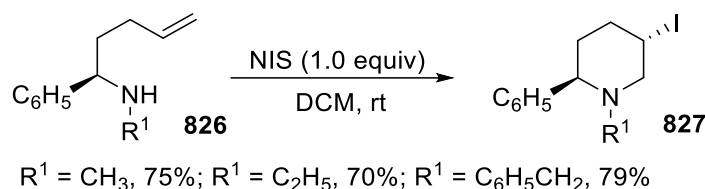
On treatment with iodine, chiral unsaturated benzylamines 828 afforded piperazine derivatives 829 in good yield and excellent stereoselection [335].

R^1 = CH$_2$C$_6$H$_5$, 74%, 99% d.e.; R^1 = CH(CH$_3$)$_2$, 75%, 99% d.e.
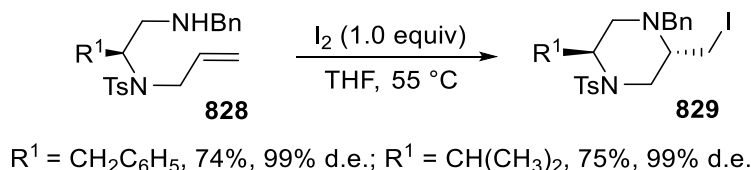
The unsaturated compound 830 afforded good yield but with low regio- and stereoselection of the bicyclic oxazolidin-2-ones 831 and 832, generated by nucleophilic substitution of iodine by the intermediate carbamate arising within the reaction by insertion of carbon dioxide at the nitrogen atom. On the other hand, compound 833 arose from an attack on the intermediate iodiranium ion by the hydroxy functionality at C-2, followed by nucleophilic substitution by a carbamate anion [391].
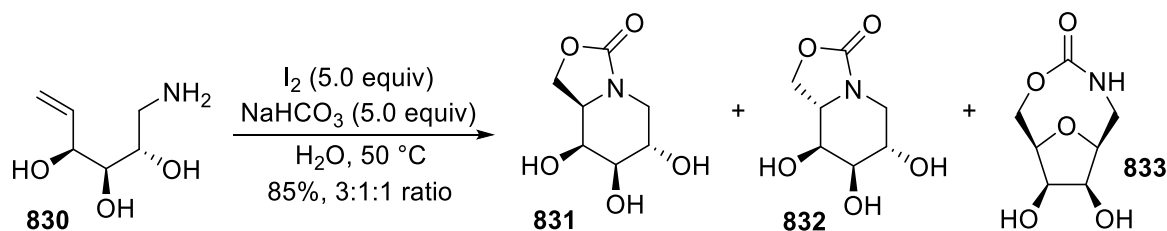
2.2.2. Cyclic N-sulphonyl amino compounds from acyclic N-sulphonyl alkenylamines.

2.2.2.1. N-sulphonyl pyrrolidines and diaza derivatives without asymmetrical induction.

When unsaturated compounds displayed a nitrogen atom substituted by a sulphonyl group, intramolecular cyclization mediated by a nucleophilic attack to haliranium ions led to saturated cyclic N-sulphonyl amines [227]. When iodine was obtained by oxidation of iodide anion performed with (diacetoxyiodo)benzene (PIDA), an iodiranium ion was generated from tosylamides 834, and the corresponding N-sulphonyl pyrrolidines 835 were isolated in excellent yield [45].
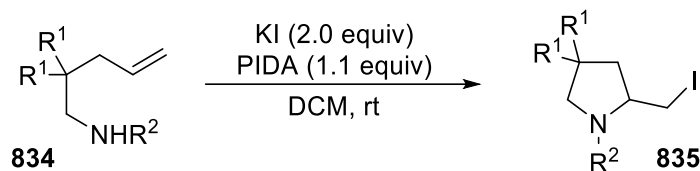
R^1 = C$_6$H$_5$, R^2 = Ts, 91%; R^1 = CH$_3$, R^2 = Ts, 97%; R^1 = H, R^2 = Ts, 92%;
R^1 = C$_6$H$_5$, R^2 = Bs, 85%; R^1 = allyl, R^2 = Ts, 96%

In addition, exploiting another environmentally friendly methodology, exploiting oxidation of the iodide anion into iodine, was carried out using I$_2$O$_5$, and N-sulphonyl derivatives 836 were converted into N-sulphonylpyrrolidines 837 in good yield [207].
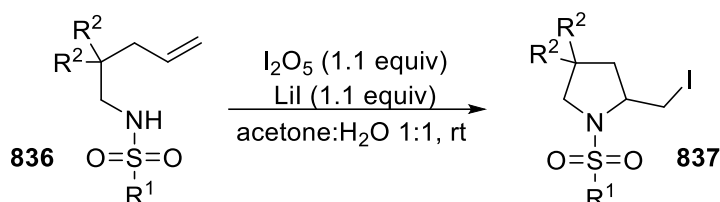
R^1 = R^2 = C$_6$H$_5$, 90%; R^1 = 4-CH$_3$-C$_6$H$_4$, R^2 = C$_6$H$_5$,89%;
R^1 = 4-CH$_3$C$_6$H$_4$, R^2 = H, 89%; R^1 = 4-CH$_3$-C$_6$H$_4$, R^2 = allyl, 89%

Iodine was also generated by the reaction of KI with hydrogen peroxide, allowing to convert of the tosyl amides 838 into the corresponding diazabicyclic derivatives 839 in moderate to good yield [392].
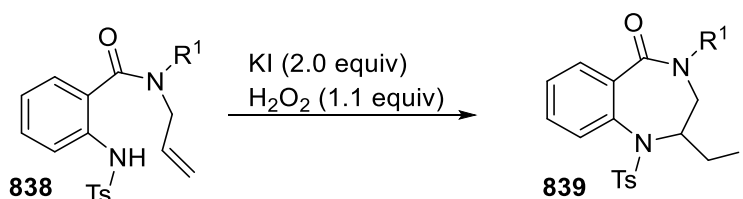
R^1 = CH$_3$, H$_2$O:DMSO 1.5:1, 60 °C, 71%;
R^1 = C$_6$H$_5$, H$_2$O:DMSO 1:4, 50 °C, 63%;
R^1 = cyclohexyl, H$_2$O:DMSO 1:5, 50 °C, 68%

In order to avoid the use of organic solvents, N-tosyl allylanilines 840 underwent cyclization in water in the presence of slight excess iodine, and the corresponding 2-iodomethyl-N-tosyldihydroindoles 841 were isolated in good yield [393].
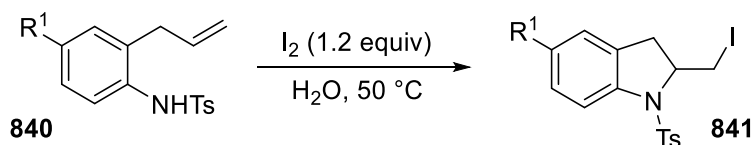
R^1 = OCH$_3$, 82%; R^1 = n-C$_4$H$_9$, 68%; R^1 = Cl, 80%; R^1 = H, 79%

The reaction rate of unsaturated N-tosyl amides 842 with NBS strongly increased in the presence of the catalyst 844 to afford N-tosyl 2-bromomethylpyrrolidines 843 in good yield, whereas poor results were observed when the catalyst was missing [279].
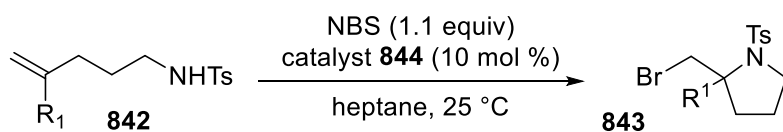
R^1 = C$_6$H$_5$, 60% (13%); R^1 = CH$_3$, 81% (19%); R1 = H, 84% (20%)

SO$_2$NHOCH$_3$ 844
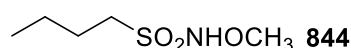
It is worth mentioning that 3-(iodomethyl)-2-methylisothiazolidine-1,1-dioxides **846** were obtained by intramolecular iodoamination of alkenyl sulfamides **845** in a basic medium, but this methodology allowed to prepare only cyclic compounds containing a five- and a six-membered ring [394].

R^1 = CH$_3$, 94%; R^1 = C$_2$H$_5$, 91%; R^1 = t-C$_4$H$_9$, 96%; R^1 = 4-CH$_3$O-C$_6$H$_4$CH$_2$, 90%
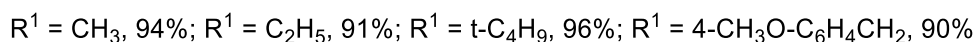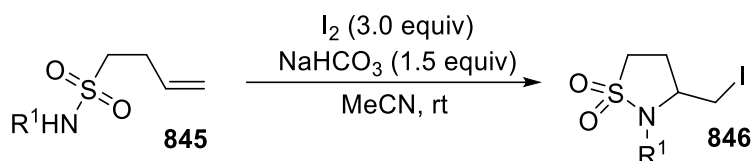
Eventually, 3,4-diiododihydropyrroles **848** were isolated in good yield when N-tosyl derivatives **847** reacted with excess iodine. The reaction was believed to proceed through an iodoallene intermediate that finally underwent a 5-endo-mode cyclization [273].

R^1 = C$_6$H$_5$, 86%; R^1 = 4-CH$_3$-C$_6$H$_4$, 91%; R^1 = 4-CH$_3$O-C$_6$H$_4$, 93%
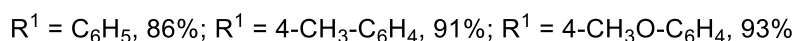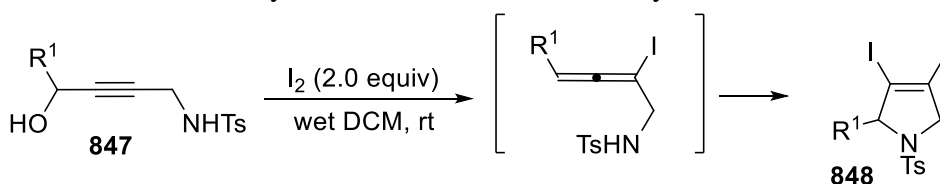
2.2.2.2. *N*-sulphonyl pyrrolidines with internal asymmetrical induction.

Starting from homoallylic tosylamides **849**, pyrrolidine derivatives **850**, displaying 2,3-trans-disubstitution, were prepared in a neutral medium in very good yield via a 5-endo-trig closure exploiting the activation of the electrophilic NBS by hexafluoroisopropanol (HFIP) [74].

R^1 = 4-CH$_3$O-C$_6$H$_4$, 92%; R^1 = C$_6$H$_5$, 86%; R^1 = 4-Cl-C$_6$H$_4$, 97%:
R^1 = 2-naphthyl, 91%; R^1 = 1-naphthyl, 85%; R^1 = 4-NO$_2$-C$_6$H$_4$, 92%
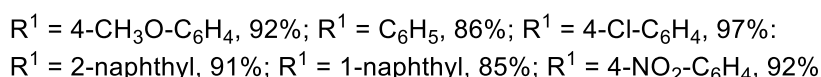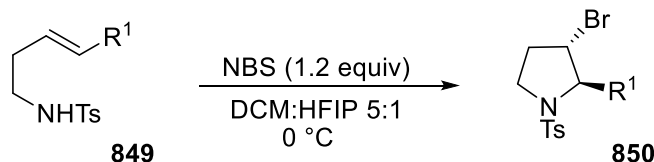
N-Tosylaminodienes **851** in a neutral medium underwent intramolecular cyclization mediated by NBS to give the corresponding N-tosyl pyrrolidines **852** in good yield and excellent regio- and stereoselection [395].

R^1 = C$_6$H$_5$, starting *E:Z* 92:8, 82%, d.r. 93:7;
R^1 = CH$_3$, starting *E:Z* 95:5, 83%, d.r. 95:5;
R^1 = H, starting *E:Z* 93:7, 79%, d.r. 97:3
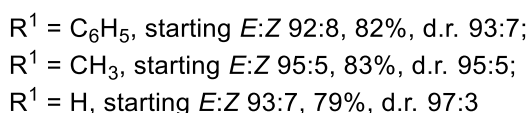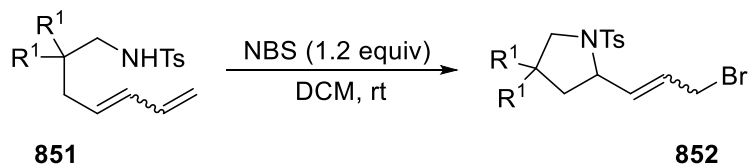
By bromocyclization mediated by NBS in the presence of DABCO, the N-arylsulphonyl derivatives **853**, containing an enyne moiety, were converted in good yield and moderate to good stereoselection via a 1,4-addition into the corresponding pyrrolidine derivatives **854** bearing an allene group [396].
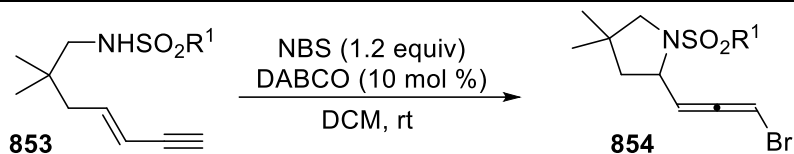
R^1 = 4-CH$_3$-C$_6$H$_4$, 83%, d.r. 83.17; R^1 = 2,4-(NO$_2$)$_2$-C$_6$H$_3$CH$_2$, 86%, d.r. 86:14
R^1 = 4-NO$_2$-C$_6$H$_4$CH$_2$, 88%, d.r. 91:9

When oxidation of bromide anion to bromine was carried out generated by Oxone®, the cyclization of the sulphonyl amides 855 proceeded in a 5-exo-trig mode, leading to pyrrolidine derivatives 856 in high yield with good stereoselection [397].
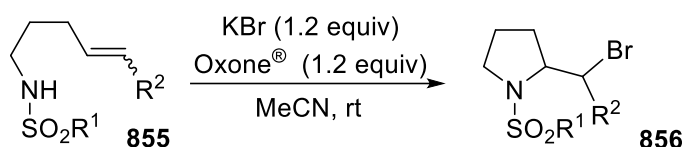
R^1 = C$_6$H$_5$, R^2 = H, 95%; R^1 = n-C$_4$H$_9$, R^2 = H, >99%;
R^1 = Ts, R^2 = (E)-CH$_3$, 89%, 77:23 d.r.; R^1 = Ts, R^2 = (Z)-CH$_3$, 90%, >99:1 d.r.

Under the same conditions, alkenoxy tosylamides 857 afforded the 5-substituted 3-bromomethyl-2-tosylisoxazolidine derivatives 858 in good yield and moderate to good 1,3-cis-diastereoselection [397].
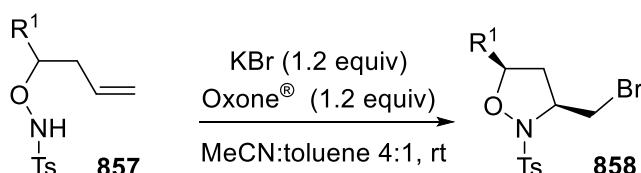
R^1 = H, 93%; R^1 = n-C$_4$H$_9$, 98%, 92:18 d.r.; R^1 = 4-CF$_3$-C$_6$H$_4$, 91%, 83:17 d.r.;
R^1 = C$_6$H$_5$, 97%, 84:16 d.r.; R^1 = 4-CH$_3$O-C$_6$H$_4$, 90%, 90:10 d.r.

Exploiting oxidation of iodide anion to iodine mediated by (diacetoxyiodo)benzene (PIDA), the unsaturated sulphoxyimines 859a,b underwent cyclization via a 5- or 6-exo-trig mode to give in good yield and with moderate stereoselection the corresponding 3-(iodomethyl)-4,5-dihydro-3H-isothiazole-1-oxides 860a or 3-(iodomethyl)-3,4,5,6-tetrahydro-1,2-thiazine-1-oxides 860b [398].
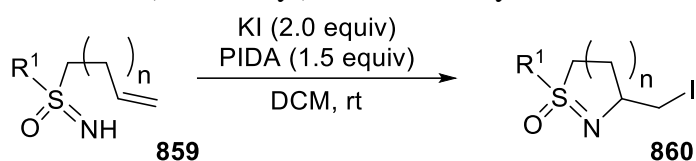
a. n = 1, R^1 = C$_6$H$_5$, 90%, 79:21 d.r.; n = 1, R^1 = 4-CH$_3$-C$_6$H$_4$, 89%, 79:21 d.r.;
b. n = 2, R^1 = C$_6$H$_5$, 92%, 77:23 d.r.; n = 2, R^1 = 4-CH$_3$-C$_6$H$_4$, 93%, 78:22 d.r.

Moreover, by cyclization carried out in basic medium, N-tosyl anilines 861 bearing at the 2 position an unsaturated chain with a disubstituted double bond, provided the substituted N-tosyldihydroindoles 862 in low yield and stereoselection [399].
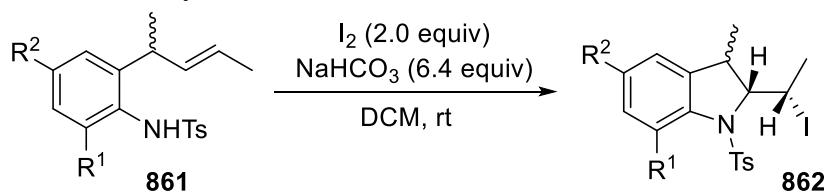
R^1 = H, R^2 = CH$_3$, 42%; R^1 = CH$_3$, R^2 = H, 31%

In the presence of excess iodine in a basic medium, the chiral tosylamide 863, by intramolecular iodocyclization proceeding in a 5-endo-trig mode, afforded with high efficiency and stereoselection the azatricyclic derivative 864 bearing three adjacent chirality centers [400].
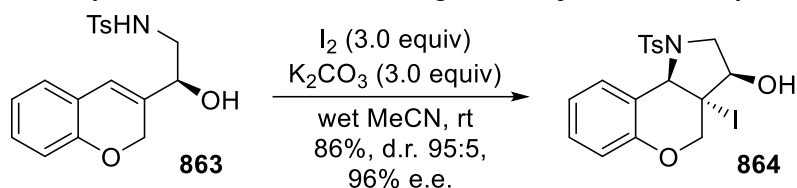
Eventually, when the N-tosylamino derivatives 865 containing a fluorine atom at the α position with respect to the double bond underwent cyclization mediated by iodine in a basic medium, N-tosyl pyrrolidines 866 were isolated in good yield and stereoselection. In the major product, both the iodomethyl group and fluorine were cis each other, owing to the directing effect of the fluorine atom [289],[401].
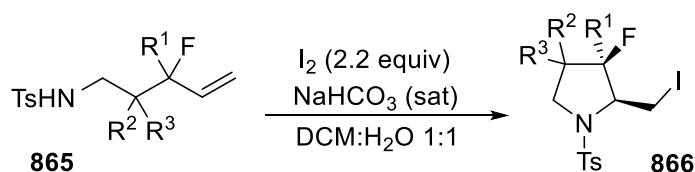
$R^1 = R^2 = R^3 = H$, 88%, d.r. 14:1 ; $R^1 = CH_3$, $R^2 = R^3 = H$, 85%, d.r. 8:1;
$R^1 = H$, $R^2 = R^3 = CH_3$, 97%, d.r. > 20:1

2.2.2.3. *N*-Sulphonyl pyrrolidines with external asymmetric induction.

When the halocyclization of unsaturated N-sulphonyl amides was carried out in the presence of appropriate chiral catalysts, N-tosyl pyrrolidines or piperidines were obtained with excellent enantioselection. Thus, compounds 867 were treated with NBS in the presence of the catalyst TRIP 612, and the substituted pyrrolidines 868 were isolated in good yield with high enantioselection [309].
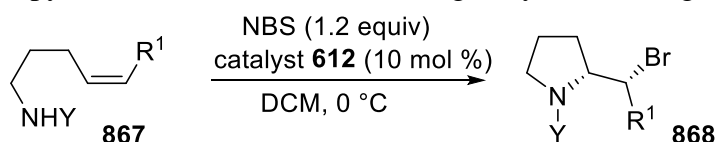
Y = Nosyl, R^1 = n-C_5H_{11}, 90%, 90% e.e.; Y = Trisyl, R^1 = n-C_5H_{11}, 76%, 89% e.e.;
Y = Nosyl, R^1 = CH_2CH_3, 81%, 87% e.e.; Y = Trisyl, R^1 = $CH_2C_6H_5$, 62%, 85% e.e.

The chiral amidophosphate catalyst 871 was effective for iodocyclization of N-sulphonyl amines 869 mediated by iodine in the presence of Lewis acid N-chlorosuccinimide (NCS), and the N-sulphonyl pyrrolidines 870 were obtained in good yield and excellent enantioselection [350].
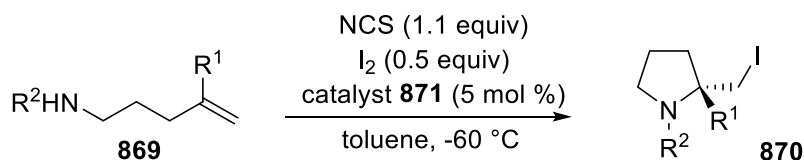
R^1 = cyclohexyl, R^2 = Ts, (- 78 °C) 95%, 99% e.e.; R^1 = C_6H_5, R^2 = Ns, 98%, 90% e.e.;
R^1 = n-C_8H_{17}, R^2 = Ns, 96%, 96% e.e.; R^1 = CH_2-cyclohexyl, R^2 = Ns, 89%, 90% e.e.
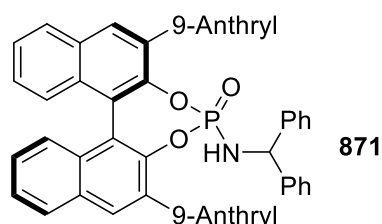
Bromocyclization of (4-nosyl)amino derivatives 872, carried out with NBS in the presence of the catalyst 874, provided excellent yield and enantioselection 2,2-disubstituted N-(4-nosyl)pyrrolidines 873 displaying the opposite configuration at C-2 with respect to 870 if the substituent of the double bond was an electron-deficient aryl group. On the contrary, when the substituent was an alkyl group, the reaction proceeded with very low asymmetric induction [402].

R^1 = 4-Cl-C$_6$H$_4$, 98%, 98% e.e.; R^1 = 4-CF$_3$-C$_6$H$_4$, 91%, 99% e.e.;
R^1 = 3-Cl-C$_6$H$_4$, 87%, 97% e.e.; R^1 = CH$_3$, 96%, 40% e.e.
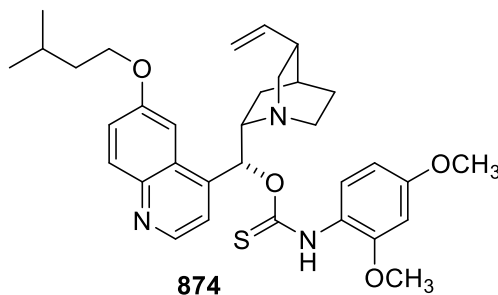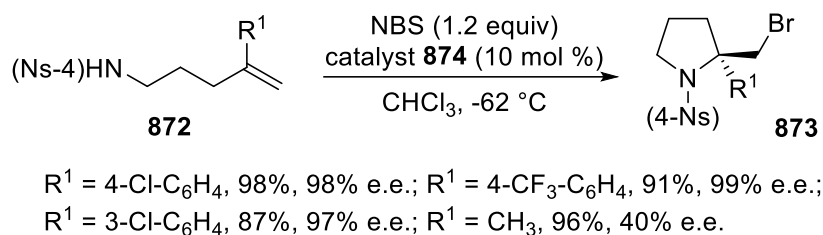
It is worth mentioning that, under the same conditions, the 4-nosyl derivative 875 afforded the N-4-nosyl isoindoline 876 in very high yield, total regio- and good enantioselection [402].
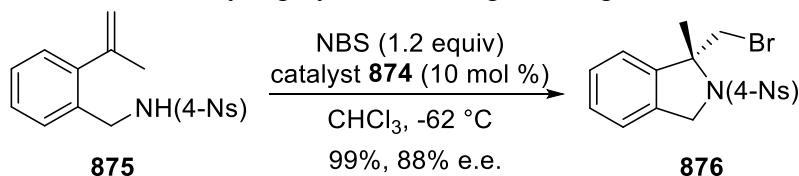
When homoallylic derivatives 877 underwent cyclization mediated by N-bromopyrrolidin-2-one (NBP) in the presence of the catalyst 879, the reaction proceeded in a 5-endo mode, providing 2,3-trans-disubstituted 3-bromopyrrolidine derivatives 878 in excellent yield and good enantioselection [403].

R^1 = C$_6$H$_5$, 91%, 90% e.e.; R^1 = n-C$_5$H$_{11}$, 95%, 85% e.e.;
R^1 = CH$_2$CH$_3$, 85%, 86% e.e.; R^1 = 2-naphthyl, 97%, 88% e.e.
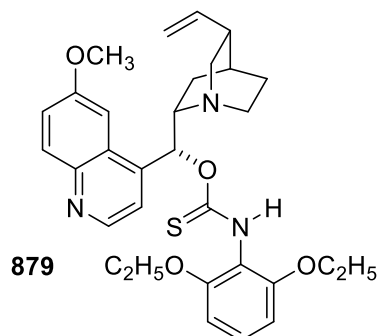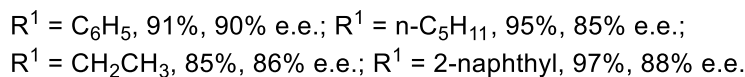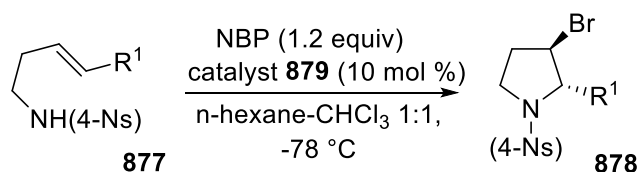
Moreover, using the catalyst 882 acting as a Lewis base, the bromocyclization of tosylamino derivatives 880, carried out with NBS, led to bromomethyl indoline derivatives 881 in good yield and enantioselection [404].
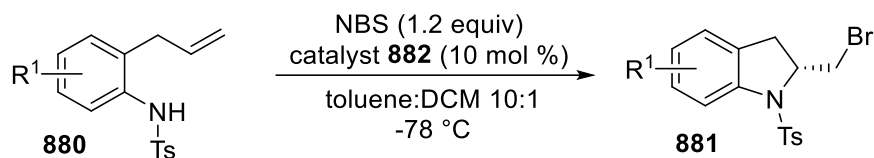
R^1 = H, 90%, 85% e.e.; R^1 = 4-CH$_3$O, 82%, 86% e.e.; R^1 = 4-t-C$_4$H$_9$, 91%, 80% e.e.
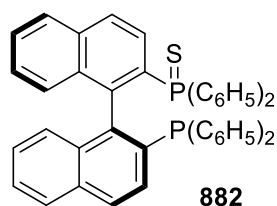
The (Z)-alkenes 883, bearing an aminosulphonyl functionality, gave N-sulphonyl pyrrolidine derivatives 884 in high yields and with high enantioselection, through a 5-exo-trig mode exclusively when N-bromopthalimide (NBPhth) was the bromine source and the chiral selenide Lewis base 885 was employed as catalyst [405].
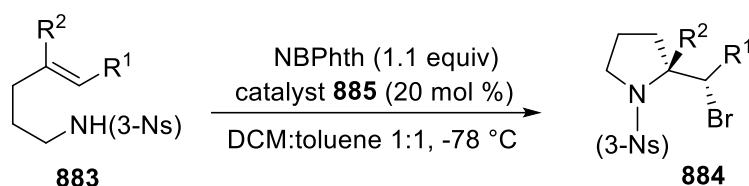
R^1 = C$_2$H$_5$, R^2 = C$_6$H$_5$, 93%, 91% e.e.; R^1 = n-C$_3$H$_7$, R^2 = C$_6$H$_5$, 82%, 91% e.e.;
R^1 = CH$_3$, R^2 = 3-Cl-C$_6$H$_4$, 85%, 83% e.e.; R^1 = CH$_3$, R^2 = C$_6$H$_5$, 90%, 92% e.e.
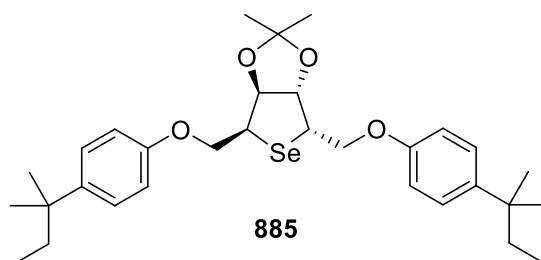
Starting from tosylamides 886 and 889, respectively, on treatment with NBS each other N-tosyl pyrrolidine derivative 887 or 890 were obtained in excellent yield and enantioselection with the opposite configuration at C-2, simply changing the diastereomeric anionic chiral Co(III) complex Δ-(S,S)-888 for Λ-(S,S)-625 [406].
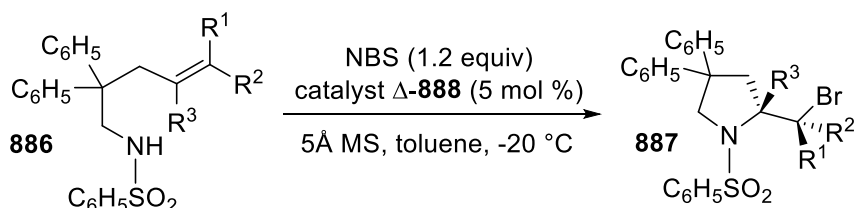
R^1 = R^2 = H, R^3 = CH$_3$, 99%, 87% e.e.; R^1 = R^3 = H, R^2 = C$_2$H$_5$, 90%, 90% e.e.;
R^1 = R^3 = H, R^2 = CH$_3$, 99%, 98% e.e.

Δ-(*S*,*S*)-**888**

R^1 = t-C$_4$H$_9$, R^2 = (CH$_3$)$_2$CH

R^1 = R^2 = H, 99%, 89% e.e.; R^1 = H, R^2 = CH$_3$, 90%, 92% e.e.;
R^1 = R^2 = CH$_3$, 47%, 92% e.e.
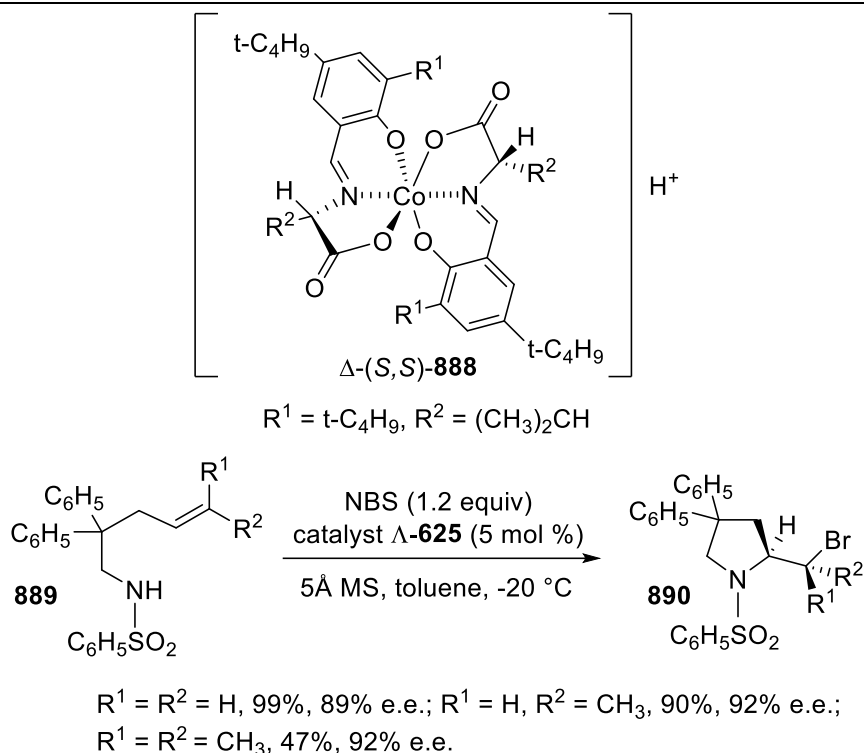
The chiral thiohydantoin catalyst 893 was effective for the cyclization of tosylamides 891, activating NIS in the presence of iodine to provide N-tosyl pyrrolidines 892 in good yield and high enantioselection [407].

a. R^1 = C$_6$H$_5$, R^2 = H, 90%, 81% e.e.; **b.** R^1 = R^2 = C$_6$H$_5$, 87%, 90% e.e.;
c. R^1 = C$_6$H$_5$, R^2 = CH$_3$, 89%, 85% e.e.

893
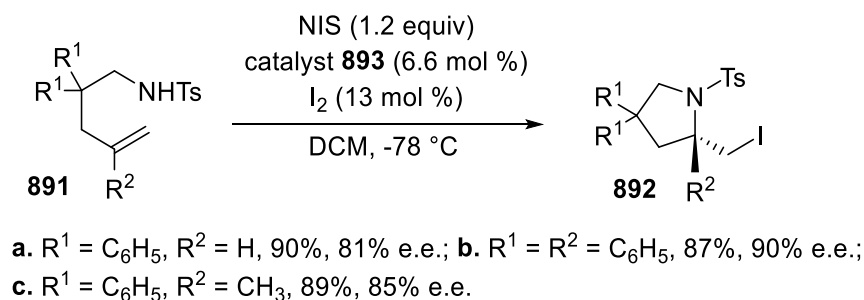
Moreover, it is worth mentioning that the regioselection of the ring closure of 891a (6-endo-trig vs. 5-exo-trig), carried out in the presence of 893, relied upon the halide added to the reaction mixture (KBr vs. KI) leading to either 894 or 892a, respectively [407].
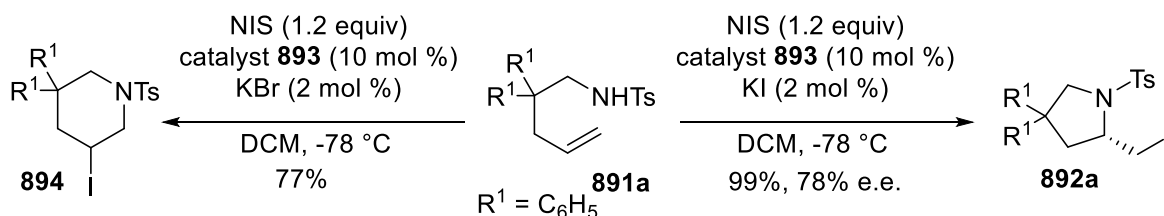
Again, a chiral anionic phase-transfer system exploiting the DABCO-derived dication 897 and catalyst TRIP 612 was employed for the cyclization of indene derivatives 895 to the corresponding tricyclic products 896, key building blocks for the synthesis of bioactive molecules that were obtained in very good yield and excellent enantioselection [319].
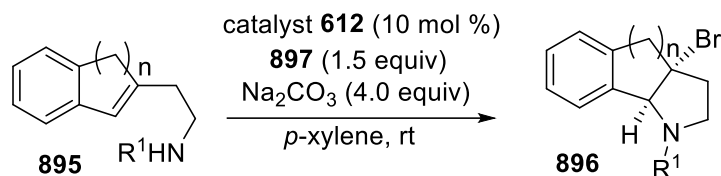
R^1 = Ts, n = 1, 98%, 95% e.e.; R^1 = 4-Br-$C_6H_4SO_2$, n = 1, 98%, 93% e.e.;
R^1 = Ts, n = 2, 96%, 93% e.e.; R^1 = 4-Br-$C_6H_4SO_2$, n = 2, 95%, 92% e.e.;
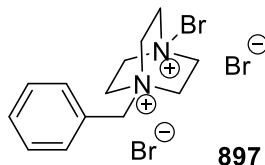
In the event, triptamine derivatives 898 underwent cyclization with N-bromoacetamide in the presence of (DHQD)2PHAL 144, to give the tricyclic compounds 899 in good yield and moderate enantioselection [408].
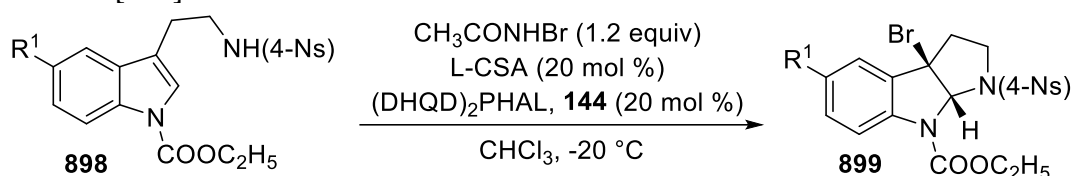
R^1 = F, 98%, 68% e.e.; R^1 = Cl, 97%, 69% e.e.; R^1 = CH_3, 96%, 73% e.e.

2.2.2.4. *N*-Sulphonyl piperidines and analogs with external asymmetric induction.

The cyclization of (E)-sulphonylamino derivatives 900, carried out with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) in the presence of catalyst 875, proceeded in 6-endo-trig mode, exclusively, leading to 2,3-trans-disubstituted piperidines 901 in high yield and good stereoselection [409].
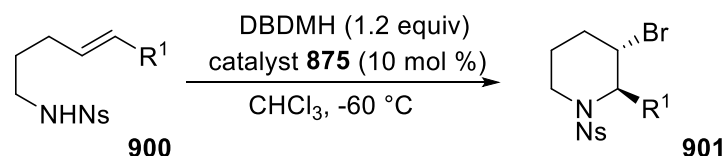
R^1 = 4-F-C_6H_4, 89%, 83% e.e.; R^1 = 4-Cl-C_6H_4, 92%, 73% e.e.;
R^1 = 3-CH_3-C_6H_4, 98%, 86% e.e.

The halofunctionalization of unsaturated sulfamate ester derivatives 902 afforded [1,2,3]oxathiazines 2,2-dioxides 903,904 and 906,907, and the reaction outcome relied on both the halogen source and the catalyst employed. In fact, when the reaction was carried out with NBS in the presence of ligands 905 and Sc(OTf)3, the compounds 903 were isolated as the major products in good yield and high enantioselection. However, when TsNCl2 was employed together with the ligand 695 and Lu(OTf)3, from the reaction, the chloro derivatives 906 were mainly isolated in good yield and excellent enantioselection with reversal of diastereoselection [410].
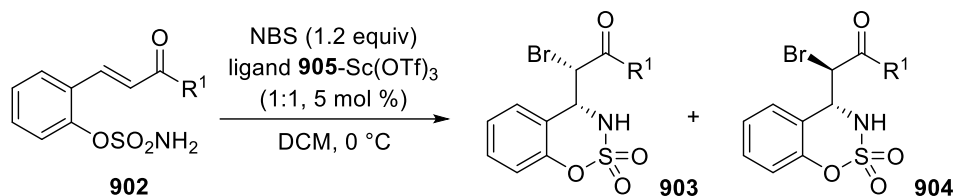
R^1 = C$_6$H$_5$, 95%, d.r. 87:13, major 95% e.e.; R^1 = 4-CH$_3$-C$_6$H$_4$, 94%, d.r. 88:12, major 96% e.e.;
R^1 = 3-CH$_3$O-C$_6$H$_4$, 95%, d.r. 89:11, major 93% e.e.; R^1 = 2-naphthyl, 91%, d.r. 90:10, major 95% e.e.
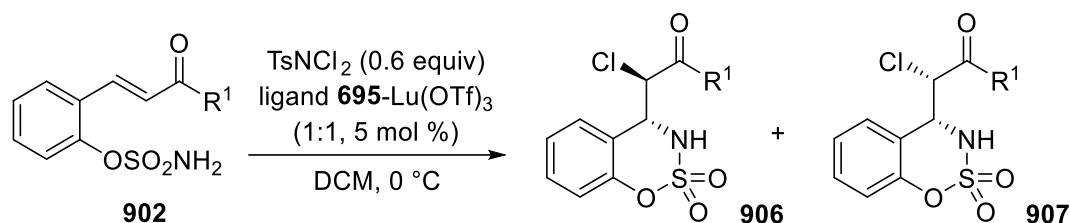
R^1 = C$_6$H$_5$, 95%, d.r. 91:9, major 98% e.e.; R^1 = 4-CH$_3$-C$_6$H$_4$, 93%, d.r. 94:6, major 99% e.e.;
R^1 = 3-CH$_3$O-C$_6$H$_4$, 91%, d.r. 92:8, major 97% e.e.; R^1 = 2-naphthyl, 92%, d.r. 94:6, major 98% e.e.

R^1 = C$_6$H$_5$CH$_2$CH$_2$
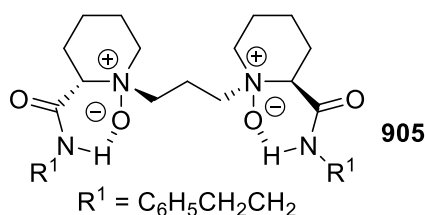
2.2.2.5. *N*-Sulphonyl 1,4-oxazines without asymmetric induction.

The N-tosylamides 908 afforded 3-(iodomethyl)-N-tosyl-3,4-dihydro-2H-benzo[b]1,4-oxazines 909 in very good yield by reaction with iodine in basic medium [411].
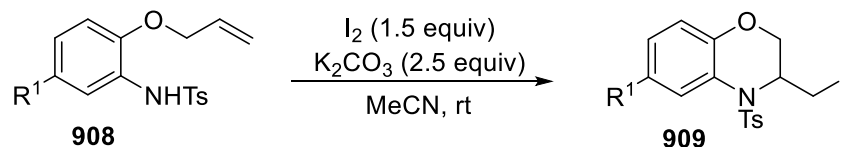
R^1 = Cl, 88%; R^1 = H, 85%; R^1 = CH$_3$, 90%; R^1 = t-C$_4$H$_9$, 92%

2.2.2.6. *N*-Sulphonyl dihydropyrazoles without asymmetric induction.

An efficient halocyclization of the unsaturated N-sulphonyl hydrazones 910 was carried out with NBS, leading to 3-substituted 5-(bromomethyl)-1-tosyl-4,5-dihydro-1H-pyrazoles 911 in good to excellent yields under mild reaction conditions [412].
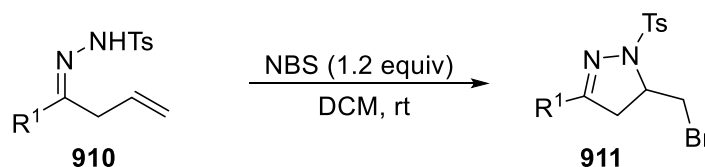
R^1 = 4-Cl-C$_6$H$_4$, 96%; R^1 = 2-Cl-C$_6$H$_4$, 83%; R^1 = 4-F$_3$C-C$_6$H$_4$, 87%;
R^1 = cyclohexyl, 92%; R^1 = (CH$_3$)$_2$CH, 98%; R^1 = CH$_2$C$_6$H$_5$, 81%

Catalyst 844 was highly effective in increasing the cyclization rate, and compound 913 was isolated in moderate yield starting from 912, whereas the yield was very low when the catalyst was missing [279].
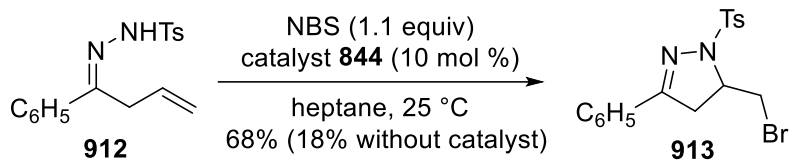
2.2.2.7. *N*-Sulphonyl dihydropyrazoles with external asymmetric induction.

In the asymmetric version of halocyclization of the unsaturated *N*-sulphonyl hydrazones, *N*-iodopyrrolidin-2-one (NIPyr) was employed in order to generate the intermediate iodiranium ion in the presence of the chiral thiourea **916**, and the nosyl hydrazones **914** gave the chiral 3,5-disubstituted 5-iodomethyl-1-nosyl-4,5-dihydro-1*H*-pyrazoles **915** in high yield and good enantioselection [413-414].
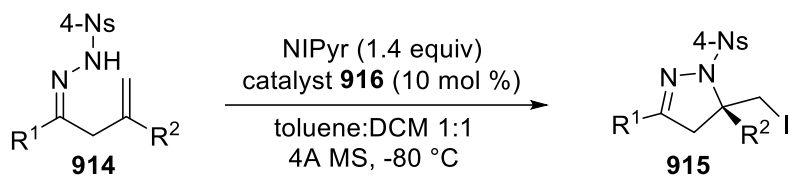
R^1 = R^2 = C$_6$H$_5$, 95%, 85% e.e.; R^1 = C$_6$H$_5$, R^2 = 4-F-C$_6$H$_4$, 88%, 83% e.e.;
R^1 = 3-Cl-C$_6$H$_4$, R^2 = 4-CH$_3$-C$_6$H$_4$, 78%, 88% e.e.
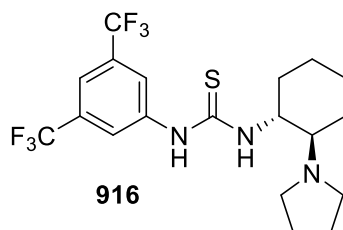
In addition, dienyl nosyl hydrazones **917** underwent cyclization mediated by NIS in the presence of catalyst **919**, to give the corresponding 1-nosyl-4,5-dihydro-1*H*-pyrazoles derivatives **918** in moderate yield buth with good enantioselection [413, 415].
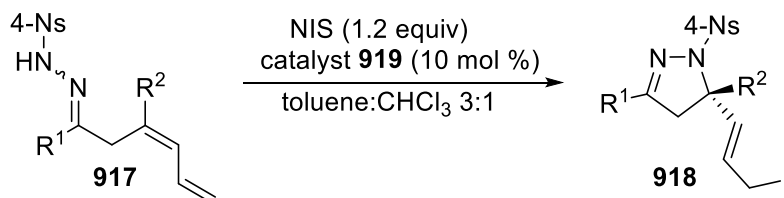
R^1 = R^2 = C$_6$H$_5$, 54%, 97% e.e.; R^1 = 4-F-C$_6$H$_4$, R^2 = C$_6$H$_5$, 61%, 82% e.e.
R^1 = 2-naphthyl, R^2 = C$_6$H$_5$, 74%, 94% e.e.
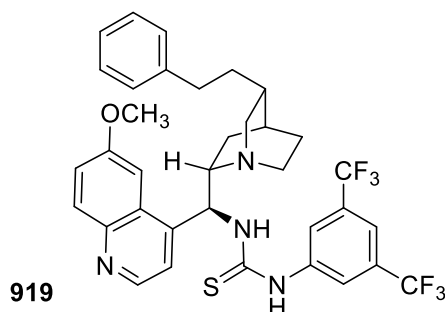
2.2.3. Cyclic *N*-acyl amines from amides of acyclic unsaturated carboxylic acids.

When the double bond was converted into a haliranium ion, unsaturated amides and carbamates reacted preferentially with the more nucleophilic oxygen atom, leading to a new C-O

bond. Due to the higher electronegativity of oxygen compared to nitrogen in an amide group, O-cyclization commonly occurs as the predominant pathway in the halocyclization of olefinic amide substrates. Consequently, there is very little or no N-cyclization [225-226]. In many cases, the subsequent hydrolysis of the cyclized products furnished the corresponding lactones, and this behavior was commonly exploited for preparing lactones in many multistep syntheses.

