Review

Chiral non Aromatic Nitrogen-Heterocycles by Asymmetric Intramolecular Haloamination and Haloamidation

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Review

Chiral Non Aromatic Nitrogen-Heterocycles by Asymmetric Intramolecular Haloamination and Haloamidation

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Abstract: This review deals with the functionalization of double bonds carried out in the presence of a chiral catalyst exploiting the intramolecular attack to haliranium ions by nucleophilic nitrogen of amides or carbamates prepared from achiral aminoalkenes, and the C-N bonds formation leads to highly enantioenriched non-aromatic heterocycles. A range of protocols are reported, emphasizing the synthesis of many natural and biologically active products of pharmacological interest prepared according to this methodology.

Keywords: non-aromatic heterocycles; haloamination; haloamidation; haliranium ion; stereoselectivity; chiral catalysts

1. Introduction

In the presence of a halenium ion source [1-3] an alkene can give rise to the corresponding intermediate haliranium ion 1 [4-5]. The subsequent nucleophilic attack by a nitrogen atom appropriately tethered on the carbon chain, occurring through an *endo*- or an *exo*-mode [6-11], leads to a variety of non-aromatic *N*-heterocycles, whose structure strongly depends on either the substrate geometry and the nucleophilic functionality involved [12-17] (Figure 1).

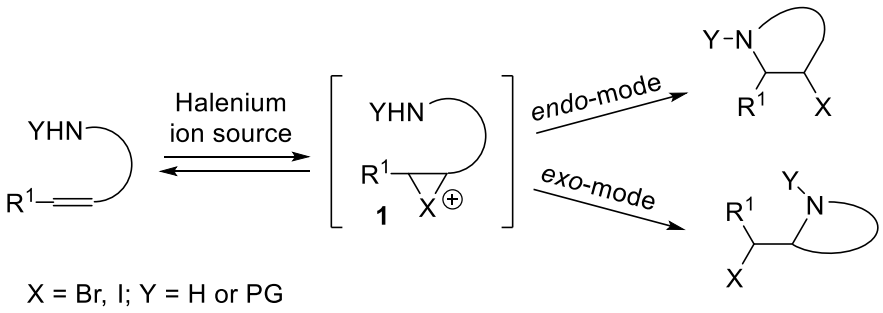

Figure 1. Formation of heterocyclic compounds via a haliranium intermediate, **1**.

The first intramolecular haloamination reactions of amino alkenes were carried out more than a century ago [18-20] and this methodology allowed to increase the molecular complexity of the starting material since a ring is created together with a halide functionality suitable for further derivatizations. In addition, when the nitrogen atom is tethered on a chiral center, two additional chiral centers can be introduced on the framework with definite configuration so that a lot of highly enantioenriched amino alkenes were easily converted into chiral polysubstituted non aromatic heterocycles generally using a source of halenium ions in a basic medium, the stereoselectivity being directed by internal asymmetric induction arising from in-tether chiral centers [21-27].

According to this methodology, a lot of highly enantioenriched amino alkenes were easily converted into chiral polysubstituted heterocycles exploiting intramolecular haloamination, generally using a source of halenium ions in a basic medium, and the stereoselectivity was directed

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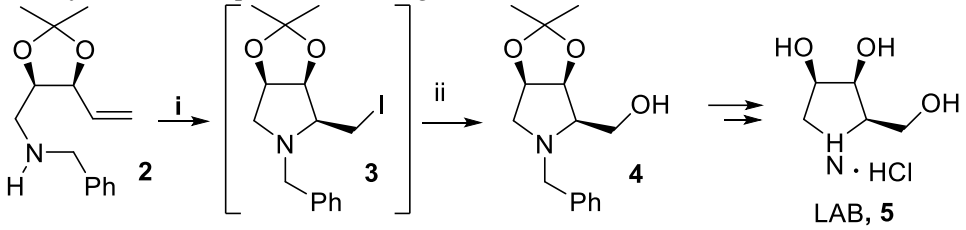
by internal asymmetric induction due to the chiral centers tethered in the substrate. On the contrary, to the best of our knowledge, starting from achiral amino alkenes, enantioselective intramolecular haloamination reactions were never carried out exploiting external asymmetric induction due to chiral catalysts, mainly derived from *Cinchona* alkaloids or BINOL, but the amino groups were always protected as sulfonyl amides or carbamates, so haloamidation is the most appropriate definition for this latter process. Within this field recently asymmetric methodologies were devised starting from achiral substrates, directed to prepare enantiomerically enriched non aromatic nitrogen-containing heterocycles, in particular natural products or bioactive molecules of therapeutic interest, and the development of improved ways directed towards the preparation of these compounds continues to be a challenging goal.

2. Asymmetric Synthesis Exploiting Substrate Directed Stereoselectivity

2.1. Polyfunctionalized Pyrrolidines

Many chiral polyhydroxy pyrrolidines isolated from natural sources, otherwise known as iminocyclitols or imino sugars, are able to inhibit glycosidases and other biologically relevant enzymes closely involved with the metabolism of *N*-linked glycoproteins [28-29]. Among the first examples of chiral amination, the aminoalkene **2**, bearing a dioxolanyl group, was used as starting material for the stereoselective synthesis of 1,4-dideoxy-1.4-manno-D-lyxitol, LAB, **5**, a potent competitive inhibitor of α-glucosidases [30-31]. The iodine-mediated cyclization proceeded according to a 5-*exo* mode in moderate yield and with total stereoselectivity leading to the iodomethyl intermediate **3** whose *cis*-2,3-disubstitution at the pyrrolidine ring, directed by the preexistent oxygenated functionality, can be explained by inspection of the transition states of the process [32-37]. Subsequently, this compound without isolation was converted in moderate yield into pyrrolidine **4** that eventually led to the expected iminosugar LAB, **5** (Scheme 1) [38].

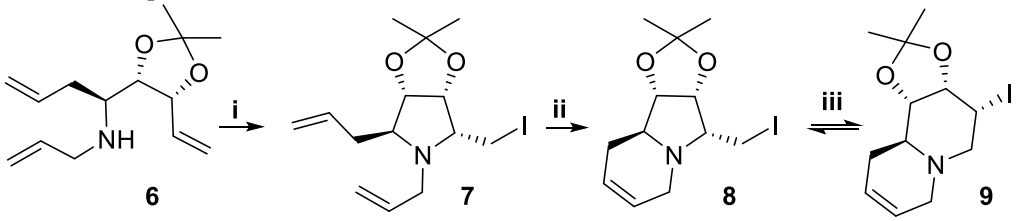


i. I_2 (1.6 equiv), $NaHCO_3$ (6.0 equiv), DME:H_2O 2:1, 0 °C,

ii. NaOH (42 equiv), $Bu_4N^+I^-$ (0.5 equiv), THF, 45% overall yield

Scheme 1. Iodocyclization leading to 1.4-dideoxy-1.4-manno-D-lyxitol, LAB, **5**.

Again exploiting the 2,3-*cis*-directing effect of ta dioxolanyl group [32-37], the iodomethyl pyrrolidine **7** was exclusively obtained in good yield with total regio- and stereoselectivity starting from secondary amine **6** and the subsequent metathesis reaction involving both the remaining allyl groups led in good yield to the iodomethyl indolizidine **8** that eventually equilibrated to the regioisomeric iodoquinolizidine **9** via an intermediate aziridine (Scheme 2) [39].



i. I_2 (1.2 equiv), $NaHCO_3$ (2.0 equiv), dioxane:H_2O 1;1, 0 °C, 87%.
ii. Grubbs' II catalyst, (0.01 equiv), CSA (1.1 equiv), DCM, -15 °C, 79%.
iii. refluxing DCM, 2 days, 2:1 equilibrium mixture.

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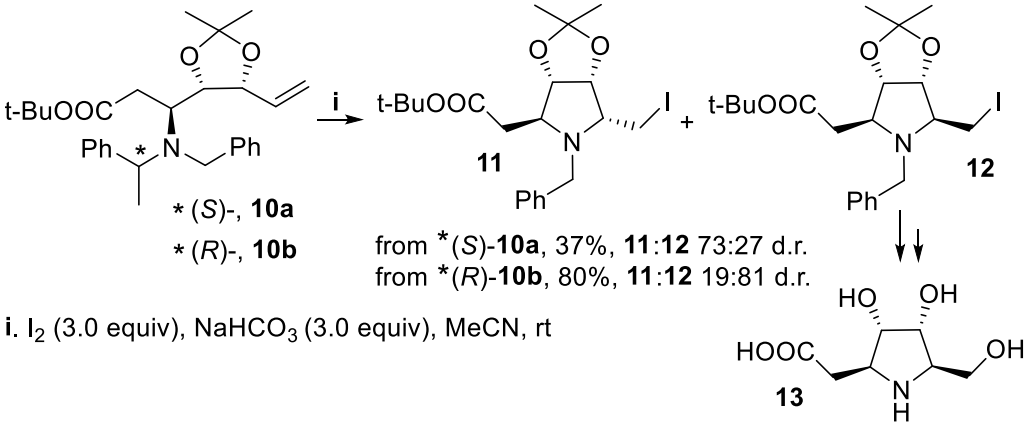
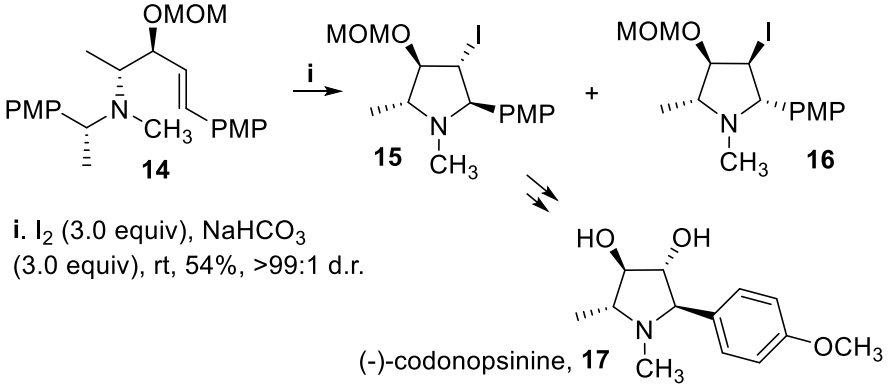
Scheme 2. Preparation of a regioisomeric mixture of iodomethyl indolizidine **8** and iodoquinolizidine **9**.