2.2.3.1. Cyclic *N*-acyl amines without asymmetric induction.

There are surprisingly few literature reports on haloaminocyclizations involving amides, and these methodologies generally require preactivation by O-silylation or O-alkylation. However, under basic conditions, the intramolecular iodoamination of o-(acylamino)styrene derivatives 920 was easily achieved to give in good yield the corresponding 1-acyl-2-(iodomethyl)benzazetine derivatives 921, potential precursors for the generation of o-quinonemethide monoimine intermediates [416].
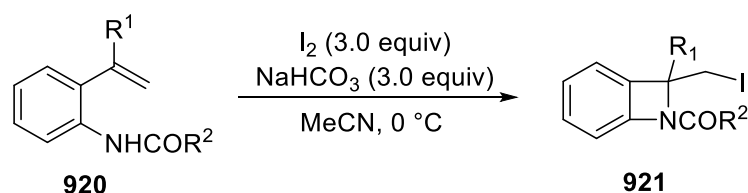
$R^1 = R^2 = CH_3$, 88%; $R^1 = CH_3$, $R^2 = C_6H_5$, 89%; $R^1 = C_6H_5$, $R^2 = CF_3$, 85%

Again, under basic conditions, amides 922 were converted in good yield into the corresponding 1,1-disubstituted isoindoline derivatives 923 [417].
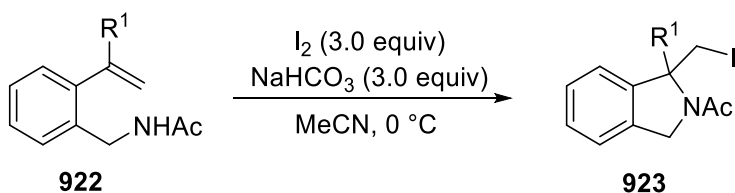
$R^1 = C_6H_5$, 87%; $R^1 = 4\text{-}CH_3O\text{-}C_6H_4$, 88%; $R^1 = CH_3$, 75%; $R^1 = CH_2CH_3$, 87%

In addition, ring allylation of aromatic amides 924, followed by in situ cyclization mediated by NBS, allowed obtaining 3-(bromomethyl)-3,4-dihydroisoquinolin-1(2H)-ones 925 in moderate yield, with bromination at the 3,4,5-trimethoxyphenyl ring. It is worth noting, however, that the pure isolated allyl derivative 926 was converted into the bicyclic derivative 927 in very good yield without bromination at the tolyl ring [418].
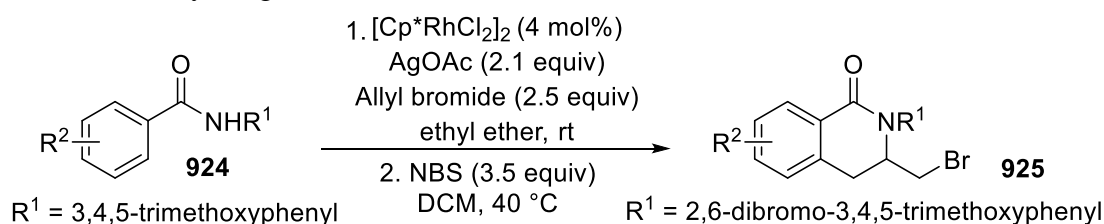
$R^2 = H$, 57%; $R^2 = 4\text{-}F$, 55%; $R^2 = 4\text{-}CH_3O$, 46%; $R^2 = 2\text{-}CH_3$, 69%
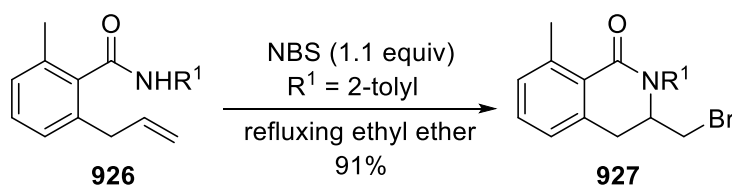
5-Endo-trig amidyl cyclization of amides 928, performed using NIS in order to generate an iodiranium ion, allowed to prepare 1,5-disubstituted 5-hydroxy-4-iodo-1,5-dihydro-2H-pyrrol-2-ones

929 in good yield. An iodide anion was eliminated to form the double bond, and water attacked the resulting cation, leading to hydroxy functionality [419-420].
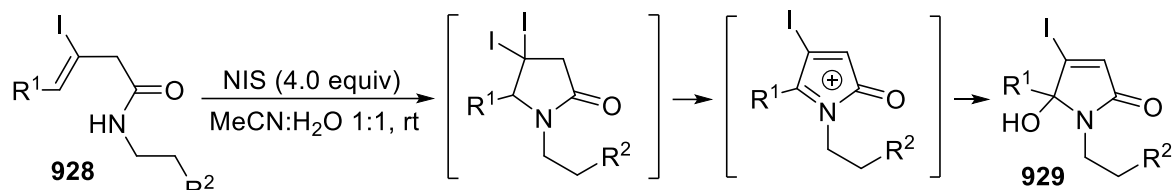
R^1 = R^2 = H, 77%; R^1 = CH$_3$, R^2 = 4-CH$_3$-C$_6$H$_4$, 76%; R^1 = CH$_3$, R^2 = 4-CH$_3$O-C$_6$H$_4$, 98%

Using t-BuOCl, converted in situ into t-BuOI by reaction with iodine, similar amides 930 afforded 1,5-disubstituted 5-hydroxy-4-iodo-1,5-dihydro-2H-pyrrol-2-ones 931 in good yield [419-420].
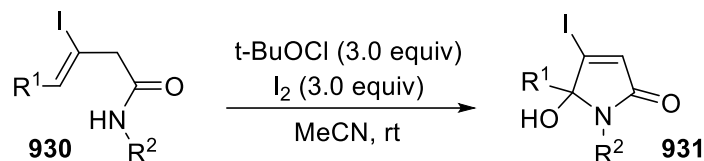
R^1 = CH$_3$, R^2 = C$_6$H$_5$, 83%; R^1 = CH$_3$, R^2 = n-C$_4$H$_9$, 70%;
R^1 = n-C$_4$H$_9$, R^2 = C$_6$H$_5$, 83%; R^1 = R^2 = n-C$_4$H$_9$, 65%

Moreover, within a synthesis of phenanthroindolizidine alkaloids, by iodocyclization performed under basic conditions, amides 932 provided iodomethyl derivatives 933 in good yield [421].
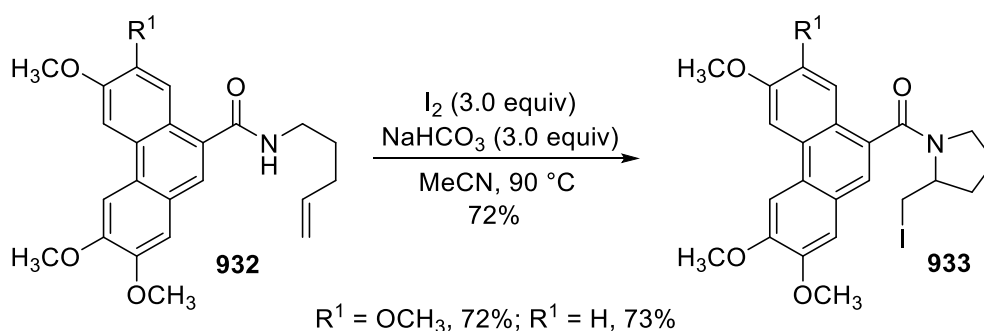
R^1 = OCH$_3$, 72%; R^1 = H, 73%

Eventually, exploiting anodic oxidation in order to generate bromine from LiBr, tryptamine amides 934 were cyclized to give the corresponding tricyclic derivatives 935 in excellent yield [422].
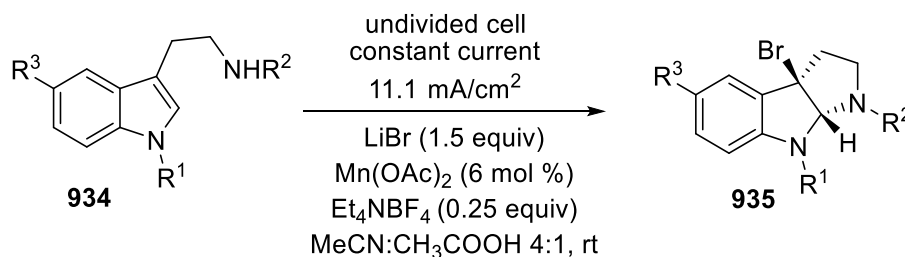
R^1 = R^2 = Ac, R^3 = H, 96%; R^1 = R^2 = Ac, R^3 = CH$_3$, 97%;
R^1 = R^2 = Ac, R^3 = OAc, 94%

2.2.3.2. Cyclic *N*-acyl amines with internal asymmetric induction.

Within a synthesis of peptomimetics, the macrocyclic amides 936, bearing a (Z)-double bond, underwent cyclization with total regioselection to give the corresponding bicyclic lactams 937 and 938 in very good yield, and stereoselection strongly relied on both the reagents and the solvent employed [423].
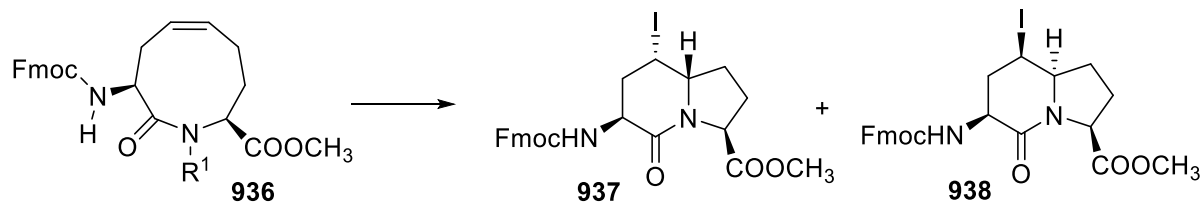
R^1 = H, I$_2$ (4.0 equiv), DIB (2.0 equiv), refluxing MeCN, 100%, d.r. 100:0
R^1 = DMB, I$_2$ (4.0 equiv), refluxing THF, 100%, d.r. 6:94

2.2.4. Cyclic N-carbamoyl amines from acyclic carbamates.

Hydroxy or amino groups tethered on an unsaturated carbon backbone were converted into carbamates, imidates, and amidines, and these functionalities allowed the introduce of a new nitrogen-carbon bond exploiting the cyclofunctionalization reaction mediated by a haliranium ion.

2.2.4.1. Synthesis of cyclic N-carbamoyl amines with internal asymmetric induction.

The iodocyclization of compound 939, bearing both carbamate and trichloroacetamide functionalities, proceeded with total chemoselection in a basic medium, leading to the N-Boc pyrrolidine 940 in good yield, exclusively, with total stereoselection due to anti-addition to the (E)-double bond [238].
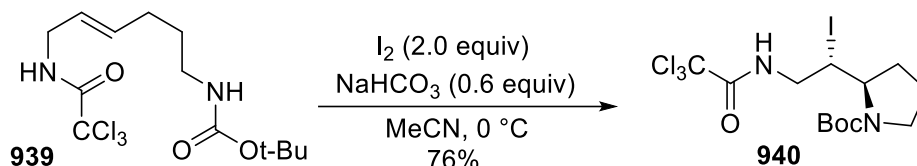
Moreover, within a total synthesis of alkaloids chimonanthine and folicanthine, the tryptophane derivative 941 reacted with NBS to afford in very good yield a mixture of exo/endo diastereomers 942 and 943 with low stereoselection [424].
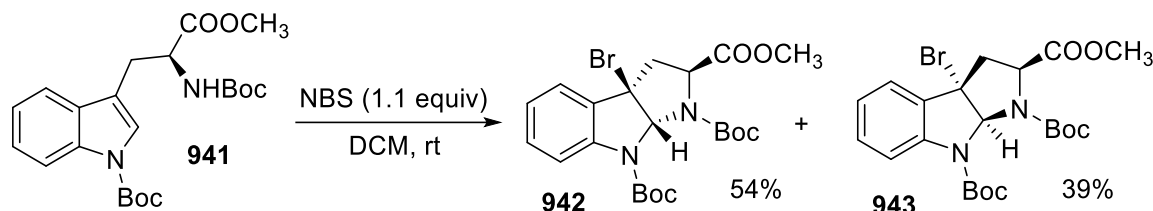
When bromine was generated by anodic oxidation of bromide ion, hexahydropyrroloindolines 945 were obtained in moderate to high yield starting from 3-substituted indoles 944 where the nitrogen of the new ring was substituted by a carbamate functionality [277].
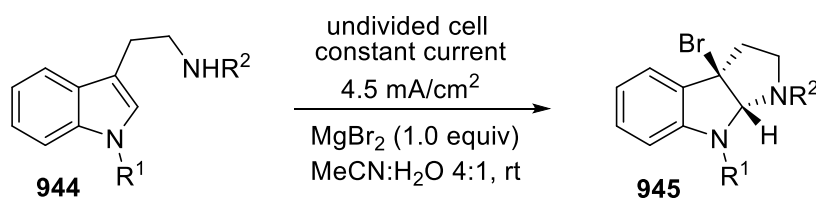
R^1 = R^2 = Boc, 61%; R^1 = Boc, R^2 = COOCH$_3$, 89%;
R^1 = Ts, R^2 = Boc, 91%; R^1 = Ts, R^2 = Cbz, 69%

Furthermore, when halogens arose from oxidation of the corresponding halides performed with Oxone®, tryptamine carbamates 946 were converted in very good yield into hexahydropyrroloindolines 947, cores of biologically active natural alkaloids [278].
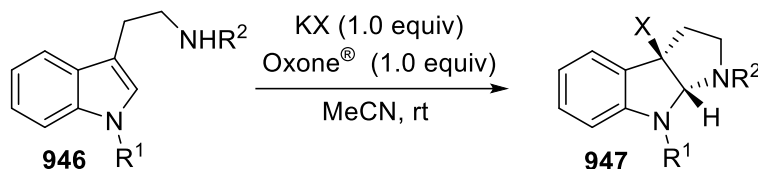
X = Br, R^1 = Boc, R^2 = COOCH$_3$, 93%; X = Br, R^1 = Ts, R^2 = Boc, 91%;
X = Cl, R^1 = Ts, R^2 = COOCH$_3$, 81%; X = Cl, R^1 = Boc, R^2 = COOCH$_3$, 85%

Chiral N-Boc aziridines 948 bearing a double bond allowed to prepare in good yield but with low regioselection mixtures of N-Boc protected chiral trisubstituted pyrrolidines 949 and piperidines 950 that were, however, obtained with nearly total diastereoselection [425].
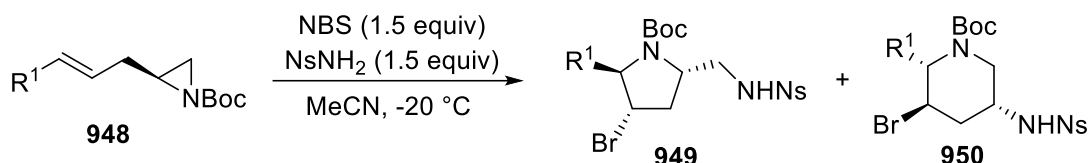
R^1 = 4-CH$_3$O-C$_6$H$_4$, 80%, 2.1 :1.0 ratio; R^1 = 4-CH$_3$-C$_6$H$_4$, 82%, 3.0:1.0 ratio;
R^1 = 4-F-C$_6$H$_4$, 82%, 2.7:1.0 ratio; R^1 = 4-t-C$_4$H$_9$-C$_6$H$_4$, 80%, 4.0:1.0

t-Butoxycarbonylamino derivatives were found to be valuable intermediates for halocyclization [426]. Thus, the reaction of chiral compounds 951, carried out with iodine in a basic medium, led to good yield without loss of chirality to highly substituted 2-oxopiperazines 952 with 2,6-cis-disubstitution [427].
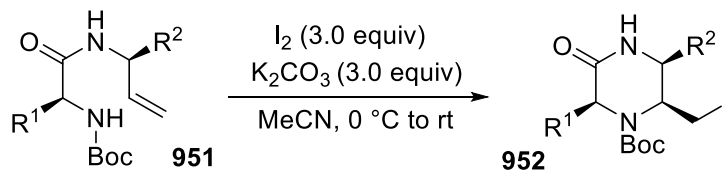
R^1 = (CH$_3$)$_2$CHCH$_2$, R^2 = (CH$_3$)$_2$CH, 70%; R^1 = R^2 = CH$_2$C$_6$H$_5$, 69%;
R^1 = R^2 = (CH$_3$)$_2$CH, 71%; R^1 = CH$_2$C$_6$H$_5$, R^2 = (CH$_3$)$_2$CHCH$_2$, 67%

The carbamates 955 were obtained as intermediates by the reaction of indolinone 953 and alkynyl carbamates 954 in the presence of catalyst 956. In the dark, a regioselective cyclization induced by iodine proceeded in a 5-exo-trig mode, leading to a novel N-C bond, and the tricyclic spiro compounds 957 were isolated in moderate yield but with excellent stereoselection [428].
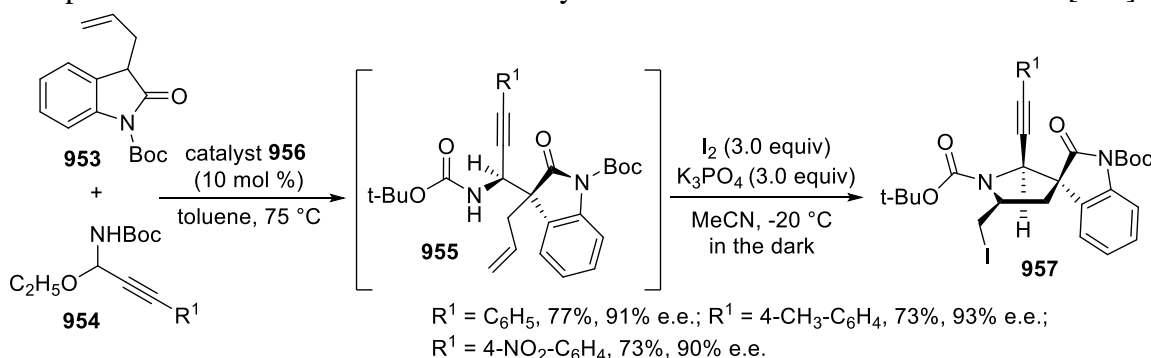
R^1 = C$_6$H$_5$, 77%, 91% e.e.; R^1 = 4-CH$_3$-C$_6$H$_4$, 73%, 93% e.e.;
R^1 = 4-NO$_2$-C$_6$H$_4$, 73%, 90% e.e.
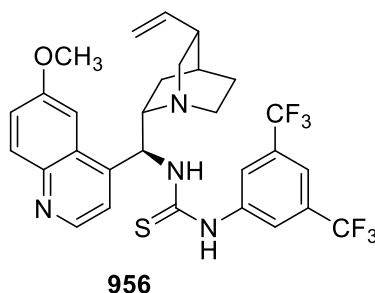
Ring closure of chiral t-Boc aziridines 958 was carried out using NBS and NsNH$_2$, and the corresponding azepanes 959 bearing three chirality centers were obtained with excellent yield and nearly total stereoselection [429].
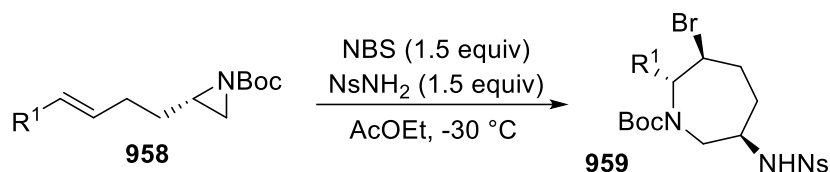
R^1 = 4-Br-C$_6$H$_4$, 82%, 99% e.e., >99% d.r.; R^1 = 3-CH$_3$-C$_6$H$_4$, 80%, 99% e.e., >99% d.r.;
R^1 = 4-Cl-C$_6$H$_4$, 83%, 99% e.e., >99% d.r.; R^1 = 4-C$_6$H$_5$-C$_6$H$_4$, 92%, 99% e.e., >99% d.r.

2.2.4.2. Cyclic *N*-carbamoyl amines with external asymmetric induction.

When the cyclization of diprotected tryptamines 960 was carried out with NBS in the presence of the catalyst Λ-(S,S)-625, acting as a Bronsted acid, the corresponding tricyclic derivatives 961 were obtained in good yield and high enantioselection [430].
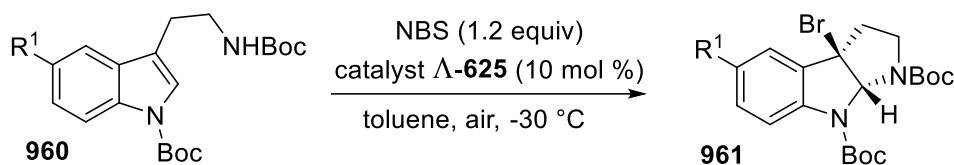
R^1 = H, 89%, 88% e.e.; R^1 = CH$_3$, 95%, 82% e.e.; R^1 = F, 78%, 80% e.e.

Using the same catalyst Λ-(S,S)-625, but changing NBS for 1,3-diiodo-5,5-dimethylhydantoin (DIDMH), the cyclization of compounds 962 to iododerivatives 963 proceeded with lower yields but with similar enantioselection [316].
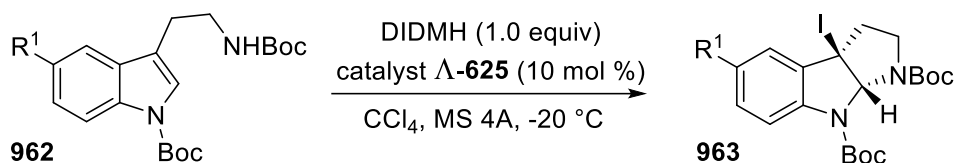
R^1 = H, 53%, 81% e.e.; R^1 = CH$_3$, 44%, 89% e.e.; R^1 = CH$_3$O, 40%, 85% e.e.

Within a synthesis of alkaloid (-)-chimonanthine, the asymmetric bromocyclization of tryptamine derivatives 964 was carried out using DABCO-derived salt 966 together with catalyst 8H-R-TRIP 967, and products 965 were recovered in high yield with excellent enantioselection [431].
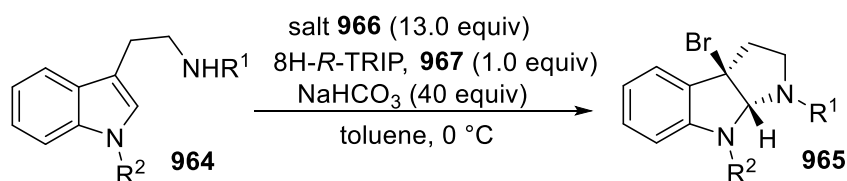
R^1 = COOCH$_3$, R^2 = Alloc, 90%, 98% e.e.; R^1 = COOCH$_3$, R^2 = Ts, 100%, 95% e.e.;
R^1 = Ts, R^2 = Boc, 95%, 92% e.e.; R^1 = Ac, R^2 = Boc, 51%, 90% e.e.
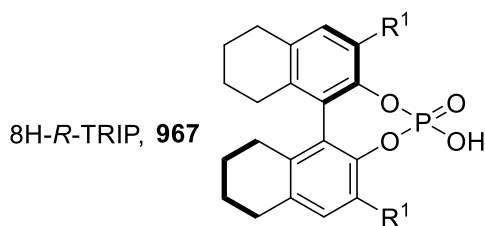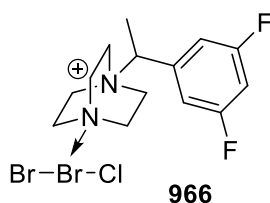
R^1 = 2,4,6-[(CH$_3$)$_2$CH]$_3$-C$_6$H$_2$

2.2.5. *N*-Sulphonyl and *N*-carbamoyl lactams from imides.

When electron-withdrawing substituents such as a sulphonyl or an acyl group lie on the amidic nitrogen atom, this latter can easily attack an intermediate haliranium ion, leading to a new C-N bond.

2.2.5.1. *N*-Sulphonyl lactams without asymmetric induction.

The bromolactamization rate of unsaturated N-sulphonyl amides induced by NBS strongly increased when a mixture of N,N-dimethylaminopyridine, urea 970, and aniline derivative 971 was used in a 60:20:20 ratio. Thus, starting from the amides 968, the corresponding lactams 969 were obtained in good yield, whereas in the absence of a co-catalyst, imino lactams arising from attack by the carbonylic oxygen were the major products [432].

n = 0, R^1 = Ts, 63%; n = 1, R^1 = Ts, 84%; n = 1, R^1 = Ns, 72%
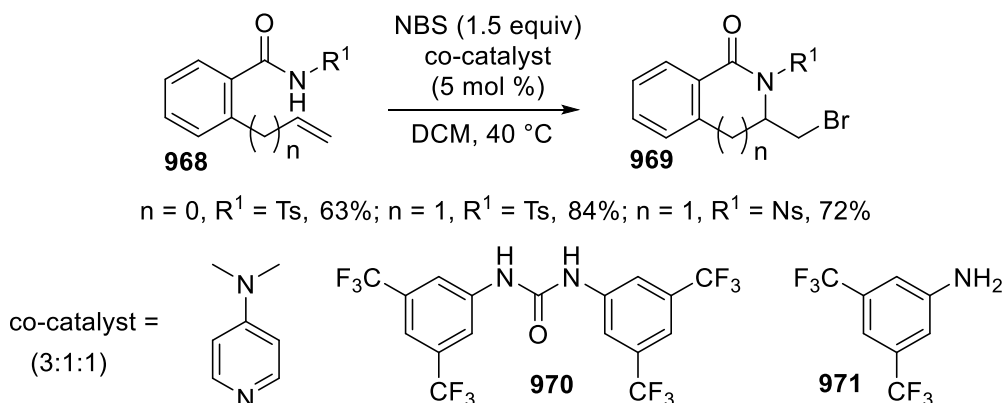
2.2.5.2. Synthesis of *N*-sulphonyl and *N*-carbamoyl lactams with internal asymmetric induction.

The tricyclic regioisomeric β-lactams 973 and 974 were isolated in high yield and with high regioselection starting from the chiral imide 972. The cyclization, carried out in a basic medium, proceeded preferentially through an SN2' mechanism at the intermediate bromiranium ion [433].
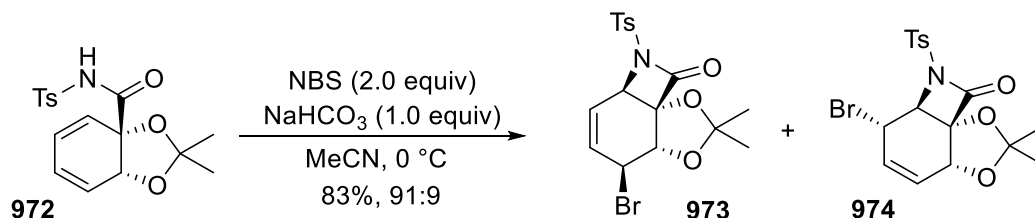
Total regio- and stereoselection were also observed when carbamate 975, bearing an imido group, underwent cyclization mediated by NBS, to provide in low-yield cis-perhydroquinoxaline 976 [434].
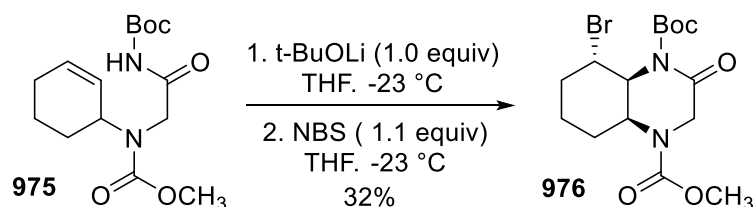
By reaction with t-BuOLi followed by NBS [429], a diastereomeric mixture of imides (S,R)-977 and (S,S)-978 afforded with excellent diastereoselection the bromolactam 979, exclusively, whereas N-Boc amide 980 remained unchanged [435].
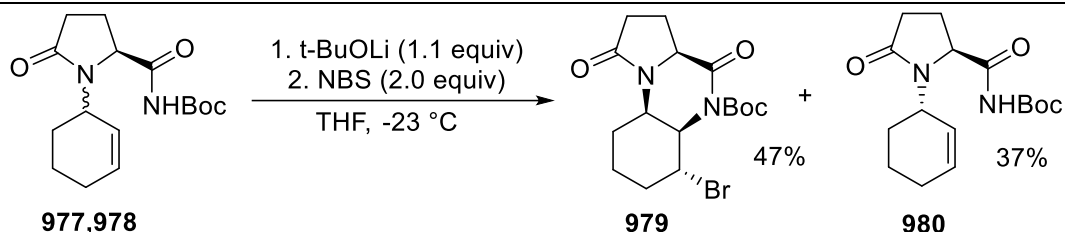
2.2.5.3. *N*-Sulphonyl lactams with external asymmetric induction.

The cyclization of compounds 981 and 984, having the amidic nitrogen substituted by a sulphonyl functionality, mediated by NBS in the presence of the catalyst 983, led to excellent yield and enantioselection to 10-bromo-2-tosyl-3,4-dihydropyrazino[1,2-a]indol-1(2H)-ones 3-bromomethyl 982 or 3-bromoalkyl substituted 985, exclusively, whereas a bromine atom was transferred to C-3 of the indole ring [436].
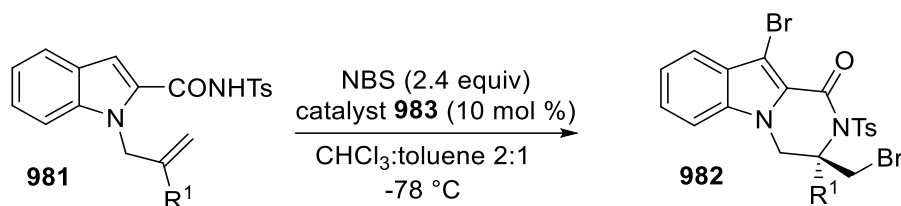
R^1 = H, 94%, 68% e.e.; R^1 = C_6H_5, 89%, 94% e.e.; R^1 = 4-CH_3-C_6H_4, 86%, 93% e.e.; R^1 = t-C_4H_9, 81%, 97% e.e.; R^1 = cyclohexyl, 98%, 96% e.e.
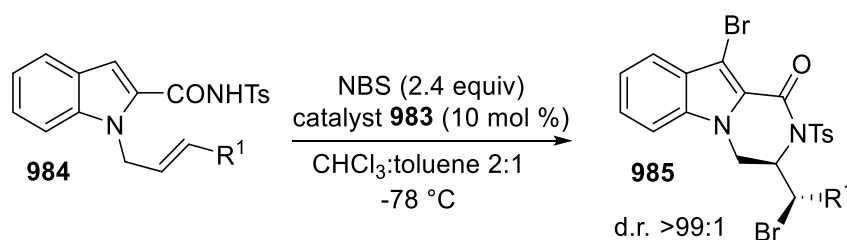
R^1 = CH_3, 72%, 91% e.e.; R^1 = C_2H_5, 97%, 92% e.e.; R^1 = n-C_3H_7, 88%, 90% e.e.
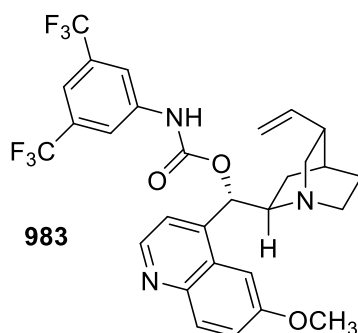
2.2.6. *N*-sulphonyl 1,3-oxazolidin-2-ones, 1,3-oxazin-2-ones, 1,3-imidazolidin-2-ones and spirolactams from *N*-sulphonyl carbamates.

2.2.6.1. Synthesis of *N*-sulphonyl 1,3-oxazolidin-2-ones without asymmetric induction.

The halocyclization of 2-arylprop-2-en-1-yl tosylcarbamates 986 was carried out first by treating with t-BuOK, followed by TsNBr2 to generate the bromiranium intermediate, and N-tosyl oxazolidin-2-ones 987 were isolated in high yield and total regioselection, whereas only nitrogen of the bidentate carbamate group attacked the bromiranium ion [437].
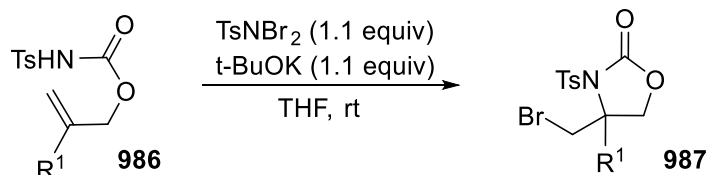
$R^1 = C_6H_5$, 88%; $R^1 = 4\text{-}F\text{-}C_6H_4$, 88%; $R^1 = 4\text{-}CH_3O\text{-}C_6H_4$, 83%

On the contrary, when N,N-dibromo-4-nitrobenzenesulfonamide in the neutral medium was employed in place of TsNBr2, the cyclization of tosylcarbamates **988** provided in good yield the dioxolanimines **989** with a totally regioselective attack of the oxygen and high (E)-stereoselection at the C=N double bond [437].
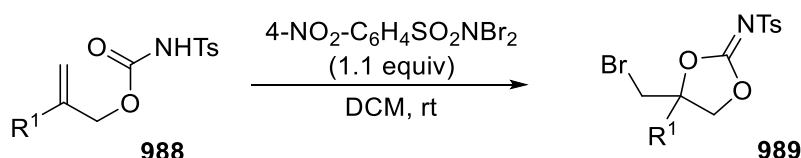
$R^1 = C_6H_5$, 89%, *E* only; $R^1 = 4\text{-}F\text{-}C_6H_4$, 73%, *E:Z* 10:1; $R^1 = 4\text{-}CH_3O\text{-}C_6H_4$, 83%, *E:Z* 9:1

2.2.6.2. Synthesis of *N*-sulphonyl 1,3-oxazolidin-2-ones with internal asymmetric induction.

In analogy with N-sulphonyl imides, N-tosyl carbamates **990** underwent halocyclization to give the corresponding substituted oxazolidin-2-ones **991** in moderate yield but with excellent stereoselection [438-439].
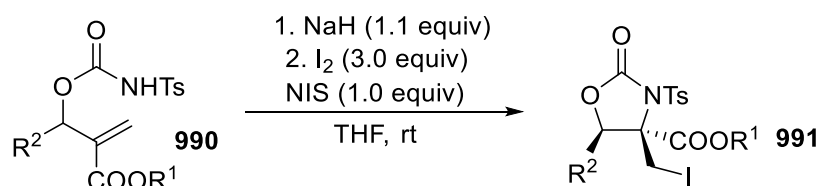
$R^1 = CH_3$, $R^2 = C_6H_5$, 75%; $R^1 = CH_3$, $R^2 = (CH_3)_2CHCH_2$, 63%, *cis:trans* 9:1);
$R^1 = t\text{-}C_4H_9$, $R^2 = C_6H_5$, 66%; $R^1 = CH_2CH_3$, $R^2 = 4\text{-}Cl\text{-}C_6H_4$, 59%

However, the process outcome strongly relied upon the nature and position of the substituents since, by cyclization, the tosylcarbamates **992** gave the corresponding cyclic products **993** in moderate yield and low stereoselection [392].
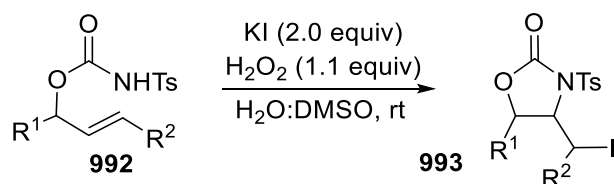
$R^1 = CH_3$, $R^2 = H$, 67%, *cis:trans* 2:1; $R^1 = n\text{-}C_3H_7$, $R^2 = H$,
60%, *cis:trans* 2.5:1; $R^1 = H$, $R^2 = n\text{-}C_3H_7$, 64%

Eventually, toluene sulphonyl carbamate **995**, generated by the reaction of enynol **994** with 4-toluenesulphonyl isocyanate, underwent cyclization with NBS in the presence of DABCO as Lewis base, leading to a mixture where N-tosyloxazolidin-2-one **996** was the major component formed with good stereoselection [396].
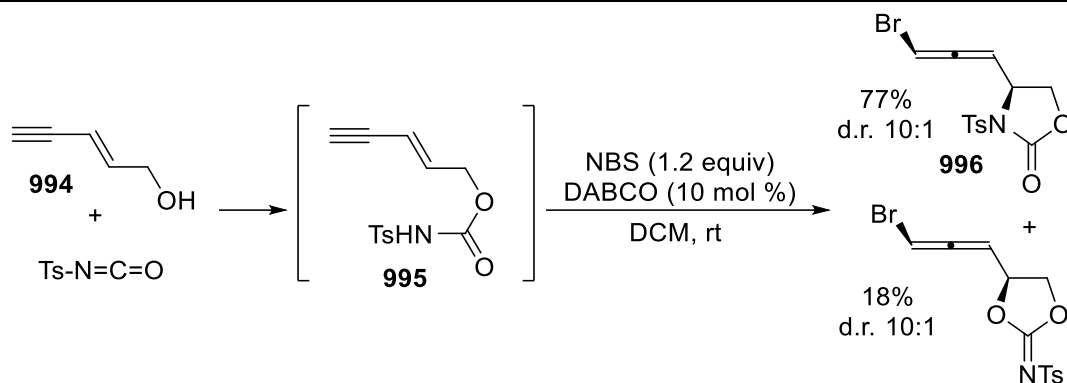
2.2.6.3. Synthesis of *N*-sulphonyl 1,3-oxazolidin-2-ones, 1,3-oxazin-2-ones, 1,3-imidazolidin-2-ones and spirolactams with external asymmetric induction.

The reaction of unsaturated (Z)-carbamates 997 was carried out with NBS in the presence of the chiral phosphine base ligand 999 and Sc triflate. The reaction proceeded with total regioselection through a 5-exo-mode cyclization, and the corresponding N-tosyl oxazolidin-2-ones 998 were isolated in good yield and excellent enantioselection [440].

R^1 = C_2H_5, 88%, 96% e.e.; R^1 = $CH_2C_6H_5$, 83%, 93% e.e.;
R^1 = $(CH_2)_3OAc$, 80%, 97% e.e.; R^1 = $(CH_2)_3Cl$, 87%, 96% e.e.
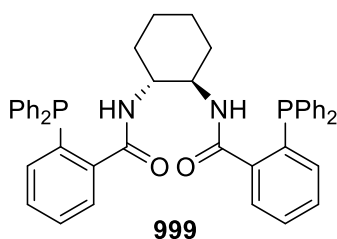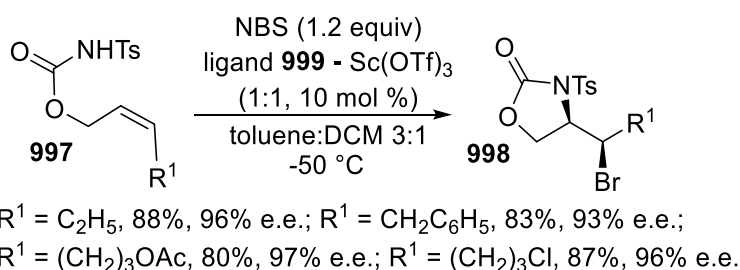
The configuration of the double bond strongly directed the regioselection of the cyclization since the (E)-carbamates 1000, treated with dibromodimethylhydantoin (DBDMH) in the presence of the phosphine oxide 1002 and Sc triflate, afforded in good yield, total regioselection and excellent enantioselection N-tosyl oxazin-2-ones 1001 exclusively, arising from a 6-endo-mode cyclization [441-442].

R^1 = C_6H_5, 86%, 95% e.e.; R^1 = $2\text{-}CH_3\text{-}C_6H_4$, 94%, 95% e.e.;
R^1 = $4\text{-}Cl\text{-}C_6H_4$, 96%, 95% e.e.; R^1 = 1-naphthyl, 75%, 99% e.e.
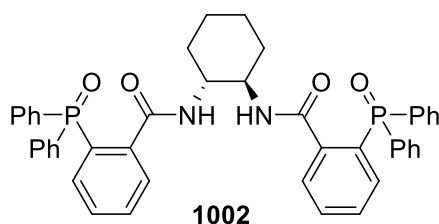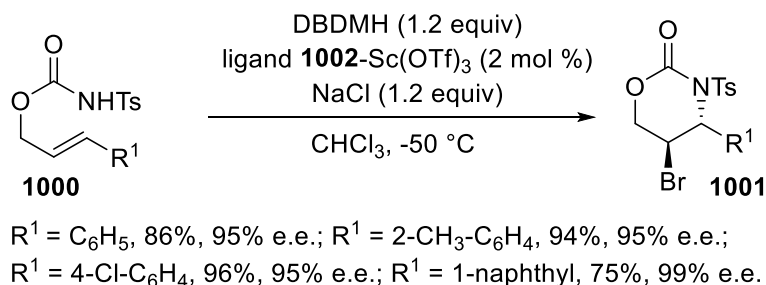
Accordingly, dienyl carbamates 1003 gave the corresponding oxazolidin-2-ones 1004 in good yield and high enantioselection [443].
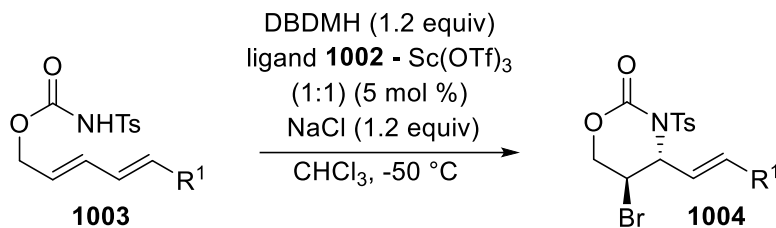
R^1 = CH$_3$, 91%, 97% e.e.; R^1 = n-C$_4$H$_9$, 79%, 93% e.e.; R^1 = CH$_2$N$_3$, 65%, 95% e.e.;
R^1 = C$_6$H$_5$, 61%, 95% e.e.; R^1 = 4-Cl-C$_6$H$_4$, 68%, 97% e.e.

In addition, homoallyl N-tosyl carbamates 1005, displaying the (E)-configuration at the double bond, underwent cyclization in a 6-exo mode, mediated by N-bromoacetamide, in the presence of the phosphine oxide 1002 and Sc triflate, to provide the corresponding oxazin-2-ones 1006 in moderate yield but with excellent enantioselection [444].
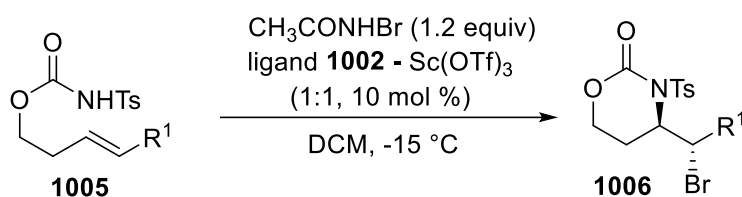
R^1 = CH$_3$, 58%, 99% e.e.; R^1 = C$_2$H$_5$, 57%, >99% e.e,;
R^1 = C$_5$H$_{11}$, 57%, >99% e.e.; R^1 = CH$_2$CH$_2$Cl, 45%, 99% e.e.

Starting from compounds 1007, under similar reaction conditions as those used for the cyclization of 1003, spiro derivatives 1008 were obtained in good yield and excellent enantioselection, exploiting the attack of a bromenium ion to the electron-rich benzofuran ring [445].
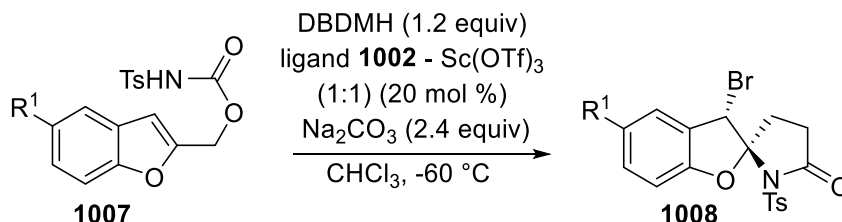
R^1 = H, 90%, 94% e.e.; R^1 = CH$_3$, 89%, 94% e.e.; R^1 = t-C$_4$H$_9$, 90%, 97% e.e.

Eventually, by reaction of allylamines 1009 with tosyl isocyanate, unsaturated N-tosyl ureas intermediates were obtained, and subsequent cyclization in situ was carried out with N-iodopyrrolidinone (NIPyr) in the presence of catalyst 1011 gave in good yield and high enantioselection the chiral N-tosylimidazolidin-2-ones 1010 [446].
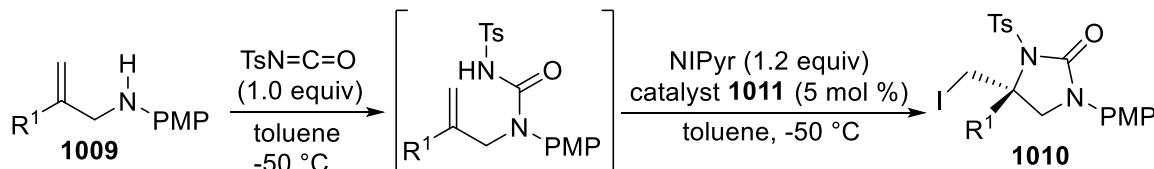
R^1 = C$_6$H$_5$, 82%, 91% e.e.; R^1 = 4-CH$_3$-C$_6$H$_4$, 97%, 92% e.e.;
R^1 = 4-F-C$_6$H$_4$, 90%, 89% e.e.; R^1 = CH$_3$, 93%, 29% e.e.

1011

R¹ = OCH₃
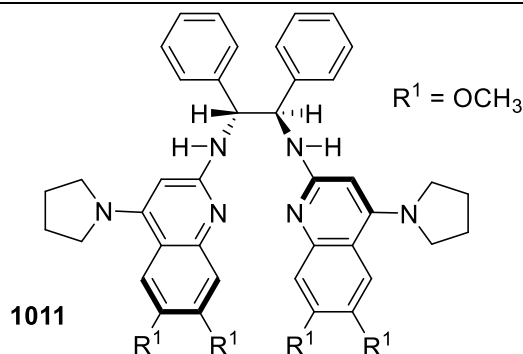
2.2.7. 4,5-Dihydro-1,3-oxazoles, 5,6-dihydro-4H-1,3-oxazines, and 1,3-oxazinan-2-ones from imidates and carbonimidothioates.

2.2.7.1. 4,5-Dihydro-1,3-oxazoles, 5,6-dihydro-4*H*-1,3-oxazines, and 1,3-oxazinan-2-ones with internal asymmetric induction.

The nucleophilic nitrogen atom of an imidate functionality created starting from an allylic or a homoallylic hydroxy group present on the substrate backbone could attack a haliranium ion, leading to a heterocyclic derivative suitable for further transformations. Thus, trichloroacetimidate 1013, after treatment with iodine in a basic medium, afforded the bicyclic derivative 1014 with complete stereocontrol arising from the configuration of the starting primary alcohol 1012 [447].

1012   **1013**   **1014**
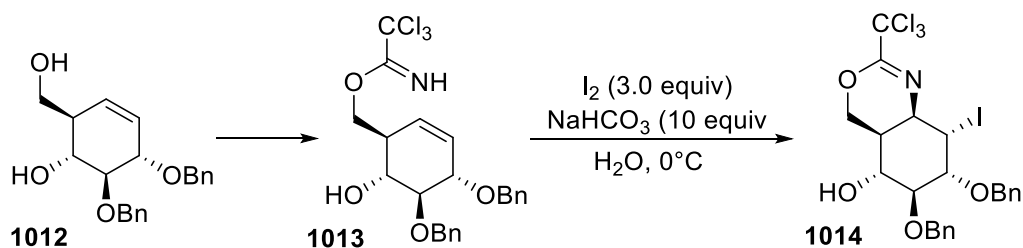
Moreover, when the imidate was prepared to start from a secondary hydroxy group lieing on a chirality center, this latter directed the stereoselective formation of the new C-N bond. Thus, the allylic trichloroacetimidate 1015 provided the corresponding bicyclic derivative 1016, isolated in moderate yield but with total stereoselection [448-449].

1015   **1016**
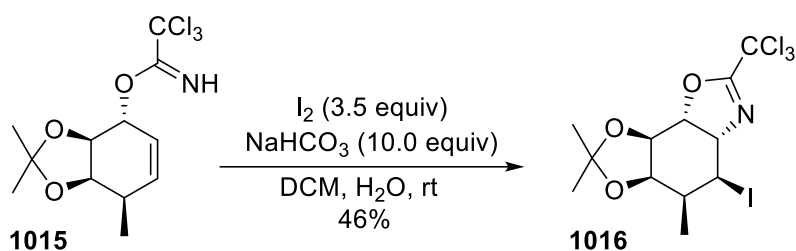
In addition, the cyclization of homoallylic trichloroacetimidates 1017 and 1019, induced by ICl, led to moderate to good yield but with total stereoselection to the bicyclic derivatives 1018 and 1020, respectively [450].

1017   **1018**
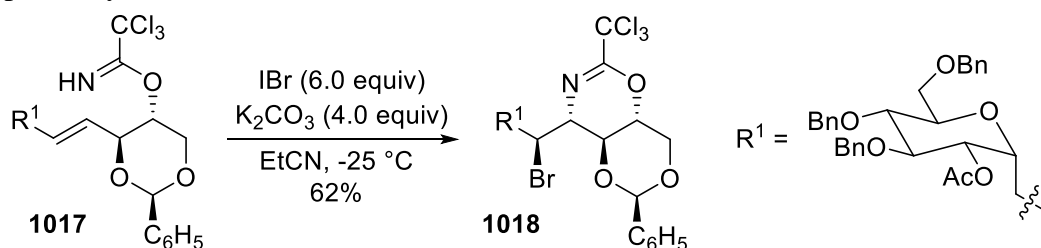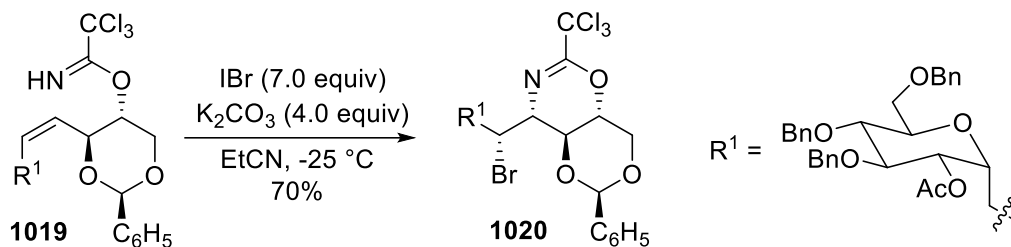
Eventually, also the thiohydroxymates 1021 and 1023 were cyclized with NBS to give the corresponding thioimidate-N-oxides 1022 and 1024 in low to moderate yield but with very low stereoselection [451].

$R^1 = H, 57\%; R^1 = OAc, 43\%$
d.r. not reported
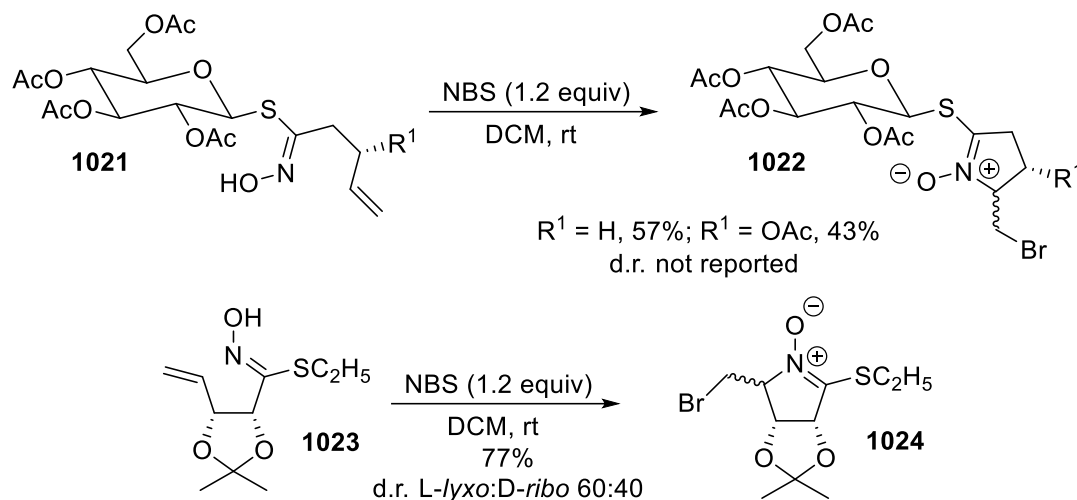
Within a total synthesis of the immunostimulant KRN7000, in alternative to trichloroacetimidates, carbonimidothioates 1025 and 1027 allowed to introduce a new C-N bond mediated by iodonium bis-sym-collidine perchlorate (IDCP), to give the corresponding heterocyclic derivatives 1026 and 1028 with total stereoselection, and the (Z)-alkene was found to be more reactive than its (E)-isomer [452].
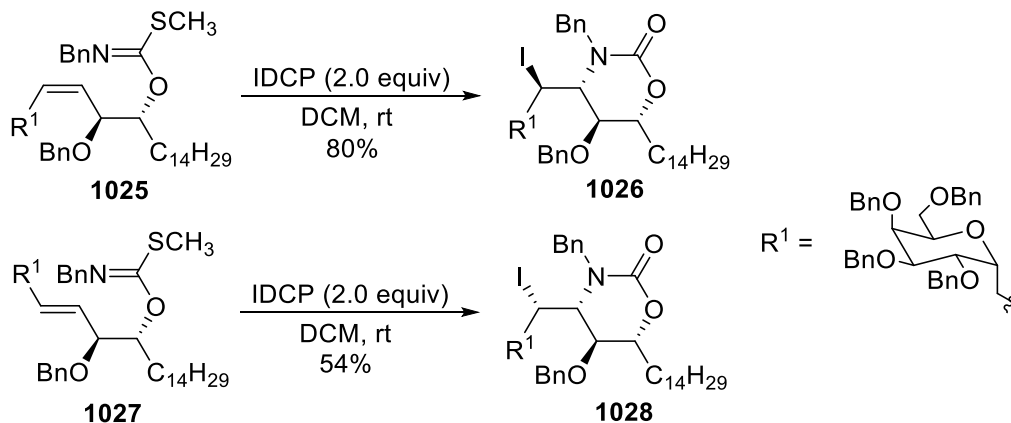
2.2.7.2. 5,6-Dihydro-4*H*-1,3-oxazines with external asymmetric induction.

Tricloroacetimidates 1029, where chirality centers are missing, underwent cyclization with NIS in the presence of catalyst 1031 to give the corresponding heterocyclic derivatives 1030 in very good yield and excellent enantioselection [453].
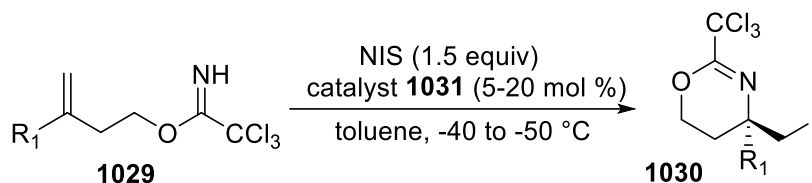
R^1 = 4-F-C$_6$H$_4$, (10 mol % **1031**, -45 °C), 86%, 90% e.e.;
R^1 = 4-Cl-C$_6$H$_4$, (5 mol % **1031**, -45 °C), 87%, 95% e.e.;
R^1 = C$_6$H$_5$, (5 mol % **1031**, -45 °C), 79%, 90% e.e.
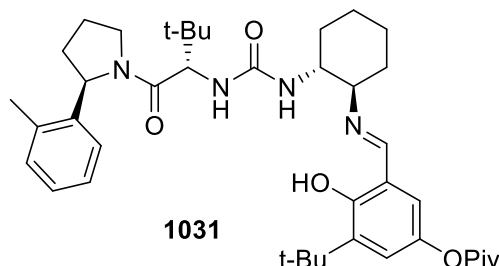
2.2.8. 4,5-Dihydrothiazoles from *S*-allyl thioimidate salts with external asymmetric induction.

In analogy with imidates obtained from allylic and homoallylic alcohols, S-allyl thioimidate salts 1032, easily prepared to start from allyl bromides and thiobenzamide, underwent cyclization mediated by NBS to give the corresponding dihydrothiazoles 1033 in moderate to good yield. It is worth mentioning that, using dichlorodiphenylhydantoin (DCPDH) in the presence of the catalyst (DHQD)2PHAL 144, the cyclization of compound 1034 to give 1035 proceeded in low yield but with good enantioselection [454].
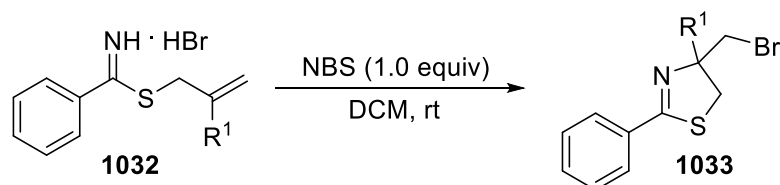
R^1 = CH$_3$, 90%: R^1 = 4-Br-C$_6$H$_4$CH$_2$, 75%; R^1 = 2-naphthyl, 57%
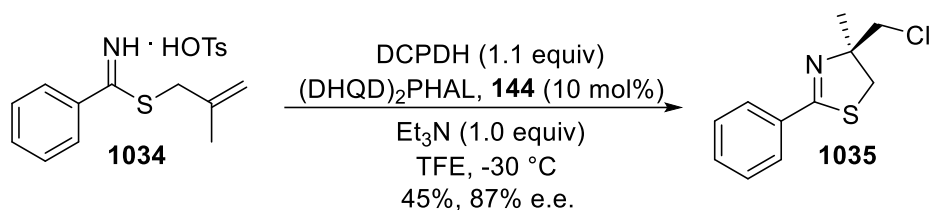
2.2.9. 2-Imino-1,3-tetrahydropyrimidines and 2-imino-1,3-imidazolidines from *N*-alkenyl guanidines and amidines.

On treatment with excess iodine in a basic medium, N-allyl and N-homoallyl guanidines 1036 and 1038, diprotected as carbamates, reacted to afford in moderate to good yield the corresponding cyclic derivatives 1037 and 1039, via a 6-endo-trig-mode or a 6-exo-trig-mode, respectively, directed by electronic factors [455-456].

1038 → **1039**

$R^1 = H, 68\%; R^1 = CH_3, 99\%$
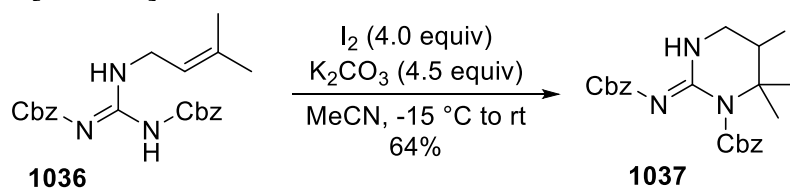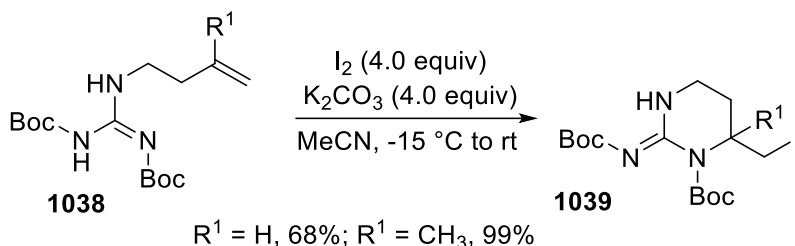
However, for monoprotected guanidine 1040, the regiochemistry of the cyclization strongly depended upon the reaction medium since neutral conditions strongly favored the 5-exo mode, leading to compound 1041, whereas, in a basic medium, the 6-endo mode was largely preferred, providing compound 1042, although the reasons for this selection are unclear [456].

1040 → **1041** + **1042**

0 equiv Na_2CO_3, 2:98; 6.0 equiv Na_2CO_3, 80:20
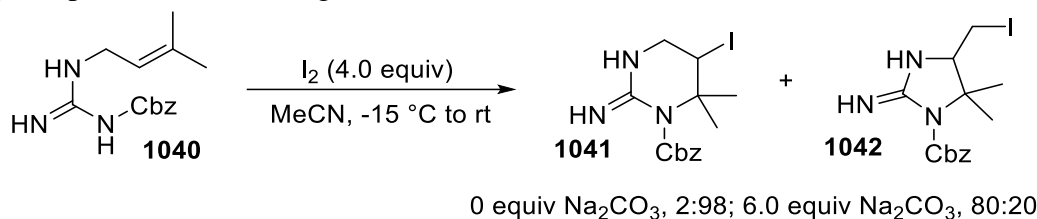
The cyclization reaction was carried out also exploiting halogen formation by oxidation of halide anions performed using Koser's reagent, hydroxy (tosyloxy)iodobenzene (HTIB). In fact, both diprotected allyl guanidines 1043 and 1045 gave in good yield the corresponding cyclic derivatives 1044 and 1046, via a 5-exo-trig-mode or a 6-endo-trig mode, respectively, again directed by electronic factors [457].

1043 → **1044**

X = Br, 89%; X = Cl, 88%

1045 → **1046**

X = Br, 57%; X = Cl, 81%
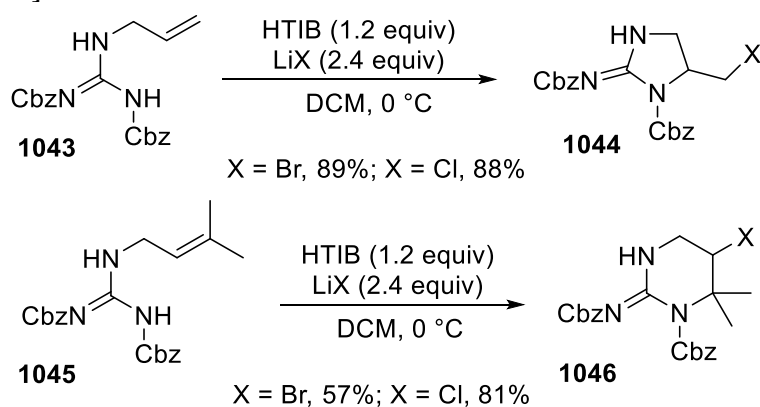
An elegant cyclization of diprotected homoallyl guanidine 1047 allowed to obtain in good yield the bicyclic compound 1048, key intermediate for the preparation of (+)-11-Saxitoxinethanoic acid [458].

1047 → **1048**

I_2 (1.2 equiv)
AgOAc (1.2 equiv)
DCM, 0 °C to rt
70%
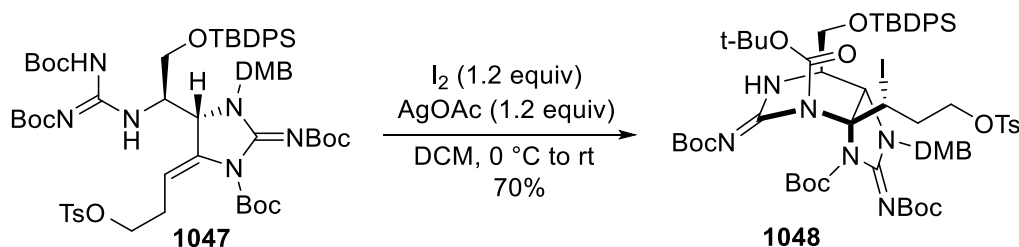
Amidines 1049, isoelectronic with imidates, on treatment with NIS were converted into the cyclic iodomethyl intermediates 1050, and subsequent attack by nitrogen at the iodomethyl group gave the corresponding 2,3-disubstituted 9,9a-dihydro-1H-imidazo[1,5-a]indol-2-ium salts 1051 in moderate to good yield [459].

R^1 = H, R^2 = methanesulfonyl, 73%; R^1 = H, R^2 = CH$_2$C$_6$H$_5$, 42%;
R^1 = C$_6$H$_5$, R^2 = methanesulfonyl, 69%; R^1 = C$_6$H$_5$, R^2 = CH$_2$C$_6$H$_5$, 77%
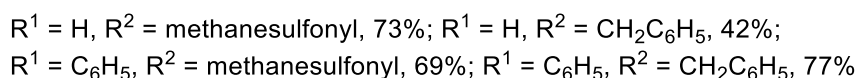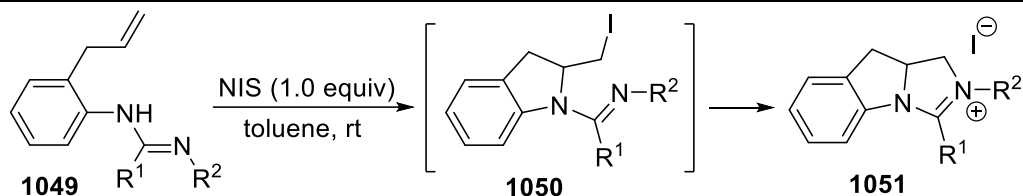
On the other hand, when the reaction was carried out in the presence of an excess of PhI(OAc)2, the amidines 1052, where substitution at the central carbon atom was missing, underwent cyclization. Still, the resulting salts were immediately oxidized to give the corresponding 2-substituted 1,2,9,9a-tetrahydro-3H-imidazo[1,5-a]indol-3-ones 1053 in moderate to good yield [460].

R^1 = methanesulphonyl, 81%; R^1 = cyclohexyl, 52%; R^1 = CH$_2$C$_6$H$_5$, 77%
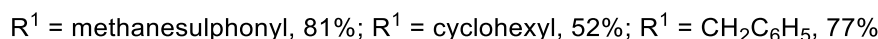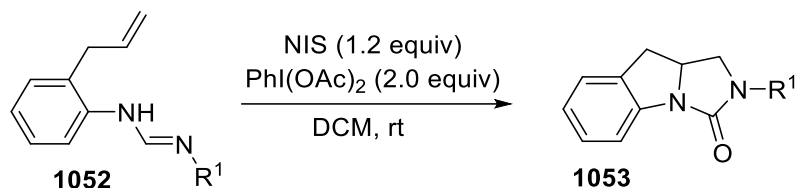
Eventually, the salts 1055, useful intermediates to N-heterocyclic carbenes (NHC), were isolated in good yield by reaction of N-allyl formamidines 1054 with an excess NIS. After cyclization, the reaction proceeded via elimination of HI, followed by aromatization and final iodination at C-2 [461].

R^1 = Mes, 72%; R^1 = Dipp, 82%
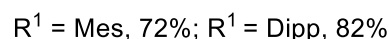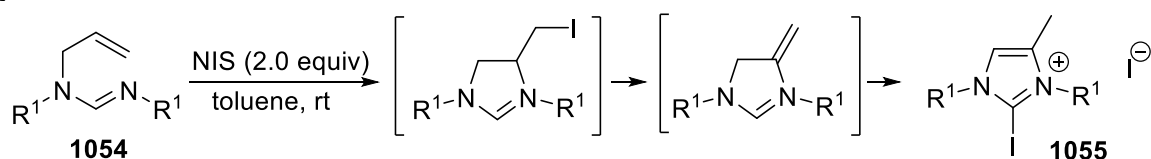
2.2.10. Polycyclic compounds from heterocycles.

A significant part of the research work concerned the halofunctionalization of double bonds involving a sp2 nitrogen atom embedded in heterocyclic compounds, leading to new C-N bonds and novel complex heterocyclic structures. However, simple allyl or homoallyl groups were tethered on the starting heterocycles, so only regioselection was involved [247]. Thus, by reaction with iodine, 3-allylthio-5H-[1,2,4]triazino[5,6-b]indole 1056 underwent cyclization at the allylic functionality in a 5-exo-mode, providing the corresponding 3-iodomethyl-3,10-dihydro-2H-[1,3]thiazolo[3',2':2,3][1,2,4]triazino[5,6-b] indolium iodide 1057 in low yield [462-463].
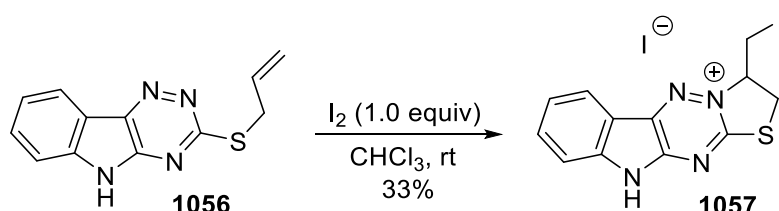
On the other hand, when cyclization was induced by bromine, the tetracyclic 3-(bromochloromethyl)-2,3-dihydro-10H-[1,3]-thiazolo[3',2':2,3][1,2,4]triazino[5,6-b]indolium bromide 1059 and 3-bromomethyl-3-methyl-3,10-dihydro-2H-[1,3]-thiazolo[3',2':2,3][1,2,4] triazino [5,6-b]indol-4-ium bromide 1061 were isolated in better yield, starting from 3-(3-chloroprop-2-en-1-ylsulfanyl-5H-[1,2,4]triazino[5,6-b]indole 1058 and 3-[(2-bromoprop-2-en-1-yl)sulfanyl]-5H-

[1,2,4]-triazino [5,6-b] indole 1060, respectively, and the five-membered ring arose from a 5-exo closure driven by electronic effects [464-466].
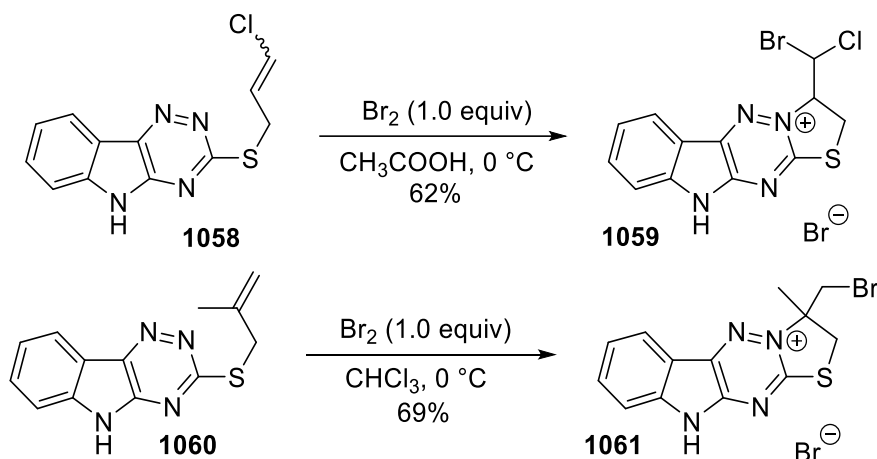
However, in the presence of stabilizing electronic factors, as it occurred for 3-(3-methyl-2-buten-1-yl)thio-5H-[1,2,4]triazino[5,6-b]indole 1062, 3-bromo-4,4-dimethyl-2,3-dihydro-11H[1,3]thiazino-[3',2':2,3][1,2,4]triazino[5,6-b]indolium tribromide 1063 was obtained in moderate yield through a 6-endo mode closure [466].
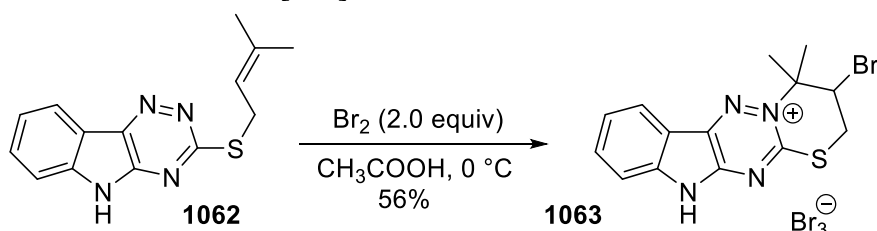
Moreover, when the 5-(homoallylthio)-3-(trifluoromethyl)-1H-1,2,4-triazole 1064 underwent cyclization mediated by iodine in a 6-exo-mode, the bicyclic 5-(iodomethyl)-3-(trifluoromethyl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b][1,3]thiazine 1065 was isolated in low yield. However, the 5-allylthio derivatives 1066 gave unexpectedly very low yields of the bicyclic 6-iodo-3-(trifluoromethyl)-1,5,6,7-tetrahydro[1,2,4]triazolo[3,4-b][1,3]thiazinium iodides 1067, according to a 6-endo mode, but the reason for this behavior remained unclear [467].

R^1 = H, 22%; R^1 = CH$_3$, 17%
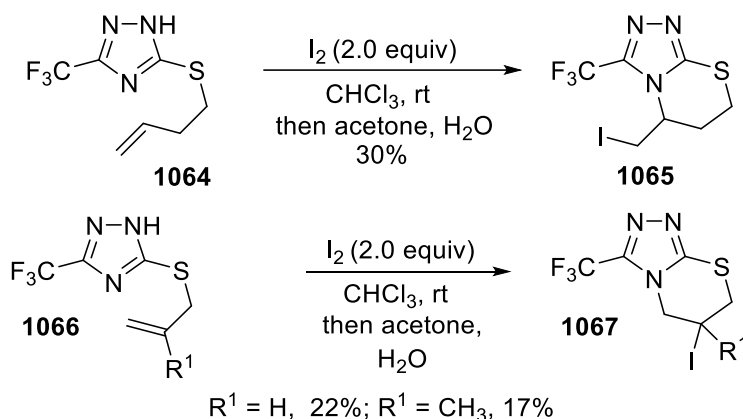
In fact, on treatment with iodine, 3-(2-methyl-2-propenyl)thio-4-methyl-1,2,4-triazole 1068 provided good yield and total regioselection the corresponding 3,6-dimethyl-6-iodomethyl-5,6-dihydro[1,3]thiazolo[3,2-b][1,2,4]triazolium iodide 1069, displaying two fused five-membered rings [468].
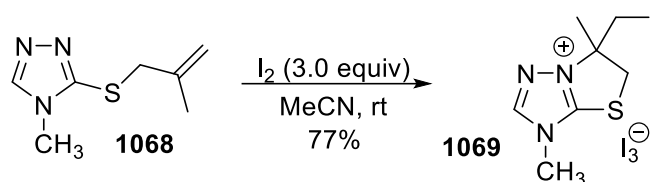
Furthermore, 2-methyl-5-((3-methylbut-2-en-1-yl)thio)-1,3,4-thiadiazole 1070, by reaction with iodine, afforded the corresponding 6-iodo-2,5,5-trimethyl-6,7-dihydro-5H-[1,3,4]thiadiazolo[2,3-b][1,3]thiazinium iodide 1071 in very good yield [469-470].
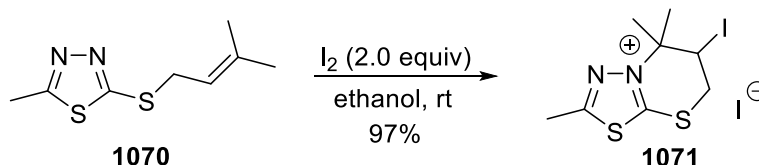
However, when 2-(allylthio)-5-methyl-1,3,4-thiadiazole 1072 underwent cyclization mediated by bromine, a regioisomeric mixture of 5-(bromomethyl)-2-methyl-5,6-dihydrothiazolo[2,3-b]-[1,3,4]thiadiazol-4-ium bromide 1073 and 6-bromo-2-methyl-6,7-dihydro-5H-[1,3,4]thiadiazolo[2,3-b][1,3]thiazin-4-ium bromide 1074 was obtained, since bias due to the bicyclic structure with two fused five-membered rings was effective [470].
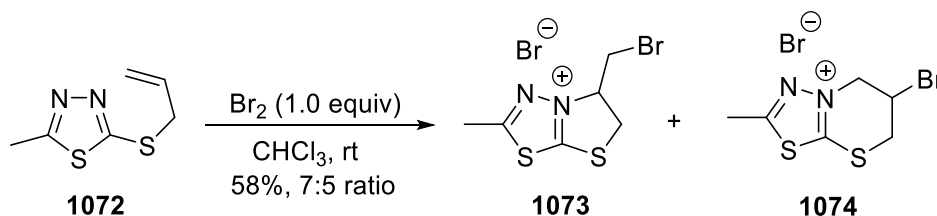
The six-membered ring formation was also observed when N-allyl-6-(bromomethyl)-5,6-dihydro[1,3]thiazolo[2,3-c][1,2,4]triazol-3-amine hydrobromide 1075 underwent cyclization mediated by bromine, leading in moderate yield via a 6-endo-mode to 7-bromo-2-(bromomethyl)-2,3,5,6,7,8-hexahydro[1,3]thiazolo[2',3':3,4][1,2,4]triazolo[1,5-a]pyrimidin-9-ium bromide 1076, exclusively, eventually converted in low yield by basic treatment into 7-bromo-2-methylene-2,3,7,8-tetrahydro-6H-[1,3]thiazolo[2',3':3,4][1,2,4]triazolo [1,5-a] pyrimidine 1077 [471].
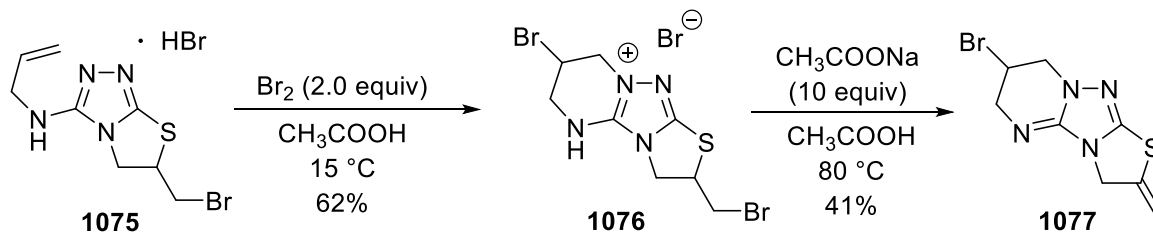
2-Allylthioquinoline 1078 underwent cyclization mediated by iodine to give the tricyclic derivative 1-iodomethyl-1,2-dihydrothiazolo[3,2-a]quinolin-10-ium triiodide 1079, but the yield was not reported [472-473], whereas under the same reaction conditions, 2-[(2-bromoallyl)thio]quinoline 1080 gave directly the elimination product 1-methylene-1,2-dihydro[1,3]thiazolo[3,2-a]quinolinium triiodide 1081 in good yield [474].
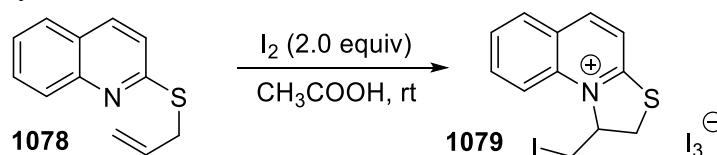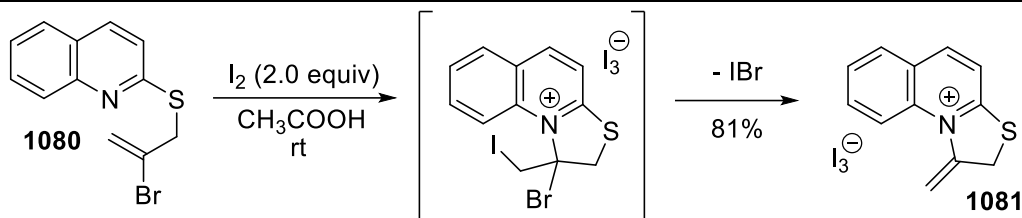
Eventually, 2-allylaminoquinoline-3-carbonitriles 1082 reacted with iodine and sodium iodide in a basic medium to afford in excellent yield of the corresponding 1-iodomethyl-1,2-dihydroimidazo[1,2-a]quinoline-4-carbonitriles 1083, suitable to be converted by subsequent elimination into [1,2-a]quinolones [475].

$R^1 = R^2 = H$, 89%; $R^1 = H$, $R^2 = CH_3$, 93%; $R^1 = CH_3$, $R^2 = H$, 92%
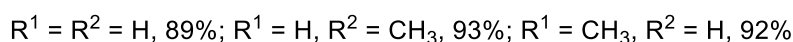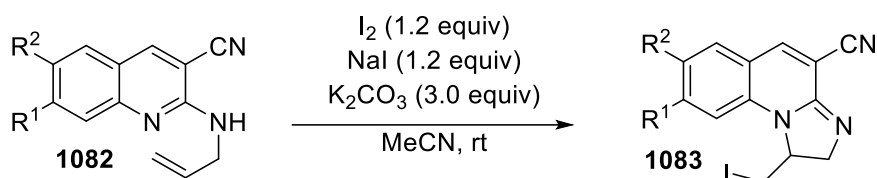
In analogy, the O-allyl derivative 4,6-dimethyl-2-(prop-2-en-1-yloxy)pyridine-3-carbonitrile 1084 was converted in excellent yield to the corresponding 8-cyano-3-iodomethyl-5,7-dimethyl-2,3-dihydro[1,3]-oxazolo[3,2-a]pyridin-4-ium triiodide 1085 [257].
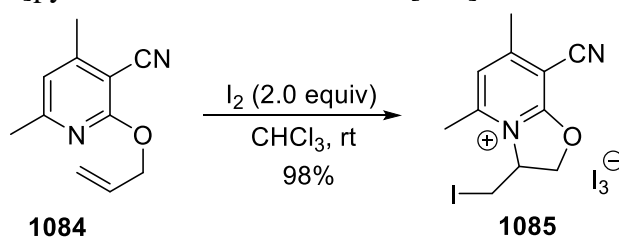
The cyclization mediated by iodine of 6-(prop-2-en-1-ylamino)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-ones 1086 proceeded in good yield via 5-exo-mode closure, to give 8-iodomethyl-7,8-dihydro-1H-imidazo[1,2-a]-pyrazolo[4,3-e]pyrimidin-4(6H)-ones 1087, and a basic treatment was required in order to remove the first formed polyiodide salt [476].

$R^1 = R^2 = H$, 82%; $R^1 = H$, $R^2 = C_6H_5$, 78%;
$R^1 = $ allyl, $R^2 = H$, 71%; $R^1 = $ allyl, $R^2 = C_6H_5$, 93%
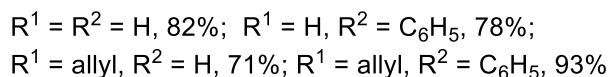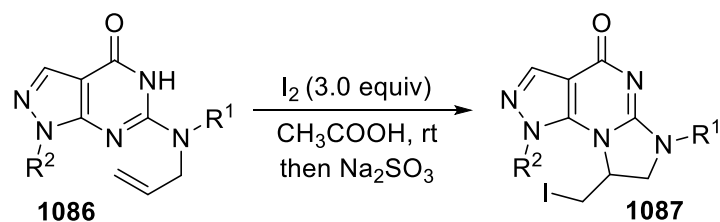
The same behavior was observed when 1-(prop-2-enyl)-6-(prop-2-enylamino)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-ones 1088 underwent cyclization to provide in good yield the tricyclic 8-(iodomethyl)-1-(prop-2-enyl)-7,8-dihydro-1H-imidazo[1,2-a]pyrazolo [4,3-e]pyrimidin-4(6H)-ones 1089. It is worth mentioning that the reaction proceeded with total regioselection, since only the allyl group bonded to the pyrimidin-4(3H)-one substructure was involved in the transformation [477].
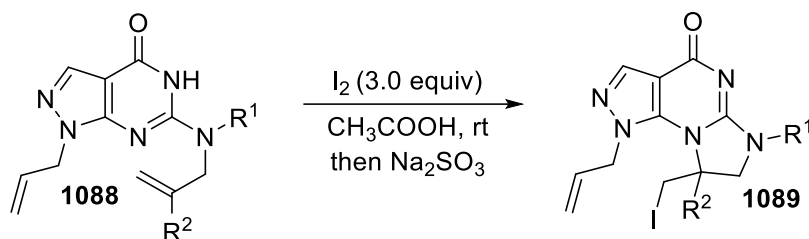
$R^1 = R^2 = H$, 86%; $R^1 = CH_3$, $R^2 = H$, 81%; $R^1 = H$, $R^2 = CH_3$, 79%

Moreover, starting from 2-[(prop-2-en-1-yl)amino]pyrido[3,2-d]pyrimidin-4(3H)-one 1090 and 2-[(3-phenylprop-2(E)-en-1-yl)amino]pyrido[3,2-d]-pyrimidin-4(3H)-one 1091, the cyclization afforded in good yield either 1-iodomethyl-2,3-dihydroimidazo[1,2-a]pyrido-[2,3-e]pyrimidin-5(1H)-one 1092, through a 5-exo-mode, or 2-iodo-1-phenyl-1,2,3,4-tetrahydro-6H-pyrido[2,3-e]pyrimido-[1,2-a]pyrimidin-6-one 1093 through a 6-endo-mode, respectively, this latter closure being directed by electronic factors due to the presence of the phenyl group [478].
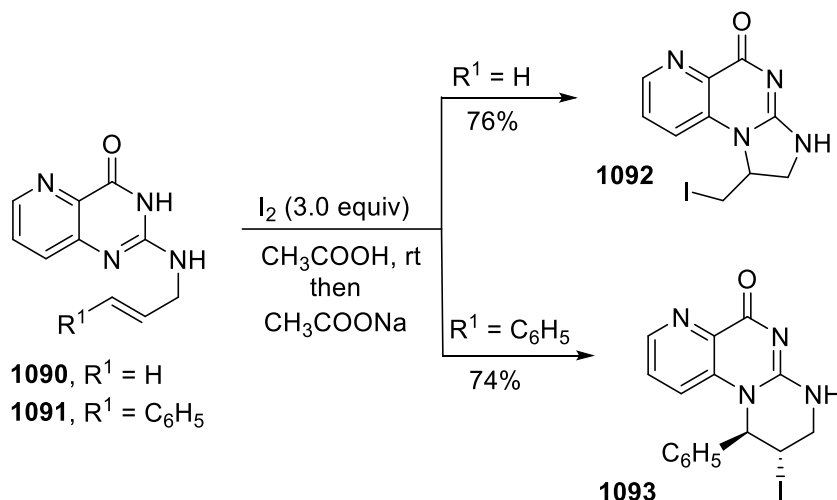
In analogy, when 2-[(prop-2-en-1-yl)thio]pyrido[3,4-d]pyrimidin-4(3H)-one, 1094, or 2-[(3-phenylprop-2(E)-en-1-yl)thio]pyrido[3,4-d]pyrimidin-4(3H)-one, 1095, were treated with excess iodine, the corresponding tricyclic derivatives 9-(iodomethyl)-8,9-dihydro-5H-pyrido[4,3-e]-[1,3]thiazolo[3,2-a]pyrimidin-5-one 1096 and 9-iodo-10-phenyl-9,10-dihydro-5H,8H-pyrido [4',3':5,6]pyrimido[2,1-b][1,3]thiazin-5-one 1097 were obtained, albeit with lower yields [479].
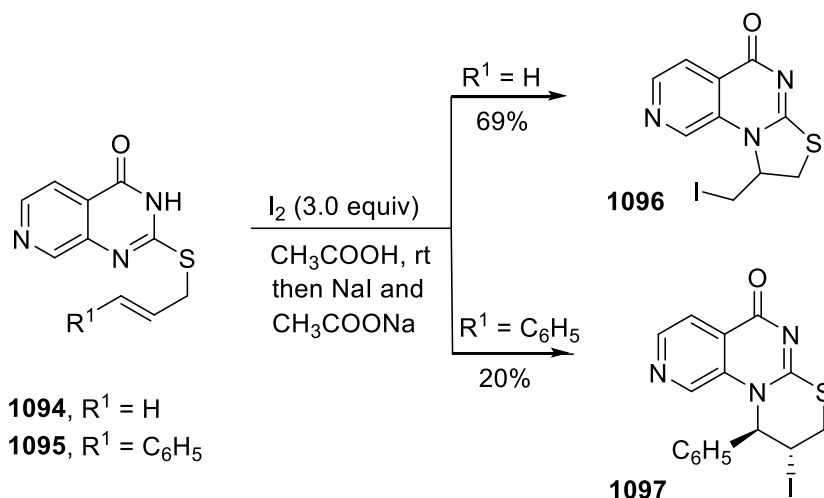
Also 6-(trifluoromethyl)pyrimidin-4(3H)-ones 1098, bearing an allylthio substituent at C-2, underwent cyclization mediated by iodine, leading in excellent yield to crystalline 3-(iodomethyl)-7-oxo-5-(trifluoromethyl)-2,3,7,8-tetrahydrothiazolo[3,2-a]pyrimidin-4-ium tri-iodides 1099 [480].

R^1 = H, (CHCl$_3$) 98%; R^1 = CH$_3$, (DCM) 98%
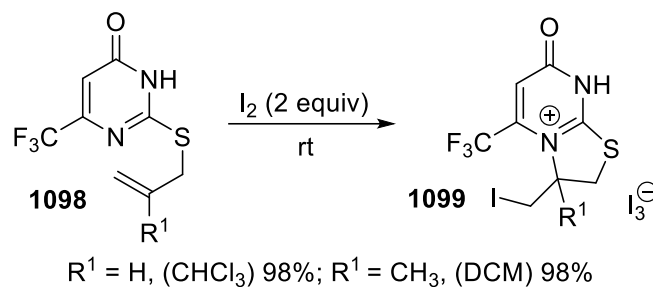
As a further example of halocyclization of allyl derivatives of nitrogen-containing heterocycles, 4-methyl-2-[(2-methylprop-2-en-1-yl)oxy]quinoline 1100, by treatment with excess iodine, afforded the corresponding 1-iodomethyl-1,5-dimethyl-1,2-dihydro[1,3] oxazolo[3,2-a]-quinolin-10-ium triiodide salt 1101 in good yield [254].
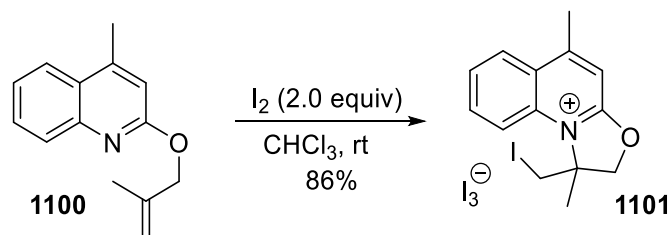
2-(But-3-en-1-ylthio)benzo[d]thiazole 1102 and 2-[(3-phenylprop-2(E)-en-1-yl)thio] benzo[d]thiazole 1104 were treated with excess iodine to give 4-(iodomethyl)-3,4-dihydro-2H-benzo[4,5]thiazolo[2,3-b][1,3]thiazin-5-ium triiodide 1103 and 3-iodo-4-phenyl-3,4-dihydro-2H-benzo[4,5]thiazolo[2,3-b][1,3]thiazin-5-ium triiodide 1105, respectively, via a 6-exo or a 6-endo closure, in agreement with structural and electronic factors [481].
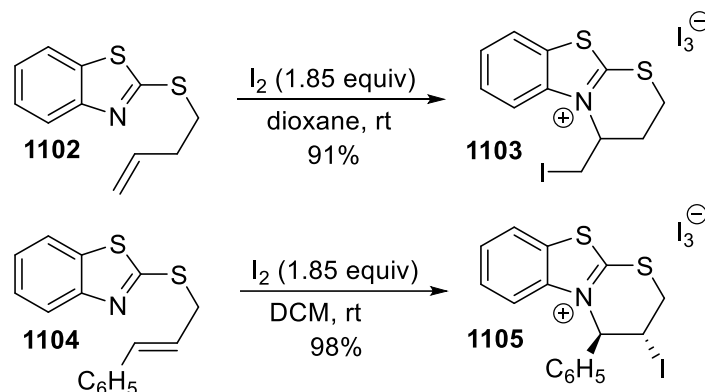
In addition, the cyclization of 6-(but-3-en-1-ylthio)-7H-purine 1106 proceeded in low yield leading to 7-(iodomethyl)-1,7,8,9-tetrahydro-[1,3]thiazino[2,3-i]purin-6-ium iodide 1107 [482].
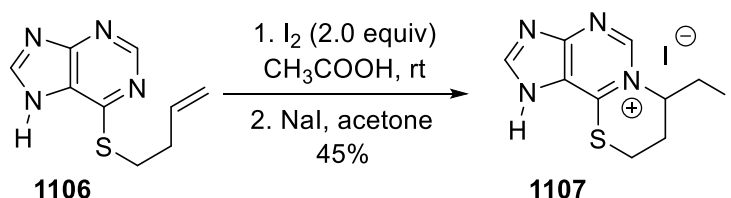
Finally, 3-iodo-imidazo[1,2-a]pyridines 1110 were prepared from N-(but-3-en-2-yl)pyridin-2-amines 1108 in moderate to good yield exploiting iodocyclization followed by C-C bond cleavage. The iodiranium ion arose from HOI, generated from I2O5 and water, and the intermediate iodomethyl group was converted into a hydroxymethyl group. This latter underwent oxidation into acyl hypoiodite 1109, and eventual decarboxylation led to product 1110 [483].
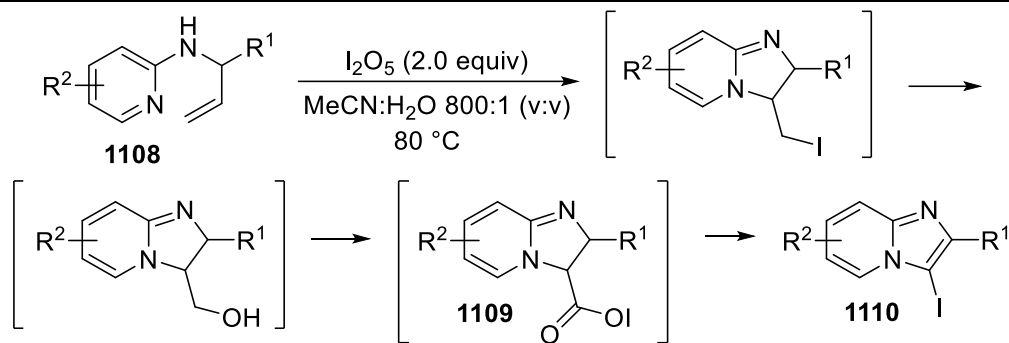
$R^1 = C_6H_5$, $R^2 = H$, 60%; $R^1 = 4\text{-}NO_2\text{-}C_6H_4$, $R^2 = H$, 89%;
$R^1 = 2$-naphthyl, $R^2 = 3\text{-}CH_3$, 57%; $R^1 = C_6H_5$, $R^2 = 3\text{-}Cl$, 61%

2.3. S-C(sp^3) and Se-C(sp^3) bond formation by an attack of sulfur and selenium nucleophiles.

2.3.1. 4-Thiomorpholine derivatives from thiols.

The attack of the sulfur of a thiol or a thioether to a haliranium ion arising from the reaction of a double bond with a halogen or a halogen donor to give a new S-C bond was scarcely reported in the literature [484-485]. However, the tosylamide 1111 underwent cyclization with bromine, leading to the corresponding 2-bromomethyl-4-tosylthiomorpholine 1112 in good yield [485].
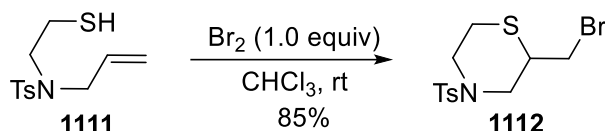
According to this procedure, a lot of unsaturated thiols 1113 were cyclized and immediately treated with DBU to provide moderate to good yield of the corresponding products 1114 containing a methylene or an alkylidene functionality [486].
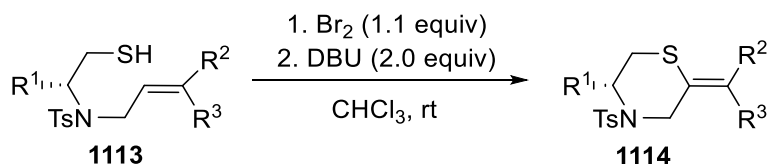
$R^1 = R^2 = R^3 = H$, 80%; $R^1 = H$, $R^2 = R^3 = CH_3$, 78%;
$R^1 = CH_3$, $R^2 = R^3 = H$, 65%; $R^1 = C_6H_5CH_2$, $R^2 = R^3 = H$, 67%

Moreover, when chiral tosylamides 1115 reacted with iodine, the corresponding 1,4-disubstituted thiomorpholine derivatives 1116 were isolated in good yield with nearly total 1,4-trans-stereoselection [335].
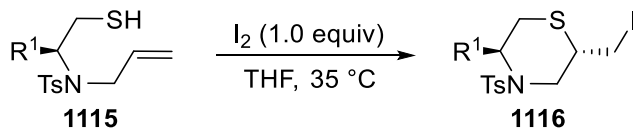
$R^1 = CH_3$, 75%, 99% d.e.; $R^1 = CH(CH_3)_2$, 75%, 99% d.e.

2.3.2. Tetrahydrothiophenes from thioethers.

Benzylthioethers 1117 were used for generating spiro compounds 1118 and 1119 in good yield but with low stereoselection via a 5-endo-trig cyclization [487-489].
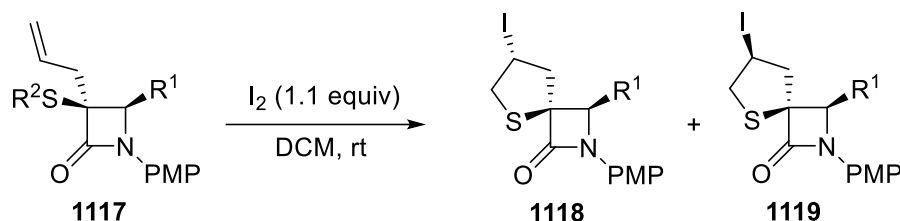
$R^1 = C_6H_5$, $R^2 = CH_2C_6H_5$, 82%, 77:23 d.r.;
$R^1 = 4\text{-}CH_3O\text{-}C_6H_4$, $R^2 = CH_2C_6H_5$, 81%, 76:24 d.r.;
$R^1 = C_6H_5$, $R^2 = CH_3$, 83%, d.r. not reported;
$R^1 = 4\text{-}CH_3O\text{-}C_6H_4$, $R^2 = CH_3$, 80%, d.r. not reported

2.3.3. (Z)-alkylidenebenzothiophen-3(2H)-ones from thioethers and dithioacetals.

It is worth mentioning that arylthioethers 1120 displayed the same reactivity as alkylthioethers to give after HI elimination the corresponding (Z)-2-arylidenebenzo[b]thiophen-3(2H)-ones 1121 and 2-aryl-4H-thiochromen-4-ones 1122 with good regio- and stereoselection but with moderate yields [490].
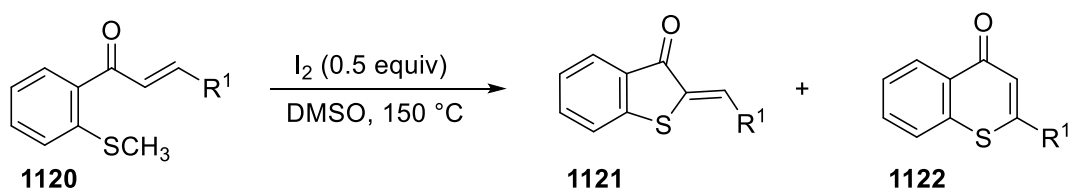
$R^1 = C_6H_5$, 73%, 90:10; $R^1 = 4\text{-}CH_3O\text{-}C_6H_4$, 56%, 81:19; $R^1 = 4\text{-}CH_3\text{-}C_6H_4$, 58%, 90:10

The preferential intramolecular addition of the sulfur atom of dithioacetals 1123 to an iodiranium ion, followed by the elimination of HI was the key step of regioselective and stereoselective formation of (Z)-2-arylidene-5-(ethylthio)-4-arylthiophen-3(2H)-ones 1124 in good yield via 5-exo-trig cyclization. Six-membered 2-(ethylthio)-3,6-diaryl-4H-thiopyran-4-ones 1125 were minor products, and the novel trick of the process was the use of a catalytic amount of iodine since the iodide formed in the reaction was oxidized to iodine by DMSO [490].
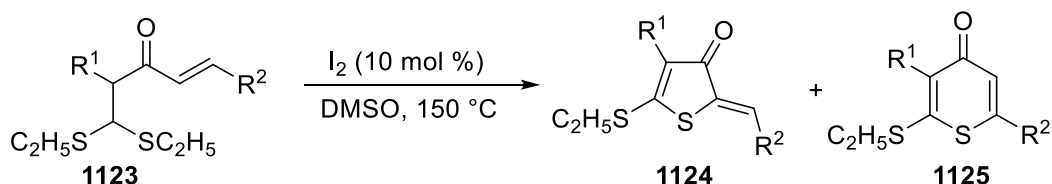
$R^1 = 4\text{-}CH_3O\text{-}C_6H_4$, $R^2 = C_6H_5$, 98%, 92:8; $R^1 = 4\text{-}CH_3O\text{-}C_6H_4$, $R^2 = 4\text{-}Cl\text{-}C_6H_4$, 90%, 97:3;
$R^1 = 4\text{-}F\text{-}C_6H_4$, $R^2 = 4\text{-}Cl\text{-}C_6H_4$, 96%, 95:5;

An efficient and practical synthetic method was devised for the preparation of 3,4-diiodo-2,5-dihydrothiophenes 1126 by electrophilic iodocyclization of S-hydroxy-2-butynyl ethanethioates 1128. The first attack of iodine, followed by the elimination of HOI, led to the intermediate iodoallenes 1127 that eventually underwent cyclization mediated by a further iodine molecule [491].
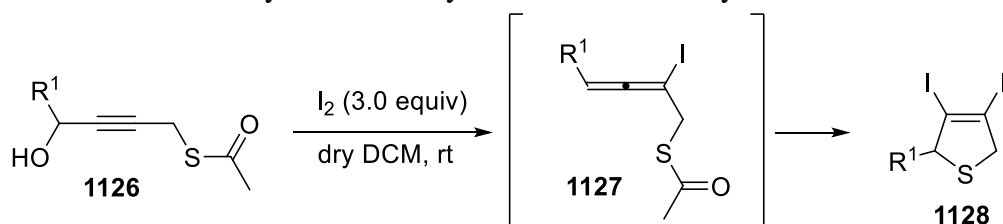
$R^1 = C_6H_5$, 89%; $R^1 = 4\text{-}CH_3\text{-}C_6H_4$, 93%; $R^1 = 4\text{-}Cl\text{-}C_6H_4$, 85%

2.3.4. 2-Alkylidene-1,3-dithiolanes and 2-imino-1,3-dithiolanes from dithioesters and dithiocarbamates.

When S-allylated α-enolic dithioesters 1129 were treated with iodine, the corresponding 2-alkylidene-1,3-dithiolanes 1130 were obtained an excellent yield. According to a 5-exo-mode directed by electronic factors, the reaction proceeded with total regioselection and high stereoselection, the newly formed double bond displaying preferential (Z)-configuration, whereas the addition of dichloromethane to the reaction mixture changed its stereochemical outcome leading to a diastereomeric E:Z-mixture [492].

R^1 = C$_6$H$_5$, 99%; R^1 = 4-Cl-C$_6$H$_4$, 99%; R^1 = 2-naphthyl, 99%
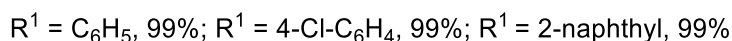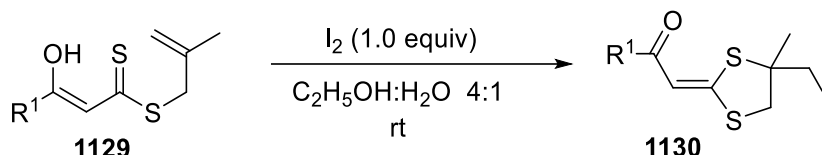
\Besides dithioesters, the thiocarbonyl sulfur of S-allyl dithiocarbamates was effective as a nucleophile for attack to haliranium ions. Thus, the dithiocarbamates 1131 were treated with iodine to give in very good yield 2-imino-1,3-dithiolanes 1132 with total regioselection, through a 5-exo-mode ring closure, but stereoselection was missing since the reaction invariably led to equimolar E:Z mixtures [493].

R^1 = C$_6$H$_5$CH$_2$, 95%; R^1 = t-C$_4$H$_9$, 100%; R^1 = C$_6$H$_5$, 90%
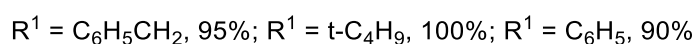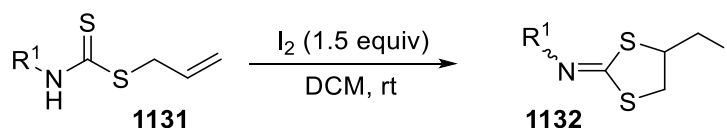
On the contrary, when S-allylselenothiocarbamates 1133 underwent cyclization mediated by iodine, 2-imino-1,3-thiaselenolanes 1134 were isolated in good yield with total regioselection but with moderate (Z)-stereoselection [494].

R^1 = C$_6$H$_5$, 90%, 85:15 Z:E; R^1 = 4-CH$_3$-C$_6$H$_4$, 83%, 83:17 Z:E;
R^1 = 2-CH$_3$-C$_6$H$_4$, 75%, 85:15 Z:E
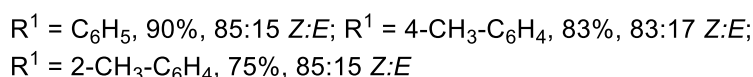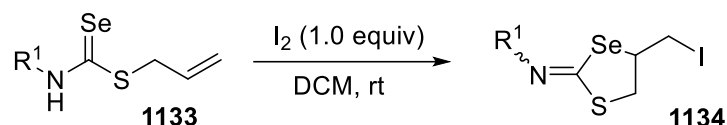
Eventually, dithiocarbamates 1135, having fully substituted nitrogen atom, underwent cyclization to provide 2-iminium-1,3-dithiolane salts 1136 in excellent yield [493].

R^1 = H, X = CH$_2$, 100%; R^1 = H, X = O, 100%; R^1 = CH$_3$, X = CH$_2$, 100%;
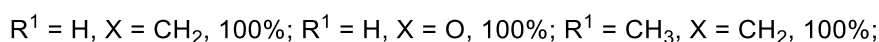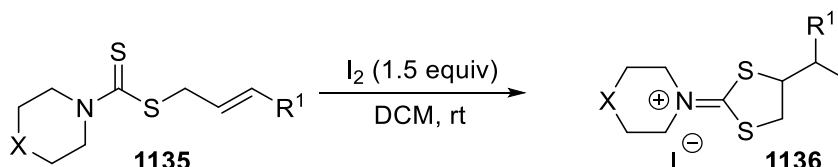
2.3.5. 1,3-Thiazolidin-2-thiones from dithiocarbamates.