A matching/mismatching effect was observed when polyfunctionalized tertiary amines **10a** and **10b** underwent stereoselective iodine-mediated cyclization proceeding in a 5-*exo* mode, together with concurrent cleavage of the phenylethylamino group. In fact, starting from (*S*)-**10a**, the product **11**, where the iodomethyl group at at C-2 was *cis*- to the oxygen of dioxolanyl substituent, was isolated in low yield as the major isomer, and the reduced yield might indicate that at the transition state the phenylethyl substituent is displayed in such a manner so as to prevent facile approach of the substrate to the iodenium ions source. On the contrary, starting from (*R*)-**10b**, having the opposite configuration at the phenylethylamino group with respect to (*S*)-**10a**, the asymmetric induction arising from the configuration of the phenylethylamino group overwhelmed the directing effect of the oxygen atom of the *cis*-dioxolane moiety and the major isomer was pyrrolidine **12**, isolated in good yield, a useful intermediate for the synthesis of the polyhydroxylated pyrrolidine β-amino acid derivative **13** (Scheme 3) [40-41].



Scheme 3. Iodoyclization leading to polyhydroxylated pyrrolidine β-amino acid derivative **13.**

The iodoamination of the *anti*-tertiary homoallylic amine **14**, displaying the (*E*)-configuration at the double bond, was carried out under the same reaction conditions leading to removal of the phenylethylamino group and proceeded as expected in a 5-*endo* mode to give the corresponding chiral 3-iodopyrrolidines **15** and **16** in moderate yield but with excellent stereoselectivity. In fact, the 2,5-*trans* isomer **15** was practically the sole product isolated, and eventually converted into the pyrrolidine alkaloid (-)-codonopsinine **17** (Scheme 4), whereas the cyclization of the (*Z*)-isomer afforded only a complex mixture. The observed stereoselectivity was explained by inspection of the two possible iodiranium ions intermediates taking into account steric interactions at the transition states between substituents at C-4 and C-5 and substituents at nitrogen atom that completely overwhelmed the directing effect of oxygen at C-4 [42-43].



Scheme 4. Iodoyclization leading to **15**, key intermediate to alkaloid (-)-codonopsinine **17**.

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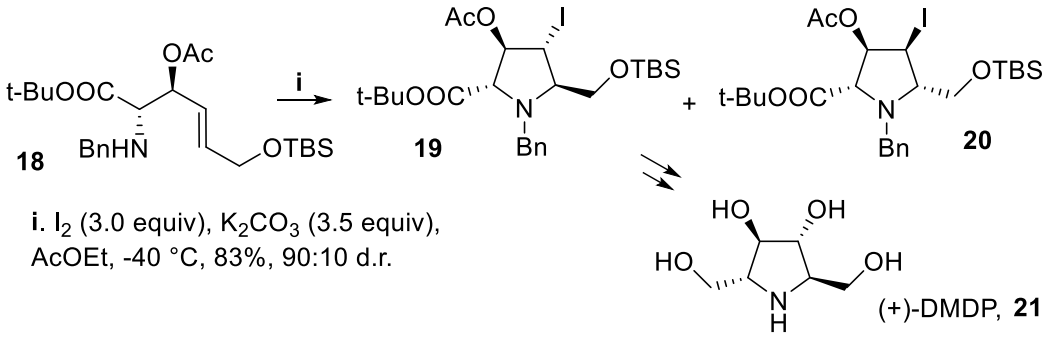
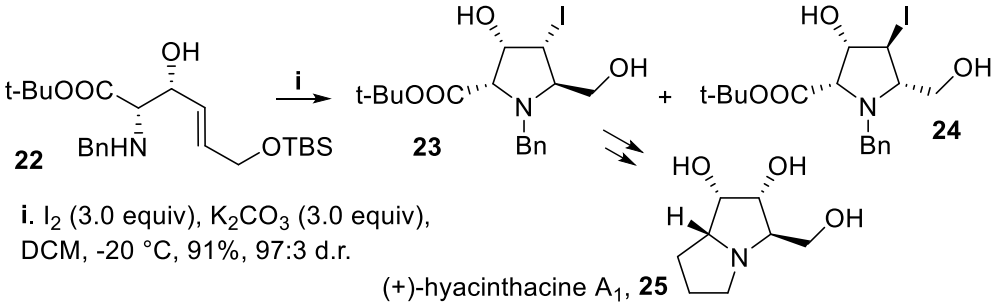
In addition, when the secondary *anti*-benzylamine **18** underwent iodocyclization according to a 5-*endo* mode, the reaction proceeded in good yield but with lower stereoselectivity, to give preferentially the isomer **19** with respect to **20**. The major isomer displayed 2,5-*trans* configuration, ascribed to steric interactions occurring at the transition state between the groups lieing at C-2 and C-5 positions, whereas the *cis*-1,2 directing effect of the acetoxy group was again largely ineffective. Compound **19** was eventually converted into a key intermediate for the synthesis of natural iminosugar (+)-DMDP, **21** [44], an *inhibitor of glucosidase I* [45] isolated from the leaves of *Derris elliptica* (Scheme 5) *[*46].



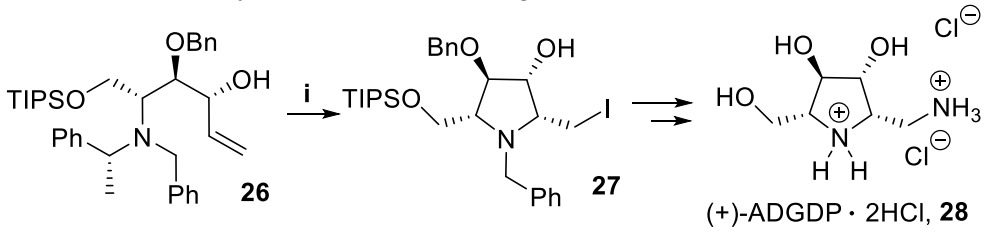
Scheme 5. Iodoyclization of *anti*-aminoalkene **18**, leading to (+)-DMDP, **21**.

On the other hand, the cyclization of compound **22**, displaying the *syn*-configuration, proceeded again in a 5-*endo* mode in good yield but with better stereoselectivity, probably owing to the 3,4-*cis*-directing effect of the hydroxy functionality matching with the 2,5-*trans*-disubstitution, leading mainly to the 2,5-*trans*-disubstituted derivative **23** [47] that was subsequently converted into a key intermediate for the synthesis of the alkaloid (+)-hyacinthacine A1, **25** (Scheme 6) [48].



Scheme 6. Iodoyclization of *syn*-aminoalkene **22**, leading to (+)-hyacinthacine A1, **25**.

However, the *bis*-homoallylic amine **26**, on treatment with iodine in a basic medium, underwent cyclization via 5-*exo* mode to give in very low yield but with nearly total stereoselectivity the polysubstituted pyrrolidine **27** where the 2,3-*cis* directing effect of the hydroxy group [32-37] overwhelmed the strain due to the resulting 2,5-*cis*-configuration, and this compound was the key intermediate to 1,2,5-trideoxy-1-amino-2,5-imino-D-glucitol, (+)-ADGDP, **28** (Scheme 7) [49].



Scheme 7. Iodoyclization of *bis*-homoallylic amine **26**, leading to (+)-ADGDP, **28**.

A different behavior was indeed observed when the *bis*-homoallylic amine **29**, diastereomeric with **26**, underwent stereoselective iodoamination to the intermediate **30**, followed by in situ

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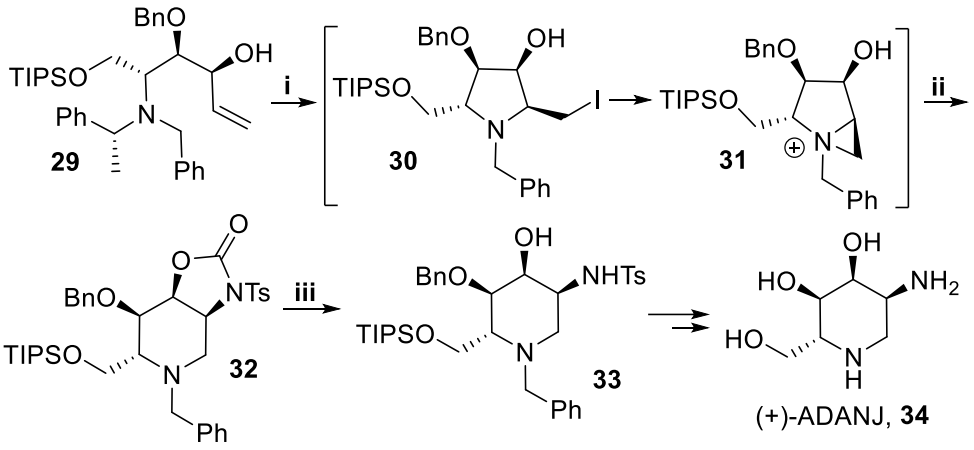
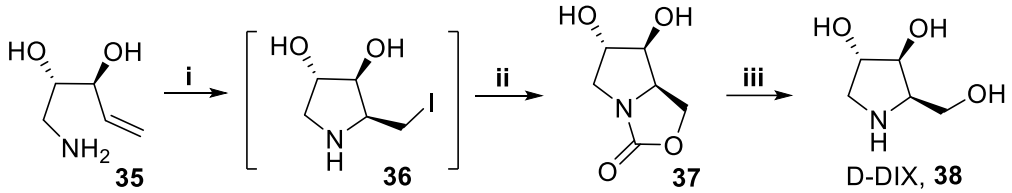
conversion into the aziridino derivative **31** that by reaction with TsNCO gave the bicyclic compound **32**. Subsequent cleavage of the oxazolidinone ring afforded the cyclic six-membered product **33**, eventually converted into (+)-ADANJ, **34**, a 2-deoxy-2-amino analogue of (+)-1-deoxyallonojirimycin (Scheme 8) [49].