By iodocyclization mediated by iodine, dithiocarbamates 1138, generated in situ starting from allylamines 1137 and CS$_2$, were converted into thiazolidine-2-thiones 1139 in moderate yield but with total regioselection [495].
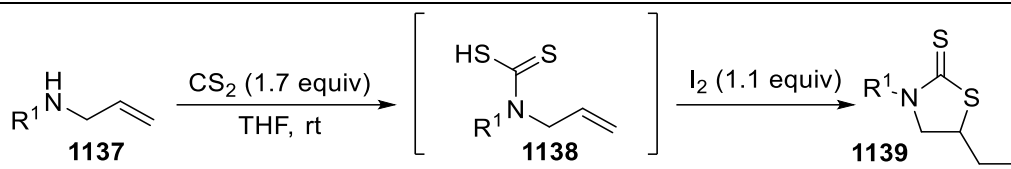
$R^1 = C_6H_5CH_2$, 60%; $R^1 = 4\text{-}CH_3\text{-}C_6H_4$, 75%; $R^1 = 4\text{-}NO_2\text{-}C_6H_4$, 68%

Moreover, the bis-allyl thiocarbamate **1140**, through two subsequent iodocyclization reactions, afforded the novel 2,6-bis(iodomethyl)-2,3,5,6-tetrahydrothiazolo[2,3-b]thiazol-4-ium iodide **1141** in moderate yield [496].
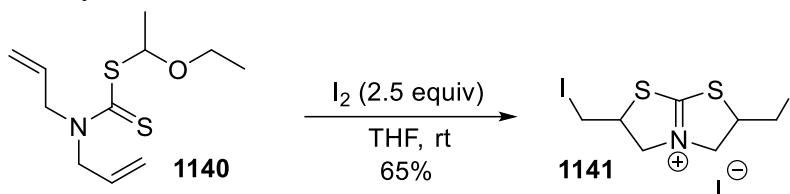
In analogy, 3-allylbenzo[d]thiazole-2(3H)-thione **1142**, on treatment with iodine, afforded the 2-(iodomethyl)-2,3-dihydrobenzo[d]thiazolo[2,3-b]thiazol-4-ium triiodide **1143** in moderate yield [497].
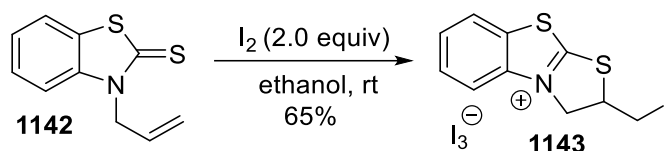
2.3.6. 4,5-Dihydro-1,3-thiazoles, 2-alkylidene-1,3-thiazolidines and furothiopyrano[2,3-*b*]quinolines from thioamides.

The intramolecular nucleophilic attack of thiocarbonyl sulfur to a haliranium ion was exploited in order to obtain thiaheterocycles [248]. Thus, thioamides **1144**, bearing an electron-releasing group, were treated with NBS to provide the corresponding 5-bromomethyl-4,5-dihydro-1,3-thiazoles **1145** in good yield [498].
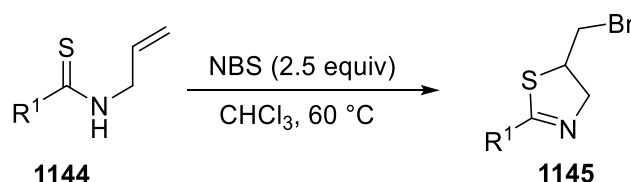
$R^1 = 4\text{-}CH_3\text{-}C_6H_4$, 90%; $R^1 = 2\text{-}CH_3\text{-}C_6H_4$, 87%; $R^1 = 1\text{-naphthyl}$, 66%; $R^1 = n\text{-}C_7H_{15}$, 83%

In the presence of an electron-withdrawing group, such as it occurred in thioamides **1146**, a further bromination gave the dibromo intermediates **1147** that underwent elimination under the reaction conditions and from the reaction mixture only the 5-bromomethyloxazoles **1148** were eventually isolated in good yield [498].
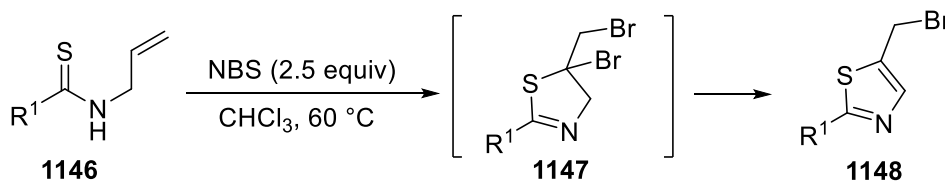
$R^1 = 4\text{-}Cl\text{-}C_6H_4$, 91%; $R^1 = 4\text{-}F\text{-}C_6H_4$, 80%; $R^1 = 4\text{-}CF_3\text{-}C_6H_4$, 61%; $R^1 = 4\text{-}NO_2\text{-}C_6H_4$, 83%

By reaction with excess iodine, N-allylthioamides **1149** regioselectively afforded the corresponding (Z)-2-(alkylidene)-5-(iodomethyl)-1,3-thiazolidines **1150** in place of the expected 4,5-

dihydro-1,3-thiazoles, owing to the presence of the ester or nitrile electron-withdrawing groups favoring the tautomeric formation of a conjugate system [499].

R^1 = COOC$_2$H$_5$, 74%; R$_1$ = CN = 91%
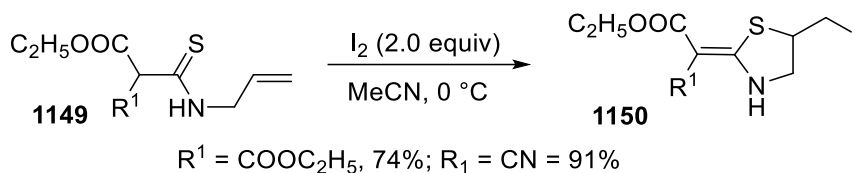
Moreover, when 3-(1-methoxybut-3-en-1-yl)quinoline-2(1H)-thiones **1151** underwent cyclization mediated by iodine, the corresponding 2-iodomethyl-4H-2,3-dihydrothiopyrano[2,3-b]quinolines **1152** were obtained in good yield [500].

R^1 = H, 85%; R^1 = CH$_3$, 88%
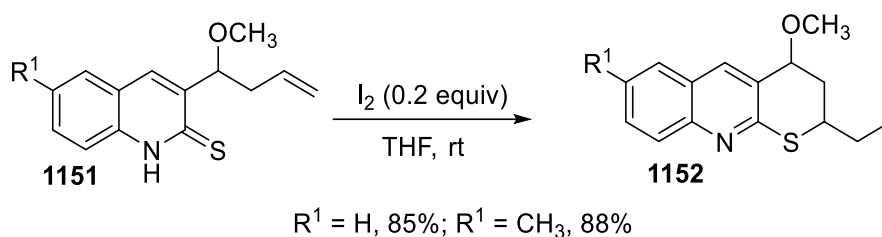
On the other hand, in the presence of a catalytic amount of iodine, quinoline-2(1H)-thiones **1153**, bearing a hydroxy functionality, underwent a further cyclization through a thiiranium ion intermediate to provide tetracyclic thiopyrano[2,3-b]quinolines **1154** in good yield exploiting the regeneration of molecular iodine [500].

R^1 = CH$_3$, 88%; R^1 = CH$_3$O, 87%; R^1 = Br, 82%
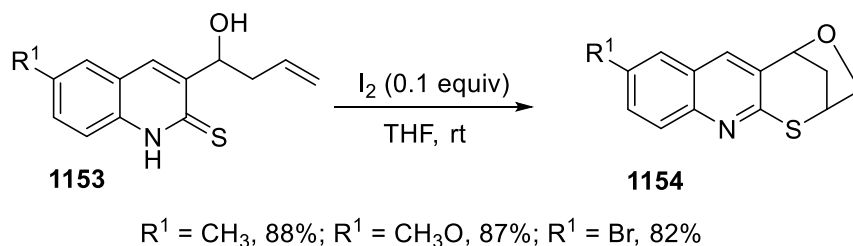
2.3.7. 2-Imino-4,5-dihydro-1,3-thiazoles and 1,3-thiazinan-2-imines from thioureas.

Also the thiocarbonyl group of thioureas was effective as a nucleophile in cyclizations mediated by haliranium ions. In fact, the thiourea **1155** reacted with iodine, leading to a good yield to the corresponding 5-iodomethyl-4,5-dihydro-1,3-thiazole **1156** [501].
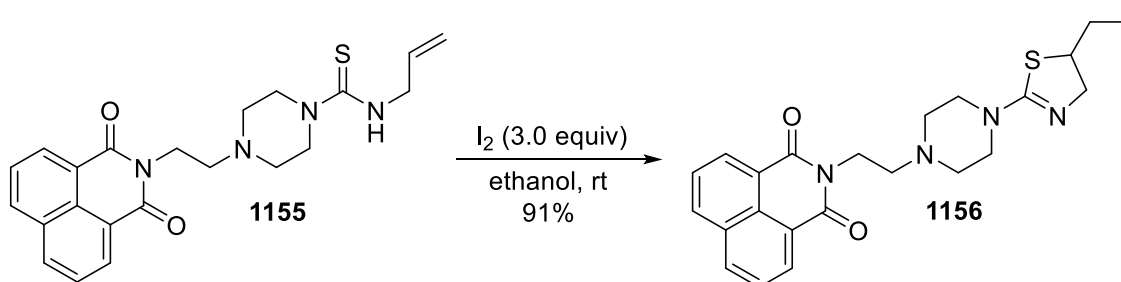
The cyclization of N-allyl thioureas **1157** was also performed using bromine, and the corresponding N,N-disubstituted 5-(bromomethyl)-4,5-dihydrothiazol-2-amine hydrobromides **1158** were isolated in good yield [502].

R^1 = R^2 = H, 86%; R^1 = H, R^2 = C$_6$H$_5$CH$_2$, 87%; R^1 = H, R^2 = C$_6$H$_5$, 86%
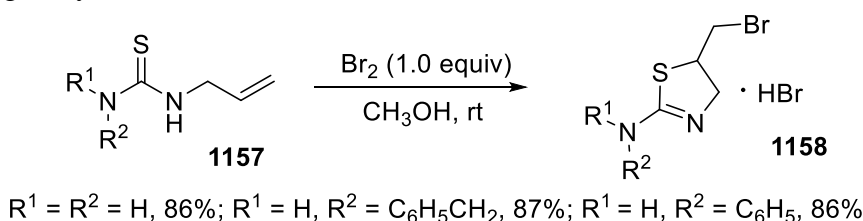
Moreover, when the reaction product arising from 1159 was treated in a basic medium, the neutral 5-(bromomethyl)-N-(pyridin-2-yl)-4,5-dihydrothiazol-2-amine 1160 was isolated in good yield [503].
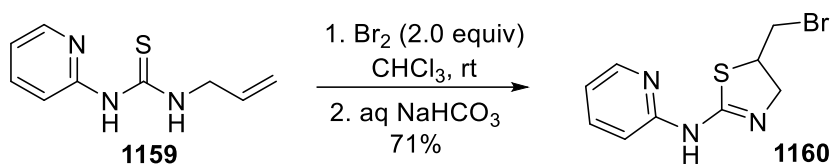
Eventually, N-acyl 5-(bromomethyl)-4,5-dihydrothiazol-2-amines 1161 were prepared in good yield by reaction of N-allyl thioureas 1162 with NBS [504].

R^1 = C_6H_5, 73%; R^1 = 3-Cl-C_6H_4, 77%; R^1 = 4-NO_2-C_6H_4, 74%
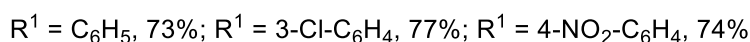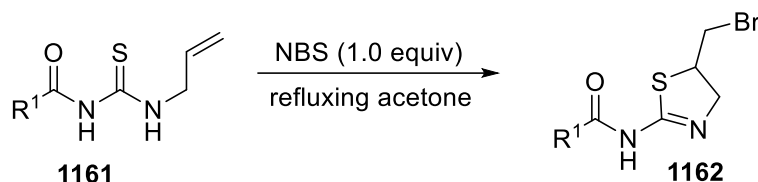
However, when the cyclization was performed starting from the allyl derivative 1163, the expected 5-iodomethyl-4,5-dihydro-1,3-thiazole was not formed since the double bond conjugated with the aromatic ring, and 2-(bromomethyl)-2,3-dihydro-5H-thiazolo[2,3-b]quinazolin-5-one 1164 was exclusively recovered in moderate yield after basic treatment [504].
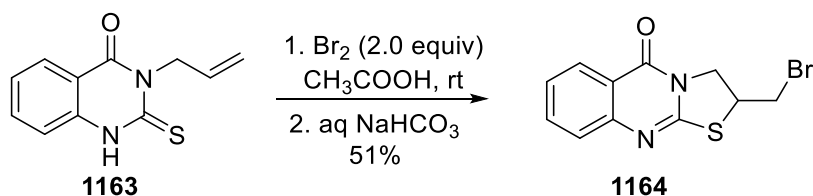
The same behavior was observed when 3-allyl-5-ethyl-6-methyl-2-thioxo-2,3-dihydropyrimidin-4(1H)-one 1165 underwent cyclization with iodine to give the bicyclic salt 6-ethyl-2-(iodomethyl)-7-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidin-8-ium triio-dide 1166 in good yield [505].
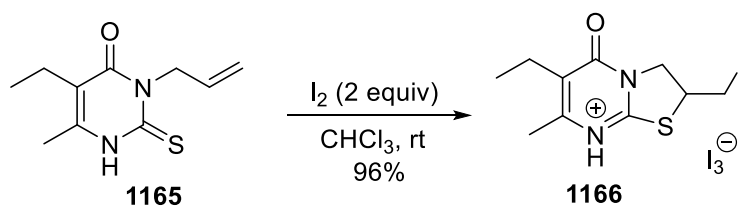
Moreover, the 4-allyl-5-aryl-2,4-dihydro-3H-1,2,4-triazole-3-thiones 1167 reacted with bromine to give salts that after basic treatment were converted in good yield and with total regioselection into the bicyclic 6-(bromomethyl)-3-aryl-5,6-dihydrothiazolo[2,3-c][1,2,4]triazoles 1168 [506].

R^1 = C_6H_5, R^2 = H, 79%; R^1 = C_6H_5, R^2 = CH_3, 68%;
R^1 = 4-Br-C_6H_4, R^2 = CH_3, 74%
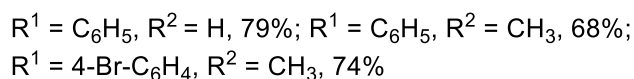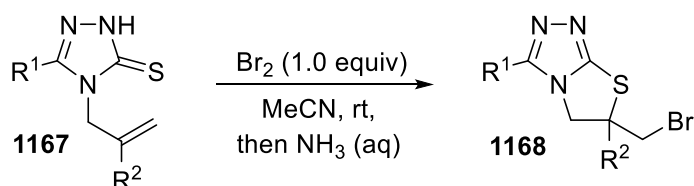
For 4-allyl-5-amino-2,4-dihydro-3H-1,2,4-triazole-3-thiones 1169, the cyclization proceeded in good yield with total regioselection, leading to the corresponding 3-amino-6-(bromomethyl)-5,6-

dihydrothiazolo[2,3-c][1,2,4]triazol-2-ium bromides 1170, with a preferential attack of the sulfur nucleophile with respect to the nitrogen [507].

R^1 = H, 78%; R^1 = CH$_3$, 68%
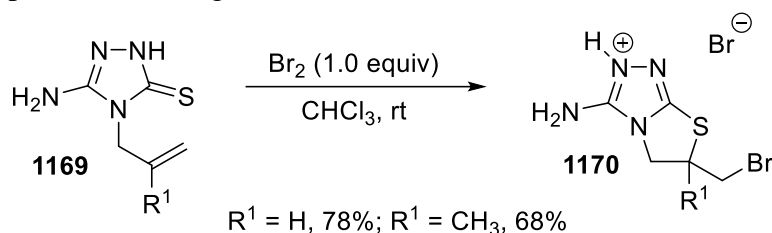
Eventually, the cyclization involving the allyl group at the C-4 of the β-lactam ring in the thioureas 1171, carried out with iodine, proceeded in a 6-exo-mode to afford the 2-imino-3-thia-1-azabicyclo[4.2.0]octan-8-one derivatives 1172 in good yield and total stereoselection [508].

R^1 = C$_6$H$_5$, 76%; R^1 = 4-CH$_3$-C$_6$H$_4$, 75%;
R^1 = 4-Cl-C$_6$H$_4$, 79%; R^1 = 4-CH$_3$O-C$_6$H$_4$, 85%
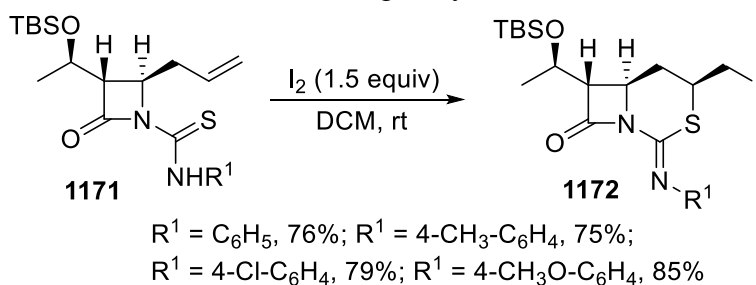
On the contrary, changing an allene group for an allyl group, the regioselection was missing, and starting from derivatives 1173, mixtures of cyclization products 1174 and 1175 were obtained, arising from either 5-exo-mode and 7-endo-mode closures, respectively [509].

R^1 = CH$_3$, R^2 = C$_6$H$_5$,   36%   36%;
R^1 = CH$_3$, R^2 = 4-Cl-C$_6$H$_4$,   18%   54%;
R^1 = C$_2$H$_5$, R^2 = 3-Cl-C$_6$H$_4$,   14%   75%
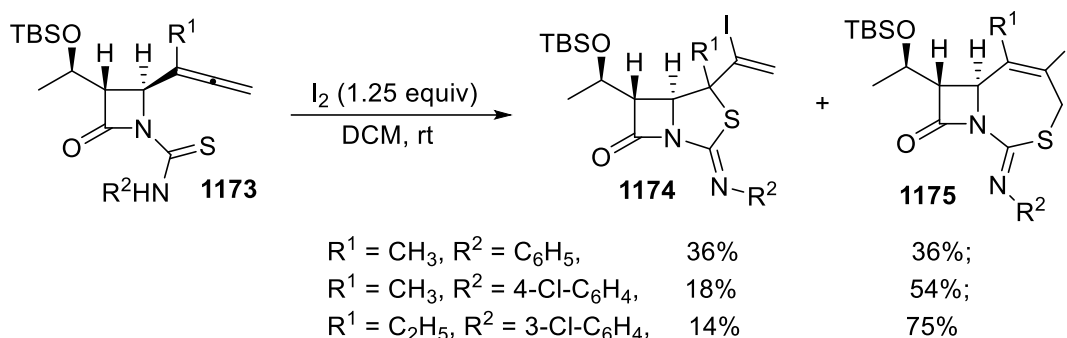
3. Intramolecular attack of nucleophiles to halirenium ions

The halocyclization of alkynes is an efficient tool leading to significant heterocyclic compounds under very mild reaction conditions and exhibits a very broad scope in terms of functional group/substituent compatibility [65, 510-513]. Since the introduced halide atom allows further elaboration mainly through palladium-catalyzed transformations, the halocyclization products are ideal substrates for further functionalization and increased molecular diversity [514-516].

3.1. O-C(sp^2) bond formation by an attack of oxygen nucleophiles.

3.1.1. Enollactones from carboxylic acids, esters, and amides.

Acetylenic substrates bearing an appropriately placed carboxy or ester group were converted by halocyclization into the corresponding enol lactones bearing a halovinyl moiety. The methodology usually exploited a variety of reagents able to generate the intermediate halirenium ion, which then underwent attack according to either *exo-* or *endo-*modes depending on the molecule geometry and electronic factors. In contrast, the introduced vinylic halogen was suitable for subsequent coupling

reactions, mainly mediated by palladium, in order to synthesize more complex heterocyclic structures [517-521].

3.1.1.1. Without asymmetric induction.

When the carboxy group and the alkynyl chain were substituents of the same carbon atom, the cyclization led to furan-2(3H)-ones, according to a 5-endo-dig mode. Thus, starting from compound 1176, the spiro enollactones 1177 were isolated in high to moderate yield, and bromine resulted in less effective than NIS for the generation of halenium ions [522].

A: X = I, 95%; **B**: X = Br, 66%
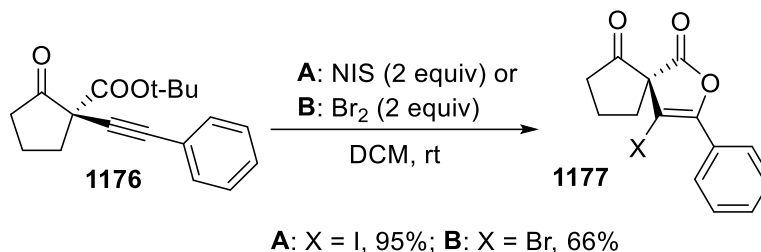
On the other hand, when both the carboxy and the alkynyl group were placed on vicinal carbon atoms, the cyclization proceeded in a 6-endo-mode, leading to 3,4-dihydropyran-2-ones. Thus, by reaction with NBS, the carboxylic acids 1178 afforded the corresponding 3,4-dihydro-2H-pyran-2-ones 1179 in good yield and total regioselection, directed by electronic factors [523].

$R^1 = R^2 = CH_3$, 75%; $R^1, R^2 = -(CH_2)_4-$, 94%; $R^1 = CH_3$, $R^2 = H$, 76%
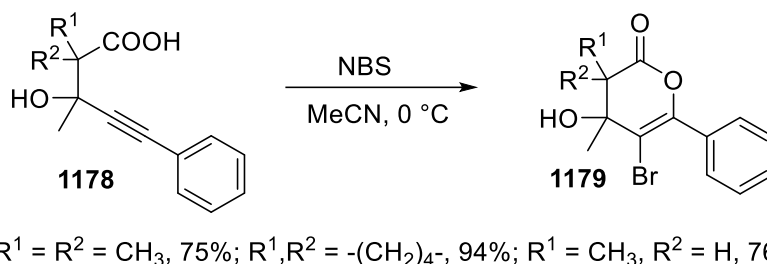
When the vicinal carbon atoms behave to an aromatic or a heterocyclic ring, the cyclization leads to fused heterocyclic compounds, and the acids 1180 and 1182 were converted in good yield to the corresponding 4-iodo-7H-thieno[2,3-c]pyran-7-ones 1181 and 5-iodo-8H-pyrano[3,4-b]pyridin-8-ones 1183, respectively [524].

$R^1 = C_6H_5$, 75%; $R^1 = 4-CH_3-C_6H_4$, 73%; $R^1 = 1$-cyclohexen-1-yl, 91%

$R^1 = C_6H_5$, 70%; $R^1 = 4-CH_3-C_6H_4$, 66%; $R^1 = C_6H_5CH_2CH_2$, 91%
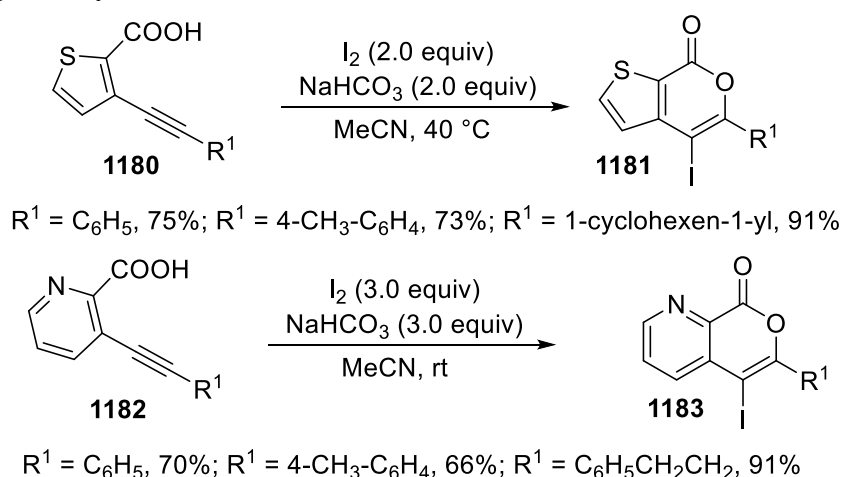
With a little modification of this methodology, the cyclization was carried out in the presence of copper(II) bromide, and compound 1184 gave the tricyclic 9-bromo-8-phenyl-6H-pyrano[4',3':4,5]thieno[3,2-b]pyridin-6-one 1185 in good yield [525].
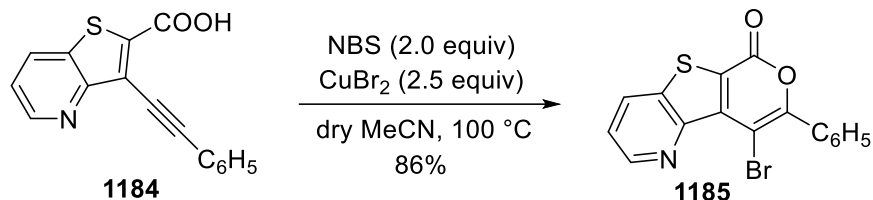
It is worth mentioning, however, that the cyclization of substrates 1186 occurred regioselectively, according to a divergent 5-exo mode or a 6-endo mode, depending on the ionic liquid employed as a solvent. Thus, using iodine in order to generate the iodirenium intermediate, isobenzofuran-1(3H)-ones 1187 or 1H-isochromen-1-ones 1188 were exclusively obtained in good yield, the former ones with total (E)-stereoselection [526].
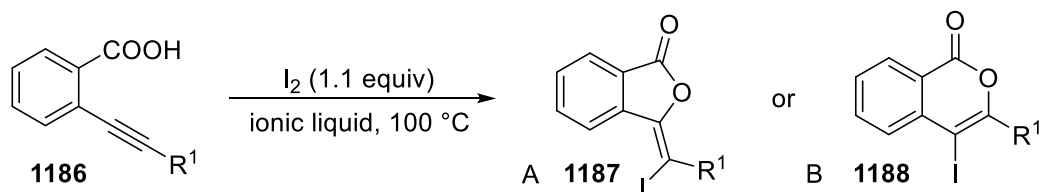
R^1 = t-C_4H_9, BmimN(CN)$_2$, A, 77%; R^1 = C_6H_5, EmimEtSO$_4$, B, 80%:
R^1 = 3-thienyl, Mor$_{1,2}$N(CN)$_2$, A, 75%; R^1 = 3-thienyl, EmimEtSO$_4$, B, 91%

On the other hand, when the carboxy group and the triple bond were separated by three atoms, as it occurred in carboxylic acids 1189, the reaction proceeded with total regioselection in a 6-exo-dig mode to give the corresponding iodomethylene-[1,4]-oxazino[4,3-a]indol-1-ones 1190 in good yield and total stereoselection, the (E)-isomer being exclusively isolated from the reaction mixture [527].
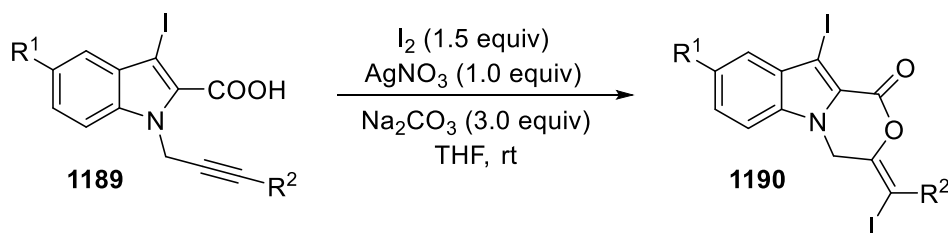
R^1 = R^2 = H, 86%; R^1 = OCH$_3$, R^2 = H, 92%, R^1 = F, R^2 = H, 80%;
R^1 = H, R^2 = CH$_3$, 79%; R^1 = H, R^2 = C_6H_5, 87%

The cyclization of (2-alkynyl)quinoline-3-carbaldehydes 1191 was carried out using excess iodine. At first, the aldehyde group was oxidized to the carboxylate, which eventually underwent cyclization according to a 6-endo-mode, and eventually, 4-iodo-1H-pyrano[4,3-b]quinolin-1-ones 1192 were obtained in good yield [528].
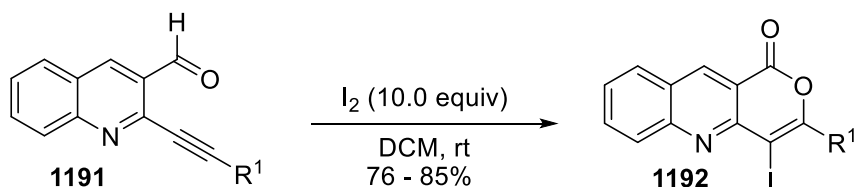
R^1 = C_6H_5; R^1 = 4-CH$_3$-C_6H_4; R^1 = n-C_4H_9; R^1 = cyclohexyl

On the other hand, when nucleophilic methanol was added to the reaction mixture in the presence of a base, (2-alkynyl)quinoline-3-carbaldehydes 1193 provided the corresponding 4-iodo-1-methoxy-1H-pyrano[4,3-b]quinolines 1194 in high yield [527].

$R^1 = C_6H_5$; $R^1 = 4\text{-}CH_3O\text{-}C_6H_4$
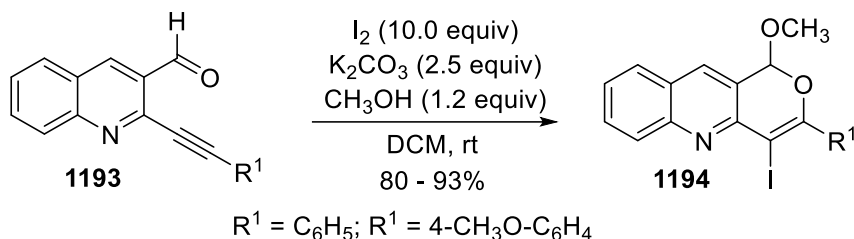
Besides the carboxy group, an ester group was also employed as the nucleophile, and the iodocyclization involving the esters 1195 led regioselectively to the corresponding tricyclic pyranones 1196 in moderate to good yield [529].
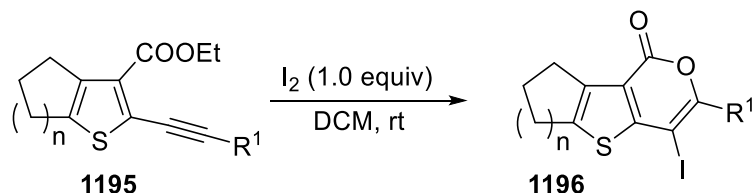
n = 1, $R^1 = C_6H_5$, 72%; n = 2, $R^1 = C_6H_5$, 80%; n = 2, $R^1 = 4\text{-}CH_3\text{-}C_6H_4$, 66%

In addition, when the reaction was carried out starting from the esters 1197, the pyrano[4,3-b]pyran-5(4H) ones 1198 were also obtained in excellent yield [530].
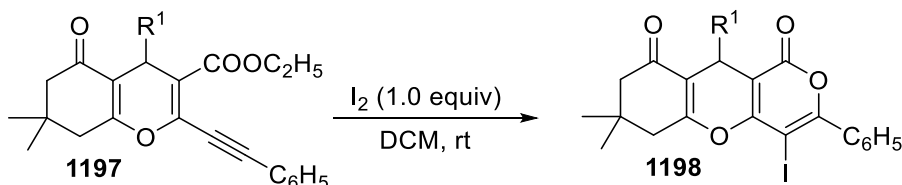
$R^1 = 3\text{-}HO\text{-}C_6H_4$, 93%; $R^1 = 4\text{-}CH_3O\text{-}C_6H_4$, 97%; $R^1 = 4\text{-}F\text{-}C_6H_4$, 88%; $R^1 = CH_3CH_2$, 85%

Within a novel synthesis of pyrazolopyrimidines, the esters 1199 underwent cyclization on treatment with excess iodine to give 10H-pyrano[4',3':3,4]pyrazolo[1,5-a]pyrimidin-10-ones 1200 in excellent yield [531].
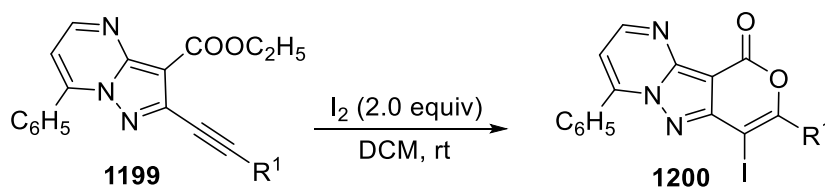
$R^1 = n\text{-}C_5H_{11}$, 92%; $R^1 = C_6H_5$, 92%; $R^1 = 1\text{-}cyclohexen\text{-}1\text{-}yl$, 93%

An effective cyclization mediated by NIS proceeding via a 6-endo-dig mode was also reported for alkynyl compounds 1201, and azulene-substituted 4-iodoisocoumarin derivatives 1202 were isolated in moderate yield [532-534].

$R^1 = R^2 = H$, 36%; $R^1 = 5\text{-}[(CH_3)_2CH]$, $R^2 = H$, 46%;
$R^1 = H$, $R^2 = 6\text{-}[(CH_3)_2CH]$, 57%
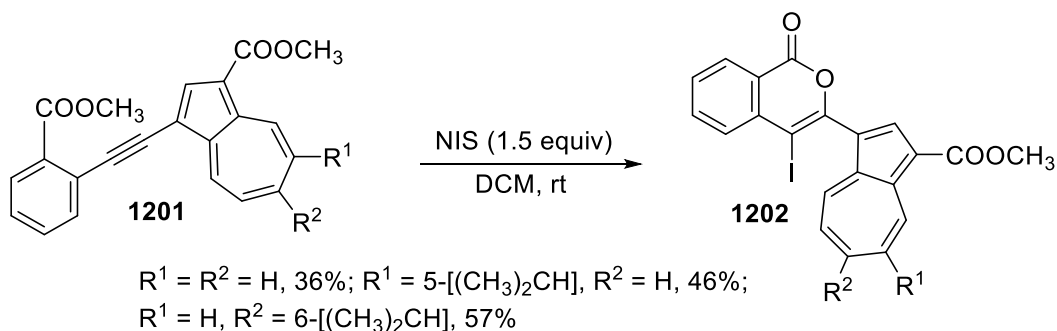
Besides halosuccinimides and iodine, other sources of halenium ions were used in order to generate a halirenium ion. In fact, the oxidation of iodide ion to iodine carried out with Oxone®, allowed to obtain good yield pyranones 1204 starting from esters 1203 [535].
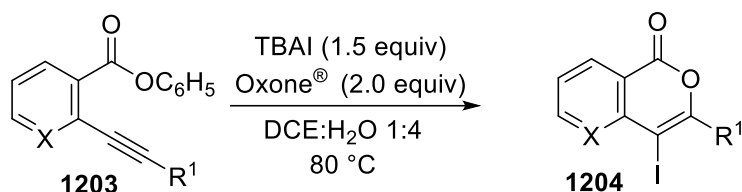
$R^1 = C_6H_5$, X = CH, 88%; $R^1 = C_6H_5$, X = N, 64%;
R^1 = 1-naphthyl, X = CH, 75%; $R^1 = n\text{-}C_4H_9$, X = CH, 69%

Also, ICl proved to be a good reagent to perform the iodocyclization of esters, and 2H-pyran-2-ones **1206** were prepared in good yield starting from enynes **1205** using ethanol as an environmentally benign solvent [536].
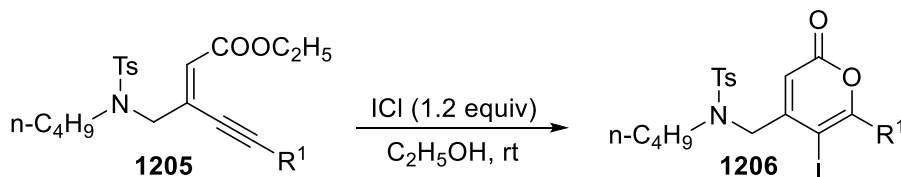
$R^1 = C_6H_5$, 85%; $R^1 = 4\text{-}C_2H_5\text{-}C_6H_4$, 70%; $R^1 = n\text{-}C_4H_9$, 75%

N-Chlorosuccinimide (NCS) together with a catalytic amount of trimethylsilyl chloride, allowed chlorocyclization of 2-alkynylbenzoates **1207**. Thus, 4-chloroisocoumarins **1208**, potent irreversible inhibitors of serine proteases and esterases, were prepared in good yield and total regioselection [537], whereas an alternative methodology exploited PhICl$_2$ as a source of chlorenium ions [531, 533, 538].
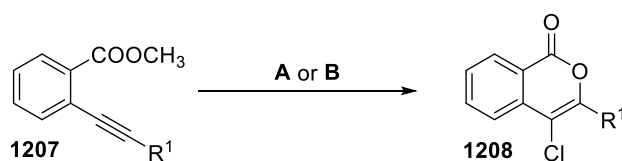
A. NCS (1.2 equiv), TMSCl (10 mol %), MeCN, 0 °C. $R^1 = C_6H_5$, 93%; $R^1 = 2\text{-}CH_3\text{-}C_6H_4$, 89%;
$R^1 = 4\text{-}Cl\text{-}C_6H_4$, 89%; $R^1 = 3\text{-}Cl\text{-}C_6H_4$, 99%; $R^1 = 2\text{-}Cl\text{-}C_6H_4$, 73%
B. PhICl$_2$ (1.2 equiv), MeCN, 70 °C. $R^1 = C_6H_5$, 70%; $R^1 = 4\text{-}CH_3O\text{-}C_6H_4$, 90%;
$R^1 = 4\text{-}CH_3\text{-}C_6H_4$, 93%; $R^1 = 4\text{-}Cl\text{-}C_6H_4$, 79%; R^1 = cyclopropyl, 55%

Moreover, through a 6-endo-dig cyclization, the ester **1209** afforded the 4-iodo-1H-benzo[4,5]thieno[2,3-c]pyran-1-one **1210** an excellent yield, although the reaction required a higher temperature owing to the electron-withdrawing effect of bromine atom [539].
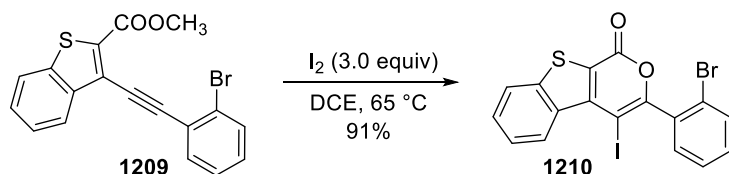
3-Iodofuro[2,3-b]chromones **1212** were obtained in moderate to good yield by iodocyclization 3-alkynyl-4-methoxycoumarins **1211**. The process involved nucleophilic attack to the iodirenium ion by the coumarin carbonyl oxygen atom to make intermediates unstable under the reaction conditions, eventually eliminating methyl iodide, leading to the furan ring [540].
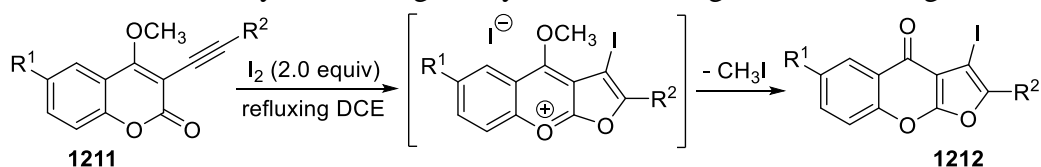
R^1 = H, $R^2 = C_6H_5$, 85%; R^1 = H, $R^2 = 4\text{-}CH_3O\text{-}C_6H_4$, 92%;
R^1 = Cl, $R^2 = C_6H_5$, 88%; R^1 = H, $R^2 = n\text{-}C_4H_9$, 60%

Eventually, exploiting the intermediate 1213 that was not isolated, the substituted 3-iodo-4H,5H-pyrano[2,3-b]chromen-5-one 1214 was obtained in moderate yield through a 6-endo-dig cyclization [541].
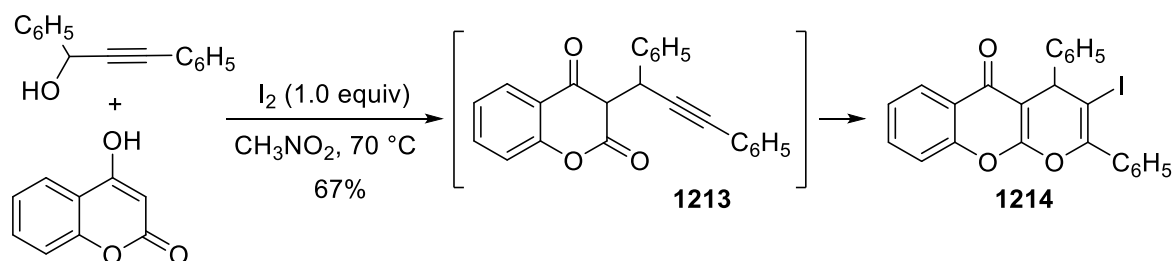
3.1.1.2. With external asymmetric induction.

The desymmetrization reaction of homodisubstituted carboxylic acids 1215 was carried out with NBS in the presence of the chiral catalyst (DHQD)2PHAL 144, to give to the chiral enol lactones 1216 in good yield and moderate to good enantioselection [542]. Similar results were observed using catalyst 1217 instead of catalyst 144 [543].
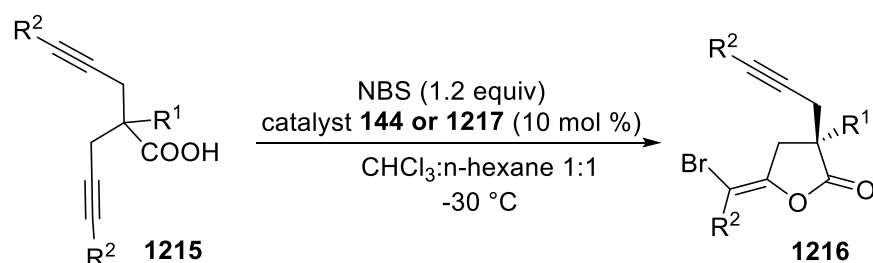
catalyst 144: R^1 = COOCH$_3$, R^2 = H, 79%, 72% e.e.; R^1 = COOCH$_3$, R^2 = CH$_3$, 91%, 90% e.e.;
R^1 = C$_6$H$_5$, R^2 = H, 90%, 70% e.e.; R^1 = C$_6$H$_5$, R^2 = 4-Cl-C$_6$H$_4$, 92%, 92% e.e.
catalyst 1217: R^1 = 4-F-C$_6$H$_4$, R^2 = H, 96%, 86% e.e.; R^1 = C$_6$H$_5$, R^2 = H, 99%, 88% e.e.;
R^1 = C$_6$H$_5$, R^2 = CH$_3$, 99%, 90% e.e.; R^1 = C$_6$H$_5$, R^2 = 4-Cl-C$_6$H$_4$, 82%, 70% e.e.
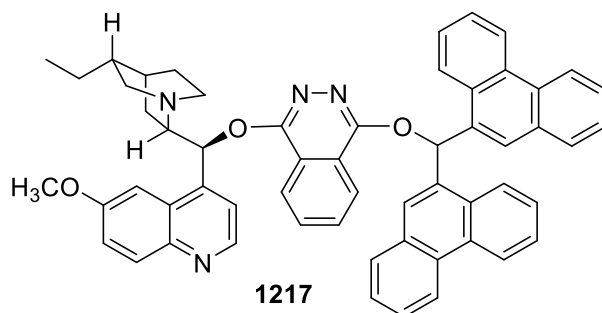
Furthermore, the cyclization of alkynoic acids 1215 leading to enol lactones 1218, carried out in the presence of catalyst 144, proceeded with similar yields but with lower enantioselection when NIS was used in place of NBS [544].
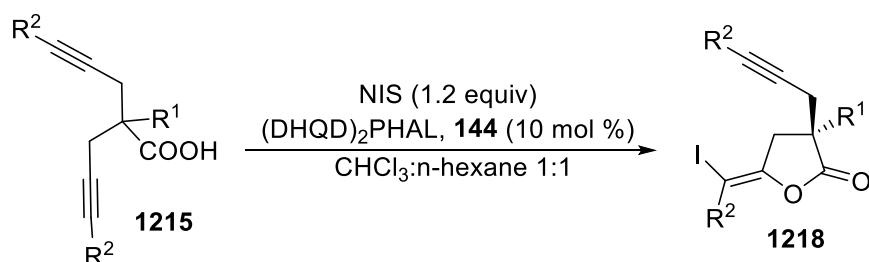
R^1 = COOCH$_3$, R^2 = H, 71%, 48% e.e.; R^1 = C$_6$H$_5$, R^2 = H, 88%, 58% e.e.;
R^1 = C$_6$H$_5$, R^2 = CH$_3$, 99%, 80% e.e.; R^1 = C$_6$H$_5$, R^2 = 4-Cl-C$_6$H$_4$, 82%, 82% e.e.

3.1.2. 4,5-Dihydro-1,3-oxazoles and imidazoles, benzo-1,3-oxazines, 1(3*H*)-iminobenzofurans and 1,3-oxazin-2-ones from amides, carbamates and ureas.

When an amidic nitrogen was substituted by a 2-alkynyl group, a 5-exo-dig cyclization occurred mediated by a halenium ion, and the resulting exocyclic double bond invariably displayed the (E)-configuration. Thus, when the amide 1219 was treated with [Py₂I]BF₄, the corresponding 5-iodoalkylidene-4,5-dihydro-1,3-oxazoles 1220 were obtained in good yield with total (E)-stereoselection [545-546].
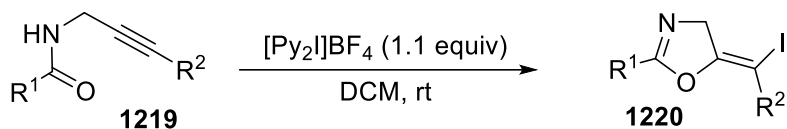
R^1 = adamantyl, R^2 = H, 65%; R^1 = (*E*)-CH=CH-C$_6$H$_5$, R^2 = H, 71%;
R^1 = R^2 = C$_6$H$_5$, 94%;

Moreover, when both nucleophilic ester and amide groups were present in the same molecule, as it occurred in compounds 1221, only 2,4-diaryl (E)-2-(oxazol-5(4H)-ylidene)-2-iodoethyl benzoates 1222 were isolated from the reaction proceeding with excellent regio- and stereoselection, the double bond displaying the (E)-configuration, exclusively [547].
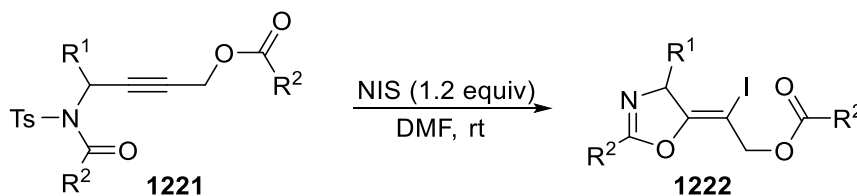
R^1 = R^2 = C$_6$H$_5$, 83%; R^1 = 2-F-C$_6$H$_4$, R^2 = C$_6$H$_5$, 83%; R^1 = 2-naphthyl, R^2 = C$_6$H$_5$, 83%

However, starting from N-propargyl amides 1223, the cyclization mediated by a combination of iodine, iodosylbenzene, and trimethylsilyl trifluoromethanesulfonate (TMSOTf), afforded the corresponding iodomethyl oxazoles 1225 in good yield via eventual oxidative aromatization of 5-(iodomethylene)-4,5-dihydrooxazole intermediates 1224 [548].
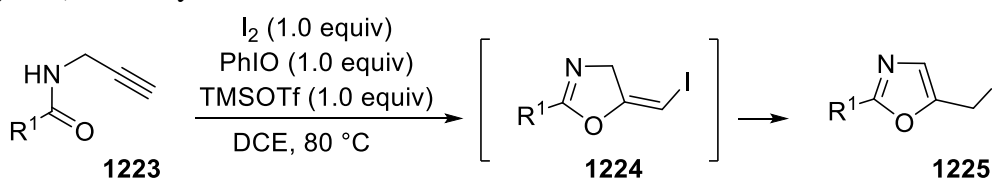
R^1 = C$_6$H$_5$, 71%; R^1 = 4-NO$_2$-C$_6$H$_4$, 71%; R^1 = 4-CH$_3$-C$_6$H$_4$, 65%

On the other hand, when the cyclization of amides 1226 was carried out under an oxygen atmosphere in the presence of a catalytic amount of iodine, the iodomethylene intermediates 1227 were cleaved exploiting visible light photocatalysis, and the corresponding aldehydes 1228 were isolated in excellent yield [549].
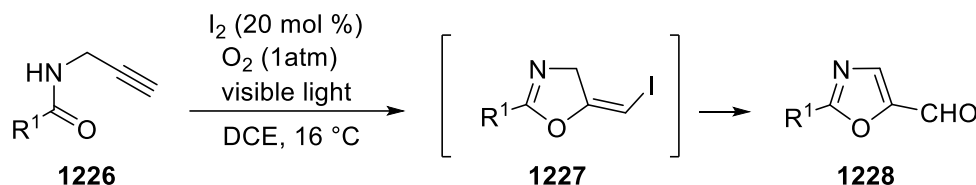
R^1 = C$_6$H$_5$, 90%; R^1 = 4-CH$_3$O-C$_6$H$_4$, 94%; R^1 = 4-CH$_3$-C$_6$H$_4$, 95%

A novel transformation involved N-tosyl propargyl amides 1229 that reacted with NIS in the presence of TMSN3. The intermediates 1230, obtained via 5-exo-dig closure, were subsequently attacked by the azido ion, eventually affording after the elimination of an N2 molecule to the 4,5-

dihydroimidazoles 1231 in low to good yield, depending on the electronic properties of the R1 substituent [550].

R^1 = C$_6$H$_5$, 80%; R^1 = 3-F-C$_6$H$_4$, 80%; R^1 = 4-CH$_3$O-C$_6$H$_4$, 38%; R^1 = CH$_3$, 36%
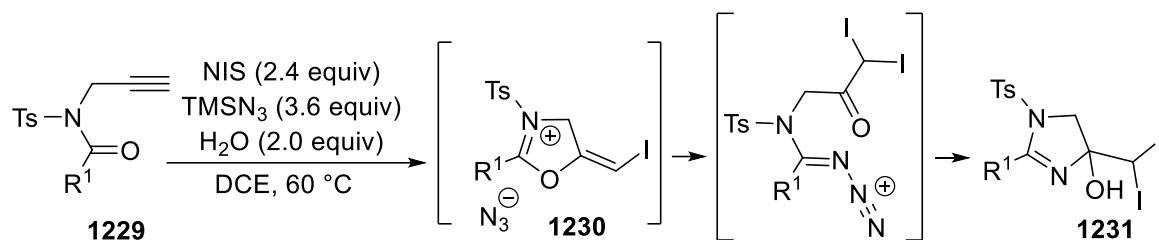
Cyclization occurring in a 6-exo-dig mode performed with excess iodine in basic medium allowed for convert in good yield of the amides 1232 into the 1,3-dihydrooxazines 1233 with total stereoselection, since the double bond displayed the (Z)-configuration, exclusively [551].