Scheme 8. Conversion of *bis*-homoallylic amine **29** to (+)-ADANJ, **34**.

It is worth mentioning that the haloamination outcome dramatically changed when a primary amine was used in place of a secondary one. In fact, when the aminoalkendiol **35** was treated with iodine in the presence of $NaHCO_3$, the bicyclic compound **37** was isolated in excellent yield and stereoselectivity [32-37], arising from insertion of a carbon dioxide molecule at pyrrolidine nitrogen, followed by intramolecular displacement of the iodide functionality of intermediate **36**. The eventual cleavage of the oxazolidin-2-one ring in a strong basic medium led in excellent yield and without any racemization to 1,4-dideoxy-1,4-imino-D-xylitol D-DIX, **38** (Scheme 9) [50-51].



Scheme 9. Synthesis of 1,4-dideoxy-1,4-imino-D-xylitol D-DIX, **38.**

Another matching/mismatching effect was observed when polyfunctionalized diastereomeric alkenols displayed different configuration at the carbon atom bearing the amino group. Thus, diastereomeric alkenylamines **39** and **42**, displaying the same configuration at C-2 and C-4, underwent cyclization in the presence of $NaHCO_3$ using iodine and NIS, respectively, as halenium sources to give, via the intermediates **40** and **43**, the corresponding bicyclic oxazolidin-2-ones **41** and **44** in high to moderate yield but with total stereoselectivity, and compound **44** was eventually converted into the iminosugar **45.** The reaction proceeded with total stereoselectivity, owing to the directing effect of the oxygenated functionality at the allylic carbon leading to the 2,3-*cis* configuration that matched with the formation of the most sTable 2,5-*trans* disubstituted product. (Scheme 10) [52-53]. On the contrary, aminoalkenes **46** and **49**, displaying opposite configuration at C-2 with respect to **39** and **42**, gave in good yield mixtures of diastereomeric bicyclic oxazolidin-2-ones **47**,**48** and **50**,**51**, respectively, but with moderate stereoselection due to mismatch between the 2,5-*cis* unfavourable configuration - with respect to the 2,5-*trans*-one - and the overwhelming *cis*-2,3-directing effect exerted by the oxygenated functionality lieing at the chiral allylic carbon (Scheme 11) [32-37],[53].

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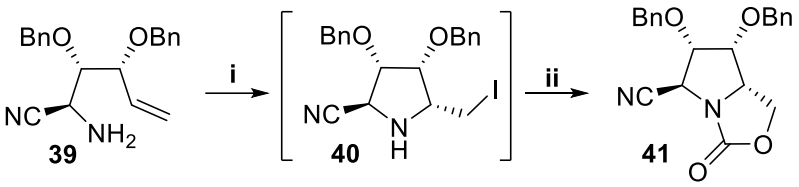
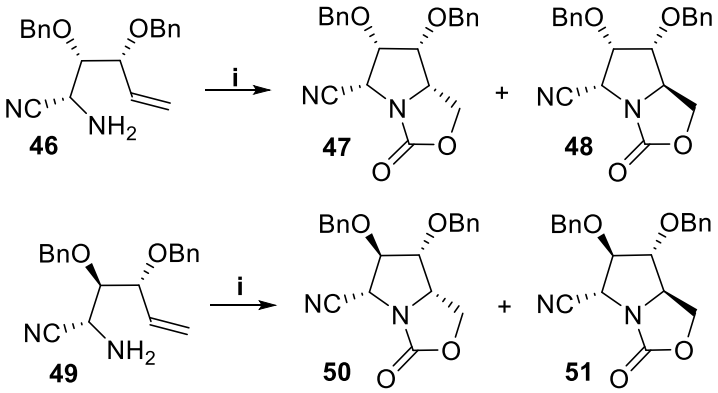
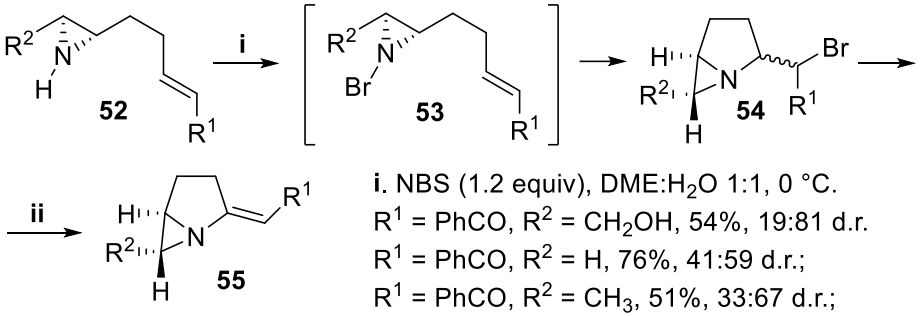


Scheme 10. Synthesis of bicyclic oxazolidin-2-ones **41** and **44** with matching effects directing stereochemistry.



Scheme 11. Synthesis of mixtures of bicyclic oxazolidin-2-ones **47**,**48** and **50**,**51** owing to mismatching effects directing stereochemistry.

The nitrogen atom of chiral unprotected aziridines was a nucleophile suitable for haloamination reactions leading to polycyclic structures containing the pyrrolidine ring. In fact, starting from compounds **52**, treatment with NBS allowed to prepare bicyclic [3.1.0]bromoderivatives **54** in good to moderate yield but and with low to moderate stereoselectivity, and the reaction seemed to proceed through an intermediate bromoaziridine **53** that attacks the double bond to give the cycloamination product [54]. Eventual elimination of HBr, carried out under basic conditions, allowed to obtain the chiral bicyclic compounds **55**, whose structure is present in azinocine antibiotics (Scheme 12) [55].



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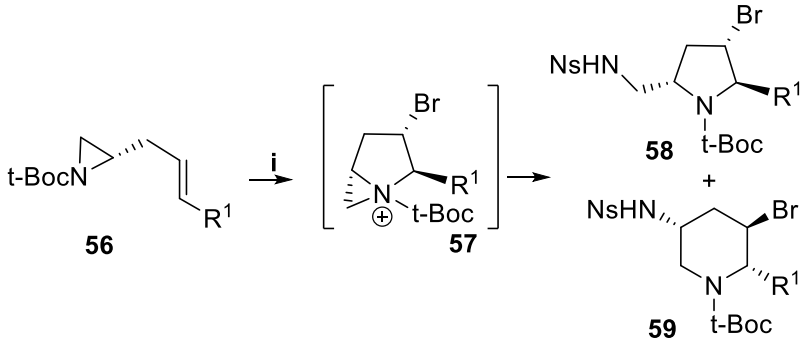
Scheme 12. Stereoselective cyclization of chiral aziridines **52** leading to bicyclic [3.1.0]bromoderivatives **55**.

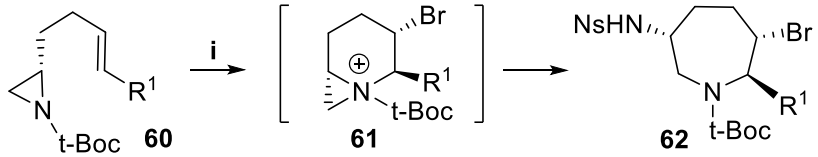
Moreover, chiral *N*-Boc aziridines **56** bearing an allyl group were treated with NBS to give at first the bicyclic aziridinium [3.1.0]intermediates **57**. Although the subsequent attack by $NsNH_2$ proceeded with low regioselectivity, either chiral *N*-t-Boc protected pyrrolidines **58** and piperidines **59** were isolated in good yield with nearly total stereoselectivity (Scheme 13) [56].



i. NBS (1.5 equiv), $NsNH_2$ (1.5 equiv), MeCN, -20 °C.
R^1 = 4-CH_3O-C_6H_4, 80%, 2.1:1.0 ratio; R^1 = 4-CH_3-C_6H_4, 82%, 3.0:1.0 ratio;
R^1 = 4-F-C_6H_4, 82%, 2.7:1.0 ratio; R^1 = 4-t-C_4H_9-C_6H_4, 80%, 4.0:1.0 ratio.

Scheme 13. t-Boc-aziridines **56** leading to regioisomeric mixtures of chiral pyrrolidines **58** and piperidines **59**.

The same reaction was carried out using NBS and nosyl amide ($NsNH_2$) starting from chiral t-Boc aziridines **60** bearing a homoallylic substituent, and the corresponding azepanes **62** displaying three chiral centres were obtained through the bicyclic intermediate **61** with excellent yield and nearly total regio- and stereoselectivity (Scheme 14) [57].



i. NBS (1.5 equiv), $NsNH_2$ (1.5 equiv), AcOEt, -30 °C.
R^1 = 4-Br-C_6H_4, 82%, 99% e.e., >99% d.r.;
R^1 = 3-CH_3-C_6H_4, 80%, 99% e.e., >99% d.r.;
R^1 = 4-Cl-C_6H_4, 83%, 99% e.e., >99% d.r.;
R^1 = 4-C_6H_5-C_6H_4, 92%, 99% e.e., >99% d.r.

Scheme 14. Stereoselective synthesis of t-Boc-azepanes **62** starting from chiral aziridines **60.**

2.2. Pyrrolidines within Polycyclic Structures

Polyhydroxylated indolizidines and quinolizidines containing a pyrrolidine ring are conformationally restricted iminocyclitols and display interesting inhibitory action against glycosidases and found potential therapeutic applications as antidiabetic, antiviral, anticancer, antimetastatic and immunoregulating agents [58]. Thus, the chiral pyrrolidine **63**, having a homoallylic substituent at C-2, was treated with NIS to give first the bicyclic intermediate **64** that without isolation, on treatment with an excess silver acetate, afforded the aziridino intermediate **65**. Ring enlargement occurring in situ allowed to convert this product in moderate yield but with nearly total stereoselectivity into the bicyclic derivative **66**, whose protecting groups were easily removed at once to give the indolizidine **67** (Scheme 15) [59].

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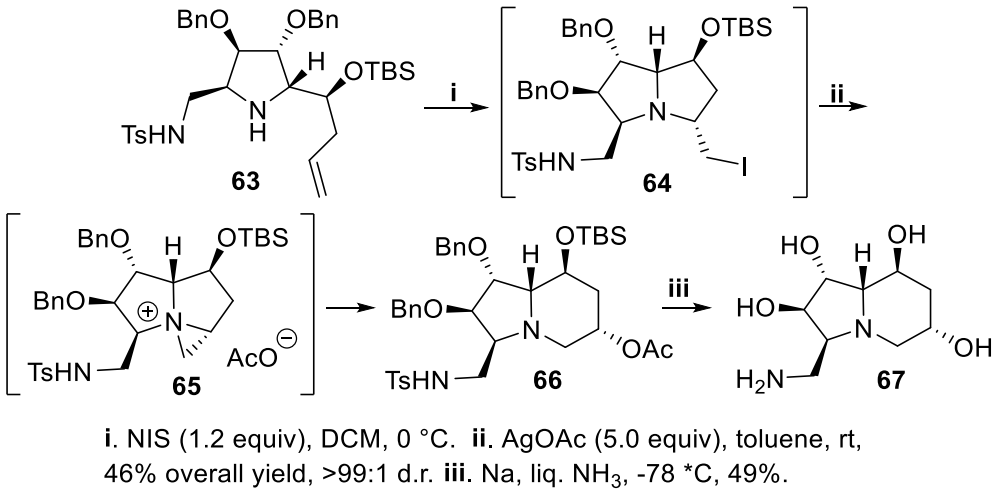

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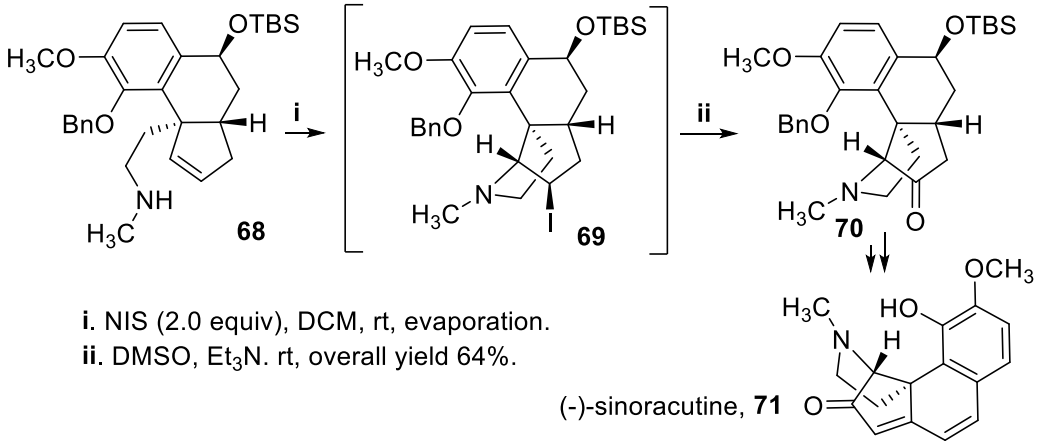
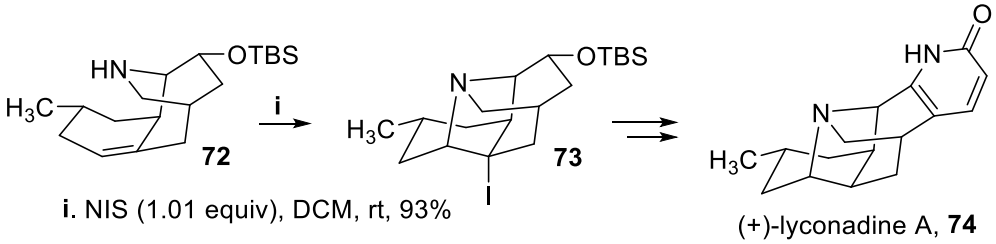
Scheme 15. Conversion of pyrrolidine **63** to the indolizidine derivative **67**.

Again directed towards preparation of polycyclic structures containing a pyrrolidine ring, the amine **68** was treated with iodine and the tetracyclic intermediate **69** was generated with total stereoselectivity. Then, exploiting a Kornblum oxidation [60], the iodide functionality was converted in moderate yield into a keto group and the *cis*-fused pyrrolidinocyclopentanone **70**, intermediate for the preparation of alkaloid (-)-sinoracutine, **71**, was eventually isolated in good yield and total stereoselectivity (Scheme 16) [61].



Scheme 16. Iodoyclization of amine **68** leading to **70**, intermediate of the synthesis of alkaloid (-)-sinoracutine, **71**.

Another iodoamination reaction carried out with NIS, starting from the chiral amine **72**, allowed to build up a pyrrolidine ring in good yield and with total stereoselectivity within the polycyclic compound **73**, key intermediate for the synthesis of alkaloid (+)-lyconadine A, **74** (Scheme 17) [62].



Scheme 17. Iodoyclization leading to **73**, a key intermediate to (+)-lyconadine A, **74**.

Exploiting a tertiary amino group tethered on a chiral center lieing in a seven-membered cycloalkene, chiral bicyclic derivatives were prepared by transannular halocyclization. Thus, within

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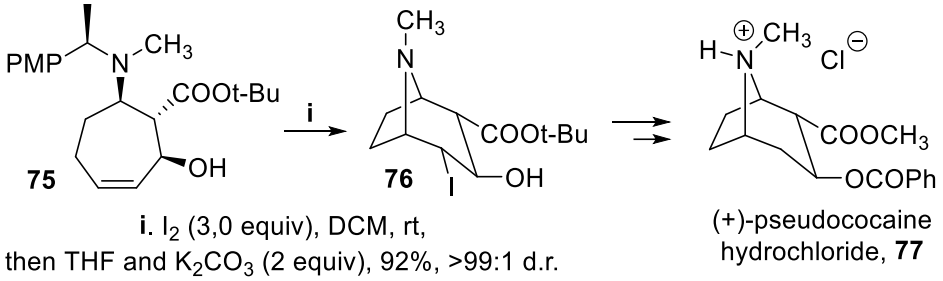
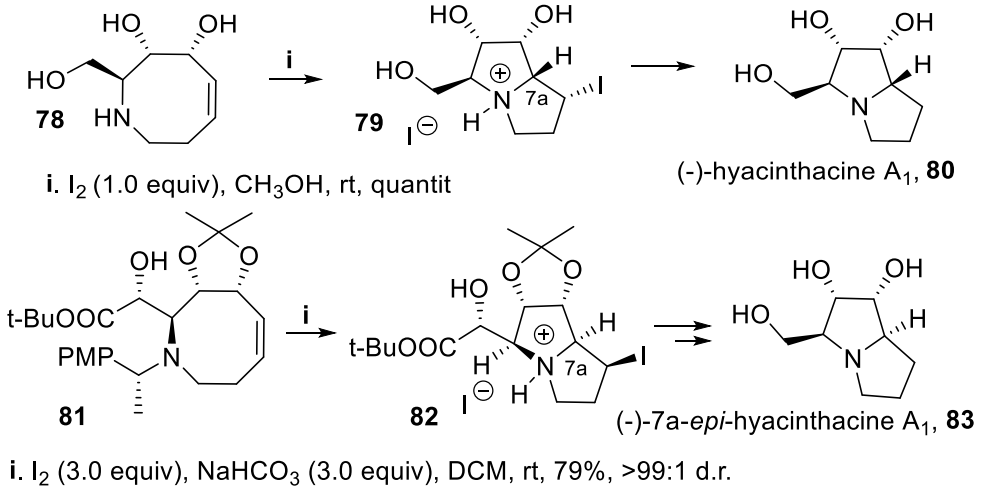
a synthesis of (+)-pseudococaine **77**, the bicyclic product **76** was isolated in very high yield and nearly total enantioselectivity starting from the tertiary amine **75** after reaction with iodine (Scheme 18) [63].



Scheme 18. Cyclization of amine **75** leading to **76**, an intermediate to (+)-pseudococaine, **77**.

In a similar approach, the compound **78**, containing a secondary amino group embedded in a eight-membered ring containing a double bond, was treated with iodine in methanol, to afford in good yield and with nearly total stereoselectivity the polyfunctionalyzed bicyclic derivative **79**, key intermediate for the synthesis of the alkaloid (-)-hyacinthacine A1, **80** [64]. However, when under the same conditions the structurally similar chiral tertiary amine **81** underwent cyclization, the attack of the nitrogen atom to iodiranium ion occurred on the opposite side of the double bond, with respect to **79**, probably due to steric bias arising from the dioxolanyl structure, so that the intermediate **82** displayed the opposite configuration at C-7a, eventually leading to (-)-7a-*epi*-hyacinthacine A1, **83** (Scheme 19) [65-66].



Scheme 19. Synthesis of (-)-hyacinthacine A1, **80**, and (-)-7a-*epi*-hyacinthacine A1, **83**, from cyclic amines **78** and **81**.