R^1 = R^2 = H, R^3 = C$_6$H$_5$, 96%; R^1 = H, R^3 = 4-Cl-C$_6$H$_4$, R^3 = n-C$_4$H$_9$, 65%;
R^1 = R^2 = 4-Cl-C$_6$H$_4$, R^3 = 4-F-C$_6$H$_4$, 83%; R^1 = CF$_3$, R^2 = R^3 = C$_6$H$_5$, 81%
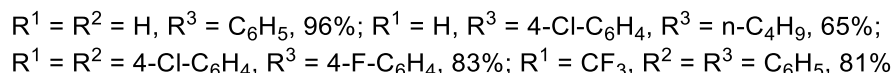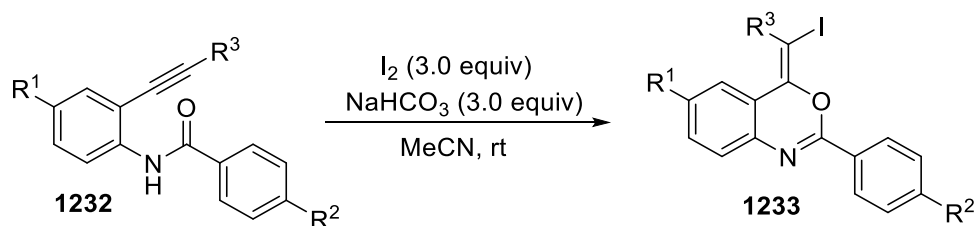
However, the reaction of amides 1234, carried out in the presence of a catalytic amount of iodine, afforded good yield and total (Z)-stereoselection dihydro-1,3-oxazines 1236, where the iodine atom was missing. In this case, iodine promoted the cyclization reaction, but it was regenerated since iodide anion favored its elimination from the cyclic intermediates 1235 [552].

R^1 = R^2 = R^3 = C$_6$H$_5$, 95%; R^1 = CF$_3$, R^2 = 4-F-C$_6$H$_4$, R^3 = C$_6$H$_5$, 88%;
R^1 = H, R^2 = C$_6$H$_5$, R^3 = 4-F-C$_6$H$_4$, 92%; R^1 = H, R^2 = 4-CF$_3$-C$_6$H$_4$, R^3 = 4-F-C$_6$H$_4$, 65%
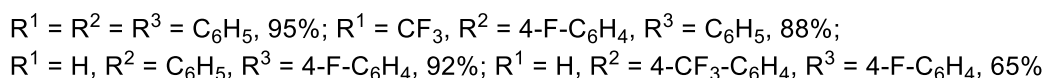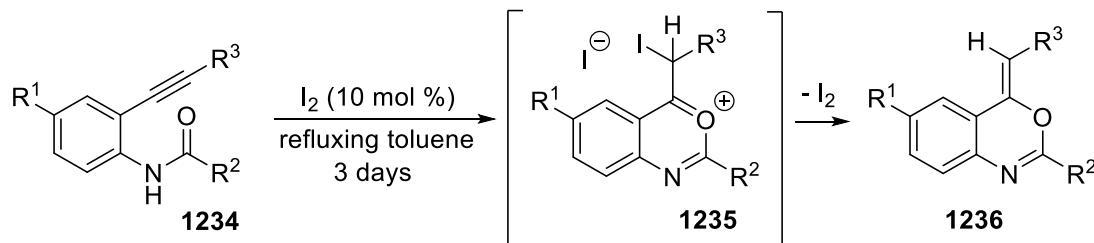
By cyclization mediated by iodine in basic medium 2-(1-alkynyl)amides 1237 afforded with moderate regioselection mixtures of imino derivatives 1238 and 1239, arising from both 5-exo-dig and 6-endo-dig closure modes, but the C=C double bond of compounds 1238 displayed the (E)-configuration, exclusively [553-555].

R^1 = R^2 = C$_6$H$_5$, 98%, 87:13; R^1 = CH$_3$, R^2 = C$_6$H$_5$, 80%, 89:11;
R^1 = C$_6$H$_5$, R^2 = 1-cyclohexen-1-yl, 69%, 23:77
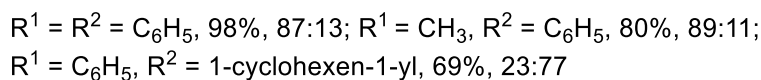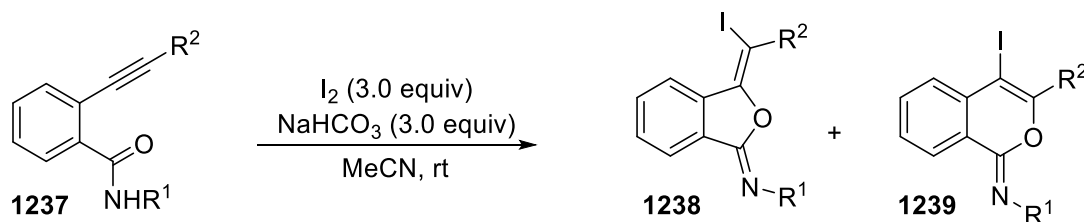
On the contrary, under the same conditions, amides 1240 cyclized with total regioselection, and imino derivatives 1241 having again (E)-configuration at the C=C double bond were exclusively isolated [553].
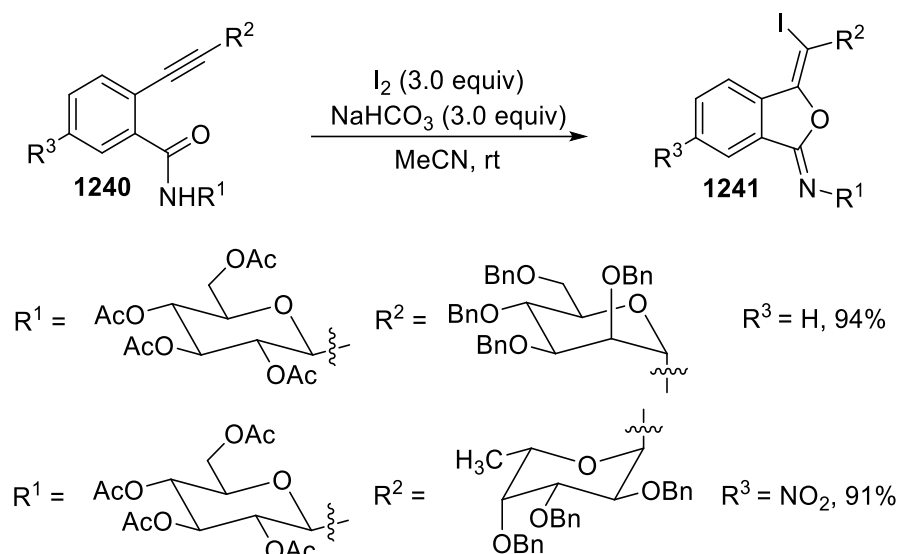
Accordingly, when iodide anion was oxidized to iodine by Oxone®, the cyclization of amides 1242, proceeding under basic conditions via 5-exo-dig mode exclusively, led first to the intermediate iminoderivatives 1243 that was eventually converted into the corresponding lactones 1244 displaying the (E)-configuration [556].

$R^1 = C_6H_5$, 70%; $R^1 = 4\text{-}CH_3\text{-}C_6H_4$, 73%; $R^1 = 2$-thienyl, 82%; $R^1 = t\text{-}C_4H_9$, 79%
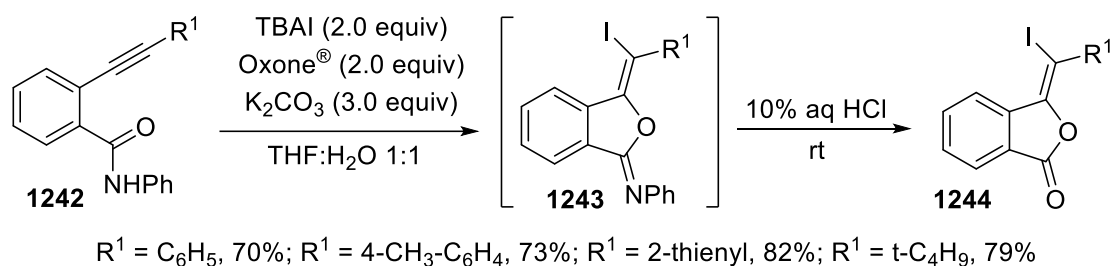
Besides the amido groups, oxycyclization to triple bonds involving halirenium ions also exploited the carbonyl group of carbamate and urea functionalities to give oxygen-containing heterocycles. In fact, the carbamate group was generated in situ starting from the amino group of compounds 1245, and reaction with carbon dioxide followed by NIS provided the oxazolidin-2-ones 1246 in good yield [231].

$R^1 = $ H, 88%; $R^1 = $ TMS, 74%
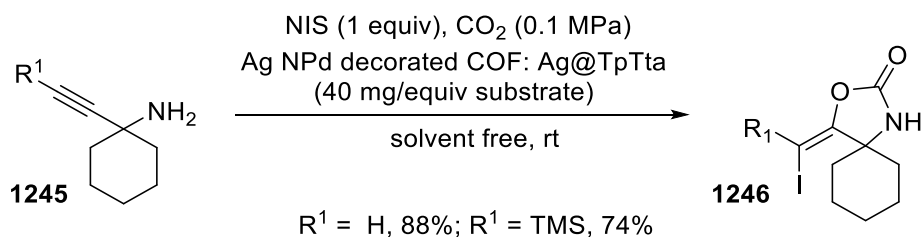
Using different sources for the generation of halirenium ions, the alkynyl carbamates 1247 underwent cyclization according to a 6-endo-dig mode to give the corresponding 5-halo-3,4-dihydro-2H-1,3-oxazin-2-ones 1248 with total regioselection, and the reaction mechanism was investigated also using computational methods [557].
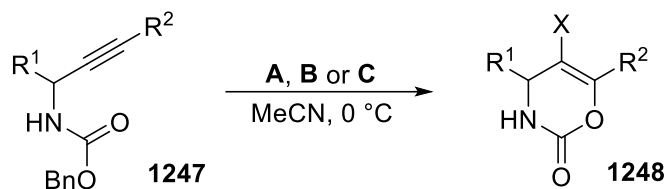
A: I$_2$ (2.0 equiv). X = I; R^1 = 4-CH$_3$-C$_6$H$_4$, R^2 = C$_6$H$_5$, 94%;
R^1 = C$_6$H$_5$, R^2 = 4-F-C$_6$H$_4$, 98%; R^1 = C$_6$H$_5$, R^2 = 2-thienyl, 98%
B: Br$_2$ (1.2 equiv).X = Br; R^1 = R^2 = C$_6$H$_5$, 93%;
R^1 = C$_6$H$_5$, R^2 = 4-F-C$_6$H$_4$, 86%; R^1 = C$_6$H$_5$, R^2 = 4-Cl-C$_6$H$_4$, 86%
C: Cl$_2$ (1.2 equiv). X = Cl; R^1 = R^2 = C$_6$H$_5$, 62%;
R^1 = C$_6$H$_5$, R^2 = 4-CH$_3$O-C$_6$H$_4$, 59%; R^1 = 4-CH$_3$-C$_6$H$_4$, R^2 = C$_6$H$_5$, 50%

When the cyclization of homopropargylic carbamates 1249 and 1251 bearing a silyl group on the triple bond was carried out by using I(coll)2PF6, the reaction proceeding in a 6-exo-dig mode led in moderate yield to 6-alkylidene-4,5-dihydro-1,3-oxazines 1250 and 1252, with total regioselection, owing to the directing effect of the substituent silyl group, whereas the double bond displayed (E)-configuration, exclusively [558].
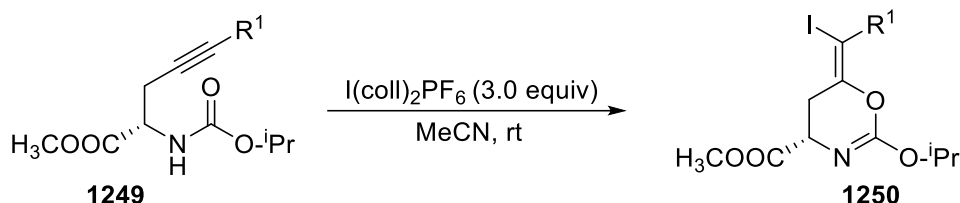
R^1 = (CH$_3$CH$_2$)$_3$Si, 73%; R^1 = (CH$_3$)$_3$Si, 64%; R^1 = [(CH$_3$)$_2$CH]$_3$Si, 60%
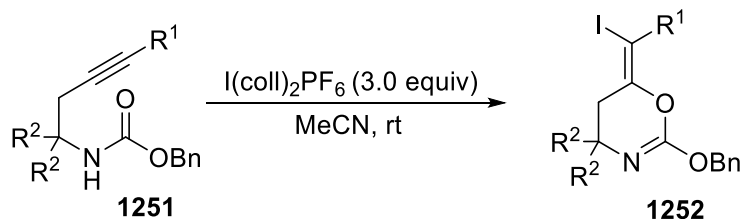
R^1 = (CH$_3$CH$_2$)$_3$Si, R^2 = H. 66%; R^1 = (CH$_3$CH$_2$)$_3$Si, R^2 = CH$_3$, 59%;
R^1 = (CH$_3$CH$_2$)$_3$Si, R^2...R^2 = (CH$_2$)$_4$, 62%

When alkynyl carbamates 1253 were treated with NIS in DCM under basic conditions, the corresponding 4-iodooxazolones 1254 were obtained in moderate to good yield through a 5-endo-dig cyclization [559].
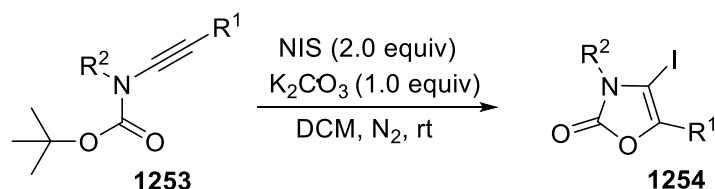
R^1 = R^2 = C$_6$H$_5$, 63%; R^1 = C$_6$H$_5$, R^2 = 3-Br-C$_6$H$_4$, 72%;
R^1 = C$_6$H$_5$, R^2 = 2-naphthyl, 53%

However, changing MeCN for DCM and in the presence of boron trifluoride, the process also involved the solvent, and via a 6-exo-dig closure, alkynyl carbamates 1255 led to 4-alkylidene-1-oxa-3,5-diazin-2-ones 1256 in good yield again with total (E)-stereoselection [559].
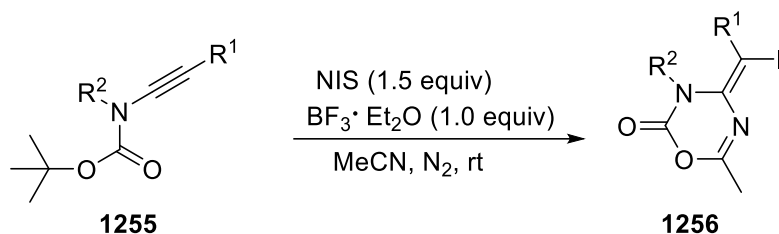
$R^1 = C_6H_5$, $R^2 = CH_2C_6H_5$, 82%; $R^1 = R^2 = C_6H_5$, 73%;
$R^1 = 4\text{-}CH_3O\text{-}C_6H_4$, $R^2 = CH_2C_6H_5$, 76%

An interesting cyclization induced by iodine involved the chiral carbamates 1259, obtained as intermediates starting from indolinones 1257 and alkynyl carbamates 1258 in the presence of catalyst 1260. Under natural light, a double cyclization occurred, the former one leading to an enolcarbamate functionality via a 6-endo dig mode and the latter one to a novel N-C bond via a 5-exo-trig mode, and tricyclic compounds 1261 were eventually isolated in moderate yield but with excellent enantioselection [428].
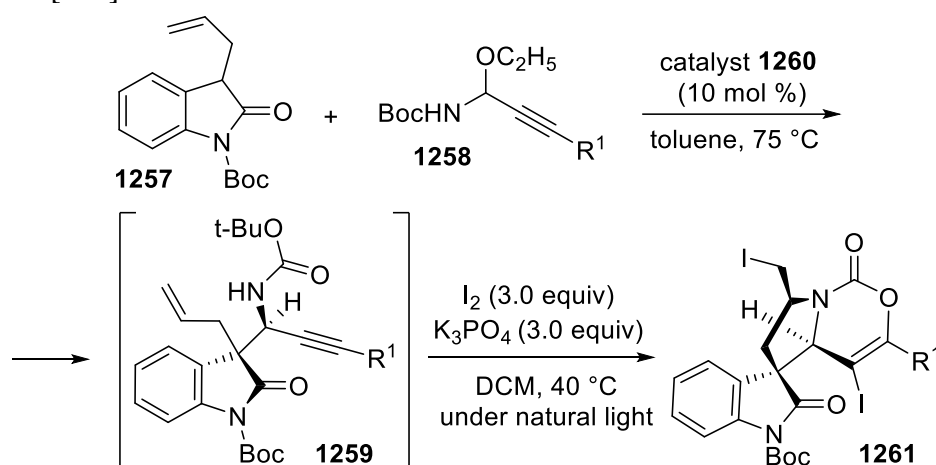
$R^1 = C_6H_5$, 65%, 90% e.e.; $R^1 = 4\text{-}CH_3\text{-}C_6H_4$, 63%, 95% e.e.;
$R^1 = 4\text{-}Br\text{-}C_6H_4$, 64%, 91% e.e.
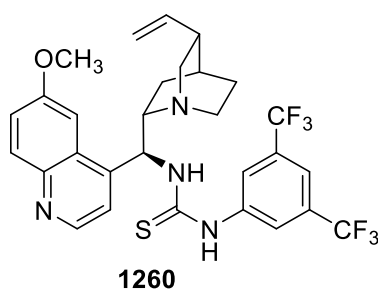
Also, the carbonyl group of ureas was effective for the oxyfunctionalization of triple bonds mediated by halirenium ions, leading to interesting and novel heterocyclic compounds. In fact, through a 5-exo ring closure, the cyclization of substituted ureas 1262, performed using iodine in basic medium, afforded in moderate yield with total regioselection of the corresponding 2-imino-5-arylidene derivatives 1263, exclusively, and the formed double bond displayed the (E)-configuration, exclusively [560].

1262 → **1263**
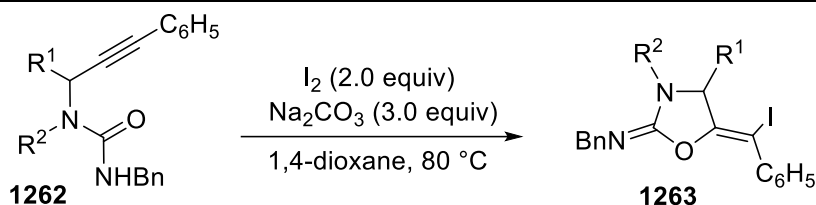
R^1 = 4-Cl-C_6H_4, R^2 = $C_6H_5CH_2$, 51%; R^1 = n-C_3H_7, R^2 = $C_5H_5CH_2$, 52%;
R^1 = 4-CH_3O-$C_6H_4CH_2$, R^2 = 4-CH_3-$C_6H_4CH_2$, 60%

Eventually, substituted ureas **1265** were obtained as intermediates by reaction of propargylamines **1264** with appropriate isocyanates, and subsequent cyclization performed with iodine gave the five-membered 2-imino-5-alkyliden derivatives **1266** in very good yield and total regio and stereoselection, the double bond having (E)-configuration [561].
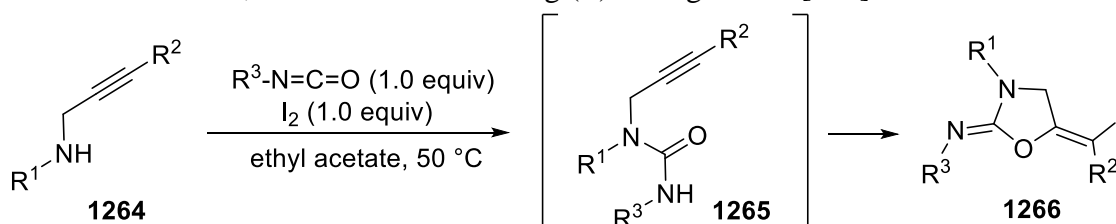
R^1 = CH_3, R^2 = H, R^3 = C_6H_5, 97%; R^1 = CH_3, R^2 = H, R^3 = 4-CH_3O-C_6H_4, 96%;
R^1 = R^2 = H, R^3 = 4-F-C_6H_4, 99%; R^1 = CH_3, R^2 = R^3 = C_6H_5, 83%

3.1.3. Dihydrofurans, dihydropyrans, and benzofurans from o-alkynyl phenols and anisols.

3.1.3.1. Dihydrofurans and 2-methylenetetrahydrofurans.

The functionalization of a triple bond mediated by nucleophilic hydroxy or alkoxy functionalities attacking in basic media a halirenium ion allowed to prepare unsaturated heterocyclic compounds containing an oxygen atom [562]. Depending on the number of carbon atoms present in the alkyl chain, dihydrofurans **1268** or dihydropyrans **1270** were obtained in good yield with total regioselection by cyclization of alkynols **1267** or **1269**, proceeding in a 5-endo or 6-endo-mode, respectively [563-564].

1267 n = 1
1269 n = 2

1268 n = 1
1270 n = 2
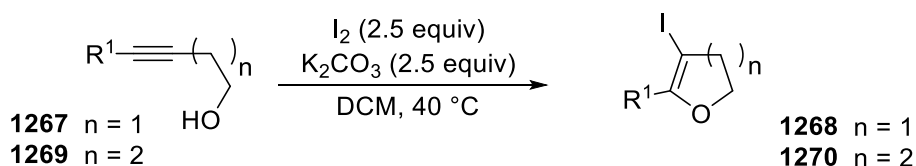
n = 1, R^1 = 4-CHO-C_6H_4, 70%; n = 1, R^1 = 3-CHO-C_6H_4, 73%;
n = 2, R^1 = 4-CHO-C_6H_4. 69%; n = 2, R^1 = 3-CHO-C_6H_4, 72%

Furthermore, in the presence of a strong base such as t-BuOK, the substrates **1271** underwent cyclization in good yield to give the corresponding dihydrofurans **1272** with total regioselection, since indoles, arising from a possible attack of the amino group, were not observed in the reaction mixture [565].
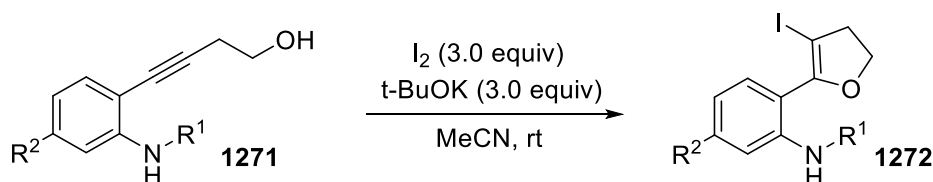
R^1 = $COOC_2H_5$, R^2 = H, 78%; R^1 = t-Boc, R^2 = H, 85%; R^1 = $COOC_2H_5$, R^2 = Cl, 71%

Moreover, without any reaction of the carbamate group, the total regio- and stereoselective cyclization of alkynol 1273, proceeding in a 5-exo-mode, led to a good yield to the chiral (Z)-5-iodomethylene tetrahydrofuran 1274, a key intermediate in the synthesis of omarigliptin, an inhibitor of dipeptidyl peptidase-4 (DPP-4) effective for the treatment of type 2 diabetes mellitus (T2DM) [566].
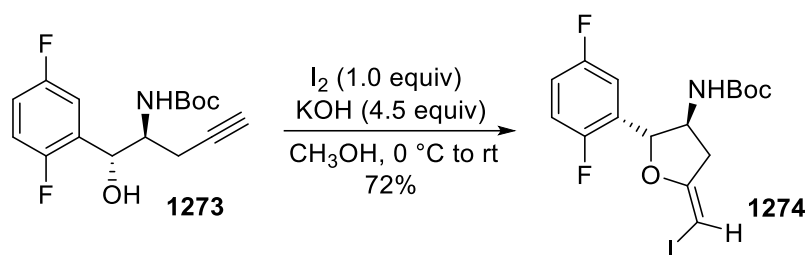
3.1.3.2. Isochromenes and 2-methylenetetrahydropyrans.

Isochromenes 1276 were regioselectively prepared to start from the alkynols 1275 via a 6-endo-dig cyclization exploiting iodine as iodirenium source in the presence of a base [567].
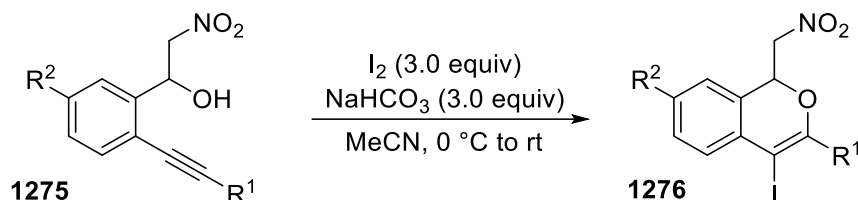
Again, the 6-endo-dig cyclization of 2-(1-alkynyl)benzylic alcohols 1277 or 2-(1-alkynyl)-3-(hydroxymethyl)pyridines 1279 led with total regioselection to the corresponding 4-iodo-1H-isochromenes 1278 or 8-iodo-5H-pyrano[4,3-b]pyridines 1280 in good yield [568].
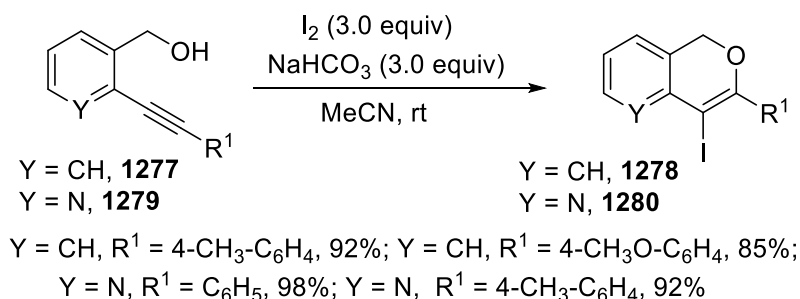
The 4-iodo-1H-isochromene 1282 was isolated in excellent yield starting from alcohol 1281, via a 6-endo-dig closure, and sulphenyl iodide stabilized on Zr(IV)-based metal-organic framework was used for the generation of an iodirenium ion [569].
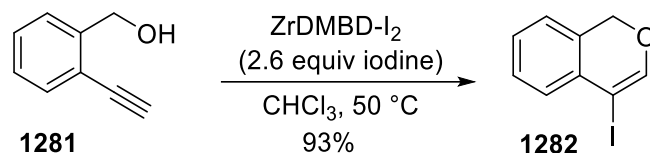
Cyclobutyl derivatives 1283 underwent a regio-divergent cyclization on changing the reaction conditions. In fact, when iodine was used in a basic medium, via cyclization proceeding in a 6-endo-dig mode, the cyclobutane-fused isochromenes 1284 were obtained in good yield and with high regioselection, aimed to minimize the angular strain, together with minor amounts of regioisomers 1285. On the contrary, starting from 1283a, NIS used together with the gold-based catalyst 1286 led to a reversal of regioselection, and the major product was the (E)-iodomethylenetetrahydrofuran 1285a, arising from a stereoselective 5-exo-dig cyclization [64].
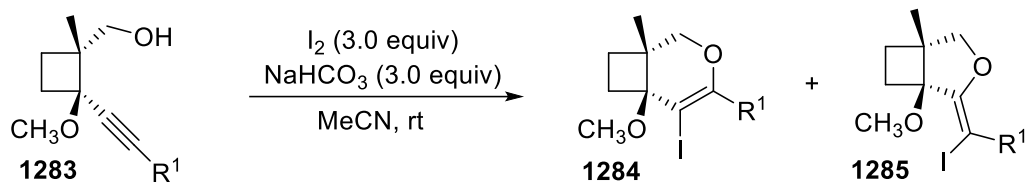
a. $R^1 = C_6H_5$, 77%, 93:7 ratio; **b.** $R^1 = 4\text{-}CH_3\text{-}C_6H_4$, 99%, >95:5 ratio;
c. $R^1 = 3\text{-thienyl}$, 83%, >95:5 ratio; **d.** $R^1 = 1\text{-cyclohexenyl}$, 51%, >95:5 ratio
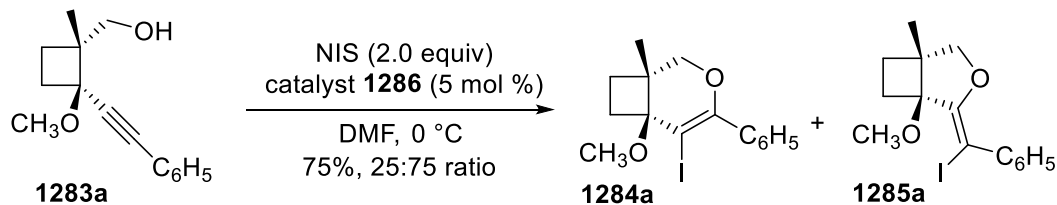
catalyst **1286** = JohnPhosAu-(MeCN)SbF$_6$

As evidenced from the preceding examples, the formation of a six-membered ring was preferred in order to avoid angular strain at the bicyclic product, although the five-membered ring formation could arise in the presence of strongly stabilizing electronic factors. In fact, when the triple bond was substituted by an electron-withdrawing group, the cyclization preferentially occurred in a 5-exo-dig mode, and mixtures of 4-iodo-1H-isochromenes 1288 and (Z)-1-(1-iodobenzylidene)-1,3-dihydroisobenzofurans 1289, displaying (Z)-configuration at the exocyclic double bond, were isolated starting from alcohols 1287 since the EWG group destabilized an incipient cation β to the aromatic ring [568].
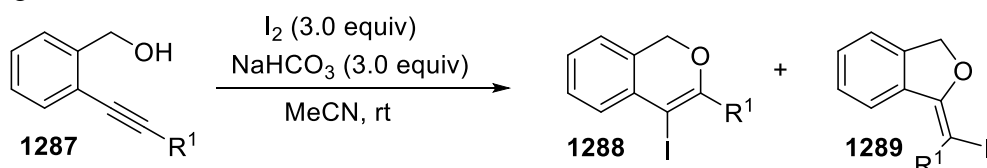
$R^1 = 4\text{-}NO_2\text{-}C_6H_4$, 88%, 25:75 ratio; $R^1 = 3,5\text{-di-}CF_3\text{-}C_6H_3$, 74%, 25:75 ratio

Chromene fused spirooxindoles 1291 were obtained in good yield by nucleophilic attack of a phenolic hydroxy group to an iodirenium intermediate, arising from the intermediate oxindoles 1290, and cyclization proceeded with total 6-endo selection, directed by electronic factors [570].
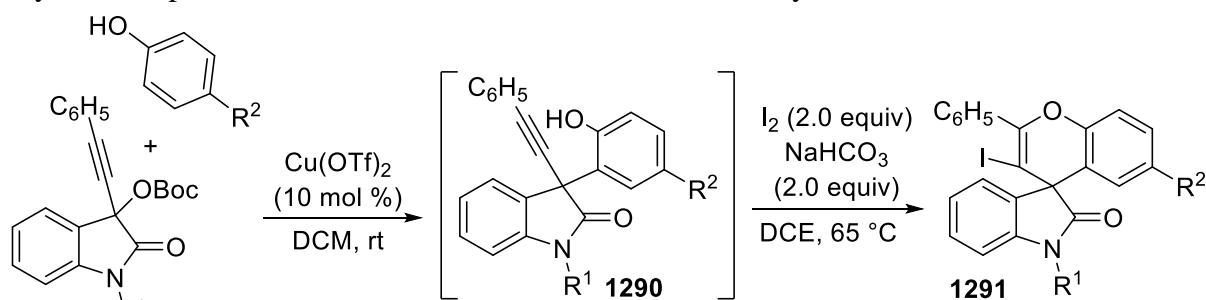
$R^1 = R^2 = CH_3$, 79%: $R^1 = CH_3$, $R^2 = CH_3O$, 84%; $R^1 = $ allyl, $R^2 = Br$, 69%

Starting from acetals 1292a,b, where the triple bond was substituted by an electron-withdrawing group, and using I(coll)2PF6 as a source of iodirenium ions, isochromenes 1293a and their analogs 5-iodo-1,2-dihydrobenzo[d]oxepines 1293b displaying a seven-membered ring were obtained in excellent yield again through 6-endo- or 7-endo-dig closures [571].

1292 → **1293**

I(coll)$_2$PF$_6$ (1.1 equiv)
DCM, rt

R^1 = -N(Ts)(CH$_3$)   **a.** n = 1, 100%;   **b.** n = 2, 94%

R^1 = -N(C=O)NCH$_3$ (benzimidazolone)   **a.** n = 1, 98%;   **b.** n = 2, 75%

R^1 = -N(pyrrolidinone)   **a.** n = 1, 87%;   **b.** n = 2, 76%
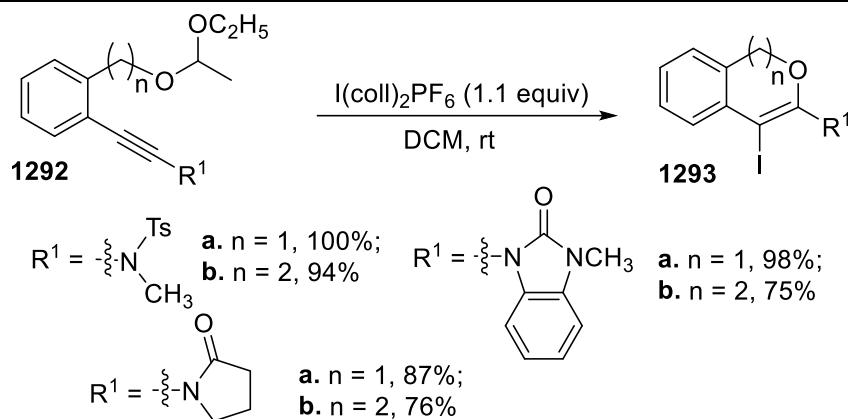
Also, a hemiacetal group was effective in intramolecularly attacking a halirenium ion obtained from a substituted triple bond, leading to a chromene. In fact, aldehydes 1294 underwent cyclization in the presence of alcohols to give the corresponding 4-iodo-1-alkoxy-1H-pyrano[4,3-b]quinolines 1295 in good yield through the formation of an intermediate hemiacetal [528],[572-573].

1294 → **1295**

R^{2}OH (1.2 equiv)
I$_2$ (2.5 equiv)
K$_2$CO$_3$ (2.5 equiv)
DCM, rt

R^1 = C$_6$H$_5$, R^2 = CH$_3$, 88%; R^1 = C$_6$H$_5$, R^2 = t-C$_4$H$_9$, 85%;
R^1 = 4-CH$_3$-C$_6$H$_4$, R^2 = CH$_3$, 93%; R^1 = n-C$_4$H$_9$, R^2 = CH$_3$, 85%;
R^1 = thiophen-3-yl, R^2 = CH$_3$, 86%
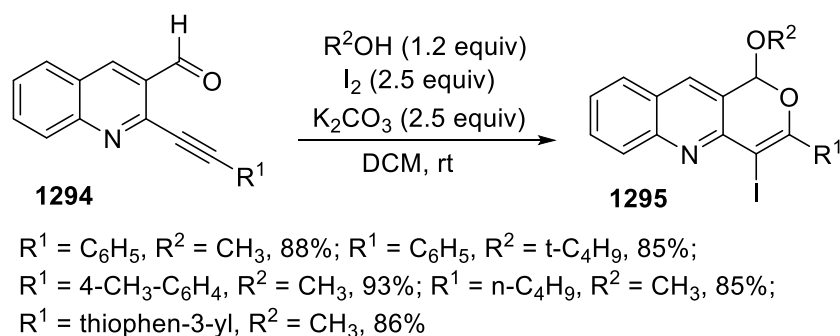
In addition, heterocyclic aldehydes 1296 bearing a triple bond substituted by a silyl group, after conversion into hemiacetals, underwent cyclization mediated by 1,3-diiodo-5,5-dimethylhydantoin (DIDMH) to give in excellent yield the corresponding 4-iodo-1-alkoxy-3-(trimethylsilyl)-1H-pyrano[4,3-b]quinolines 1297 [574].

1296 → **1297**

DIDMH (1.1 equiv)
R^{1}OH
H$_2$O, rt

R^1 = CH$_3$, 95%; R^1 = CH$_3$CH$_2$, 92%; R^1 = (CH$_3$)$_2$CH, 86%; R^1 = n-C$_4$H$_9$, 92%;
R^1 = t-C$_4$H$_9$, 91%; R^1 = cyclohexyl, 88%; R^1 = CH$_2$C$_6$H$_5$, 84%
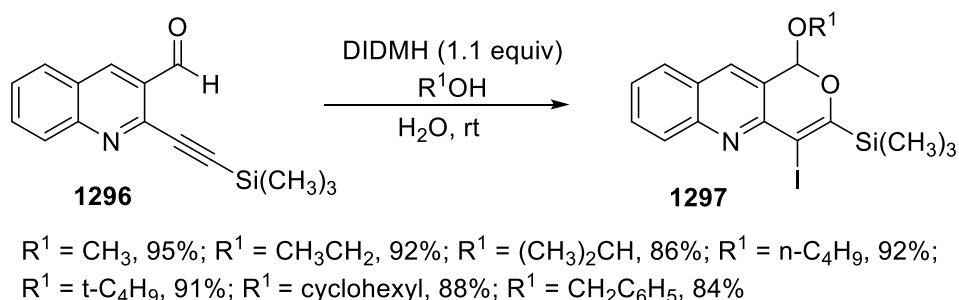
Eventually, the cyclization of the diol 1298, proceeding in a 6-exo-dig mode, led to good yield and stereoselection to the 2-iodomethylenetetrahydropyran 1299, displaying exclusively the (Z)-configuration at the double bond [575].

1298 → **1299**

NIS (1.3 equiv)
THF, rt
93%, Z:E 91:9
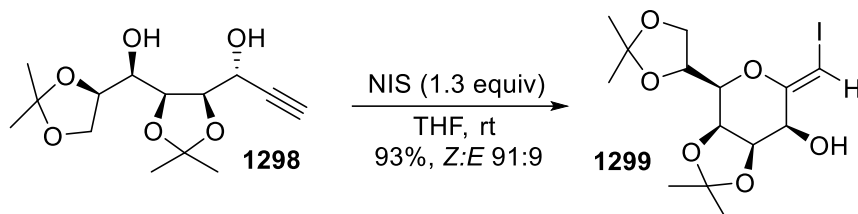
3.1.3.3. Benzofurans from o-alkynyl phenols and anisoles.

When the hydroxy phenolic groups and the alkynyl chain were placed on adjacent carbons of an aromatic ring, as it occurred for compounds 1300, 3-iodobenzofurans 1301 were obtained in

excellent yield via a 5-endo-dig cyclization, but an excess NIS and a Lewis base such as triphenylphosphine were required [576-578].

$R^1 = C_6H_5$, 96%; $R^1 = 4\text{-}CH_3O\text{-}C_6H_4$, 97%; $R^1 = t\text{-}C_4H_9$, 91%
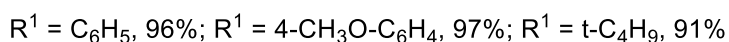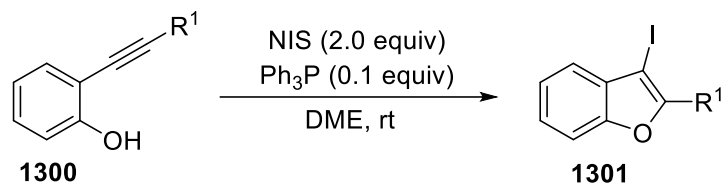
Also, methyl ethers of phenols (anisoles) were allowed to prepare 3-iodobenzofurans by cyclization involving an intermediate iodirenium ion. In fact, novel benzofuranyl benzimidazole derivatives 1303 were obtained in good yield when compounds 1302 underwent cyclization mediated by ICl [579].

$R^1 = C_6H_5$, 85%; $R^1 = 4\text{-}CH_3\text{-}C_6H_4$, 80%
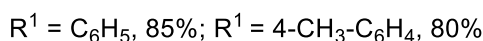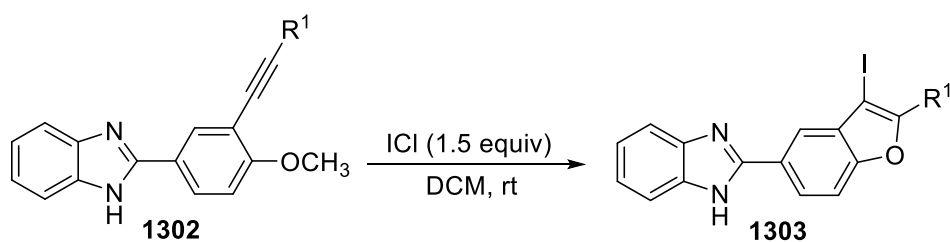
Again mediated by ICl, the cyclization of compound 1304 provided the 3-iodo-2-phenylfuro[2,3-b]quinoxaline 1305 in very good yield [580].
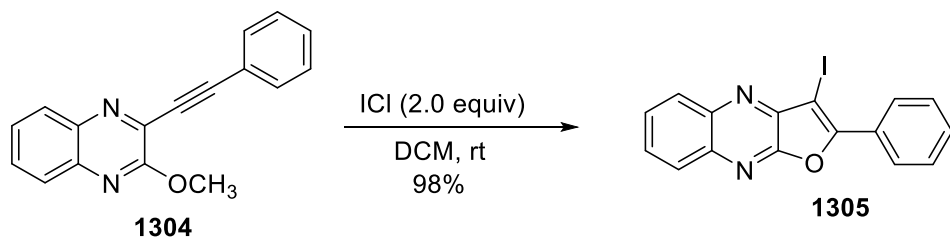
When the reaction was carried out using iodine under basic conditions, both ethers 1306 and 1308 afforded the corresponding 3-iodobenzofuran derivatives 1307 and 1309 in very good yield [578].

$R^1 = 4\text{-}CH_3OC_6H_4$, 100%; $R^1 = 4\text{-}CH_3\text{-}C_6H_4$, 92%; $R^1 = n\text{-}C_4H_9$, 89%
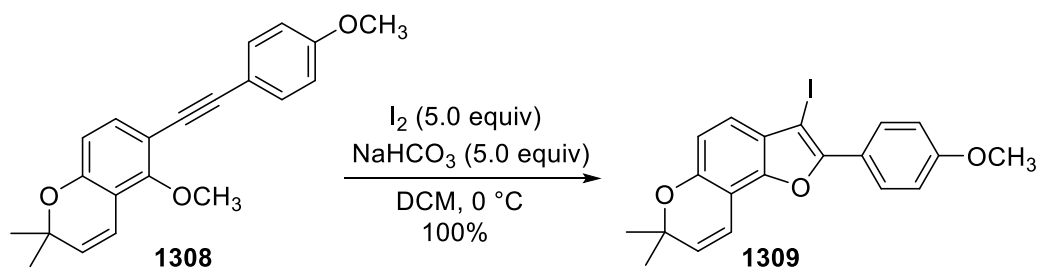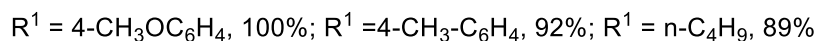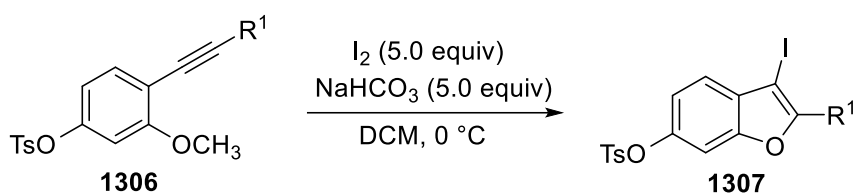
Under the reaction conditions leading to 3-iodobenzofurans an acetonide-protecting group remained unchanged, and methoxy derivative 1310 was easily converted into 1311 in high yield [581].
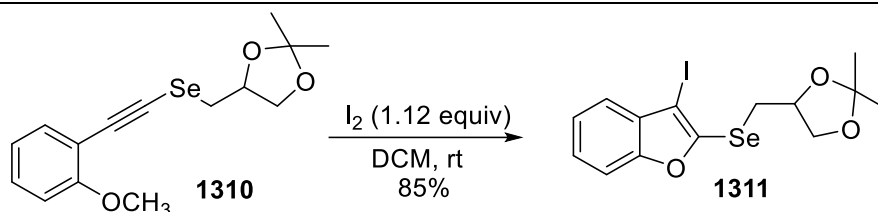
Eventually, the bis-iododerivative 1313, suitable for further modifications according to the Sonogashira reaction, was obtained in moderate yield starting from compound 1312, where two triple bonds and two methoxy substituents were in the appropriate position for the cyclization [582].
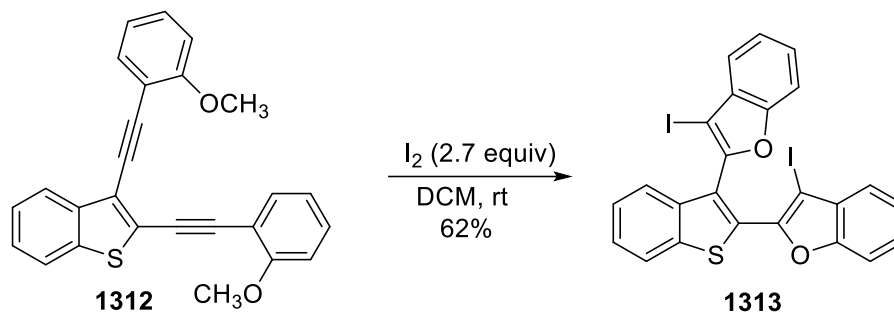
However, when the triple bond or the aromatic ring was substituted by an electron-withdrawing group, as it occurred for anisols 1314, the cyclization required higher temperatures to give the corresponding 3-iodobenzofurans 1315 in good yield [583].

R^1 = NO_2, 90%; R^1 = $COOC_2H_5$, 85%
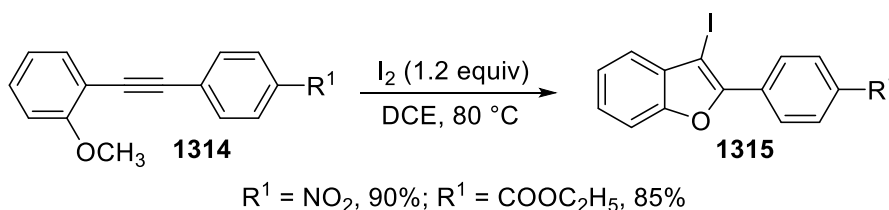
Accordingly, owing to the presence of an electron-withdrawing iodo substituent at the aromatic ring, a higher temperature was needed in order to convert in very good yield the ethers 1316 into the corresponding 3-iodobenzofurans 1317 [584].

R^1 = H, R^2 = C_6H_5, 97%; R^1 = CH_3, R^2 = C_6H_5, 99%;
R^1 = CH_3, R^2 = $n\text{-}C_4H_9$, 75%; R^1 = H, R^2 = 4-CH_3-C_6H_4, 99%
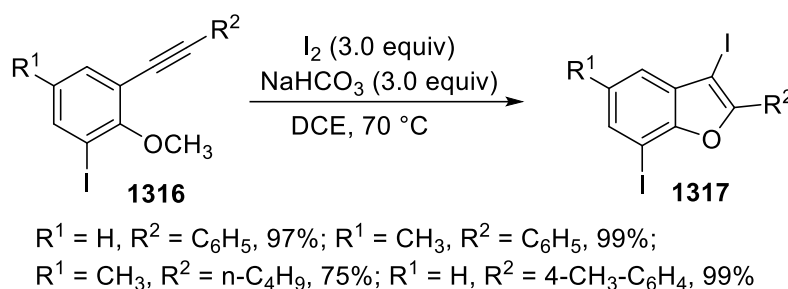
It is also worth noting that some novel reaction methodologies were introduced for converting 2-alkynyl anisoles into 3-iodobenzofurans. In fact, under mechanochemical conditions in the absence of a solvent, electrophilic cyclization of 2-alkynylanisoles 1318, carried out with equimolar amounts of iodine, led to a good yield to 3-iodobenzofurans 1319 [585].

R^1 = C_6H_5, 78%; R^1 = 4-F-C_6H_4, 83%; R^1 = 2-CH_3-C_6H_4, 78%
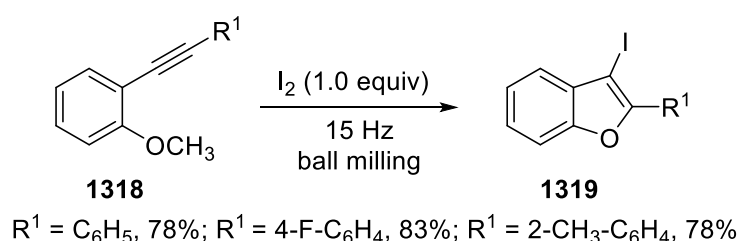
The reaction was also performed in water, and a mixture of NaI and CuSO4 was employed in order to generate iodine. Appropriate amounts of γ-cyclodestrin were needed in order to solubilize

the alkynylanisoles as guests, and starting from compounds 1320, 3-iodobenzofurans 1321 were isolated in very good yield [586].

R^1 = H, >95%; R^1 = OCH$_3$, >95%
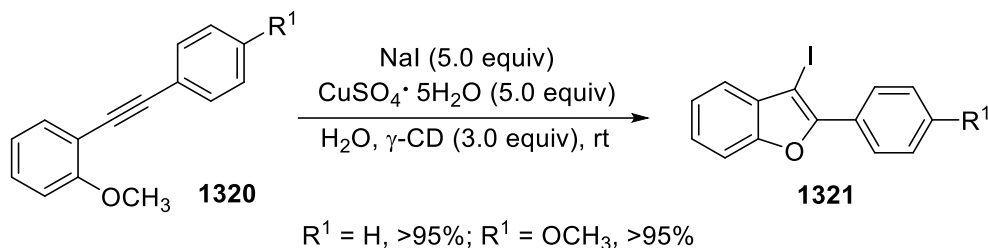
3-Iodobenzofurans were also formed as intermediates within cascade reactions aimed to prepare more complex derivatives. Thus, Pd-catalyzed Suzuki substitution of vinylic iodine of 3-iodobenzofurans 1323 generated in situ afforded in good yield 2,3-disubstituted benzofurans 1324, starting from compounds 1322 [587].