Within the enantioselective synthesis of the diazatricyclic core of alkaloid TAN1251C, **87**, a muscarinic antagonist of potential interest in the treatment of ulcer [67], the spiro derivative **84** underwent cyclization mediated by iodine to provide with low stereoselectivity a mixture of compounds **85** and **86**, but the reaction yield was not reported (Scheme 20) [68].

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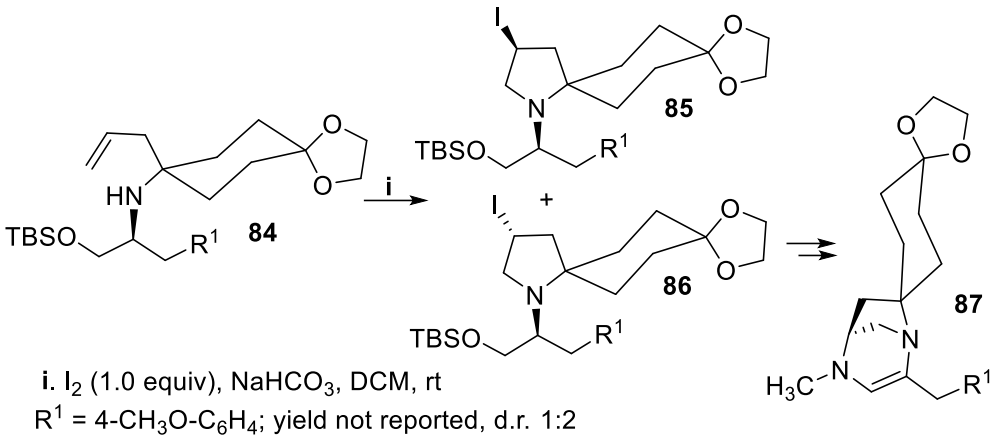
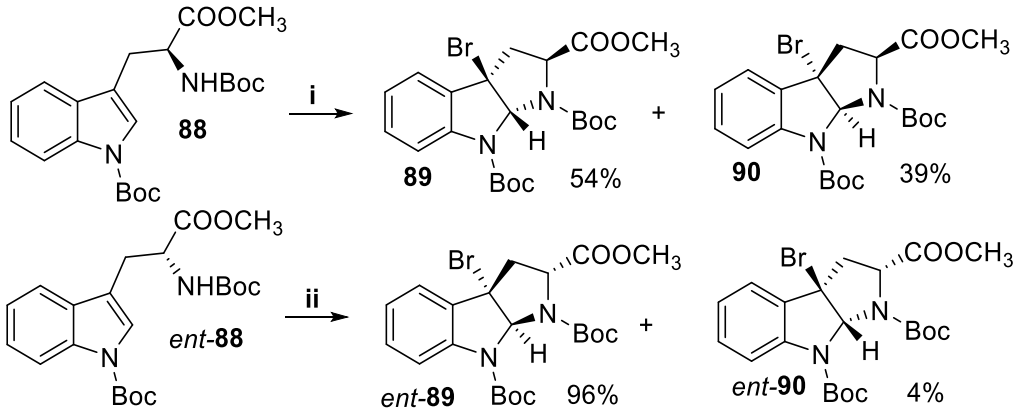


Scheme 20. Synthesis of spiroderivative **85**, intermediate of diazatricyclic core of alkaloid TAN1251C, **87.**

Eventually, within a total synthesis of pyrrolidineindoline alkaloids, the (*S*)-tryptophane derivative **88** reacted with NBS to afford in good yield a mixture of diastereomers **89** and **90** with low stereoselectivity [69] whereas the reaction of (*R*)-tryptophane derivative *ent*-**88** with NBS, carried out in the presence of pyridinium *p*-toluene sulphonate (PPTS), afforded compound *ent*-**89** in good yield and excellent diastereoselectivity (Scheme 21) [70].



Scheme 21. Cyclization of tryptophane derivatives **88** and *ent*-**88**, intermediates to pyrrolidineindoline alkaloids.

2.3. Piperidine, Morpholine and Piperazine Derivatives

In analogy with aminoalkenols **14, 17, 21** and **24** [42-43], the primary amine **91** afforded in good yield but with low regio- and stereoselection the bicyclic oxazolidin-2-ones **92** and **93**, generated by nucleophilic substitution of iodine by the intermediate carbamate anion arising from insertion of carbon dioxide at the nitrogen atom. On the other hand, compound **94** arose from attack to the intermediate iodiranium ion by the hydroxy functionality at C-2, followed by nucleophilic substitution by a carbamate anion. However, the major product **92** was eventually converted into 1-deoxygalactonojirimycin (DGJ), **95**, (Scheme 22) [40] which is presently undergoing clinical evaluation for the treatment of Fabry's disease [71].

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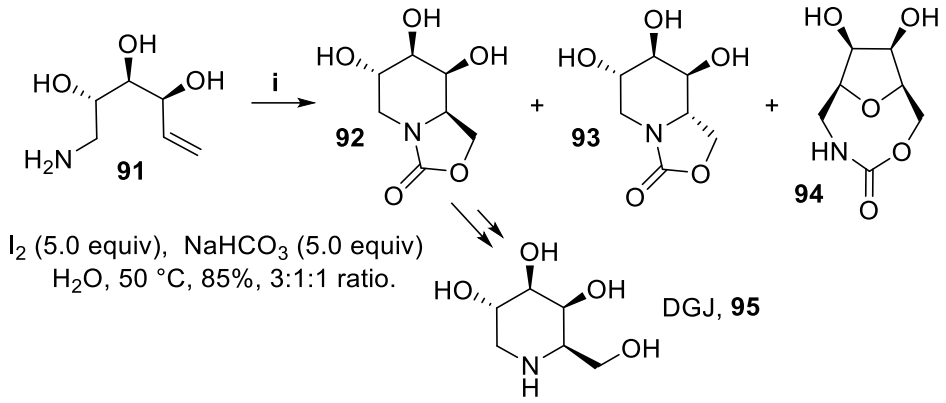
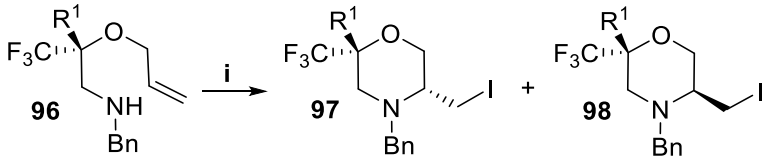


Scheme 22. Iodoamination leading to 1-deoxygalactonojirimycin (DGJ), **95.**

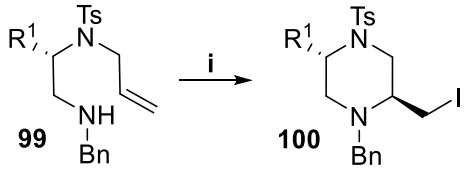
A variety of natural products and biologically and pharmaceutically active compounds contain a C-substituted morpholine subunit, and in medicinal chemistry trifluoromethyl morpholines deserved particular attention, owing to the substituent that can deeply affect their metabolic properties [72-73]. Thus, enantiopure allylic amino ethers **96**, where a trifluoromethyl group lies at a quaternary carbon adjacent to the oxygen atom, underwent cyclization mediated by iodine under basic conditions according to a 6-*exo*-mode, to give in good yield the corresponding diastereomeric iodomethylmorpholines **97** and **98**, but the stereoselectivity of the process was very low or missing (Scheme 23) [74].



i. I_2 (3.0 equiv), K_2CO_3 (3.0 equiv), MeCN, rt.
R^1 = Ph, 90%, 63:37 d.r.; R^1 = C_2H_5, 76%, 53:47 d.r.

Scheme 23. Synthesis of chiral trifluoromethyl morpholines by iodocyclization.

Besides morpholine derivatives, many compounds containing disubstituted piperazine ring were reported to display a broad spectrum of pharmacological activities [75]. Thus, chiral unsaturated benzylamines **99**, prepared in the enantiomerically pure form starting from (*S*)-amino acids, were treated with iodine, to afford 2,5-*trans*-disubstituted piperazine derivatives **100** in good yield and excellent stereoselectivity according to a 6-*exo*-mode cyclization (Scheme 24). The stereochemical outcome was explained by inspection of the conformational preferences for the chair-like transition states of the reaction, since in the higher energy transition state leading to the *cis*-isomer a strong interaction between the iodomethyl group and the tosyl group occurs, that is missing in the lower transition state leading to the *trans*-isomer [76].



i. I_2 (1.0 equiv), THF, 55 °C.
R^1 = $CH_2C_6H_5$, 74%, 99% d.e.; R^1 = $CH(CH_3)_2$, 75%, 99% d.e.

Scheme 24. Stereoselective iodocyclization of chiral trifluoromethyl morpholines **99**.

2.4. Substituted Guanidines

The marine alkaloids of the batzelladine family, isolated from the *Batzella* genus, contain a tricyclic guanidine core with substituents of varying complexity, and batzelladines A-F exhibit

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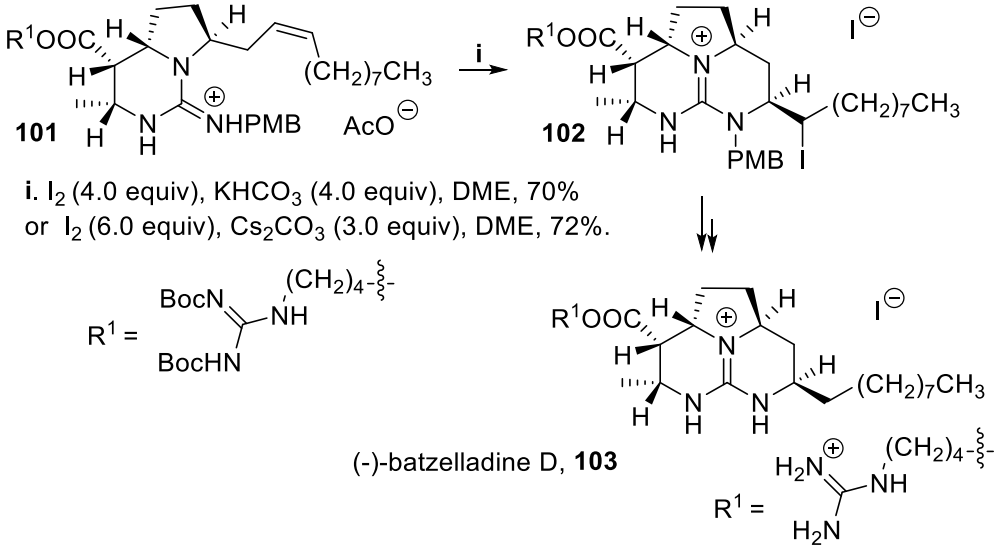
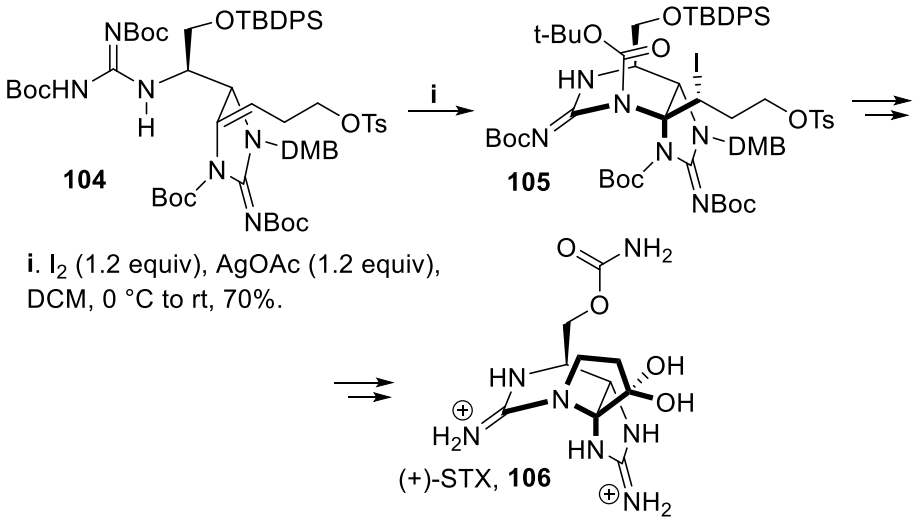
interesting biological antiviral activity in the inhibition of the binding of HIV gp120 to human CD4 [77]. Within a total synthesis of batzelladine D, **103**, the intermediate **101** was treated with iodine in a basic medium and the tricyclic intermediate **102** was isolated in good yield and with total stereoselectivity, the asymmetric induction being due to the chiral centers present in the starting material (Scheme 25) [78-79].



Scheme 25. Iodoyclization of **101**, leading to **102**, key intermediate to alkaloid (-)-batzelladine D, **103**.

A guanidinium group is present also in saxitoxin (STX) **106** and its analogs, a family of naturally occurring tricyclic guanidium alkaloids produced by some dinoflagellates which share the common chemical feature of high affinity and ion flux blockage capacity for voltage gated sodium channels (Na$_V$s), so that these compounds became interesting pharmacological targets [80].



Scheme 26. Stereoselective synthesis of the bicyclic compound **105**, intermediate to (+)-saxitoxin, STX, **106.**

Thus, within a synthesis of saxitoxin (STX), **106**, the first representative of this alkaloids family to be isolated, the diprotected homoallyl guanidine **104** underwent cyclization mediated by iodine to give in good yield and with total stereoselectivity the bicyclic compound **105**, that was eventually converted into the (+)-saxitoxin, STX, **106** (Scheme 26) [81].

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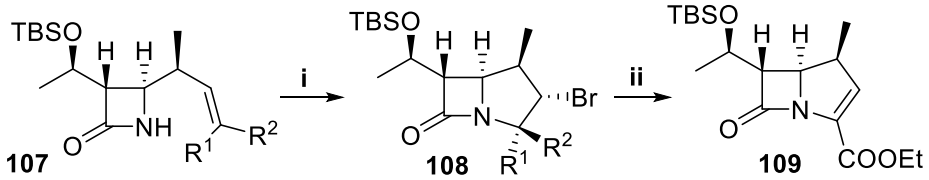
2.5. Penems and Lactams

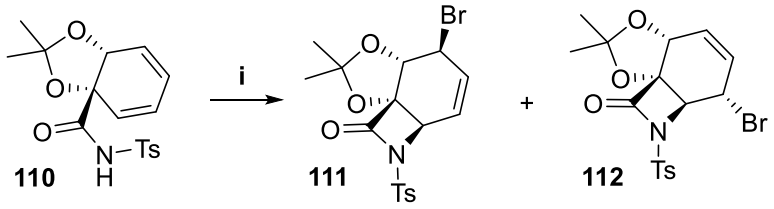
The bicyclic 1β-methylcarbapenem skeleton was built starting from the β-lactam **107** using a bromoamidation reaction directed by molecular geometry, that was carried out with NBS under mild conditions, to give in excellent yields and with total stereoselectivity the bicyclic compounds **108**, [82] eventually converted in good yield into carbapenem **109** (Scheme 27) [83].



i. NBS (1.1 equiv), MeCN, rt. **ii**. CH_3COCl-NaI, MeCN, 75%.
R^1 = OEt, R^2 = COOEt, 97%; R^1 = COOEt, R^2 = OEt, quantit.

Scheme 27. Stereoselective synthesis of the bicyclic lactams **108.**

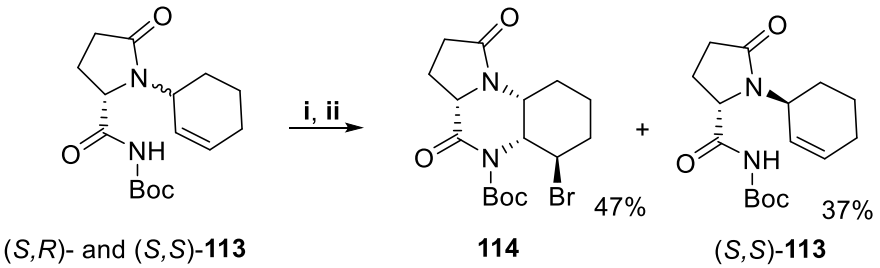
However, the intramolecular halolactamization was generally carried out exploiting an imide functionality, since the electron withdrawing tosyl or carboxylate groups favor nucleophilic attack by the nitrogen, whereas simple amides prefer to attack a haliranium ion with the more nucleophilic oxygen atom [84-87]. Thus, the bromocyclization of the chiral tosylamide **110** was carried out in a basic medium leading to a regioisomeric mixture of tricyclic β-lactams **111** and **112** that were isolated in high yield and with high stereoselectivity although the reaction proceeded preferentially through a S_N2' mechanism at the intermediate bromiranium ion (Scheme 28) [88].



i. NBS (2.0 equiv), $NaHCO_3$ (1.0 equiv), MeCN, 0 °C, 83%, 91:9.

Scheme 28. Stereoselective synthesis of bicyclic lactams **111** and **112**.

Furthermore, an equimolar inseparable diastereomeric mixture of imides (*S,R*)- and (*S,S*)-**113** was treated with t-BuOLi, and subsequent addition of NBS [89] allowed to isolate with excellent diastereoselectivity the bromolactam **114**, exclusively, whereas *N*-Boc imide (*S,S*)-**113** remained unchanged and this behavior was attributed to the different conformational flexibility of starting imides **113** (Scheme 29) [90].



i. t-BuOLi (1.1 equiv). **ii**. NBS (2.0 equiv), THF, -23 °C.

Scheme 29. Stereodifferentiation of imides (*S,R*)- and (*S,S*)-**113**.

Eventually, within a synthesis of indolizidinone dipeptide mimetics, the macrocyclic unsaturated amides **115a,b** underwent transannular stereodivergent halocyclization with total regio-

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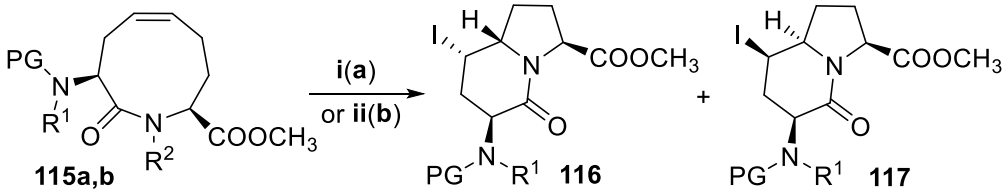
and stereoselectivity, depending on the reagents, the solvent employed and the substituent of the nitrogen atom. In fact, treatment of **115**a with iodine and (diacetoxyiodo)benzene (DIB) in refluxing MeCN afforded the bicyclic lactam **116**, exclusively, whereas the amide **115b** by reaction with iodine in refluxing THF led in good yield and total stereoselectivity to the diastereomeric lactam **117** (Scheme 30) [91].

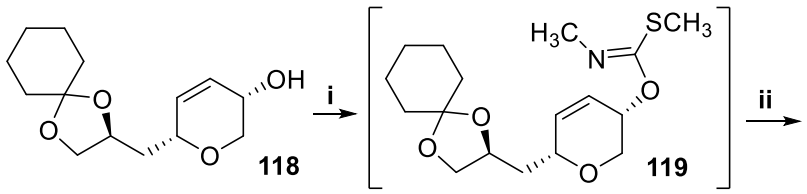


(**a**) PG,R^1 = Phth, R^2 = H. **i**. I_2 (4.0 equiv), DIB (2.0 equiv), refluxing MeCN, 78%, d.r. 100:0. (**b**) PG = o-Brosyl, R^1 = CH_3, R^2 = DMB. **ii**. I_2 (4.0 equiv), refluxing THF, 79%, d.r. 0:100.