R^1 = CH$_3$, R^2 = R^3 = C$_6$H$_5$, 87%; R^1 = H, R^2 = 4-CH$_3$-C$_6$H$_4$, R^3 = 4-F-C$_6$H$_4$, 80%;
R^1 = CH$_3$, R^2 = 4-CH$_3$-C$_6$H$_4$, R^3 = 4-CH$_3$CH$_2$-C$_6$H$_4$, 89%
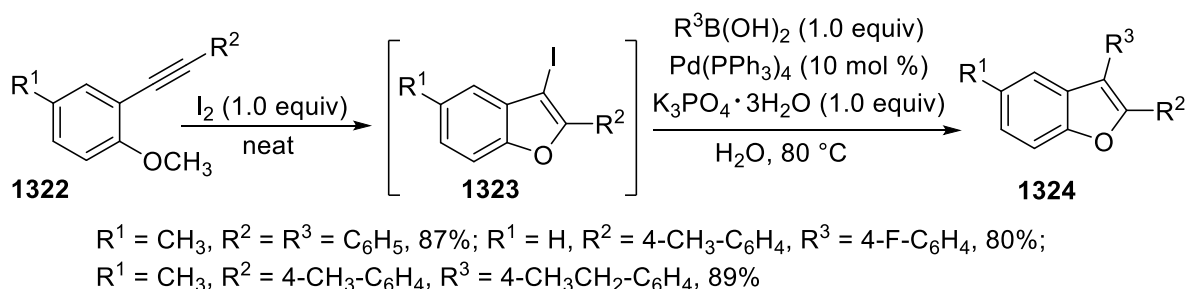
In addition, 3-trifluoromethylbenzofurans 1326 were synthesized in moderate to good yield via tandem iodocyclization and trifluoromethylation of 2-alkynylanisoles 1325 [588].

R^1 = 4-CH$_3$-C$_6$H$_4$, 72%; R^1 = 4-CH$_3$O-C$_6$H$_4$, 76%; R^1 = 4-Cl-C$_6$H$_4$, 64%
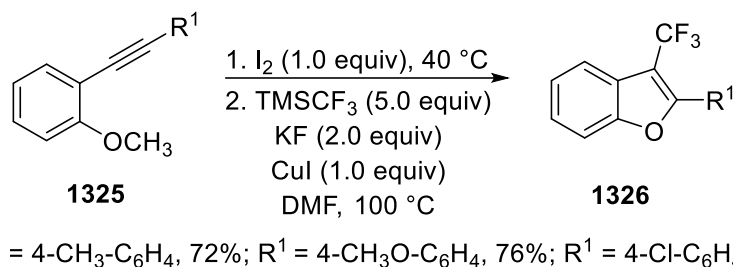
Eventually, when the cyclization was performed in water in the presence of PhS-SPh, the 3-sulfur substituted benzofurans 1328 were isolated in excellent yield starting from alkynyl anisoles 1327 via iodine-mediated cascade annulation reaction [589].

R^1 = R^2 = C$_6$H$_5$, 93%; R^1 = C$_6$H$_5$, R^2 = 4-Br-C$_6$H$_4$, 95%;
R^1 = 4-CH$_3$-C$_6$H$_4$, R^2 = 4-Br-C$_6$H$_4$, 97%
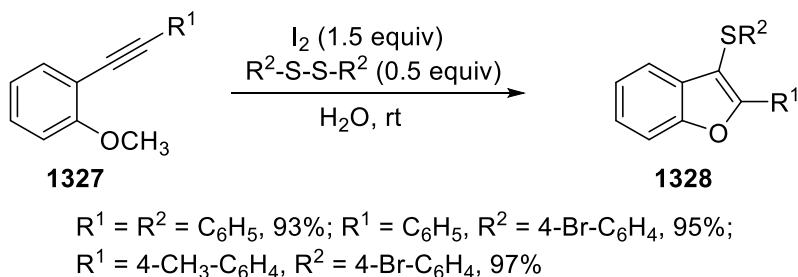
The cyclization was carried out also starting from substrates bearing two groups competing for the cyclization reaction. Thus, starting from 1329, the 3-iodobenzofuran 1330 was isolated with total regioselection, whereas a regioisomeric mixture of compounds 1332 and 1333 was obtained starting from 1331, with preferential ring closure of the alkoxycarbonyl group, whereas compound 1333 presumably resulted from acid-promoted cyclization by HI even in the presence of excess base [590].
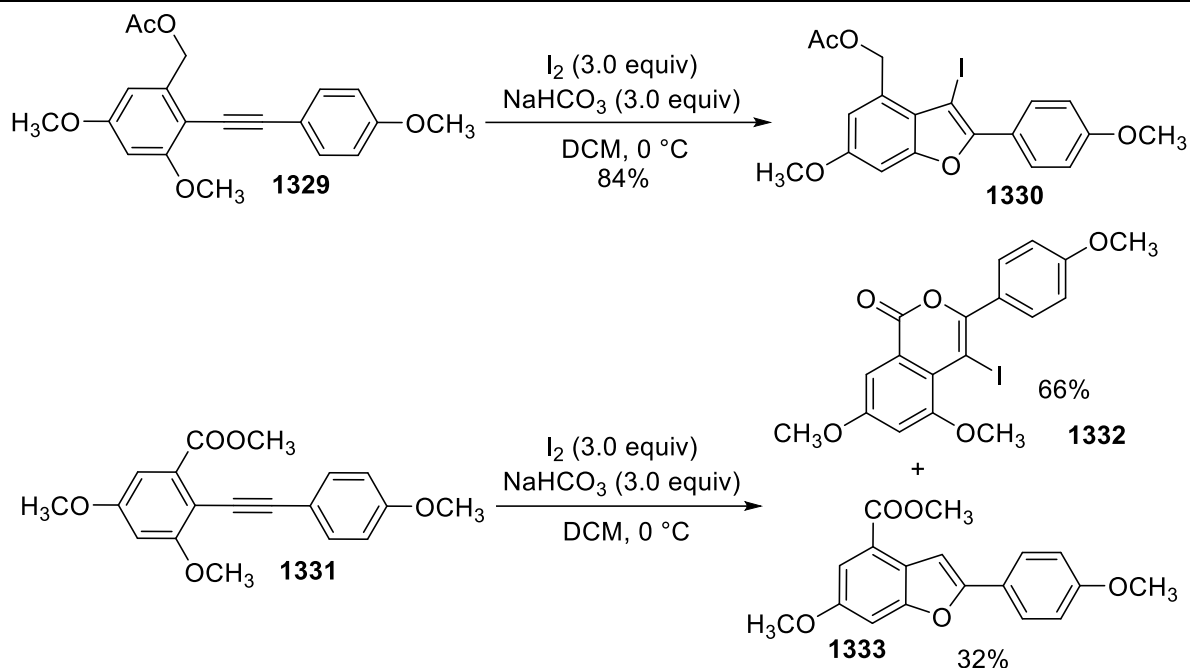
The same behavior was observed when the 3-alkynyl-2-(methylthio)benzo[b]thiophene 1334 was treated with excess iodine, 4-iodo-3-(2-methylthio)benzo[b]thiophen-3-yl-1H-isochromen-1-one 1335 was the sole product formed in a quantitative yield via 6-endo-dig cyclization, owing to the exclusive attack of the carboxylate group [539].
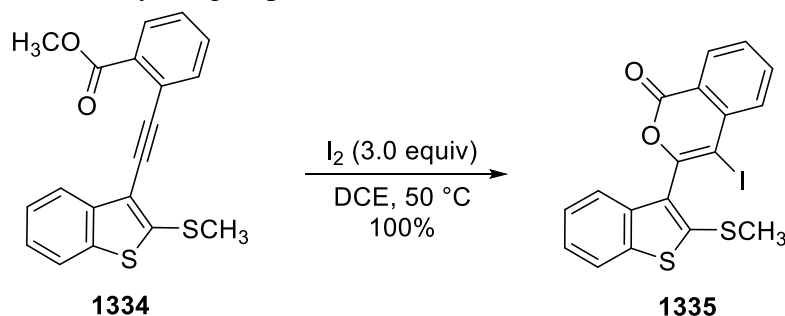
Besides ethers, acetals were used in order to obtain the cyclization of alkynyl derivatives to 3-iodobenzofurans. In fact, by cyclization mediated by I(coll)2PF6, the acetals 1336 afforded in excellent yield to the corresponding 3-iodobenzofurans 1337 [591].
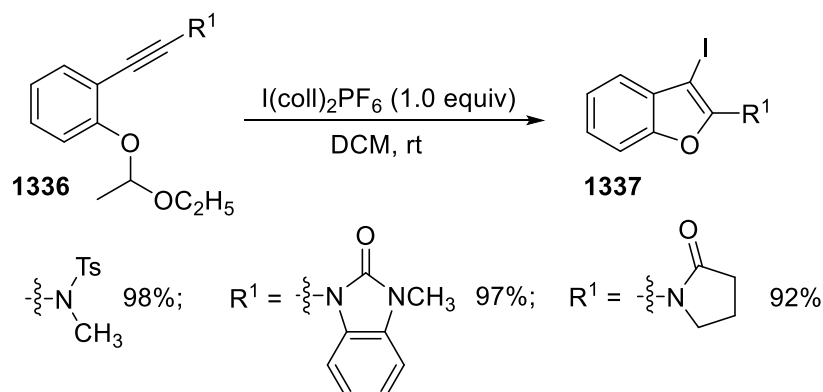
When two different functionalities suitable for cyclization were present on the same aromatic ring, as in compound 1338, the cyclization occurred with total regioselection, and only the acetal functionality reacted to give 3-iodobenzofuran 1339 [592].
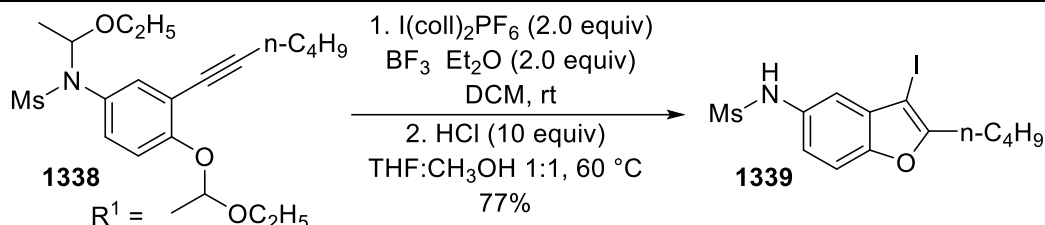
3.1.3.4. Miscellaneous heterocycles.

An unusual reaction involved at first a 5-endo-dig cyclization of alkynols 1340, mediated by PhIO, and subsequent attack to the intermediate cation by the benzonitrile employed as solvent provided the tetrahydrofuro[2,3-d]oxazoles 1341 in good yield [593].

$R^1 = CH_3$, 77%; $R^1 = C_2H_5$, 61%; $R^1 = n-C_3H_7$, 61%
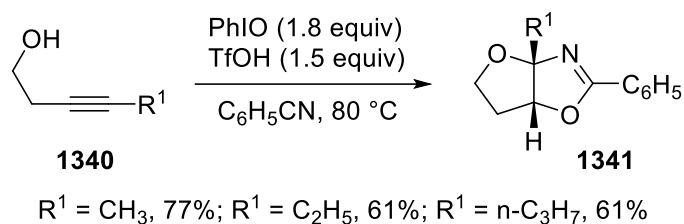
Within total syntheses of the F-furan fatty acids F5 and F6, the alkynyl diol 1342 was treated with excess iodine in a basic medium to give in good yield the corresponding iodofuran 1343, probably by an initial attack to an iodirenium ion in a 5-endo-dig mode, followed by elimination of water under the reaction conditions [594].
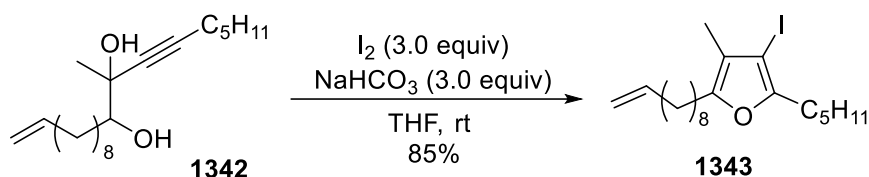
Also, OMOM ethers of alcohols and phenols were useful for iodocyclization. In fact, on treatment with iodine, ethers 1344 afforded in good to moderate yield the corresponding 4-substituted 3-iodo-4-furan-2(5H)-ones 1345, whereas starting from ethers 1346 the 3-iodo-2H-chromen-2-ones 1347 were efficiently prepared [595].

$R^1 = n-C_7H_{15}$, 85%; $R^1 = F-C_6H_4$, 85%; $R^1 = C_6H_5$, 60%

$R^1 = R^2 = H$, 72%; $R^1 = H$, $R^2 = OCH_3$, 85%; $R^1 = C_6H_5$, $R^2 = OCH_3$, 80%
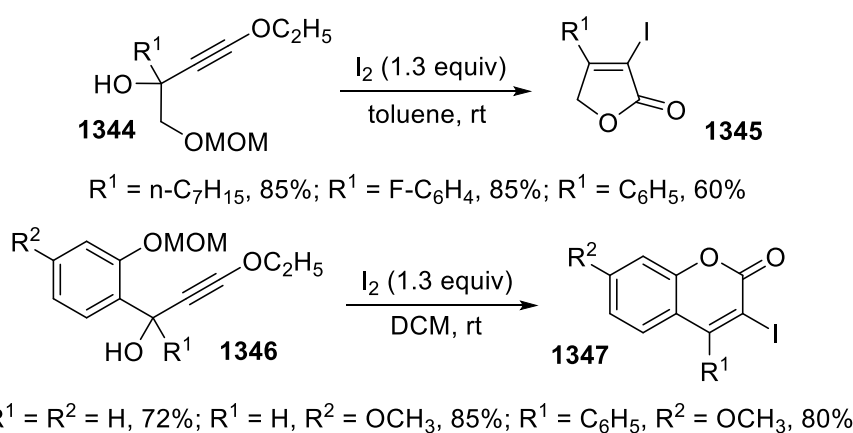
Starting from N-tosyl-N-alkynyl hydroxylamines 1350, prepared in situ from alkynols 1348 and tosylhydroxylamine 1349, 4-iodo-2-tosyl-2,3-dihydroisoxazoles 1351 were synthesized in moderate yield via 5-endo-dig cyclization induced by iodine [596].

R^1 = R^2 = R^3 = C$_6$H$_5$, 53%; R^1 = R^2 = 4-Cl-C$_6$H$_4$, R^3 = C$_6$H$_5$, 63%;
R^1 = R^2 = C$_6$H$_5$, R^3 = 4-Br-C$_6$H$_4$, 67%
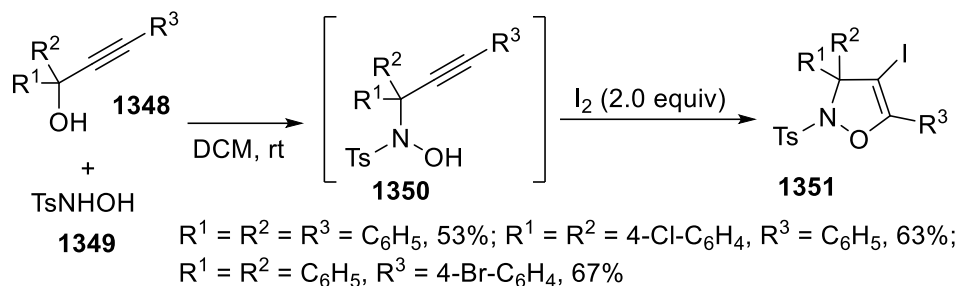
4-Iodoisoxazol-3(2H)-ones 1353 bearing an amide group were obtained in very good yield by iodocyclization of compounds 1352 mediated by 1,3-diiodo-5,5-dimethylhydantoin (DIDMH), proceeding in a 5-endo-mode, followed by a Ritter-type amidation involving the solvent acetonitrile [597].

R^1 = 4-CH$_3$O-C$_6$H$_4$, 92%; R^1 = 4-CH$_3$-C$_6$H$_4$, 84%; R^1 = 1-naphthyl, 97%
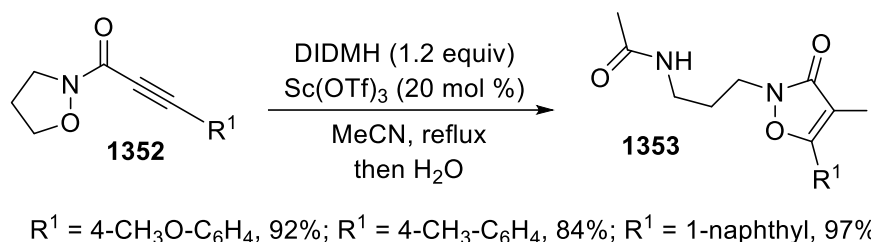
Eventually, a 6-endo-dig cyclofunctionalization carried out with NIS allowed to convert compound 1354 into the corresponding benzo[4,5]thieno-[2,3-c][1,2]oxaphosphinine 1355 in good yield [598].
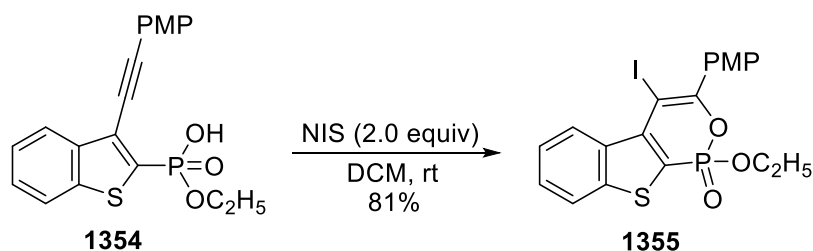
However, the conversion of alkynylphosphonic monoesters 1356 into 2-alkoxy-1,2-oxaphosphinane 2-oxides 1357 performed with NBS required catalysis by DMAP. The reaction proceeded in moderate yield but with total regioselection for six-membered ring products arising from a 6-exo-dig halocyclization, whereas the double bond was formed practically without stereoselection [599].

R^1 = C$_2$H$_5$, R^2 = C$_6$H$_5$, R^3 = H, 60%, 1:2 *E:Z;*
R^1 = CH$_3$, R^2 = C$_6$H$_5$, R^3 = H, 65%, 1:2 *E:Z*
R^1 = C$_2$H$_5$, R^2 = R^3 = C$_6$H$_5$, 50%, 1:1.5 *E:Z*
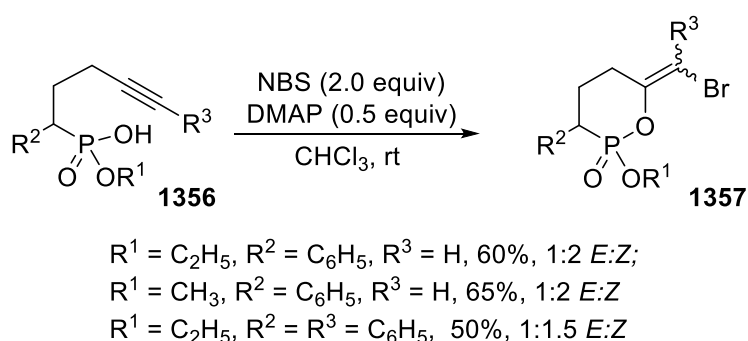
3.1.4. Furans from enynol acetates.

Enynol acetates 1358 afforded the corresponding 3-iodofurans 1359 in very good yield through an iodirenium ion, the acetate group being removed from the enolic oxygen by the nucleophilic iodide anion [600].
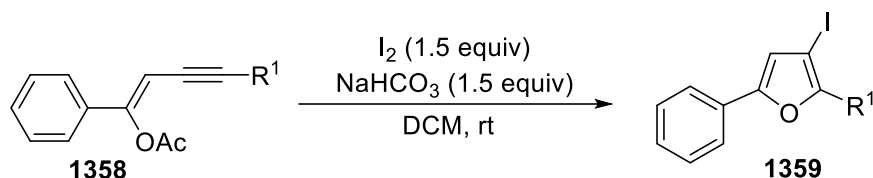
$R^1 = C_6H_5$, 94%; $R^1 = 3\text{-}CH_3\text{-}C_6H_4$, 95%; R^1 = cyclohexyl, 88%; $R^1 = n\text{-}C_6H_{13}$, 85%

The cyclization rate of enynols acetates 1360 and 1362 increased when the ring was substituted by an electron-releasing group, and the 3-iodofurans 1361 and 1363 were isolated in good yield, irrespective of the configuration of the starting double bond, although (E)-enynes 1362 seemed to be a little more reactive than (Z)-ones 1360 [601].
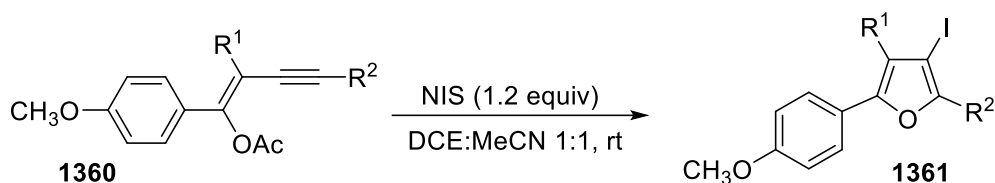
$R^1 = R^2 = C_6H_5$, 61%; $R^1 = C_6H_5$, $R^2 = n\text{-}C_4H_9$, 67%; $R^1 = 4\text{-}F\text{-}C_6H_4$, $R^2 = C_6H_5$, 59%
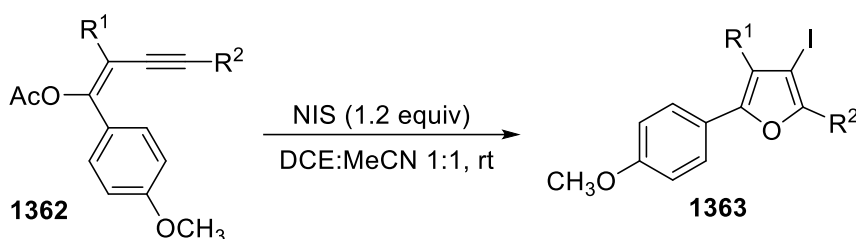
$R^1 = n\text{-}C_4H_9$, $R^2 = 4\text{-}CH_3O\text{-}C_6H_4$, 82%; $R^1 = C_6H_5$, $R^2 = n\text{-}C_4H_9$, 69%;
$R^1 = n\text{-}C_4H_9$, $R^2 = 4\text{-}F\text{-}C_6H_4$, 93%

3.1.5. Furans, dihydrofurans, and pyrans from ketones and aldehydes.

Besides the oxygen of carboxylic acids and their derivatives and ethers, also the carbonyl oxygen of ketones and aldehydes was effective as a nucleophile for the functionalization of triple bonds [602]. Thus, the reaction of 2-(1-alkynyl)-2-cyclohexen-1-ones 1364 with nucleophilic alcohols, induced under basic conditions by iodine, which generated an iodirenium ion, gave highly substituted furans 1365 in good to excellent yields [603-605].
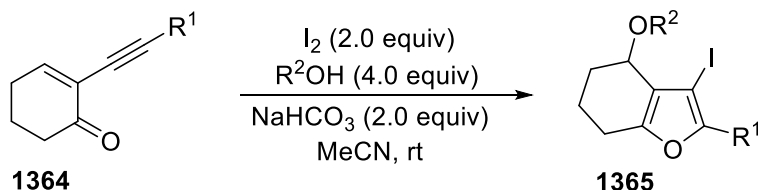
$R^1 = C_6H_5$, $R^2 = (CH_2)_2OH$, 83%; $R^1 = 4\text{-}CN\text{-}C_6H_4$, $R^2 = (CH_2)_2OH$, 89%;
$R^1 = C_6H_5$, $R^2 = (CH_2)_5OH$, 65%; $R^1 = 4\text{-}CH_3O\text{-}C_6H_4$, $R^2 = (CH_2)_3OH$, 67%

Starting from ketones 1366, cyclization carried out using iodine allowed to obtain the corresponding 3-iodo-4-(trifluoromethyl)-4H-pyrans 1367 in good yield since the iodirenium ion was attacked by the enolic form of the ketone and formation of the six-membered ring was favored via 6-endo-dig closure [606].
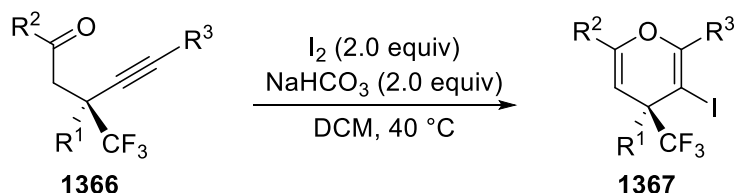
R^1 = R^2 = R^3 = C$_6$H$_5$, 70%; R^1 = 4-CH$_3$-C$_6$H$_4$, R^2 = R^3 = C$_6$H$_5$, 78%;
R^1 = R^2 = C$_6$H$_5$, R^3 = 4-CH$_3$O-C$_6$H$_4$, 90%

The mode of cyclization of substrates where a chain bearing a triple bond was tethered to a cyclic β-diketone strongly depended on the ring size of the diketone. In fact, two different oxabicyclic compounds, 1369 and 1371, were obtained with total regioselection starting from 1368 or 1370 via 5-exo-dig or 6-endo-dig modes, respectively, and the preference could be probably ascribed to angular strain at the transition state [541].

R^1 = C$_6$H$_5$, 88%; R^1 = 4-CH$_3$O-C$_6$H$_4$, 81%; R^1 = 4-F-C$_6$H$_4$, 89%
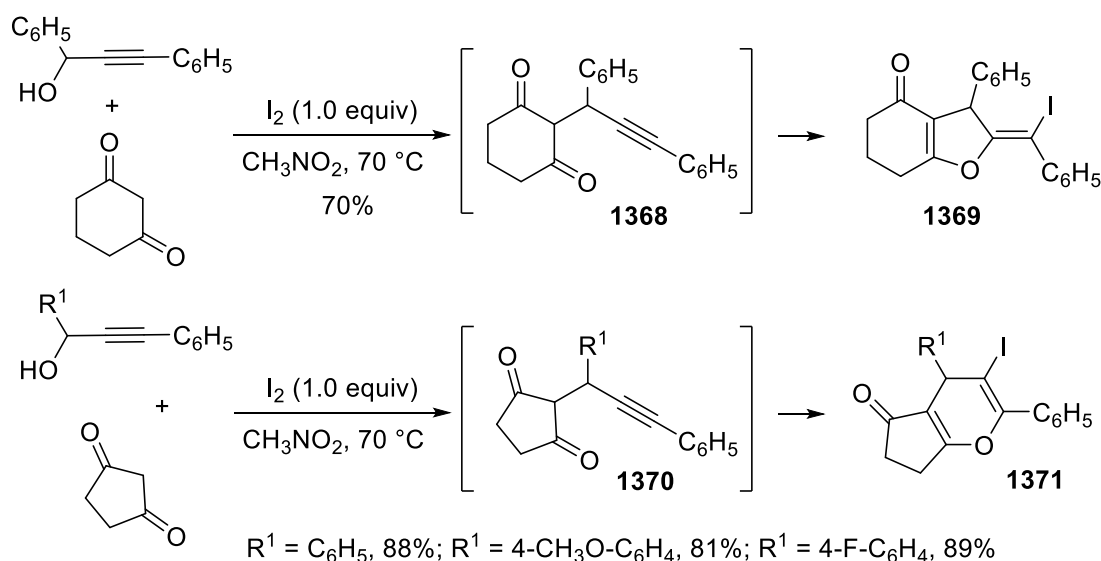
In addition, starting from compound 1372, through a 5-exo-dig cyclization, the spirooxyindole 1373 obtained an excellent yield [607].
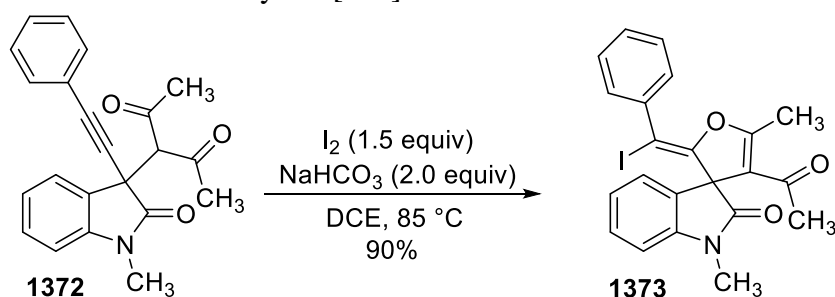
The cyclization of 2-fluoroalk-3-yn-1-ones 1374 to give substituted furans 1375 was carried out by using NIS or, in the alternative, NBS, and the addition of both Lewis acids ZnBr2 and AuCl to the reaction mixture allowed to increase significantly the reaction yield [608].
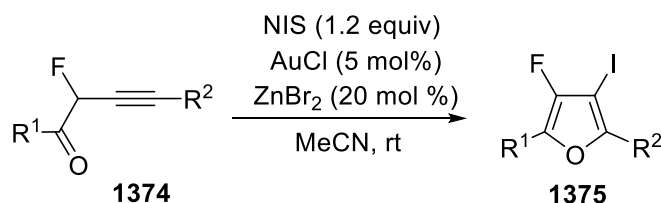
R^1 = C$_6$H$_5$, R^2 = 4-CH$_3$-C$_6$H$_4$, 76%; R^1 = 4-Br-C$_6$H$_4$, R^2 = 4-CH$_3$-C$_6$H$_4$, 69%;
R^1 = C$_6$H$_5$, R^2 = cyclopropyl, 70%; R^1 = 4-F-C$_6$H$_4$, R^2 = 4-CH$_3$-C$_6$H$_4$, 68%

3-Formyl-4-iodofurans 1377 were obtained by iodocyclization of α-alkynyl β-alkoxy enones 1376 in moderate to good yield. The enol ether functionality first directed an attack of the carbonyl oxygen to the intermediate iodiranium ion that eventually underwent cleavage under the reaction conditions [609].

$R^1 = R^3 = CH_3$, $R^2 = C_6H_5$, 87%; $R^1 = R^3 = CH_3$, $R^2 = 4\text{-}CH_3O\text{-}C_6H_4$, 88%;
$R^1 = R^2 = C_6H_5$, $R^3 = C_2H_5$, 45%
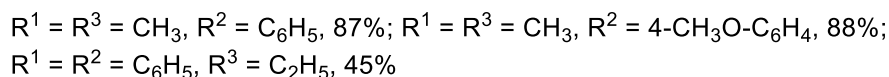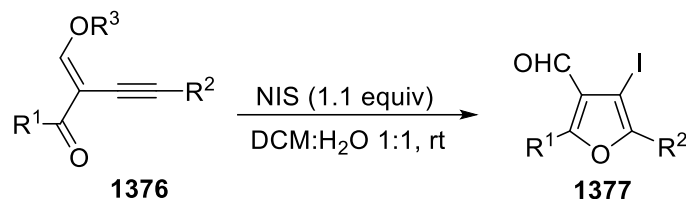
In the presence of iodine, compounds 1378 initially formed a six-membered ring via 6-endo-dig cyclization, followed by a further cyclization leading eventually to the spiro derivatives 1379 in moderate to good yield [610].

$R^1 = 4\text{-}CH_3OC_6H_4$, 87%; $R^1 = 4\text{-}CH_3\text{-}C_6H_4$, 86%;
$R^1 = n\text{-}C_5H_{11}$, 75%; $R^1 = 4\text{-}NO_2\text{-}C_6H_4$, 38%
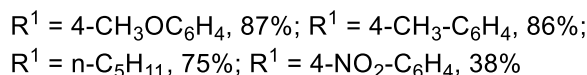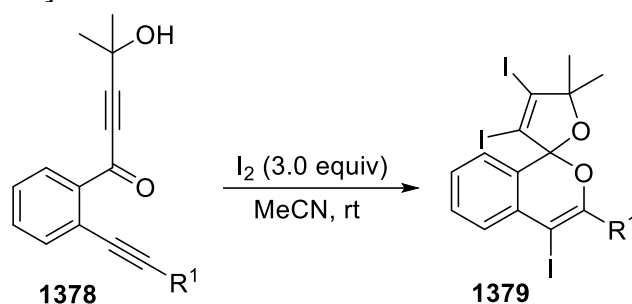
3.1.6. Polycyclic compounds from heterocycles.

The oxygen atom of the carbonyl group of furopyrimidine nucleosides 1380, bearing a 5-alkynyl substituent, was able to attack an iodirenium ion, leading in good yield to the corresponding bicyclic products 1381 via a cyclization proceeding in a 5-endo-trig mode [611].

$R^1 = 4\text{-}CH_3\text{-}C_6H_4$, 92%; $R^1 = 4\text{-}n\text{-}C_5H_{11}\text{-}C_6H_4$, 76%
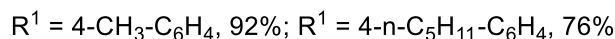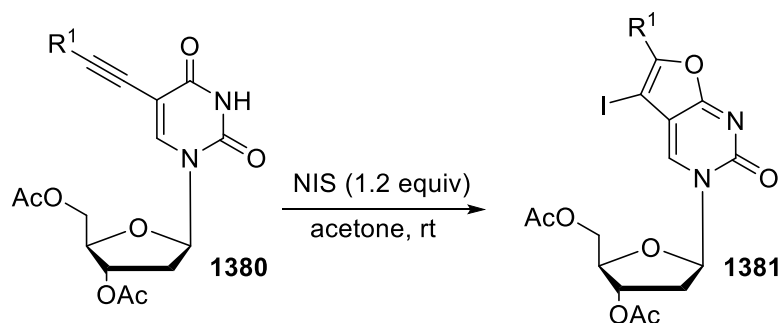
3.2. N-C(sp²)-bond formation by an intramolecular attack of nitrogen nucleophiles to halirenium ions.

3.2.1. 3-Iodopyrroles, 3-iodoindoles, 3-iodoquinolines from alkynyl amines.

N-substituted 2-nitro-1,4-diphenylbut-3-yn-1-amines **1383**, synthesized by conjugate addition of anilines to the activated 1,3-enyne **1382**, underwent iodocyclization to give fully substituted 3-iodopyrroles **1384** in good yield [612-613].
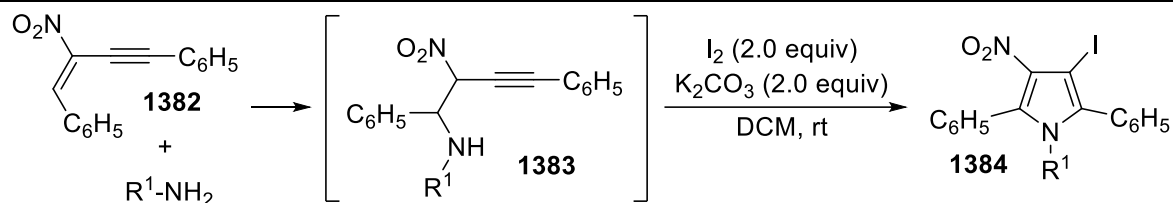
R^1 = C$_6$H$_5$, 82%; R^1 = 2-Br-C$_6$H$_4$, 60%; R^1 = 4-CH$_3$CH$_2$-C$_6$H$_4$, 75%; R^1 = 4-CF$_3$-C$_6$H$_4$, 71%

Moreover, when the anilines **1385**, bearing a 2-alkynyl substituent, were treated with a small amount of iodine, the intermediates **1386** were first formed. Still, the iodide anion arising from the reaction generated iodine again so that only the 2-substituted indoles **1387**, where iodine was missing, were isolated in good yield [614-615].
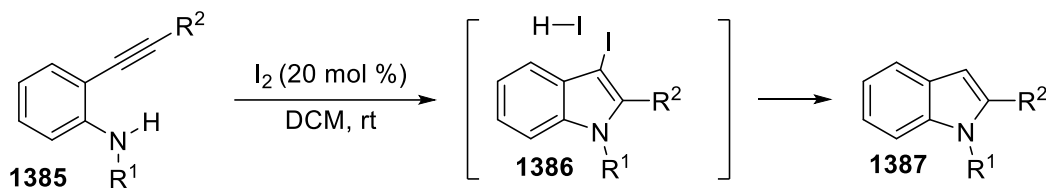
R^1 = 2-NO$_2$-C$_6$H$_4$, R^2 = C$_6$H$_5$, 96%; R^1 = 2-NO$_2$-C$_6$H$_4$, R^2 = 1-naphthyl, 98%;
R^1 = 2-NO$_2$-C$_6$H$_4$, R^2 = 4-CH$_3$O-C$_6$H$_4$, 97%; R^1 = 2-NO$_2$-C$_6$H$_4$, R^2 = n-C$_4$H$_9$, 44%

When the cyclization was carried out starting from *N,N*-dialkyl anilines, an alkyl group was eventually removed from the nitrogen, leading to an iodoalkane. In fact, 2-substituted 3-iodo-1*H*-pyrrolo[2,3-*b*]pyridines **1389** were obtained in very good yield by reaction with excess iodine through a 5-*endo*-dig closure starting from *N,N*-dimethylamino derivatives **1388** [616].
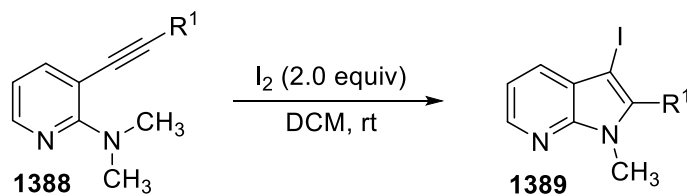
R^1 = C$_6$H$_5$, 93%; R^1 = 3-thienyl, 93%; R^1 = 4-CH$_3$-C$_6$H$_4$, 97%

According to the same methodology, 3-iodo-1-methyl indoles **1391** were prepared in moderate yield through a 5-*endo*-dig closure when 4-substituted 2-alkynyl anilines **1390** were treated with excess iodine [617].
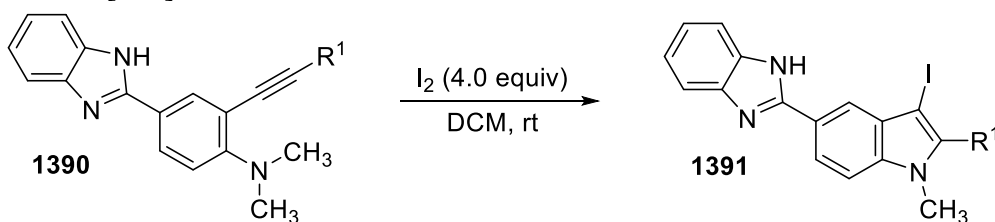
R^1 = C$_6$H$_5$, 30%; R^1 = 4-CH$_3$-C$_6$H$_4$, 40%; R^1 = n-C$_3$H$_7$, 60%; R^1 = n-C$_4$H$_9$, 60%

Within an elegant approach to enediynes embedded into a heterocyclic core, the diynes **1392** were treated with iodine to give in moderate yield 2-alkynyl-3-iodoindoles **1393**, suitable for a further Sonogashira coupling with acetylenes [618].

R^1 = C_6H_5, 65%; R^1 = $(CH_2)_4OH$, 75%
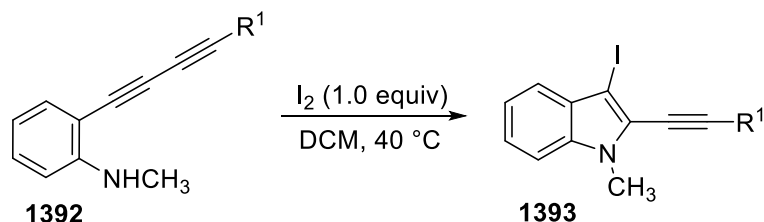
The reaction of *N,N*-dimethyl 2-[2-(2-alkynylphenyl)ethynyl]anilines **1394**, carried out with a little excess iodine, afforded first the intermediates 3-iodoindoles **1395** that in the presence of iodine underwent carbocyclization, to provide in moderate to good yield the 6-substituted 5-iodo-11-methyl-11*H*-benzo[*a*]carbazoles **1396** [619].

R^1 = 4-CH_3-C_6H_4, 95%; R^1 = 4-Br-C_6H_4, 54%; R^1 = 4-NO_2-C_6H_4, 95%
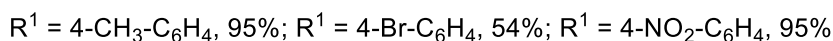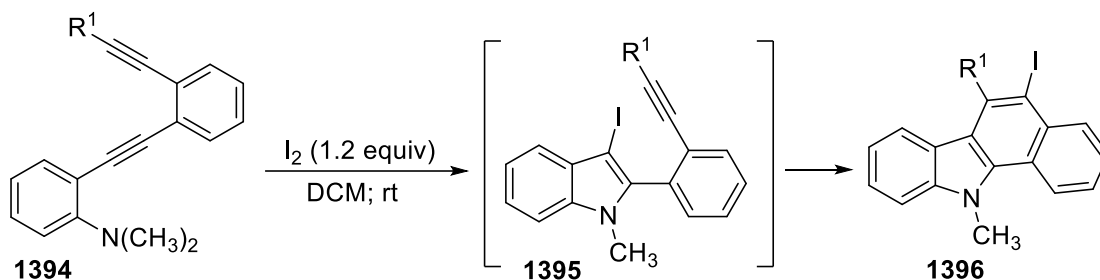
Moreover, within a formal synthesis of Oxopropaline G, dimethylaniline derivatives **1397** were treated with iodine to give in good yield the tricyclic 4-(iodomethyl)-9-methyl-2-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indoles **1398**. The mechanism proceeded *via* a cascade electrophilic cyclization initiated by an attack of the nitrogen atom to the iodirenium ion arising from the triple bond, followed by carbon-carbon bond formation and eventual attack of iodide anion to the resulting primary cation [620].

R^1 = H, 90%; R^1 = CH_3, 92%; R^1 = Cl, 90%; R^1 = NO_2, 85%
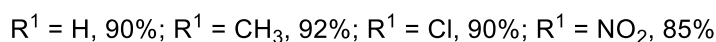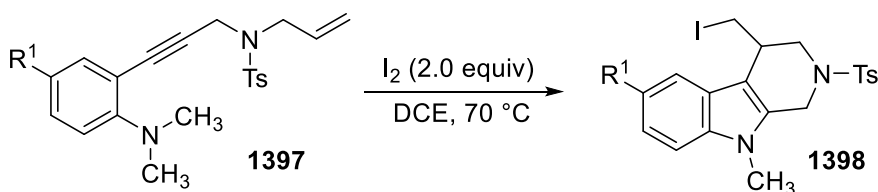
It is worth noting however that removal of an alkyl group did not occur when the 5-(prop-2-yn-1-ylthio)pyrimidin-4(3*H*)-ones **1399** were treated with an excess iodine, the corresponding salts (*E*)-7-(iodomethylene)-4-oxo-2-phenyl-4,6,7,8-tetrahydro-3*H*-pyrimido [5,4-*b*][1,4] thiazin-8-ium iodides **1400** being exclusively formed in good yield as (*E*)-stereoisomers through a 6-*exo*-dig closure [621].

R^1 = C_6H_5, R^2 = CH_3, 90%; R^1 = 4-CH_3-C_6H_4, R^2 = CH_2CH_3, 92%;
R^1 = 2-CH_3-C_6H_4, R^2 = n-C_3H_7, 84%
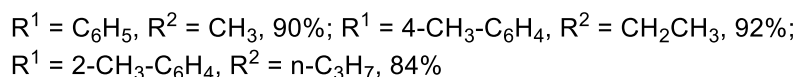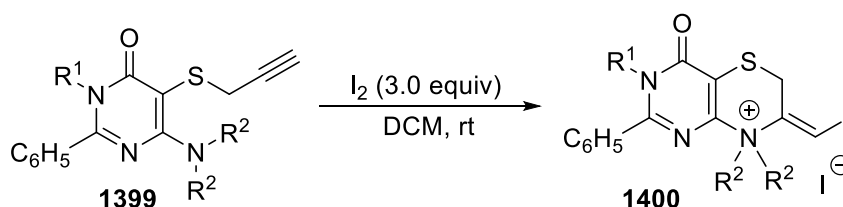
Amino alkynols **1402**, obtained by nucleophilic addition starting from 2-aminoaryl ketones **1401**, were treated with excess iodine to provide disubstituted 3-iodoquinolines **1403** in good yield [622].

R^1 = H, R^2 = CH$_2$CH$_3$, 75%; R^1 = H, R^2 = (CH$_2$)$_3$CH$_3$, 81%;
R^1 = R^2 = C$_6$H$_5$, 69%; R^1 = C$_6$H$_5$, R^2 = (CH$_2$)$_6$CH$_3$, 81%
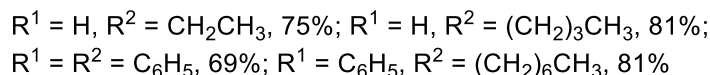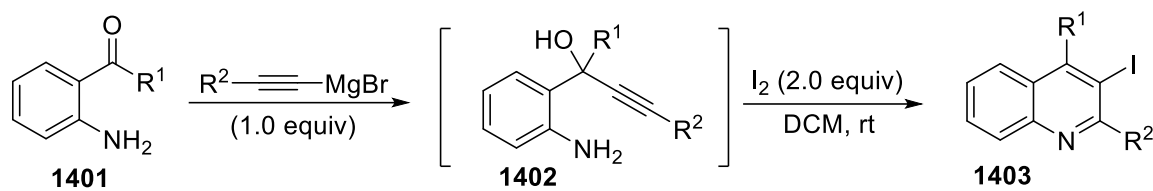
Exploiting a similar methodology, trisubstituted 3-iodoquinolines **1406** were prepared in good yield starting from aminobenzophenones **1404** that were converted into the intermediates **1405** [623].

R^1 = C$_6$H$_5$, R^2 = H, 90%; R^1 = 4-CH$_3$-C$_6$H$_4$, R^2 = H, 94%; R^1 = 4-CH$_3$O-C$_6$H$_4$, R^2 = H, 95%;
R^1 = C$_6$H$_5$, R^2 = Cl, 93%; R^1 = n-C$_5$H$_{11}$, R^2 = Cl, 83%; R^1 = cyclopropyl, R^2 = Cl, 92%
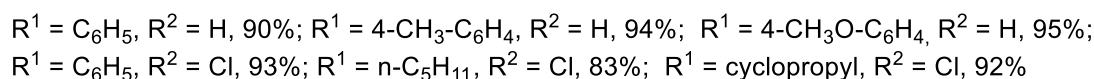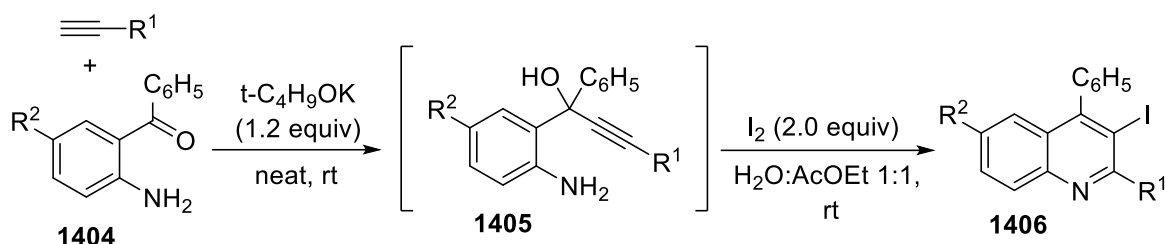
In order to introduce a functionalization at the aromatic ring, the alkynyl derivatives **1407** were sequentially treated first with a diazonium salt and then with iodine to give, through a cyclization proceeding in a 6-*endo*-mode, the corresponding 3-iodo-6-diazenyl quinolines **1408** in good yield, whose diazo group could be easily changed for other functionalities [624].

R^1 = C$_6$H$_5$, R^2 = 4-NO$_2$-C$_6$H$_4$, 67%; R^1 = C$_6$H$_5$, R^2 = 4-F-C$_6$H$_4$, 68%;
R^1 = C$_6$H$_5$, R^2 = 2-I-C$_6$H$_4$, 71%; R^1 = 4-CH$_3$-C$_6$H$_4$, R^2 = 4-Cl-C$_6$H$_4$, 69%
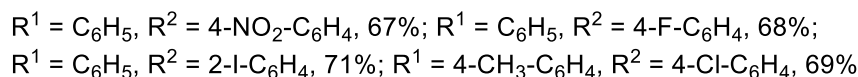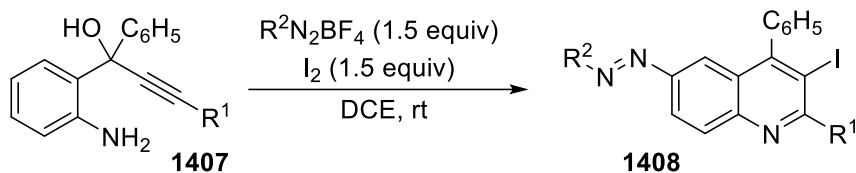
3.2.2. Pyrazoles from hydrazones.

By reaction with excess iodine in a basic medium, phenylhydrazones of 2-alkynyl aldehydes 1409 afforded the corresponding 4-iodopyrazoles 1410 in good yield, and cyclization proceeded through a 5-endo-dig mode [625-626].

R^1 = C$_6$H$_5$, 80%; R^1 = 4-CH$_3$-C$_6$H$_4$, 85%;
R^1 = 3-thienyl, 83%; R^1 = ferrocenyl, 90%
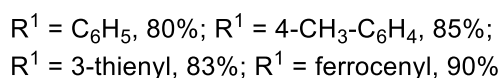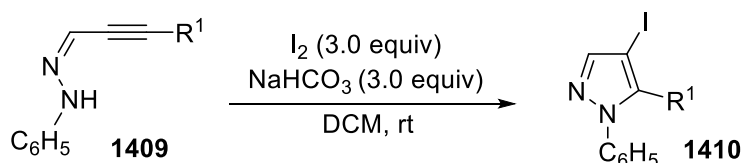
Moreover, amines 1411 at first by N-nitrosation were converted into intermediates 1412. These compounds underwent cyclization mediated by iodine, proceeding in a 5-endo-mode, to give in good yield the corresponding 4-iodopyrazole N-oxides 1413 [627].

R^1 = 3-Br-C_6H_4, R^2 = 2,4-CH_3O-C_6H_3-CH_2CH_2, 73%
R^1 = 4-Br-C_6H_4, R^2 = 2,4-CH_3O-C_6H_3-CH_2CH_2, 75%
R^1 = 4-CN-C_6H_4, R^2 = 2,4-CH_3O-C_6H_3-CH_2CH_2, 71%
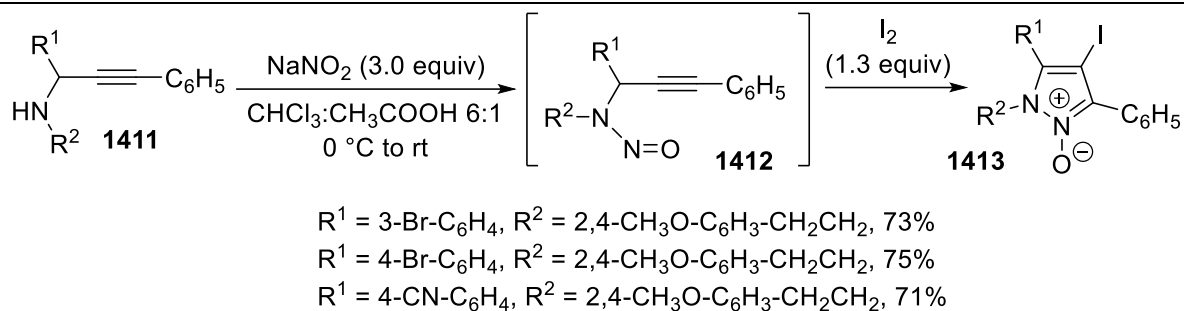
3.2.3. Miscellaneous heterocycles from amines.

A cyclization proceeding in a 5-exo-dig mode allowed to prepare in good yield and total stereoselection (E)-2-(bromomethylene)-2,3-dihydro-1H-imidazo[1,2-a]pyridin-4-ium bromide 1415 starting from the propargyl pyridinium salt 1414 using bromine in acetic acid as source of bromiranium ions [384].
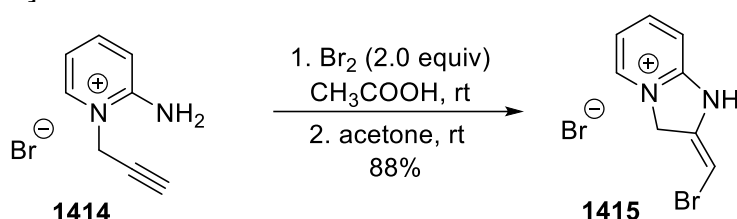
Moreover, the reaction of N-propargyl derivatives 1416 through an unusual 7-exo-dig mode gave the corresponding (Z)-6-(iodomethylene)-5,6,7,11b-tetrahydro-1H,3H-benzo[f]thiazolo[3,4-d][1,4]diazepin-3-ones 1417 in good yield and total stereoselection [389].

R^1 = H, 92%; R^1 = OCH_3, 82%
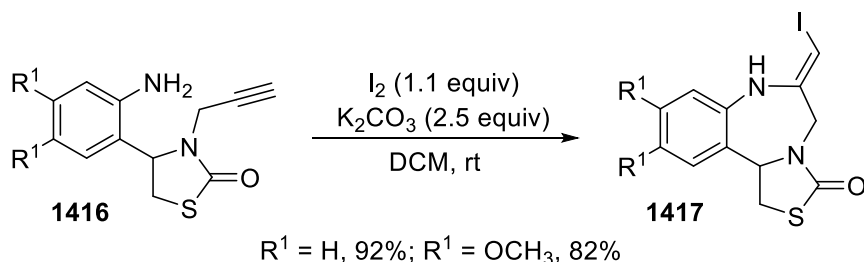
3.2.4. Dihydropyrroles, indoles, and quinolines from N-sulphonylamino derivatives.

The compounds 1418, containing both a carbamate and a tosylamino group, were treated with iodine in a basic medium, and 1-tosyl-3-iodo-2,3-dihydro pyrroles 1419 were the sole products isolated in good yield from the reaction that proceeded with total regioselection. However, both functionalities could react via a 5-endo-dig mode [628]. The same behavior was observed when compound 1418a underwent cyclization mediated by ICl in a basic medium to afford moderate yield but again with total regioselection of the corresponding 1-tosyl-3-iodo-2,3-dihydro pyrrole 1419a [629].
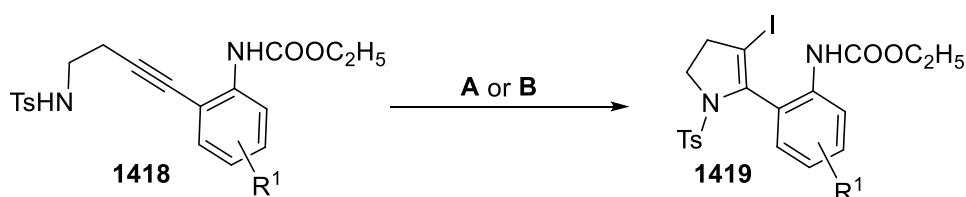
A. I_2 (3.0 equiv), K_2CO_3 (3.0 equiv), MeCN, rt;
a. R^1 = H, 75%; **b.** R^1 = 4-CH_3, 73%; **c.** R^1 = 3-CH_3O, 70%; **d.** R^1 = 4-NO_2, 63%
B. ICl (3.0 equiv), Na_2CO_3 (3.0 equiv), THF, 0 °C; **a.** R^1 = H, 68%

The reaction of tosylamino derivatives 1420 was carried out using NIS, and the addition of triphenylphosphine acting as a Lewis base promoted cyclization that proceeded under mild conditions to give the corresponding 3-iodo-1-tosyl-1H-indoles 1421 in excellent yield [576].
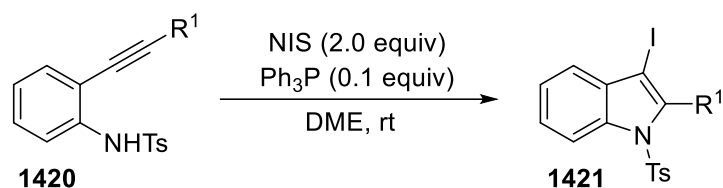
R^1 = C$_6$H$_5$, 98%; R^1 = 4-CH$_3$O-C$_6$H$_4$, 99%; R^1 = cyclopropyl, 96%

The cyclization of alkynyl tosylamides 1422 was carried out in a basic medium and led to 2-substituted 1-iodo-3-tosylpyrano[3,2-e]indol-7(3H)-ones 1423 in good yield [630].
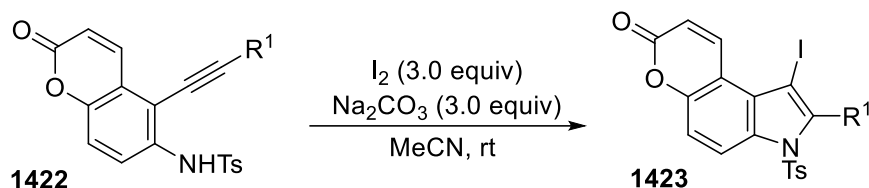
R^1 = C$_6$H$_5$, 81%; R^1 = 4-CH$_3$O-C$_6$H$_4$, 81%; R^1 = n-C$_6$H$_{13}$, 96%

The cyclization of tosylamino derivatives 1424 mediated by iodine proceeded with total regioselection via a 6-endo-dig mode. Subsequent aromatization and loss of the tosyl group led to excellent yield to 3-iodoquinoline derivatives 1425 [631].
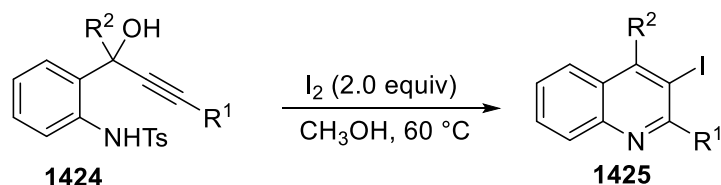
R^1 = R^2 = C$_6$H$_5$, 93%; R^1 = 4-CH$_3$-C$_6$H$_4$, R^2 = C$_6$H$_5$, 94%;
R^1 = 3-CH$_3$O-C$_6$H$_4$, R^2 = C$_6$H$_5$, 84%

In analogy, when compound 1426 was treated with iodine in DCM, the corresponding 2-ethoxy-3-iodo-4-methylquinoline 1427 was isolated in moderate yield [632].
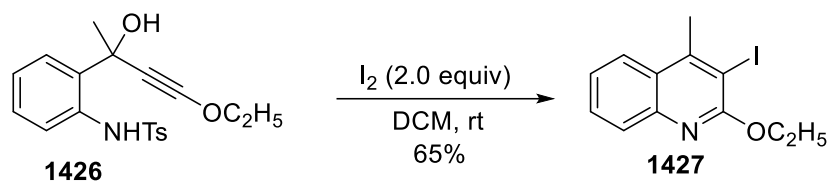
On the contrary, the cyclization of tosylamides 1428, carried out with an excess NIS, proceeded in a 5-exo mode leading to the corresponding intermediates 1429 whose hydroxy functionality was oxidized by NIS to provide 2-(iodomethylene)indolin-3-ones 1430 in very good yield but with low stereoselection [633].
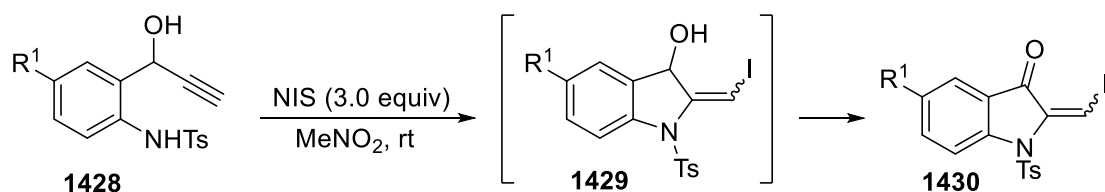
R^1 = H, 87%, d.r. 5:1; R^1 = CH$_3$, 92%, d.r. 2:1; R^1 = Br, 85%. d.r. 2:1

Moreover, when tosylamides 1431, having a tertiary hydroxy functionality in place of a secondary one, were treated under the same conditions, the reaction proceeded through a complex mechanism to give the corresponding 3-(diiodomethyl)indolin-2-ones 1432 in good yield [632].

1431 → **1432**
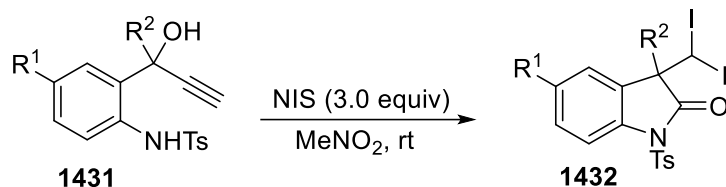
R^1 = Cl, R^2 = C_6H_5, 98%; R^1 = CH_3, R^2 = C_6H_5, 88%; R^1 = H, R^2 = CH_3, 67%

However, when the cyclization of N-tosylamino derivatives **1433** was carried out under an oxygen atmosphere in the presence of a little amount of iodine, the intermediates **1434** were first formed exploiting the visible light photocatalysis, and subsequent cleavage by iodide anion afforded in good yield the corresponding indole aldehydes **1435** with concurrent regeneration of iodine [549].

1433 → **1434** → **1435**
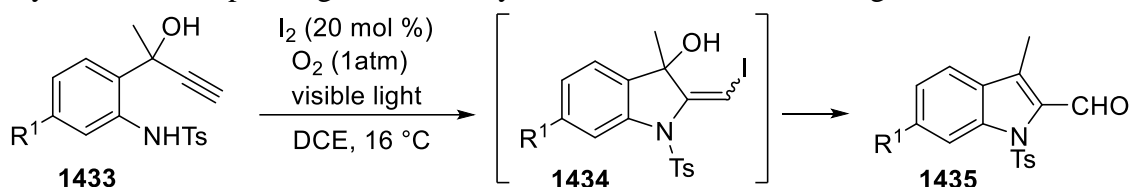
R^1 = H, 75%; R^1 = CH_3, 76%; R^1 = Cl, 73%

In addition, 4-iodo-1-tosylpyrazoles **1437** were obtained in good yield from N-propargyl-N′-tosylhydrazines **1436** by treatment with iodine under basic conditions. Moreover, when the reaction was carried out under mildly acidic conditions, again starting from N-propargyl-N′-tosylhydrazines **1436**, removal of the tosyl group occurred, and 4-iodopyrazoles **1438** were isolated in moderate yield [634].

1436

I_2 (5.0 equiv)
$NaHCO_3$ (5.0 equiv)
MeCN, 70 °C → **1437**
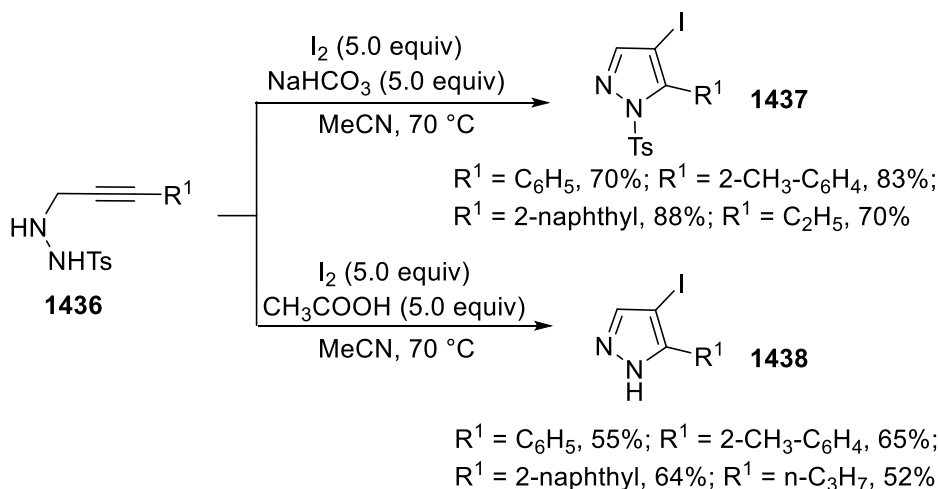
R^1 = C_6H_5, 70%; R^1 = 2-CH_3-C_6H_4, 83%;
R^1 = 2-naphthyl, 88%; R^1 = C_2H_5, 70%

I_2 (5.0 equiv)
CH_3COOH (5.0 equiv)
MeCN, 70 °C → **1438**

R^1 = C_6H_5, 55%; R^1 = 2-CH_3-C_6H_4, 65%;
R^1 = 2-naphthyl, 64%; R^1 = n-C_3H_7, 52%

Eventually, the iodocyclization of 3-(alkynyl)thiophene-2-sulfonamides **1439**, carried with iodine in a basic medium and proceeding according to a 6-endo-dig mode, provided 4-iodo-2H-thieno[3,2-e][1,2]thiazine 1,1-dioxides **1440** in good yield [635].

1439

I_2 (2.5 equiv)
K_2CO_3 (3.0 equiv)
DCM, rt → **1440**
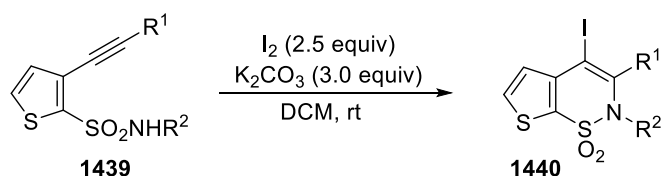
R^1 = C_6H_5, R^2 = CH_3, 78%; R^1 = C_6H_5, R^2 = C_2H_5, 74%;
R^1 = cyclohexyl, R^2 = CH_3, 72%; R^1 = cyclopentyl, R^2 = CH_3, 75%

3.2.5. Isoindolin-1-ones and polycyclic enamides from amides.

A halirenium ion arising from a triple bond and a halenium ion were also attacked by amidic nitrogen. Thus, amides **1441a**, on treatment with iodine and phosphazene superbase P4-t-Bu,

underwent cyclization via 5-exo-dig mode to give in very good yield and total stereoselection of the corresponding 3-(1-iodoalkylidene)isoindolin-1-ones 1442a, where the double bond displayed the (Z)-configuration, exclusively [636]. On the other hand, when n-BuLi was used in place of phosphazene superbase, the amides 1441b afforded isoindolin-1-ones 1442b in slightly lower yield but again with total (Z)-stereoselection [637].
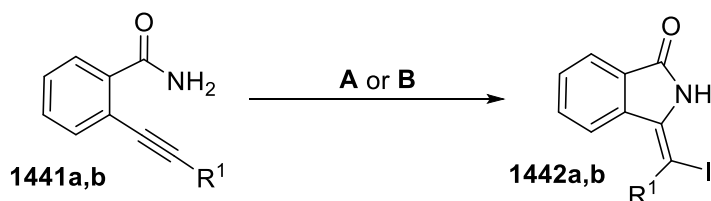
A: I$_2$ (3.0 equiv), P$_4$-t-Bu (1.0 equiv), THF, rt
a: R^1 = C$_6$H$_5$, 87%; R^1 = 4-F-C$_6$H$_4$, 81%; R^1 = cyclohexyl, 94%
B: n-BuLi (1.2 equiv), I$_2$ (3.0 equiv), THF, 0 °C
b: R^1 = C$_6$H$_5$, 67%; R^1 = 4-CH$_3$-C$_6$H$_4$, 71%; R^1 = 4-F-C$_6$H$_4$, 69%

The amides 1444 reacted with the alkynols 1443 to give the alkynyl intermediates 1445 that were not isolated, but directly treated with an excess iodine to give the seven-membered enamides 1446 in moderate yield, exploiting an unusual 7-endo-dig cyclization mode [638].

R^1 = 4-CH$_3$O-C$_6$H$_4$CH$_2$, R^2 = 4-CH$_3$-C$_6$H$_4$, 72%;
R^1 = C$_6$H$_5$CH$_2$, R^2 = 3,4-(CH$_3$O)$_2$-C$_6$H$_3$, 68%;
R^1 = t-C$_4$H$_9$, R^2 = 3,4-(CH$_3$O)$_2$-C$_6$H$_3$, 60%
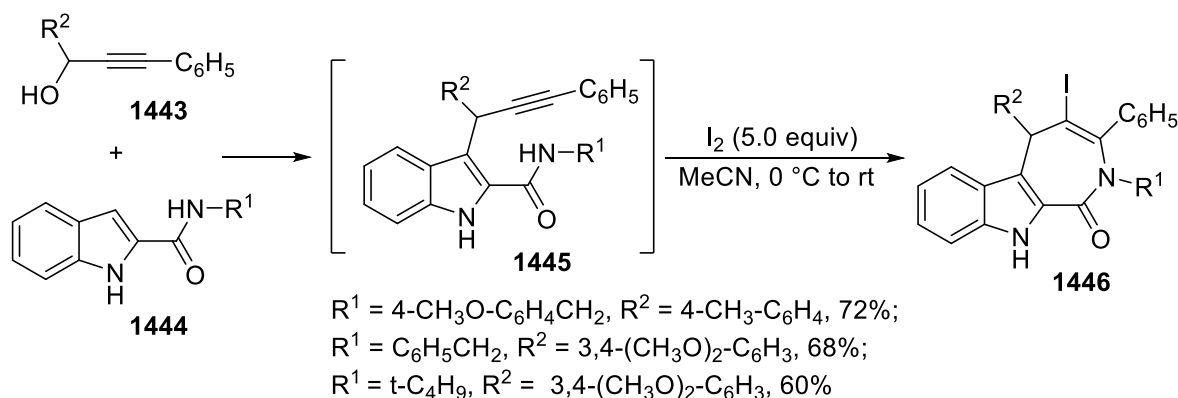
3.2.6. Pyrrolinones, pyrroles, pyrazoles, isooxazoles, and their dihydro derivatives from carbamates.

A lot of examples reported in the literature concerned the cyclization of carbamates mediated by halirenium ions to give enecarbamates with the formation of a new C-N bond. Thus, the enantioenriched ynones 1447, prepared to start from chiral amino acids, underwent cyclization with iodine in a basic medium, favored by microwave irradiation, to provide tert-butyl (S)-4-iodo-3-oxo-2,3-dihydro-1H-pyrroles 1448 in moderate to good yield with minor loss of configuration [639].
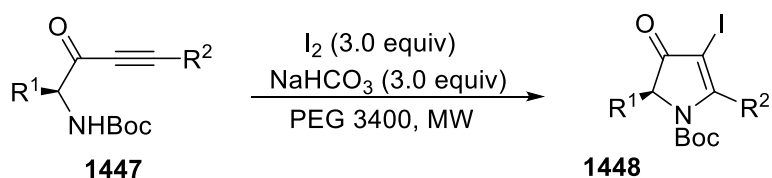
R^1 = (CH$_3$)$_2$CH, R^2 = C$_6$H$_5$, 65%; R^1 = (CH$_3$)$_2$, R^2 = n-C$_4$H$_9$, 80%;
R^1 = (CH$_3$)$_2$CH, R^2 = cyclopropyl, 64%

Again, promoted by microwave irradiation, the cyclization of compounds 1449 induced by iodine in a basic medium and proceeding via a 5-endo mode, after elimination of water, gave fully substituted 3-iodopyrroles 1450 in moderate to good yield [640].

R^1 = (CH$_3$)$_2$CHCH$_2$, 81%; R^1 = C$_6$H$_5$CH$_2$, 67%; R^1 = CH$_3$, 66%
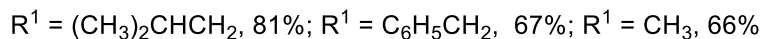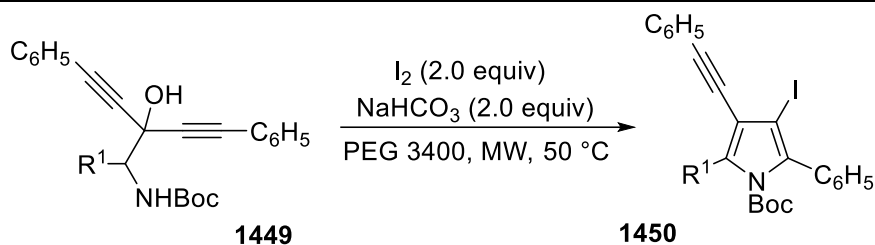
Some iodine-containing reagents used for cyclization are both iodinating and oxidizing agents, thus enabling the divergent synthesis of pyrroles, pyrazoles, isoxazoles, and their 2,5-dihydro products. Thus, chiral alkynyl carbamates 1451 by reaction with IPy2PF6, through a 5-endo-dig mode, gave the corresponding (R)-4-iodo-2,3-dihydro-1H-pyrroles 1452 in moderate to good yield. On the contrary, when I(coll)2PF6 was employed, that is, both an iodinating and an oxidating agent, oxidation followed cyclization, and 3-iodopyrroles 1453 were isolated in excellent yield [641].

R^1 = C$_6$H$_5$, 83%; R^1 = 2-thienyl, 64%;
R^1 = 2-naphthyl, 93%

R^1 = 2-CH$_3$O-C$_6$H$_4$, 90%; R^1 = 2-thienyl, 88%;
R^1 = 1-naphtyl, quantit
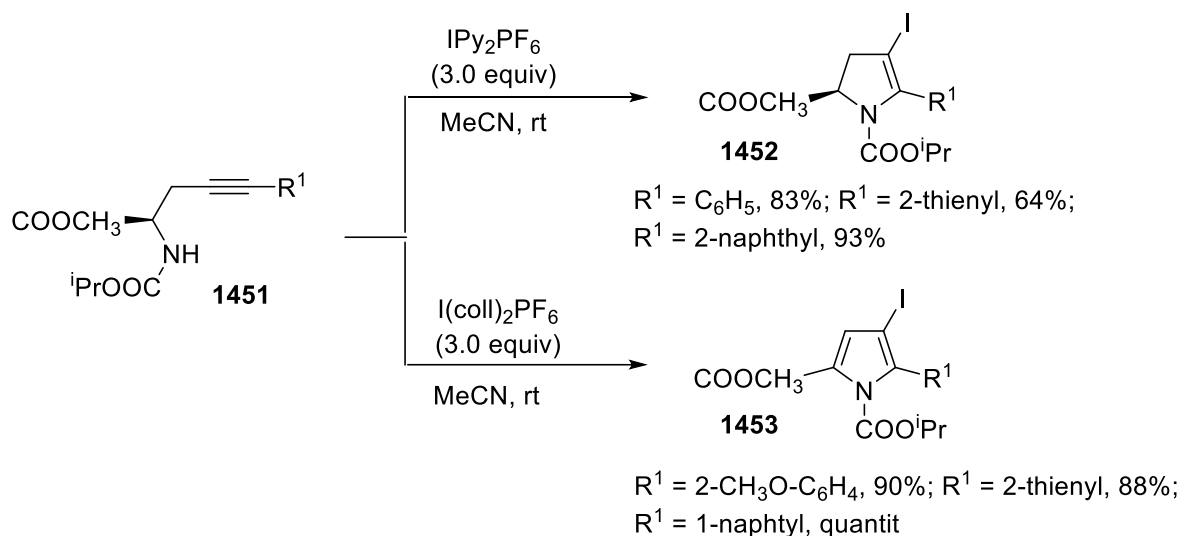
Moreover, 2-trifluoromethyl-1,3-enynes 1454 reacted first with benzylamine to give alkynyl amines 1455 and their cyclization in situ, induced by excess NIS and followed by aromatization, provided 3-iodo-4-trifluoromethylpyrroles 1456 in good yield [642].

R^1 = C$_6$H$_5$, 87%; R^1 = 4-CH$_3$O-C$_6$H$_4$, 82%; R^1 = 4-Cl-C$_6$H$_4$, 85%
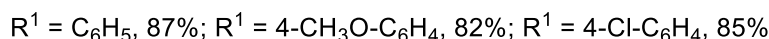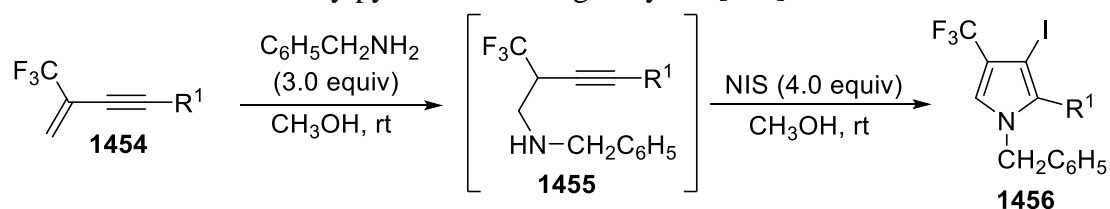
A similar behavior was observed for iodocyclization of the hydroxylamine-derived alkynyl carbamates 1457. In fact, these compounds reacted with an excess of I(coll)2PF6 to afford only 4-iodo-isoxazole-2(5H)-carboxylates 1458, according to a 5-endo-dig closure. On the contrary, when the reaction was carried out with NIS in the presence of a strong Lewis acid as boron trifluoride, the cyclization was followed by aromatization with loss of the carbamate functionality, leading to the isoxazoles 1459 in very good yield [643].

I(coll)$_2$PF$_6$
(2.0 equiv)
DCM, rt

1458

NIS
(2.5 equiv)
BF$_3$· OEt$_2$
(2.5 equiv)
DCM, 0 °C

R^1 = C$_6$H$_5$, R^2 = OBn, 83%;
R^1 = 2-thienyl, R^2 = OBn, 64%;
R^1 = 2-naphthyl, R^2 = OBn, 93%

1459

R^1 = 2-CH$_3$O-C$_6$H$_4$, R^2 = ^{i}Pr, 90%;
R^1 = 2-thienyl, R^2 = ^{i}Pr, 88%;
R^1 = 1-naphtyl, R^2 = ^{i}Pr, quantit

1457
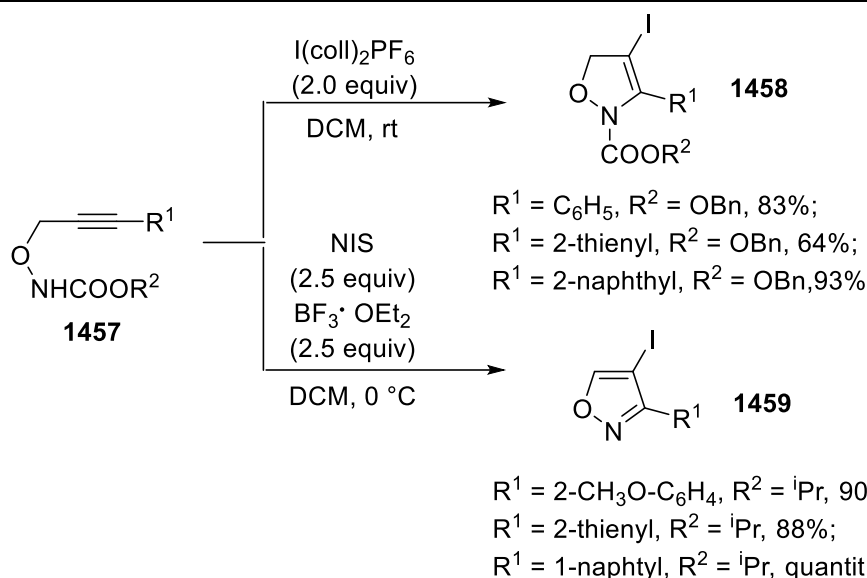
According to the same experimental protocols, by reaction with I(coll)2PF6 carbamates 1460, derived from alkynyl hydrazines, via a 5-endo-dig closure afforded the corresponding diisopropyl 4-iodo-1H-pyrazole-1,2(3H)-dicarboxylates 1461 in good yield, whereas the reaction carried out with NIS in the presence of boron trifluoride after aromatization led to isopropyl 4-iodo-1H-pyrazole-1-carboxylates 1462 in excellent yield [644].

I(coll)$_2$PF$_6$
(2.0 equiv)
DCM, rt

1461

R^1 = 2-CH$_3$O-C$_6$H$_4$, quantit.;
R^1 = 2-thienyl, 88%; R^1 = n-C$_4$H$_9$, 60%

NIS
(3.0 equiv)
BF$_3$· OEt$_2$
(3.0 equiv)
DCM, 0 °C

1462

R^1 = 2-CH$_3$O-C$_6$H$_4$, 99%;
R^1 = 2-thienyl, 91%; R^1 = 1-cyclohexenyl, 70%

1460
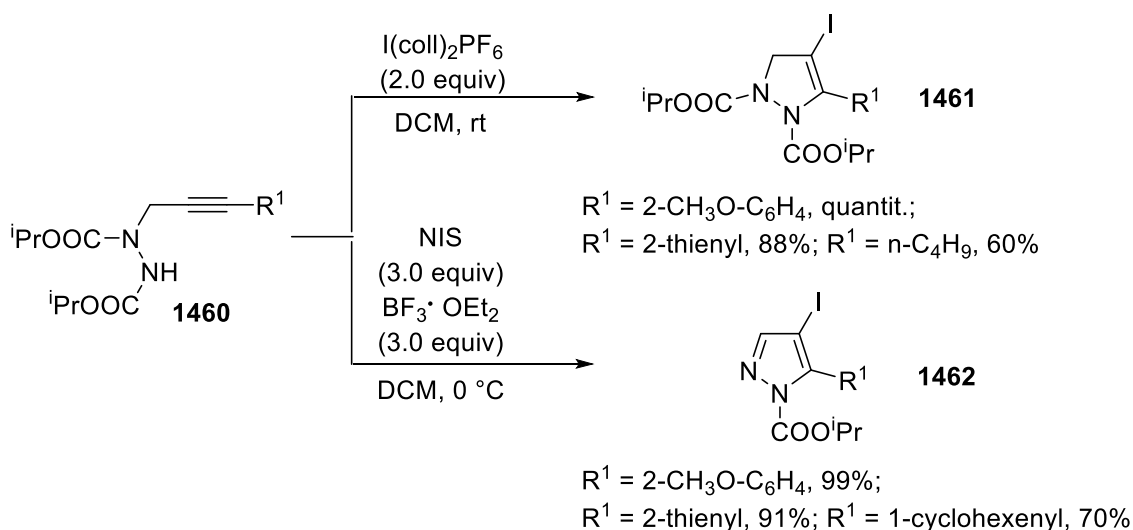
Also, the reaction outcome of carbamates 1463, tethered on an indole structure, was directed by the employed reagent. In fact, in a basic medium, the iodocyclization led to moderate to good yield to 2,4-disubstituted diethyl 3-iodo-1H-pyrido[2,3-b]indole-1,9(4H)-dicarboxylates 1464 and the reaction proceeded in a 6-endo-mode. On the contrary, when the same products reacted with iodine in the presence of ICl, the 2,4-disubstituted ethyl 3-iodo-9H-pyrido[2,3-b]indole-9-carboxylates 1465 were isolated, and a carbamate functionality was lost [645].

R^1 = 4-Cl-C$_6$H$_4$, R^2 = C$_6$H$_5$, 61%;
R^1 = 4-CH$_3$CH$_2$O-C$_6$H$_4$, R^2 = 4-CH$_3$-C$_6$H$_4$, 73%

R^1 = 4-Cl-C$_6$H$_4$, R^2 = C$_6$H$_5$, 86%;
R^1 = 4-CH$_3$CH$_2$O-C$_6$H$_4$, R^2 = 4-CH$_3$-C$_6$H$_4$, 90%
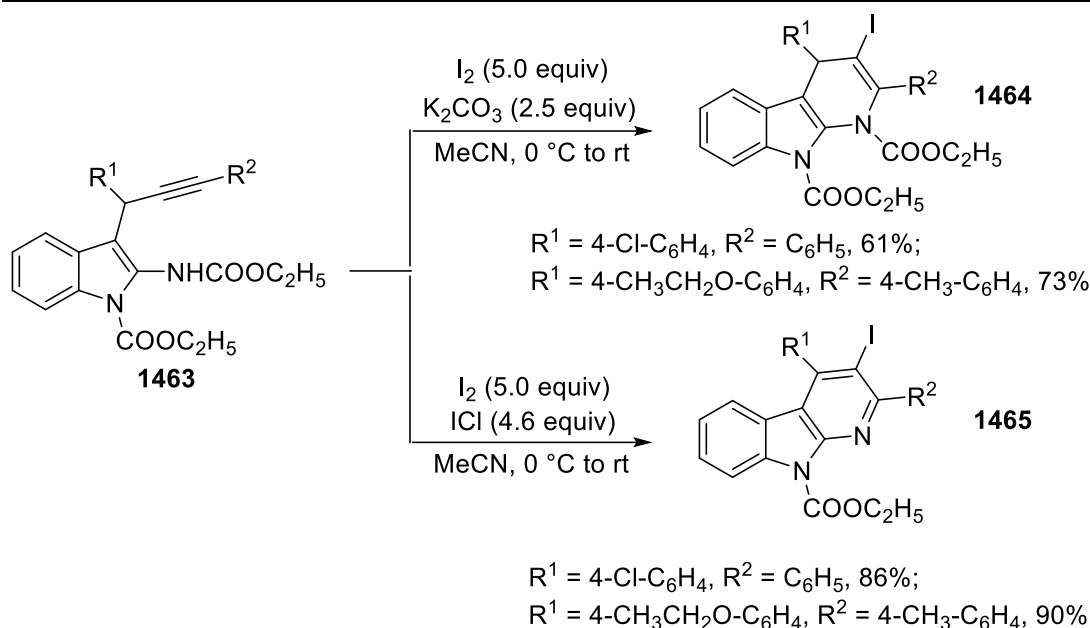
3.2.7. 4-Alkylidene-1,3-oxazolidin-2-ones from *N*-sulphonyl carbamates.

On treatment with NBS in the presence of a catalytic amount of copper(II) chloride, N-tosyl alkynyl carbamates 1466 were easily converted into the corresponding 4-alkylidene-3-tosyl-1,3-oxazolidin-2-ones 1467. The reaction proceeded in good yield and with total stereoselection, the configuration of the double bond being assigned as (E) exclusively [646].
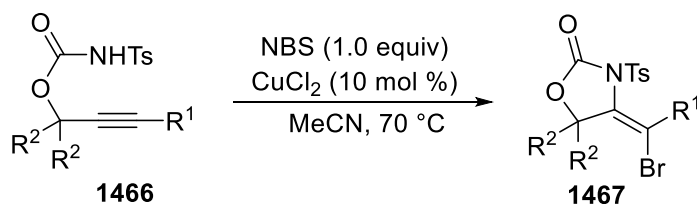
R^1 = R^2 = H, 75%; R^1 = H, R^2 = CH$_3$, (40 °C) 92%; R^1 = n-C$_3$H$_7$, R^2 = H, 73%

3.2.8. Imidazolidin-2-imines from *N*-alkynyl guanidines.

In analogy with amines and amides, the nitrogen of alkynyl guanidines attacked iodirenium ions to give heterocyclic derivatives via a 5-exo-dig closure. In fact, the substituted guanidines 1469, obtained by reaction of alkynylamines 1468 with carbodiimides, were treated in situ with iodine in a basic medium to afford the corresponding (2Z,4E)-4-(1-iodoalkylidene)-1,3-imidazolidin-2-imines 1470 in good yield and total (2Z,4E)-stereoselection [561].
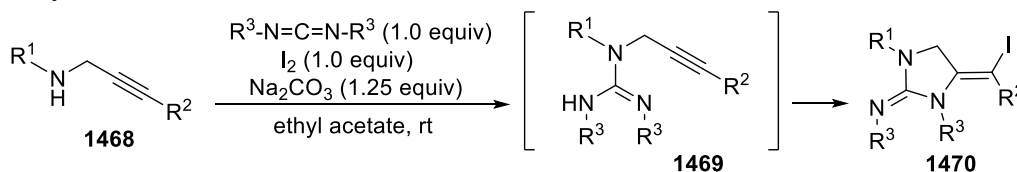
R^1 = CH$_3$, R^2 = H, R^3 = 4-CH$_3$-C$_6$H$_4$, 84%; R^1 = CH$_2$C$_6$H$_5$, R^2 = H, R^3 = 4-CH$_3$-C$_6$H$_4$, 78%;
R^1 = t-C$_4$H$_9$, R^2 = C$_6$H$_5$, R^3 = 4-CH$_3$-C$_6$H$_4$, 75%

3.2.9. Indole and quinolinone derivatives from imines.

N-(2-Alkynylphenyl)imines 1471 allowed to prepare in good yield ring-fused indoles 1472 by cyclization mediated by NIS proceeding via a 5-endo mode, followed by nucleophilic attack to the carbon of the starting imine by a tethered hydroxy functionality [647].
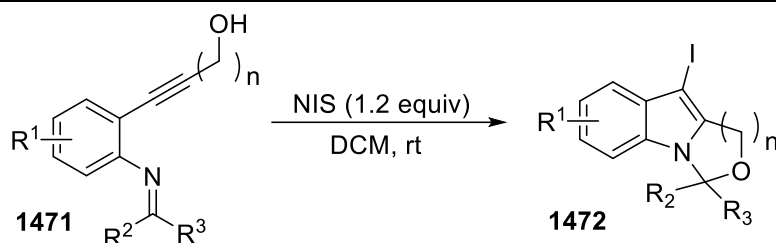
R^1 = H, R^2 = R^3 = C$_6$H$_5$, n = 1, 63%; R^1 = R^2 = H, R^3 = C$_6$H$_5$, n = 2, 62%;
R^1 = H, R^2 = R^3 = C$_6$H$_5$, n = 2, 94%; R^1 = 4-CH$_3$, R^2 = R^3 = C$_6$H$_5$, n = 2, 70%

In addition, starting from the imines 1473, the iodocyclization mediated by NIS proceeding in a 6-endo mode provided the corresponding 3-iodoquinolin-4(1H)-ones 1474 in moderate to good yield, DCM being the choice solvent for the reaction [647].
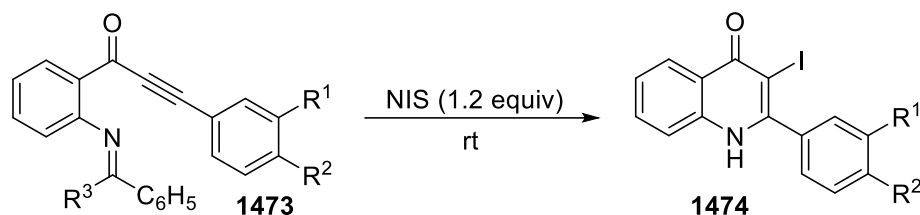
R^1 = R^2 = H, R^3 = OCH$_3$, 58% (MeCN); R^1 = H, R^2 = OCH$_3$, R^3 = OCH$_3$, 61% (MeCN);
R^1 = O^{i}Pr, R^2 = R^3 = OCH$_3$, 90% (DCM); R^1 = O^{i}Pr, R^2 = OCH$_3$, R^3 = C$_6$H$_5$, 95% (DCM)

3.2.10. Nitrogen-containing polycyclic compounds from heterocycles.

Also, nitrogen atoms embedded in aromatic rings were able to attack halirenium ions generated from triple bonds, leading to polycyclic structures [247]. Thus, starting from the pyridine derivatives 1475, the ethyl 3-aroylindolizine-1-carboxylates 1476 were obtained in moderate to good yield, followed by a reaction with water and elimination of the iodine atom [648].
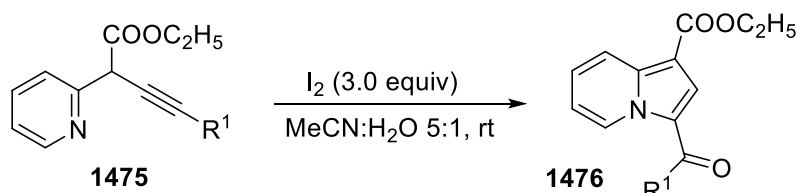
R^1 = C$_6$H$_5$, 80%; R^1 = 4-NO$_2$-C$_6$H$_4$, 83%;
R^1 = 4-CH$_3$O-C$_6$H$_4$, 25%; R^1 = 3-CH$_3$O-C$_6$H$_4$, 63%

Moreover, the cyclization mediated by bromine of 2-(prop-2-yn-1-ylthio)nicotinic acid 1477, leading to the 3-(bromomethylene)-8-carboxy-2,3-dihydrothiazolo[3,2-a]pyridin-4-ium tribromide 1478, proceeded in a 5-exo-dig mode with total chemoselection and regioselection. In fact, only the pyridinic nitrogen attacked the intermediate bromirenium ion, whereas the carboxy group was not involved in the reaction, but the formation of bromomethylene functionality occurred without stereoselection [649].
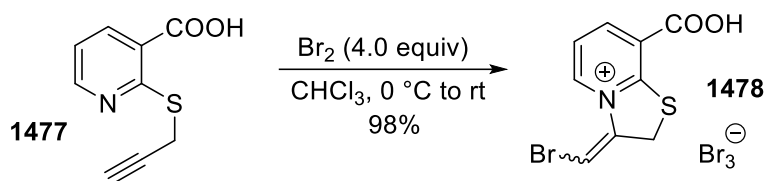
In a similar cyclization 8-(prop-2-ynylsulfanyl)quinoline 1479, on treatment with iodine or bromine, afforded the corresponding salts 1480a,b in excellent yield, and cyclization proceeded in a 6-exo-dig mode owing to structural bias, but the double bond of the halomethylene functionality was formed with total (E)-stereoselection [650].
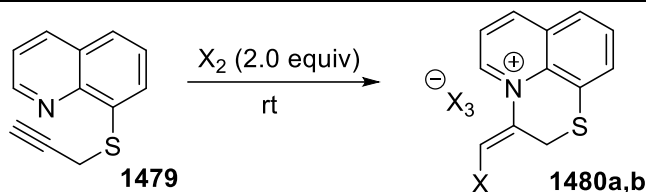
a. X = I, ethyl ether, 85%; **b.** X = Br, DCM, 93%

The compound 1481, arising from 2-thioquinoline, on treatment with iodine, gave the dication 1482 whose yield was not reported, but the structure was assigned by X-ray diffraction analysis [651].
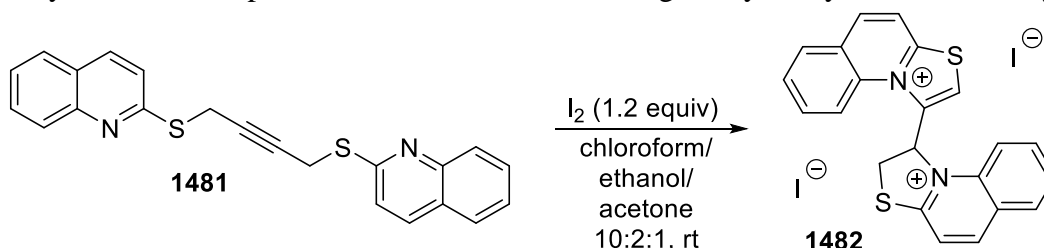
The cyclization of 4-alkynyl-1-methoxy-1H-pyrano[4,3-b]quinolines 1483was carried out with excess iodine to afford in good yield pyrrolo[1,2a]quinolones 1484, via 5-endo-dig cyclization followed by cleavage of the enolacetal functionality, leading to two carbonyl groups [652].

R^1 = 4-CH$_3$-C$_6$H$_4$, R^2 = C$_6$H$_5$, 81%;
R^1 = R^2 = C$_6$H$_5$, 80%; R^1 = cyclohexyl, R^2 = C$_6$H$_5$, 70%
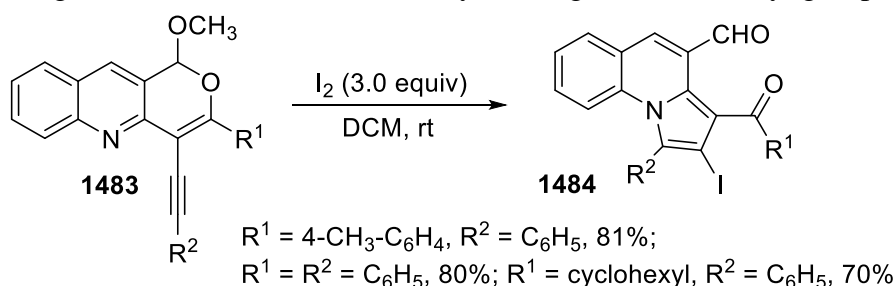
Eventually, pyridine derivatives 1485 underwent iodocyclization with iodine in a basic medium, followed by shift 1,2 of the methyl group, to give 2-iodo indolizinones 1486 in excellent yield [653].
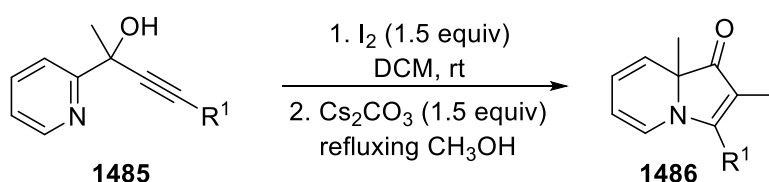
R^1 = C$_6$H$_5$, 99%; R^1 = 4-CH$_3$-C$_6$H$_4$, 97%; R^1 = 3-thienyl, 93%

The reaction of 3-aryl-5-(prop-2-ynylthio)-1H-1,2,4-triazoles 1487 was carried out with NIS, to give in moderate yield the corresponding (E)-5-(iodomethylene)-3-aryl-5,6-dihydrothiazolo[2,3-c][1,2,4]triazoles 1488 in moderate yield but with total stereoselection, the double bond displaying only the (E)-configuration [654].
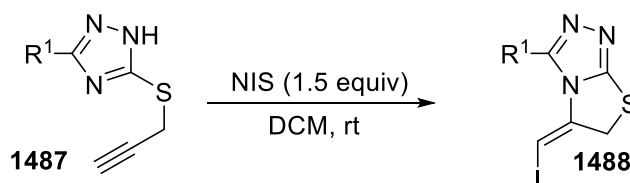
R^1 = 4-CH$_3$-C$_6$H$_4$, 55%; R^1 = 4-CF$_3$-C$_6$H$_4$, 58%; R^1 = 4-CH$_3$O-C$_6$H$_4$, 59%

On the contrary, 3-aryl-4-phenyl-5-(prop-2-yn-1-ylthio)-4H-1,2,4-triazoles 1489, where a hydrogen atom on nitrogen is missing, afforded the corresponding salts 1490 in moderate to good yield with total stereoselection, the newly formed double bond displaying again the (E)-configuration, exclusively [655].

1489   **1490** C_6H_5
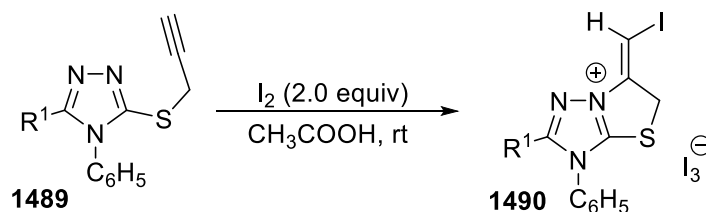
$R^1 = C_6H_5$, 82%, $R^1 = 4\text{-}Br\text{-}C_6H_4$, 77%; $R^1 = CH_2C_6H_5$, 62%

2-(But-3-yn-1-yl)-1H-benzo[d]imidazoles **1491** underwent cyclization mediated by iodine in the presence of AgNO₃, and the regiochemistry of the process strongly relied on structural features. In fact, 4-unsubstituted alkynes afforded in good yield the substituted (E)-1-(iodomethylene)-2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazoles **1492** through a 5-exo mode closure, with total (E)-stereoselection at the double bond. On the contrary, the reaction of 4-substituted alkynes proceeded in a 6-endo mode, leading to the substituted 2-iodo-3,4-dihydrobenzo[4,5]imidazo[1,2-a]pyridines **1493**, exclusively [656].

1491   **1492**   or   **1493**

$R^1 = R^2 = H$, 94%; $R^1 = H$, $R^2 = C_6H_5$, 90%;

$R^1 = CH_3$, $R^2 = H$, 90%; $R^1 = H$, $R^2 = 4\text{-}CH_3OC_6H_4$, 90%;

$R^1 = Cl$, $R^2 = H$, 94% $R^1 = Cl$, $R^2 = C_6H_5$, 82%
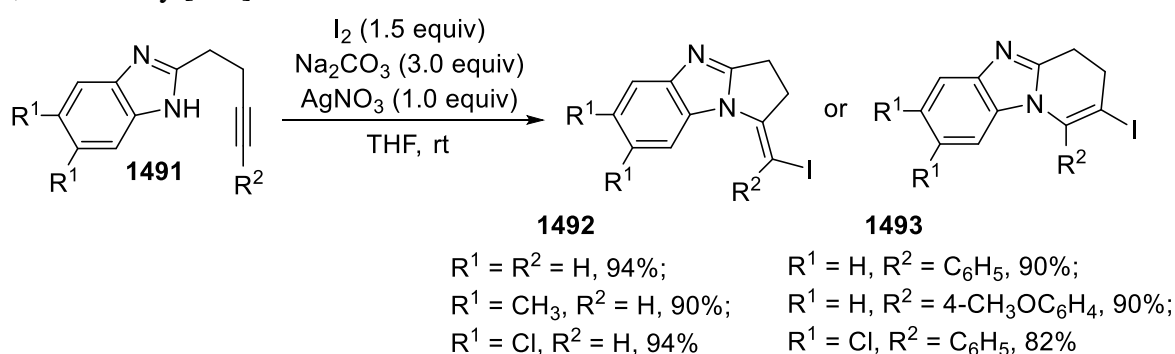
When the 2-substituent of 1H-benzo[d]imidazole was a 4-pentyn-1-yl group, as in **1494**, formation of a 6-membered ring was preferred over the 7-membered ring, and the tricyclic compounds **1495** were exclusively obtained through a regioselective and stereoselective 6-exo-dig mode of cyclization, with (E)-configuration of the double bond [656].

1494   **1495**

$R^1 = R^2 = H$, 93%; $R^1 = Cl$, $R^2 = H$, 90%; $R^1 = H$, $R^2 = C_6H_5$, 81%
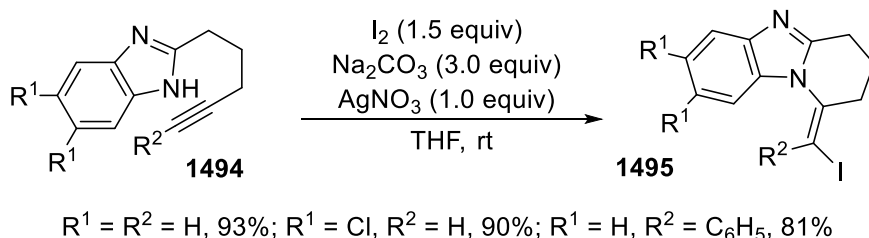
A similar behavior was observed for the cyclization of 2-alkynyl-1H-benzo[d]imidazoles **1496**. In fact, when the triple bond was substituted by an aryl group, the reaction always proceeded in excellent yield through a 6-endo-dig mode to give cations **1497**, whereas via a 5-exo-dig cyclization, the cations **1499** were obtained from unsubstituted or alkyl substituted alkynes **1498** with total (E)-stereoselection [657].