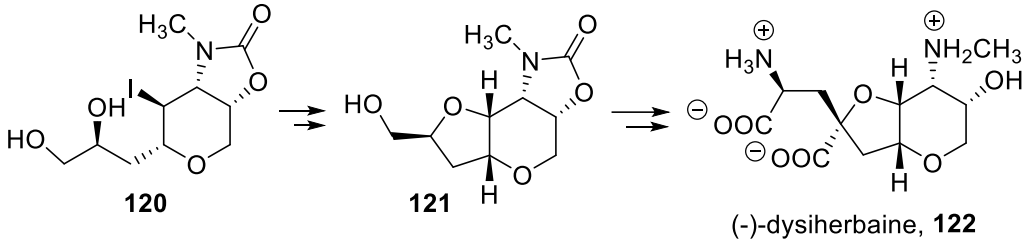
Scheme 30. Stereodivergent transannular bromoamidation leading to dipeptide mimetics **116** or **117**.

2.6. 1,3-Oxazolidin-2-Ones and 4,5-Dihydrooxazoles

The enantiomerically pure allylic alcohol **118** was treated with methyl thiocyanate followed by iodomethane, to give the intermediate carbonimidothioate **119** that by reaction with *N*-iodosuccinimide in basic medium afforded in moderate overall yield the corresponding oxazolidinone **120.** This latter compound was isolated with total stereoselectivity, directed by the preexisting chiral center, and was further elaborated to give the *cis*-fused hexahydrofuro [3,2-*b*]pyran **121**, key intermediate [92] of a total synthesis of neuroexcitotoxin (-)-dysiherbaine, **122** (Scheme 31) [93].



i. (a) NaH, CH_3NCS, THF, rt , (b) CH_3I.
ii. NIS, $NaHCO_3$, $CHCl_3$, rt, overall 51%.



Scheme 31. Intramolecular cyclization leading to **121**, key intermediate to alkaloid (-)-dysiherbaine, **122**.

The iodocyclization of the enantiomerically pure trichloroacetimidate **123** containing a 1,4-dioxane moiety again occurred with chirality transfer starting from the preexisting allylic chiral center, and the reaction proceeded in good yield and total stereoselectivity to give the *trans*-4,5-dihydrooxazole **124** that was converted at first into (+)-polyoxamic acid **125** and then to the known lactone **126** (Scheme 32) [94].

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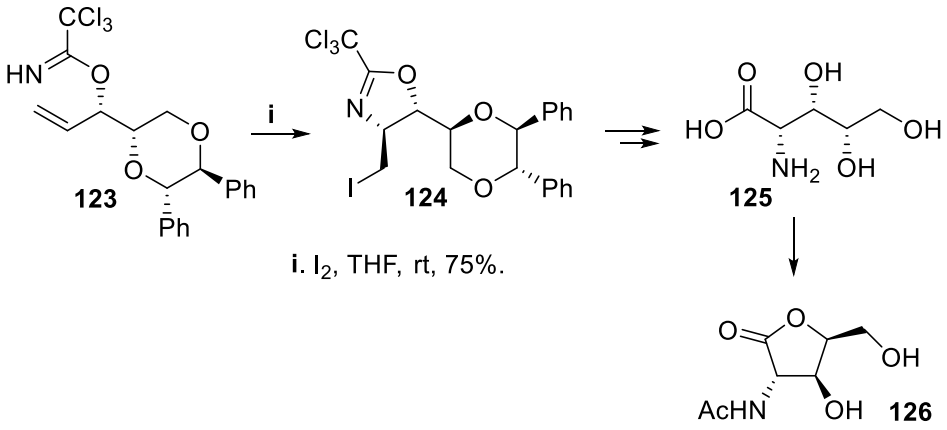
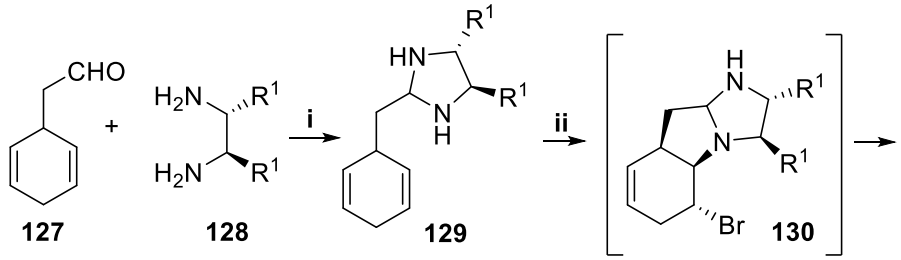


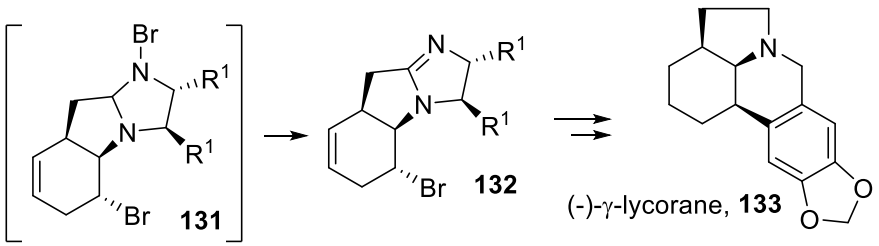
Scheme 32. Synthesis of (+)-polyoxamic acid **125** and lactone **126** starting from imidate **123**.

2.7. 4,5-Dihydroimidazoles

The chiral imidazolidine **129**, prepared by reaction of 2-(cyclohexa-2,5-dien-1-yl)acetaldehyde **127** with chiral diamine **128**, underwent bromoamination with desymmetrization through diastereotopic group selection [95-99]. In fact, using an excess NBS this compound was converted at first into the chiral tricyclic imidazolidine **130**, whereas a further bromination at the nitrogen atom gave the intermediate **131**. The subsequent elimination reaction led in moderate yield but with total stereoselectivity to the tricyclic compound **132**, containing a 4,5-dihydroimidazole moiety, that was eventually converted into (-)-γ-licorane, **133** [100], a degradation product of several members of the caranine family of alkaloids (Scheme 33) [101].



R^1 = PMP. **i.** DCM, rt, quantit. **ii.** NBS (2.1 equiv), DCM, 0 °C, 57%.



Scheme 33. Desymmetrization via bromoamination of chiral imidazolidine **129** leading to (-)-γ-licorane **133**.

3. Asymmetric Synthesis Exploiting Stereoselectivity Directed by an Added Chiral Catalyst

3.1. N-Sulfonyl and Carbamoyl Pyrrolidines, Indolines and Hexahydropyrrolo [2,3,-b]indoles (HPI)

Enantiomerically pure substituted pyrrolidines and their derivatives are components of many pharmaceutically relevant molecules [102-104]. Among them, either 2-substituted 3-halopyrrolidine and 2-halomethylpyrrolidine derivatives appeared to be attractive advanced intermediates towards

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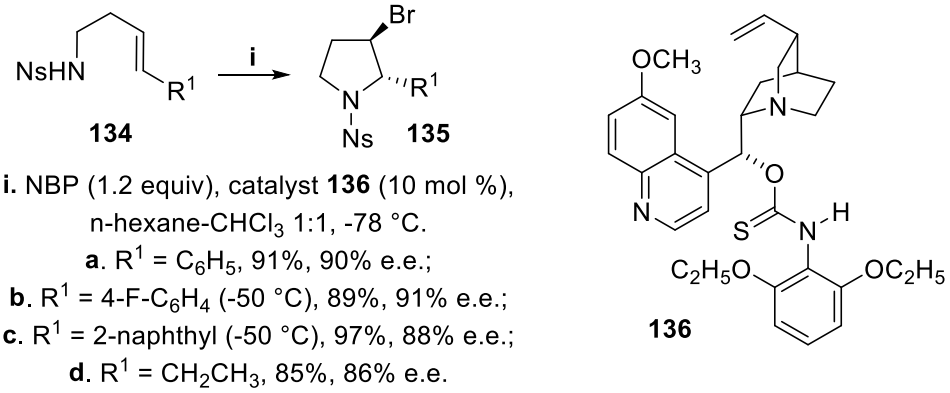
the synthesis of substituted hydroxypyrrolidines that display strong inhibitory activity against a lot of phosphoribosyltransferases [105].

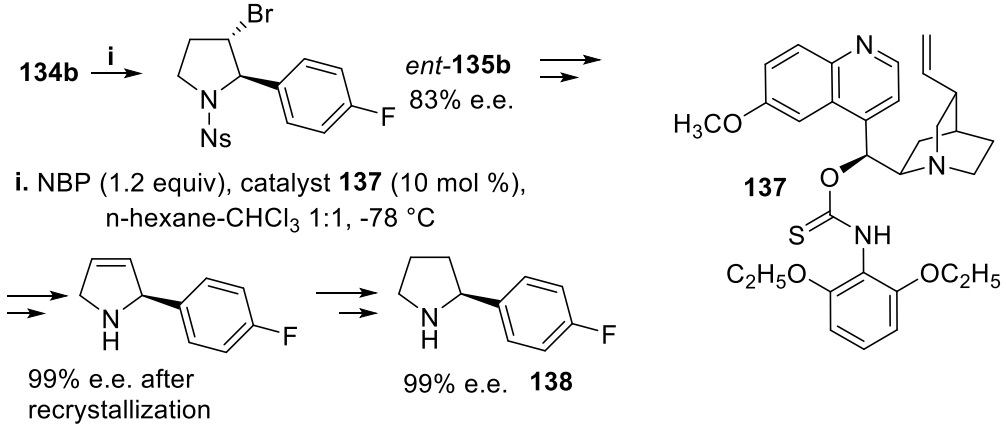
Thus, the homoallylic nosylamides **134** were treated with *N*-bromopyrrolidin-2-one (NBP) in the presence of the catalyst **136** and the cyclization reaction proceeded in a 5-*endo* mode, providing 2,3-*trans*-disubstituted 3-bromopyrrolidine derivatives **135** in excellent yield and good enantioselectivity. After inspection of the possible transition states, where a charge pair formation was hypothised between the quinuclidine nitrogen of the catalyst and bromenium ion, together with binding of the nosyl amide and bromenium ion stabilized by Lewis basic sulphur, the stereoselectivity was ascribed to a strong repulsive interaction between 2,6-diethoxyphenyl group of the catalyst and the aryl or alkyl substituent of the substrate, missing in the most favored TS but occurring in the less favored one (Scheme 34) [106].



i. NBP (1.2 equiv), catalyst **136** (10 mol %), n-hexane-$CHCl_3$ 1:1, -78 °C.
a. R^1 = C_6H_5, 91%, 90% e.e.;
b. R^1 = 4-F-C_6H_4 (-50 °C), 89%, 91% e.e.;
c. R^1 = 2-naphthyl (-50 °C), 97%, 88% e.e.;
d. R^1 = CH_2CH_3, 85%, 86% e.e.