1496   **1497**

$R^1 = C_6H_5$, 84%, $I_3^{\ominus}$ 10%, $I^{\ominus}$ 74%; $R^1 = 4\text{-}CH_3C_6H_4$, 92%, $I_3^{\ominus}$ 6%, $I^{\ominus}$ 84%;

$R^1 = 4\text{-}CH_3OC_6H_4$, 92%, $I_3^{\ominus}$ 7%, $I^{\ominus}$ 85%

R^1 = H, 92%; R^1 = C(CH$_3$)$_2$OH, 100%
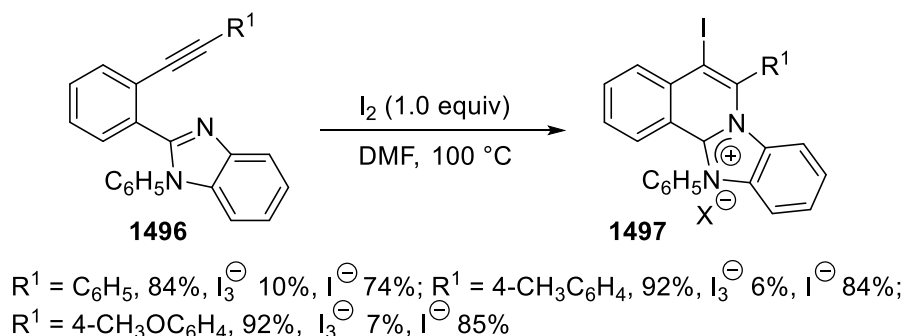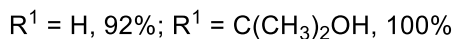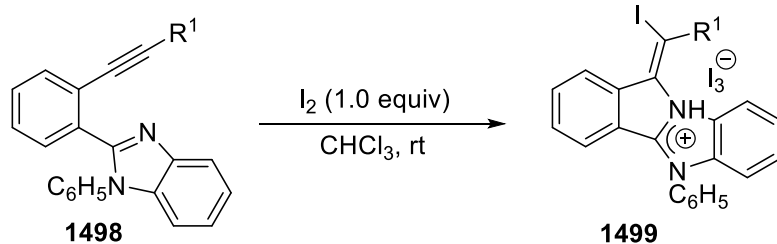
With excess iodine and in the presence of a catalytic amount of CuI, the 2-(2-ethynylphenyl)-1H-benzo[d]imidazole derivatives 1502, prepared from 2-alkynyl benzaldehydes 1500 and benzene-1,2-diamine 1501, were directly transformed in moderate yield via a 6-endo-dig cyclization into substituted 5-iodobenzo[4,5]imidazo[2,1-a]isoquinolines 1503 using iodine in the presence of a catalytic amount of CuI [658].

R^1 = C$_6$H$_5$, R^2 = CH$_3$, 71%; R^1 = C$_6$H$_5$, R^2 = F, 70%; R^1 = n-C$_6$H$_{13}$, R^2 = H, 58%
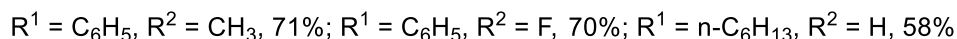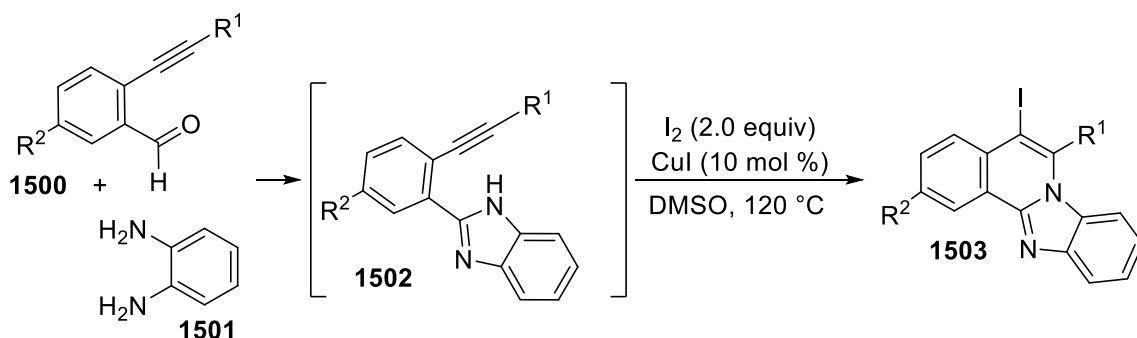
When 6-amino-2-(prop-2-yn-1-ylthio)pyrimidin-4(3H)-one 1504 underwent cyclization mediated by iodine, 5-amino-3-(iodomethylene)-7-oxo-2,3,7,8-tetrahydrothiazolo [3,2-a]pyrimidin-4-ium iodide 1505 was obtained through a 5-exo-dig mode in moderate yield but with total stereoselection, the double bond displaying (Z)-configuration, exclusively [659].
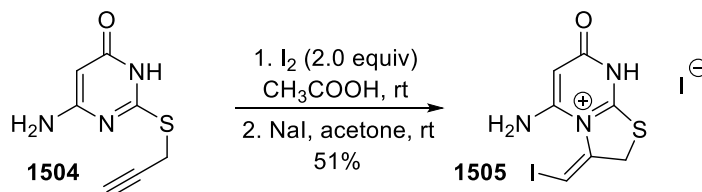
On the other hand, when 2-(prop-2-yn-1-ylthio)pyrido[3,4-d]pyrimidin-4(3H)-one 1506, containing the same reacting substructure, was treated with iodine, after basic treatment, the corresponding tricyclic derivative 9-(iodomethylene)-8,9-dihydro-5H-pyrido[4,3-e]thiazolo[3,2-a]pyrimidin-5-one 1507 was obtained in low yeld but with total (Z)-stereoselection [478].
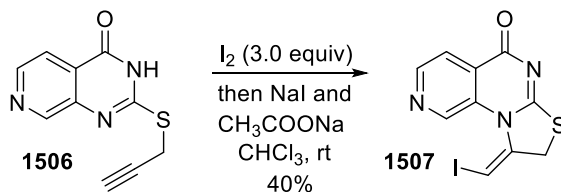
3.3. S-C(sp^2) and Se-C(sp^2) bond formation by an attack of sulfur and selenium nucleophiles.

3.3.1. 3-Iodothiophenes from thiols and thioethers and 3-iodoselenophenes from selenides.

The attack of thiols and thioethers to a halirenium ion was exploited with the aim of preparing dihydrothiophene and thiophene derivatives [660]. Thus, the cyclization of 1-mercapto-3-alkyn-2-ols

1508a, mediated by excess iodine in basic medium, allowed to obtain fully substituted 3-iodothiophenes 1509a in good yield via a 5-endo-dig closure [661]. Moreover, fully substituted 3-iodothiophenes 1509b were isolated in moderate to good yield starting from thiols 1508b when an ionic liquid such as EmimEtSO4 was employed as a solvent in the absence of a base [662]. In alternative to ionic liquids, a mixture of choline chloride-glycerol was also effective in providing fully substituted 3-iodothiophenes 1509c in good yield starting from thiols 1508c [663].
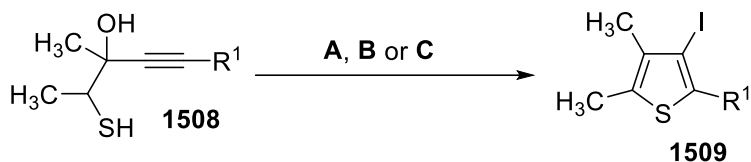
A. I_2 (2.0 equiv), $NaHCO_3$ (2.0 equiv), MeCN, rt
a: R^1 = C_6H_5, 71%; R^1 = 4-CH_3-C_6H_4, 83%; R^1 = n-C_4H_9, 67%
B. I_2 (2.0 equiv), $EmimEtSO_4$, rt
b: R^1 = 3-thienyl, 62%; R^1 = n-C_4H_9, 95%; R^1 = t-C_4H_9, 64%
C. I_2 (1.2 equiv), choline chloride:glycerol 1:2, rt
c: R^1 = C_6H_5, 80%; R^1 = n-C_4H_9, 72%; R^1 = 4-CH_3-C_6H_4, 78%

In analogy, starting from homopropargyl selenides 1510, on treatment with iodine the corresponding 5-substituted 4-iodo-2,3-dihydroselenophenes 1511 were obtained, suitable to be converted into selenophenes by further reaction with DDQ [664-666].
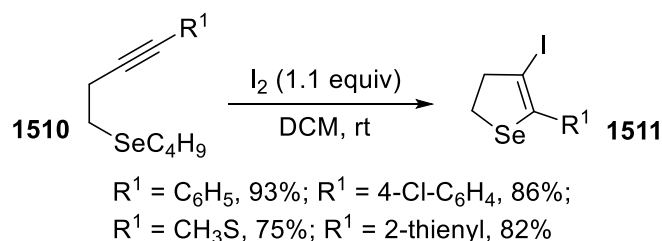
R^1 = C_6H_5, 93%; R^1 = 4-Cl-C_6H_4, 86%;
R^1 = CH_3S, 75%; R^1 = 2-thienyl, 82%

On the other hand, the cyclization of selenoethers 1512, displaying three carbon atoms within selenium and the triple bond, was carried out with iodine and proceeded in a 5-exo-dig mode. The corresponding 2-[iodo(aryl)methylene)]tetrahydroselenophenes 1513 were obtained in good yield with total regio- and (E)-stereoselection, a mixture E:Z being observed only when the substituent was 2-methylphenyl group, clearly owing to steric hindrance [667].
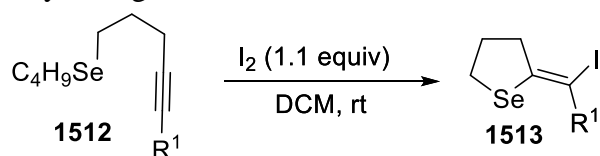
R^1 = C_6H_5, 93%; R^1 = 4-CH_3-C_6H_4, 77%; R^1 = 2-naphthyl, 85%;
R^1 = 2-CH_3-C_6H_4, 90%, 5.5:1 d.r. *E:Z*

On the other hand, the cyclization of enynyl thioethers 1514 led to the disubstituted 3-iodothiophenes 1515 in moderate to good yield [668-669].
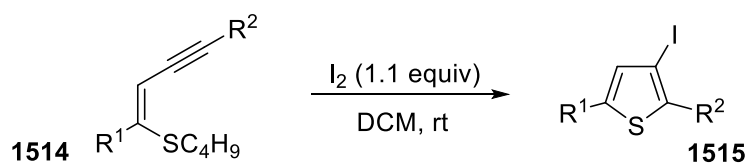
In a green process, the halogen was generated by oxidation of halide anions with Cu(II), and either thioethers 1516 and selenoethers 1518 displaying an enyne moiety gave the corresponding 3-iodothiophenes 1517 or selenophenes 1519, respectively, in excellent yield [670].

Y = S, **1516**
Y = Se, **1518**

Y = S, **1517**
Y = Se, **1519**
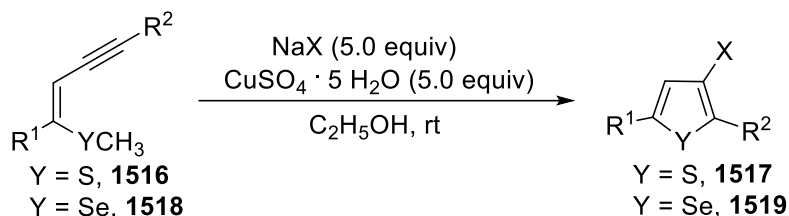
Y = S, R^1 = R^2 = C$_6$H$_5$: X = Cl, 92%; X = Br, 86%; X = I, 90%;
R^1 = R^2 = 3-thienyl, X = Cl, 91%; X = I, 91%
Y = Se, R^1 = R^2 = C$_6$H$_5$: X = Cl, 81%; X = I, 95%

Starting from 4,5-dihydroselenophene derivatives 1520a (X = S), containing an enyne moiety, the cyclization carried out with iodine proceeding in a 5-exo-dig mode allowed to prepare in moderate to good yield 5-substituted 3-iodo-4,5-dihydroselenopheno[2,3-b]thiophenes 1521a. On the contrary, starting from 4,5-dihydroselenophene derivatives 1520b (X = Se), 3-iodo-4,5-dihydroselenopheno[2,3-b]selenophenes 1521b were isolated in moderate to good yield, suitable for further elaboration by means of Sonogashira reaction [671].

1520a,b → **1521a,b**

I$_2$ (1.1 equiv)
DCM, rt
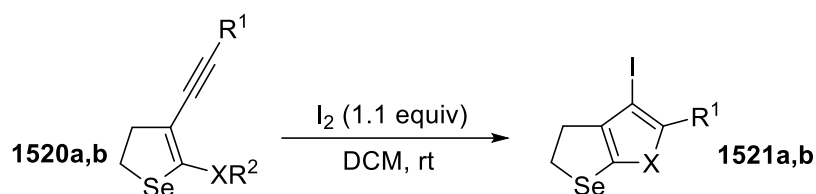
a. X = S, R^1 = C$_6$H$_5$, R^2 = CH$_3$, 70%; X = S, R^1 = t-C$_5$H$_9$, R^2 = CH$_3$, 40%;
b. X = Se, R^1 = C$_6$H$_5$, R^2 = n-C$_4$H$_9$, 72%; X = Se, R^1 = n-C$_5$H$_{11}$, R^2 = n-C$_4$H$_9$, 35%

Moreover, butylselenyl propargyl alcohols 1522 reacted with iodine to provide at first 2,3-dihydroselenophenes 1523, which by elimination of water were converted in good yield into 2-aryl 3-iodo-4,5,6,7-tetrahydrobenzo[b]selenophenes 1524 [672].

1522   **1523**   **1524**

I$_2$ (1.0 equiv)
DCM, 40 °C
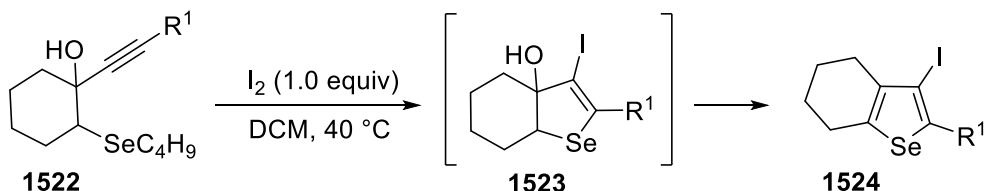
R^1 = C$_6$H$_5$, 77%; R^1 = 4-Cl-C$_6$H$_4$, 68%;
R^1 = 2-CH$_3$O-C$_6$H$_4$, 90%; R^1 = 1-naphthyl, 90%

Again, substituted 3-iodoselenophenes 1526 were obtained in good yield by reaction of (Z)-selenoenynes 1525 with iodine in the presence of alcohols [665],[673].

I$_2$ (1.5 equiv)
R^{1}OH (3.0 equiv)
DCM, rt

1525   **1526**
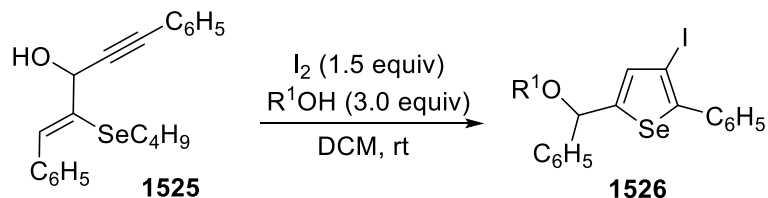
R^1 = C$_2$H$_5$, 80%; R^1 = n-C$_4$H$_9$, 72%; R^1 = CH$_3$, 78%; R^1 = C$_6$H$_5$CH$_2$, 87%

3.3.2. (*E*)-4-(Bromomethylene)-1,3-oxathiolanes from thioethers

By reaction with bromine, the 3-(benzylthio)-3-(prop-2-yn-1-yloxy)azetidin-2-ones 1527 gave the spirans 1528 in low yield with total stereoselection, the double bond displaying the (E)-configuration, exclusively [674].

$R^1 = C_6H_5$, 48%, $R^1 = 4\text{-}Br\text{-}C_6H_4$, 31%
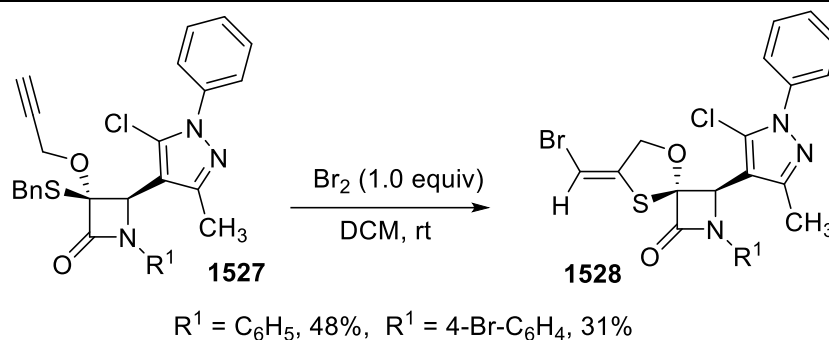
3.3.3. Benzothiophenes and benzoselenophenes from thioanisoles and selenoanisoles.

The most frequently reported ring closure leading to substituted benzothiophenes or benzoselenophenes involved an aryl thioether or selenoether [664, 675] where an alkynyl group was tethered on the aromatic ring at 2-position [521, 676-679]. Thus, exploiting a 5-endo-closure, the cyclization of thioethers 1529 afforded 3-iodobenzo[b]thiophenes 1530 in excellent yield [680-682].
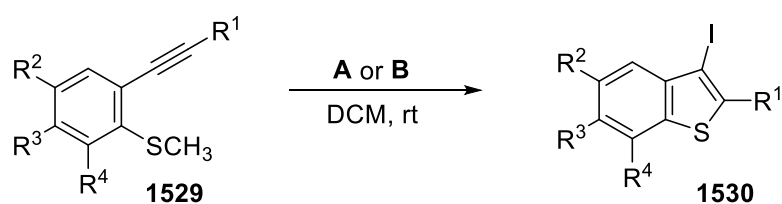
A: I_2 (1.25 equiv). $R^1 = C_6H_5$, $R^2 = R^3 =$ H, $R^4 = OCONEt_2$ 90%;
$R^1 = 4\text{-}CH_3O\text{-}C_6H_4$, $R^2 = R^3 =$ H, $R^4 = OCONEt_2$ 91%;
$R^1 = n\text{-}C_6H_{13}$, $R^2 = R^3 =$ H, $R^4 = OCONEt_2$ 92%;
B: I_2 (1.5 equiv). $R^1 = 4\text{-}CH_3S\text{-}C_6H_4$, $R^2 = OCH_3$, $R^3 = R^4 =$ H, 92%;
$R^1 = 3\text{-}CH_3O\text{-}C_6H_4$, $R^2 = OCH_3$, $R^3 = R^4 =$ H, 89%;
$R^1 = C_6H_5$, $R^2 = R^3 = R^4 =$ H, 91%

Moreover, according to a green methodology, iodide ion was oxidized to iodine by Fe(III) chloride, and 3-iodobenzo[b]thiophenes 1532 were obtained in very good yield starting from thioanisoles 1531 [683].
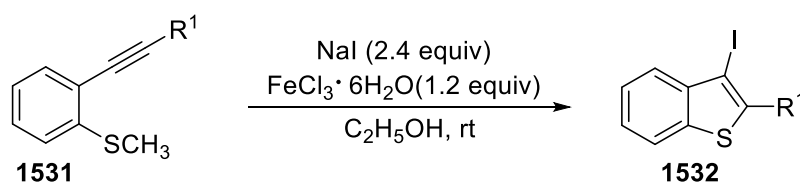
$R^1 = (CH_3)_3Si$, 92%; $R^1 = CH_2OH$, 86%; $R^1 = CH_2OCH_3$, 97%;
$R^1 = $ H, 56%; $R^1 = $ 1-cyclohexenyl, 83%

Furthermore, within the preparation of a new ligand for palladium, the bis-methylthio ether 1533 underwent cyclization mediated by iodine to give an excellent yield to the corresponding 2-[3-iodo-4-(methylthio)benzo[b]thiophen-2-yl)]pyridine 1534 [684].
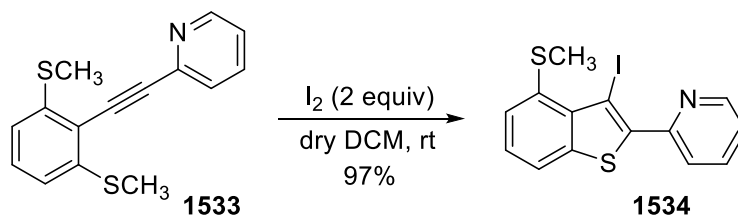
Within a new approach to desketoraloxifene analogs, the iodocyclization of thioether 1535, containing a methoxy group suitable for cyclization, afforded 3-iodobenzo[b]thiophene 1536 in good

yield with total regioselection, the corresponding 3-iodobenzofuran being not detected in the reaction mixture [685].

1535 → **1536**
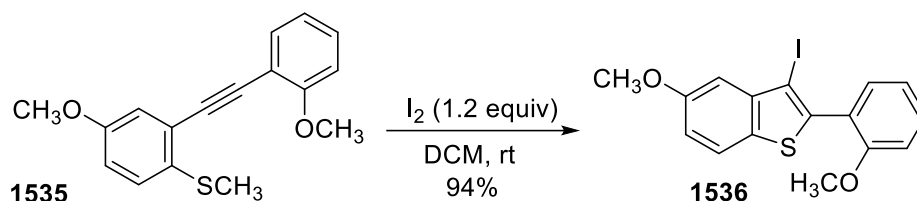
Depending on the alkyne substitution, different groups can lie at the 2-position of 3-iodobenzothiophenes arising from the cyclization of thioanisoles or selenoanisoles. Thus, in the presence of iodine and using alcohol as the solvent, the thioanisoles 1537 afforded a good yield 3-iodobenzothiophenes 1538, where the alkyl chain at C-2 bears an alkoxy group [686].

$R^1 = C_6H_5$, $R^2 = CH_3$, 78%; $R^1 = C_6H_5$, $R^2 = C_6H_5CH_2$, 84%;
$R^1 = CH_3$, $R^2 = C_6H_5CH_2$, 74%
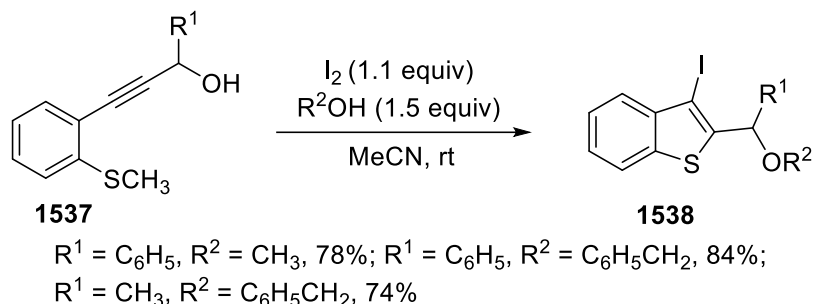
In analogy, starting from the selenoanisoles 1539 where the triple bond was substituted by a chain containing a chirality center, the 3-iodobenzo[b]selenophene derivatives 1540 were prepared in low yield, together with the products 1541, arising from cleavage of the protecting group [687].

a. n = 1, **1540a**, 60%, **1541a**, 37%;
b. n = 2, **1540b**, 38%, **1541b**, 47%
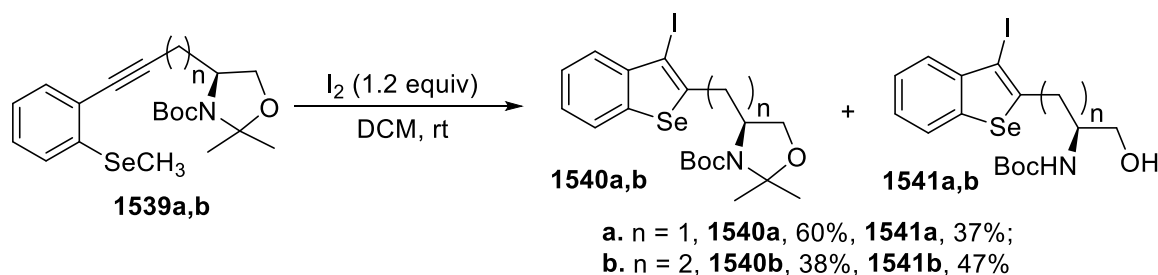
Eventually, starting from propargylic alcohols 1542, after an initial 5-exo-dig closure leading to intermediates 1543, the benzo[b]selenophene derivatives 1544, bearing a carbonyl group as a substituent at C-2, were isolated in moderate to good yield by reaction with iodine [665, 688].

$R^1 = C_6H_5$, 82%; $R^1 = 4\text{-Cl-}C_6H_4$, 69%; $R^1 = 4\text{-CH}_3\text{O-}C_6H_4$, 72%; $R^1 = H$, 68%
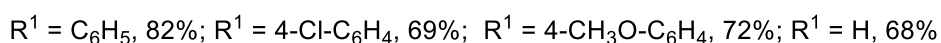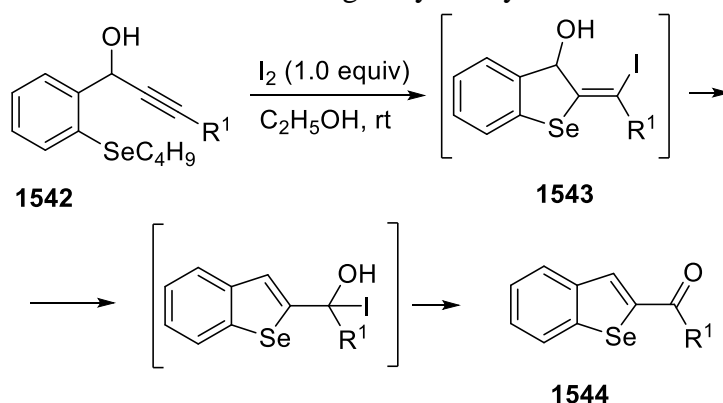
Moreover, when a diyne chain was placed at the 2-position of the aromatic ring of compounds 1545, the cyclization carried out at room temperature provided 3-iodobenzo[b]thiophenes 1546 displaying a triple bond suitable for further transformations using Pd-mediated coupling [689].

$R^1 = C_6H_5$, 95%; $R^1 = (CH_2)_2OH$, 94%;
$R^1 = (CH_2)_5OH$, 93%; $R^1 = TMS$, 82%
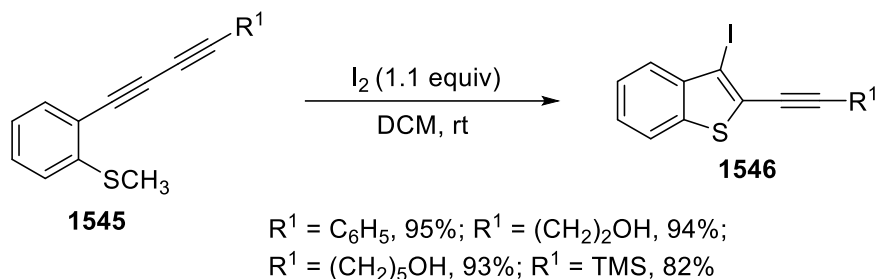
However, when the triple bond was substituted by an electron-withdrawing group, the iodocyclization required higher temperatures. Thus, the thioethers 1547 and 1549 afforded in good yield the corresponding 2-substituted 3-iodobenzo[b]thiophenes 1548 and 1550, respectively [539].

$R^1 = N(CH_3)_2$, 99%; $R^1 = OCH_3$, 92%; $R^1 = 2\text{-Br-}C_6H_4$, 100%
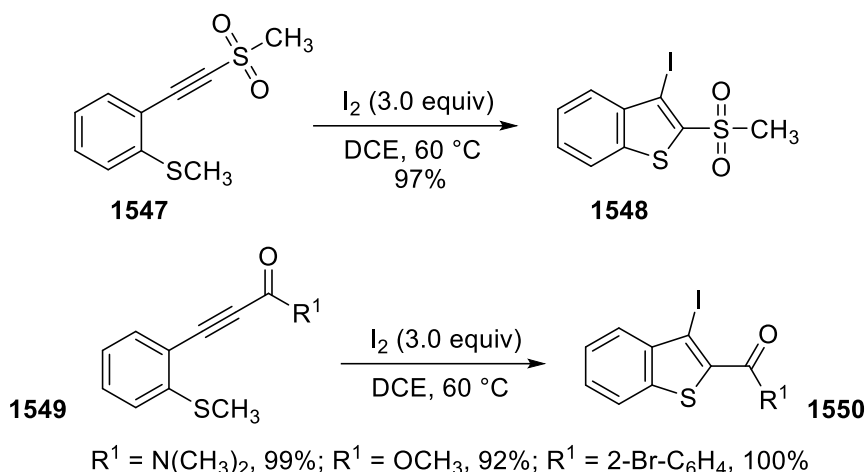
In order to prepare complex heterocyclic systems, depending on the substitution pattern at the aromatic ring, the cyclization of the thioethers 1551a,b, carried out with bromine, allowed to obtain in good yield 3-bromo-2-arylthieno[2,3-b]pyridines 1552a or 3-bromo-2-arylthieno[3,2-b]pyridines 1552b [690].

a. Y = N, Z = CH, $R^1 = C_6H_5$, 83%; Y = N, Z = CH, $R^1 = C_6H_5$, 73%;
b. Y = CH, Z = N, $R^1 = C_6H_5$, 89%; Y = CH, Z = N, $R^1 = 4\text{-CH}_3\text{O-}C_6H_4$, 98%
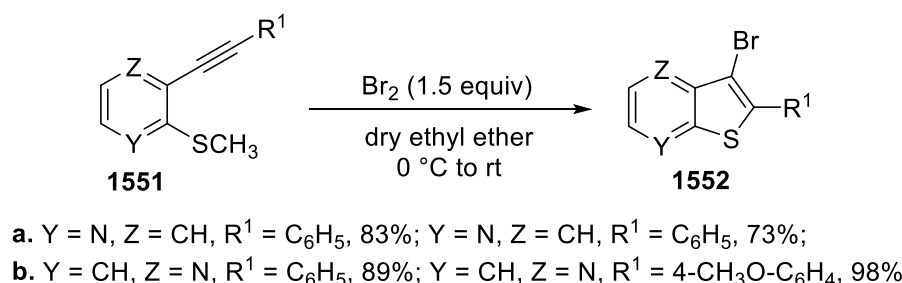
Furthermore, the cyclization of 2-(methylthio)-3-(phenylethynyl)quinoxaline 1553, carried out with ICl, allowed to prepare in good yield 3-iodo-2-phenylthieno[2,3-b]quinoxaline 1554 [691].
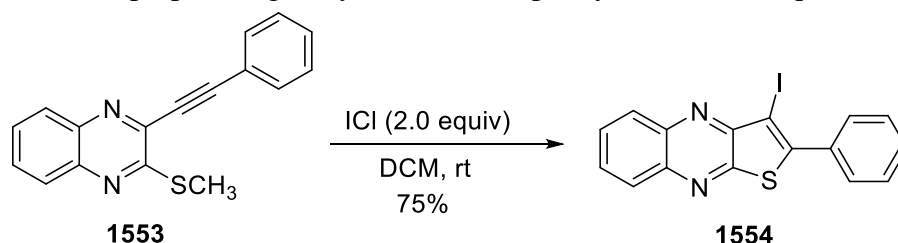
Also, NIS was effective for the cyclization of thioethers or selenoethers 1555 and 1557 via 5-endo-dig mode, and the corresponding thieno[2,3-b]quinoline 1556 and selenopheno[2,3-b]quinoline derivatives 1558 were isolated in moderate to good yield [692].
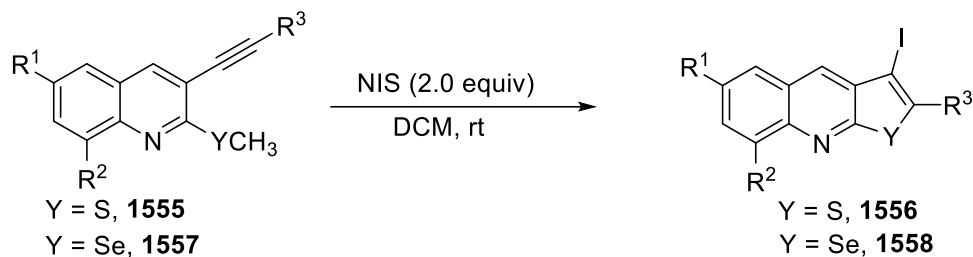
Y = S: $R^1 = CH_3$, $R^2 = R^3 = H$, 69%; $R^1 = R^3 = H$, $R^2 = CH_3$, 72%;
$R^1 = R^2 = R^3 = H$, 61%; $R^1 = R^2 = H$, $R^3 = Br$, 84%;
Y = Se: $R^1 = CH_3$, $R^2 = R^3 = H$, 64%; $R^1 = CH_3$, $R^2 = H$, $R^3 = Br$, 72%;
$R^1 = R^2 = R^3 = H$, 60%; $R^1 = R^2 = H$, $R^3 = Br$, 71%;

In addition, N-alkynyl-2-(butylselenyl)imidazoles 1559 were treated with iodine to give a good yield of the corresponding 2-substituted 3-iodoimidazo[2,1-b][1,3]selenazoles 1560, according to a 5-endo-dig closure [693].
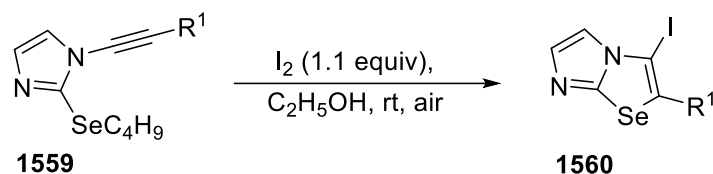
$R^1 = C_6H_5$, 86%; $R^1 = 4\text{-}CH_3\text{-}C_6H_4$, 78%; $R^1 = n\text{-}C_5H_{11}$, 78%

The cyclization of thioethers 1561 led to halogenated benzo[b]naphtho[2,1-d] thiophene derivatives 1562 in good yield, at first via formation iodiranium ion, followed by the formation of a new C-C bond with the catalysis of Au and eventual attack by thioether functionality to give the tetracyclic structures [694].
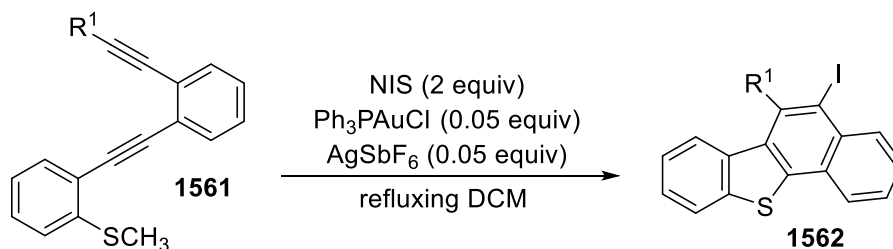
$R^1 = n\text{-}C_5H_{11}$, 82%; $R^1 = 4\text{-}CH_3\text{-}C_6H_4$, 80%; $R^1 = 4\text{-}CH_3OC_6H_4$, 67%

A reiterative iodocyclization was also used for the preparation of complex heterocyclic compounds. In fact, by halocyclization of 1563, the 3-iododerivative 1564 was at first prepared, followed by alkynylation to give the derivative 1565. A subsequent iodocyclization afforded the tricyclic derivative 1566 that, by a further alkynylation, gave 1567, eventually converted by iodocyclization into the tetracyclic compound 1568 in excellent yield [695].

1566 → **1567** $\xrightarrow{\substack{I_2 \ (1.3 \ equiv) \\ TBAI \ (0.3 \ equiv) \\ DCE, \ 80 \ °C \\ R^1 = C_6H_5, \ 99\%}}$ **1568**
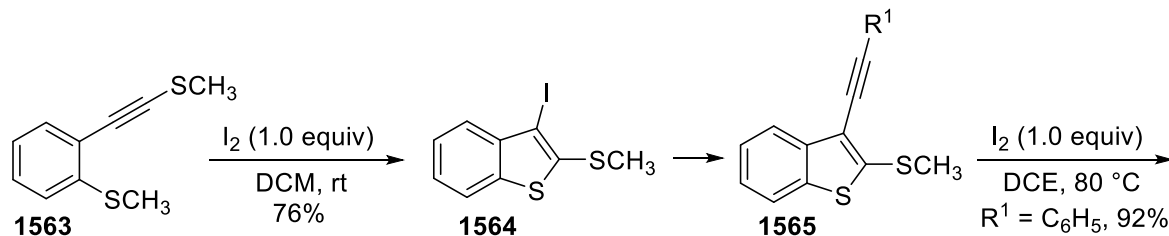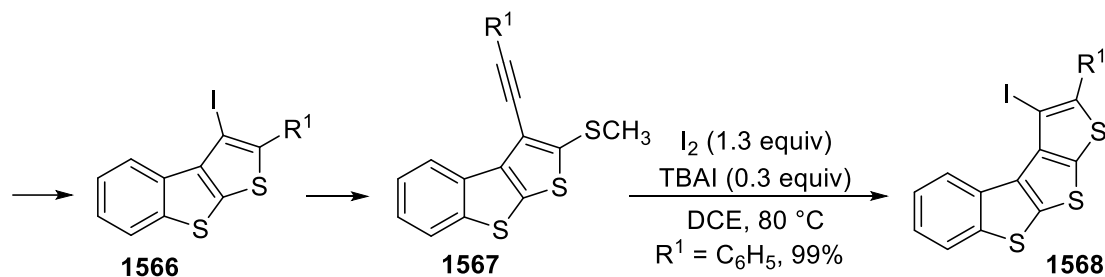
Eventually, both bis(3-iodobenzo[b]thiophen-2-yl)(phenyl)phosphine oxide 1570 and tris(3-iodobenzo[b]thiophen-2-yl)(phenyl)phosphine oxide 1572 were obtained by cyclization of compounds 1569 and 1571, respectively, carried out with excess iodine [598].

1569 $\xrightarrow{\substack{I_2 \ (5.0 \ equiv) \\ DCE, \ 50 \ °C \\ 82\%}}$ **1570**

1571 $\xrightarrow{\substack{I_2 \ (10.0 \ equiv) \\ DCE, \ 50 \ °C \\ 82\%}}$ **1572**
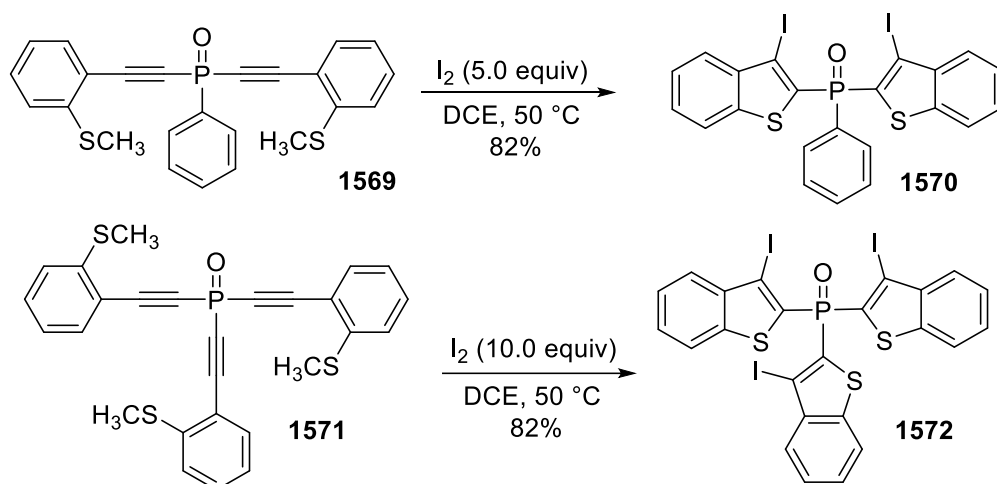
3.3.4. 1,4-dihydro-2*H*-benzo[*d*][1,3]thiazin-2-imines from thioureas.

Alkynyl thiocyanate 1573 was treated with primary amines to give in situ the intermediate thioureas 1573 that underwent cyclization by iodine to provide in good yield the corresponding 4-(1-iodopentylidene)-1,4-dihydro-2H-benzo[d][1,3]thiazin-2-imines 1575 with total stereoselection (E) at the C=C double bond [696].

1573 $\xrightarrow{\substack{R^1NH_2 \ (1.1 \ equiv) \\ I_2 \ (1.3 \ equiv) \\ Cs_2CO_3 \ (1.5 \ equiv) \\ DCE, \ 65 \ °C}}$ **1574** → **1575**
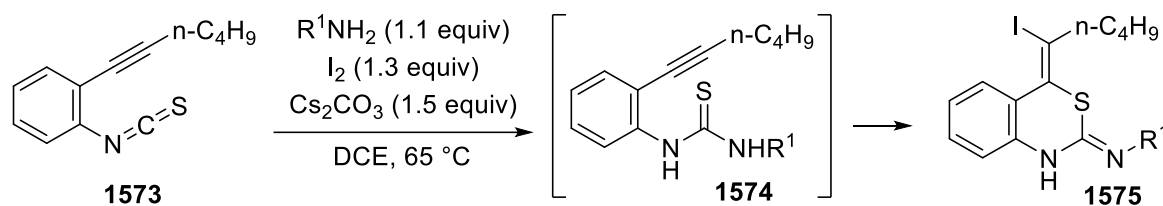
$R^1 = C_6H_5$, 84%; $R^1 = CH_2C_6H_5$, 81%; $R^1 = $ cyclohexyl, 81%

On the contrary, when secondary amines reacted with thiocyanate 1576, the corresponding intermediate thioureas 1577 by cyclization mediated by iodine gave the 4-(1-iodopentylidene)-4H-benzo[d][1,3]thiazin-2-amines 1578 in good yield and total (E)-stereoselection at the C=C double bond [696].

1576 $\xrightarrow{\substack{R^1R^2NH \ (1.1 \ equiv) \\ I_2 \ (1.3 \ equiv) \\ Cs_2CO_3 \ (1.5 \ equiv) \\ DCE, \ 65 \ °C}}$ **1577** → **1578**
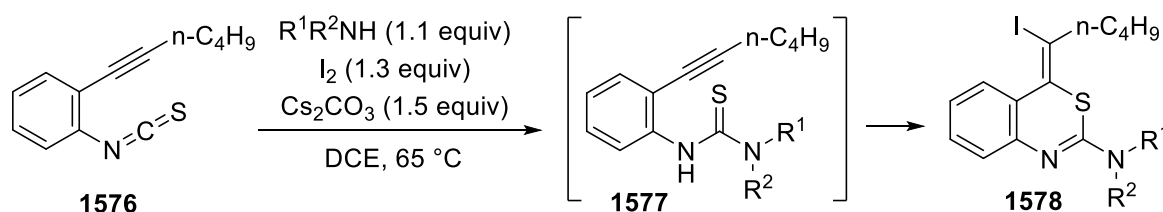
$R^1...R^2 = $ -(CH_2)_5-, 89%; $R^1...R^2 = $ -(CH_2)_4-, 88%; $R^1 = R^2 = C_2H_5$, 90%

In addition, when the thioureas 1579 bearing an unsubstituted allene group were treated with iodine, the cyclization proceeded with total regioselection, and 3,4-dihydro-2H-1,3-thiazin-2-imine derivatives 1580 were isolated in moderate yield [508].

$R^1 = C_6H_5$, 70%; $R^1 = 3\text{-}CH_3\text{-}C_6H_4$, 72%; $R^1 = 3\text{-}Cl\text{-}C_6H_4$, 69%
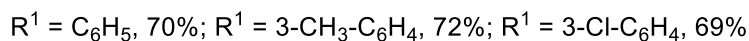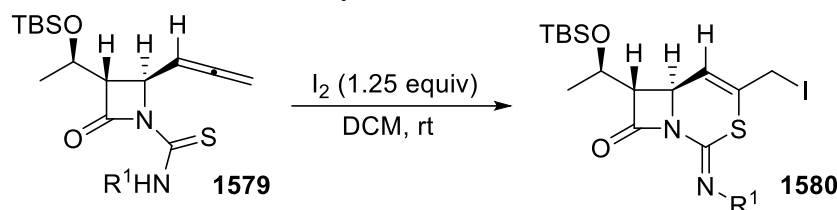
3.3.5. 3-Iodothiophenes from dithioacetals and xanthates.

Starting from 1-(1,3-dithian-2-yl)propargylamines 1581, 4-amino-3-iodothiophenes 1583 were obtained in moderate to good yield by cyclization mediated by iodine via the intermediates 1582, and the reaction proceeded regioselectively in a 5-endo-mode [697].

X = O, $R^1 = 4\text{-}CH_3\text{-}C_6H_4$, $R^2 = C_6H_5$, 74%; X = CH_2, $R^1 = 4\text{-}CH_3\text{-}C_6H_4$, $R^2 = C_6H_5$, 44%;
X = O, $R^1 = R^2 = C_6H_5$, 69%; X = C_2H_5N, $R^1 = 4\text{-}CH_3\text{-}C_6H_4$, $R^2 = C_6H_5$, 61%
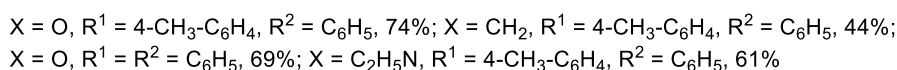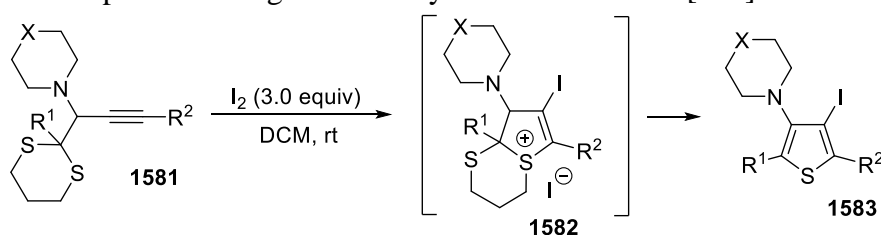
Moreover, in boiling, DMSO bromoenynes 1584 were first converted into the xanthates 1585 that eventually provided in good yield the substituted 3-iodothiophenes 1586 via iodocyclization proceeding in a 5-endo-dig mode, exploiting the in situ formation of iodine arising from the decomposition of ammonium iodide [698].

$R^1 = C_6H_5$, $R^2 = R^3 = n\text{-}C_3H_7$, 87%; $R^1 = 4\text{-}Br\text{-}C_6H_4$, $R^2 = R^3 = n\text{-}C_3H_7$, 82%;
$R^1 = 4\text{-}C_2H_5\text{-}C_6H_4$, $R^2 = R^3 = n\text{-}C_4H_9$, 86%; $R^1 = C_6H_5(CH_2)_3$, $R^2 = R^3 = n\text{-}C_3H_7$, 72%
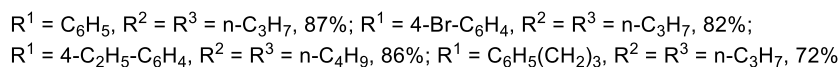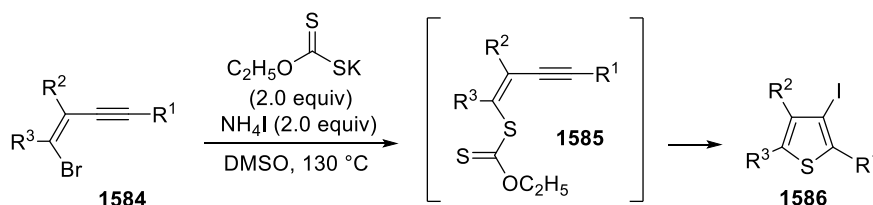
3.3.6. Miscellaneous sulfur and selenium-containing heterocycles.

Starting from alkynyl thioethers 1587 and selenoethers 1589a,b, 4-iodo-3-aryl-1H-isothiochromenes 1588 and 1H-isoselenochromenes 1590a,b were respectively isolated in moderate to good yield by iodocyclization proceeding in a 6-endo-dig mode [699].

X = S, **1587**
X = Se, **1589a,b**

X = S, **1588**
X = Se, **1590a,b**

1587, $R^1 = 4\text{-}CH_3\text{-}C_6H_4$, $R^2 = CH_3$,
1589a. $R^1 = C_6H_5$, $R^2 = n\text{-}C_4H_9$
1589b. $R^1 = 3\text{-}CH_3\text{-}C_6H_4$, $R^2 = n\text{-}C_4H_9$

1588, $R^1 = 4\text{-}CH_3\text{-}C_6H_4$, 55%;
1590a. $R^1 = C_6H_5$, 69%;
1590b. $R^1 = 3\text{-}CH_3\text{-}C_6H_4$, 70%
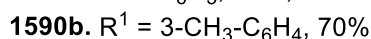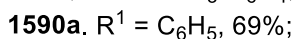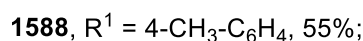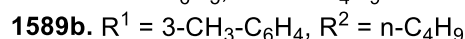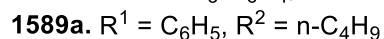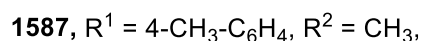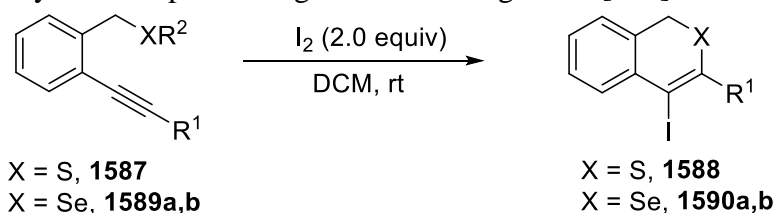
5. Conclusions

For more than a hundred years after the first electrophilic halocyclization reaction [700], the carbon-heteroatom bond-forming reactions were a central theme of organic synthesis. Thus, novel methodologies involving attack to haliranium and halirenium ions by nucleophilic functionalities containing O, N, S, and Se directed to prepare valuable heterocyclic intermediates as well as complex natural products were continuously developed. These reactions were carried out under relatively mild conditions and tolerated a wide variety of functional groups, thus avoiding protection group chemistry, and proceeded in excellent yields with high regio- and stereoselection. However, despite the impressive increase in the number of publications that recently appeared in the literature on the preparation of heterocycles via electrophilic cyclization exploiting catalytic and/or asymmetric methodologies, many interesting problems wait to be solved, and we hope that the present review can be useful to inspire solutions to some of the remaining challenges.

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Conflicts of Interest

The authors declare no conflict of interest.

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