Scheme 34. Bromocyclization leading to 3-bromopyrrolidine derivatives **134** exploiting catalyst **136**.

Moreover, the compound **134b** underwent bromoamidation under the same conditions, but using catalyst **137**, pseudoenantiomeric with **136**, and the reaction proceeded with high enantioselectivity leading to *ent*-**135b** that was eventually converted into the enantiomerically pure pyrrolidine **138**, a component of the selective Kv1.5 blocker BMS-394136, but the chemical yields of the synthetic steps were not reported (Scheme 35) [107].



i. NBP (1.2 equiv), catalyst **137** (10 mol %), n-hexane-$CHCl_3$ 1:1, -78 °C

Scheme 35. Synthesis of pyrrolidine **138**, a component of the selective Kv1.5 blocker BMS-394136.

Enantioenriched 2-halomethyl pyrrolidine derivatives were useful intermediates for the synthesis of highly bioactive benzazepinones [108-109]. It is worth noting that the cyclization of unsaturated tosylamide **139**, carried out with NIS in the presence of catalyst **142**, proceeded in a regiodivergent mode on addition of different potassium halides to the reaction mixture. In fact, when a small amount of KI was used, the cyclization according to a 5-*exo*-trig mode afforded the expected 2-iodomethyl pyrrolidine **140**, exclusively, isolated in good yield and high stereoselectivity. Conversely, in the presence of a small amount of KBr, only the corresponding piperidine derivative **141** was obtained, via a 6-*endo*-trig mode, but the stereoselectivity of the process could not be ascertained owing to the rapid decomposition of the product. In order to obtain a deeper insight

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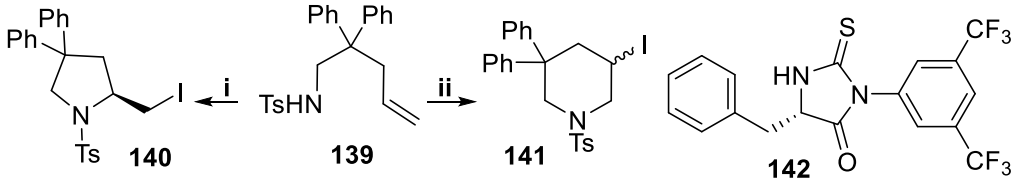
about the interaction of the additives with the catalyst, some variable temperature NMR experiments were carried out that evidenced a KBr effect on the binding between the substrate **139** and the catalyst **142**. The different regioselectivity of the iodoamidation was ascribed to this interaction, but the real mechanistic changes leading to switch of the regiochemistry remained unclear (Scheme 36) [110].



i. NIS (1.2 equiv), catalyst **142** (10 mol %), KI (2 mol %), DCM, -78 °C, 99%, 78% e.e.
ii. NIS (1.2 equiv), catalyst **142** (10 mol %), KBr (2 mol %), DCM, -78 °C, 77%.

Scheme 36. Regiodivergent cyclization of tosylamide **139** in the presence of catalyst **142** due to the added halide.

Tosylamides **143a,b**, prepared starting from 2-allylanilines, underwent stereoselective iodoamidation according to the preceeding protocol to give indolines (2,3-dihydro-1*H*-indoles), whose heterocyclic structure occurs either in the class of natural indole-terpenoid alkaloids [111-112] and in candidates for drugs [113]. The cyclization of tosylamide **143a** (R^1 = H) proceeded in moderate yield and with high stereoselectivity in the presence of catalyst **142** alone or in the presence of KBr, to give 2-iodomethyl indoline **144** although a better yield was obtained on adding iodine [114]. On the contrary, the tosylamide **143b** (R^1 = Cl) afforded the indoline **145** in good yield and high stereoselectivity in the absence of KBr, whose addition dramatically decreased the yield of the cyclization, and this result was again ascribed to interactions between the catalyst and the additive. Eventually, it is worth mentioning that the configuration of **144** was opposite to that of **145**, but the reason of the different outcome was not ascertained (Scheme 37) [110].

i. NIS (1.2 equiv), catalyst **142** (10%) DCM, -78 °C.
a. R^1 = H: no additive, 57%, 87% e.e.; KBr (2 mol %), 58%, 87% e.e.;
I_2 (2 mol %), 89%, 80% e.e.

ii. NIS (1.2 equiv), catalyst **142** (10%) DCM, -78 °C.
b. R^1 = Cl: no additive, 86%, 88% e.e.; KBr (2 mol %), 14%, 89% e.e.

Scheme 37. Stereodivergent synthesis of 2-iodomethyl indolines **144** and **145**.

Also NBS was effective for halocyclization of tosylamides **146**, carried out in the presence of BINOL-derived catalyst **148** acting as a Lewis base, to give bromomethyl indoline derivatives **147** in good yield and with high enantioselectivity. The stereochemistry of the reaction strongly relied on the electronic density of the aromatic ring, since higher enantioselectivity was observed for tosylamides bearing an ERG at C-4 of the aromatic ring, with respect to tosylamides substituted at C-5, while the opposite effect was observed when an EWG was present (Scheme 38) [115].

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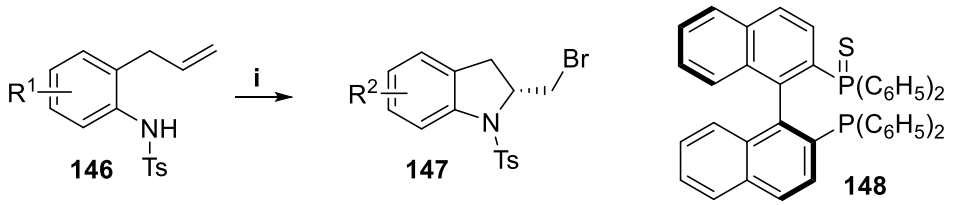
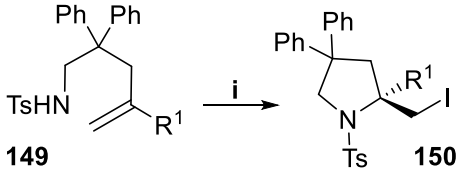


i. NBS (1.2 equiv), catalyst **148** (10 mol %), toluene:DCM 10:1, -78 °C.
R^1 = H, 90%, 85% e.e.; R^1 = 4-OCH_3, 82%, 86% e.e.; R^1 = 5-OCH_3, 84%, 34% e.e.;
R^1 = 4-F, 80%, 74% e.e.; R^1 = 5-F, 78%, 82% e.e.; $R^{1.}$ = 4-t-Bu, 91%, 80% e.e.

Scheme 38. Synthesis of 2-bromomethyl indolines **147** mediated by catalyst **148**.

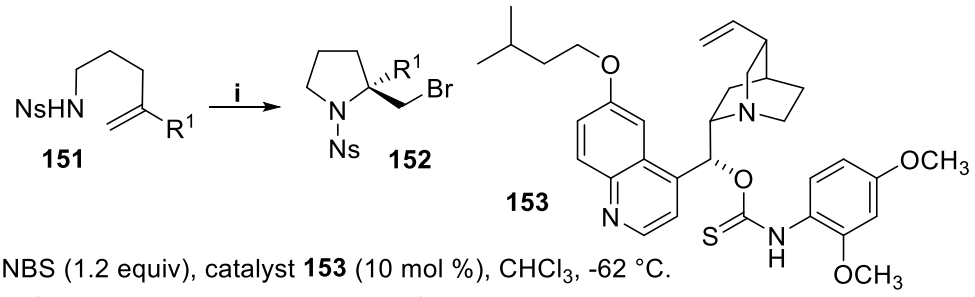
Homoallylic tosylamides **149** containing a *gem*-disubstituted double bond underwent iodoamidation mediated by NIS activated by a small amount iodine [109] in the presence of the chiral thiohydantoin catalyst **142**, and *N*-tosyl 2-iodomethylpyrrolidines **150** were obtained in good yield and high enantioselectivity (Scheme 39) [110].



i. NIS (1.2 equiv), catalyst **142** (6.6 mol %), I_2 (13 mol %), DCM, -78 °C.
R^1 = H, 90%, 81% e.e.; R^1 = C_6H_5, 87%, 90% e.e.; R^1 = CH_3, 89%, 85% e.e.

Scheme 39. Synthesis of 2-iodomethylpyrrolidine derivatives **18** mediated by catalyst **10**.

The bromocyclization of similar (4-nosyl)amino derivatives **151**, carried out with NBS in the presence of the catalyst **153**, provided in excellent yield and enantioselectivity *N*-(4-nosyl)pyrrolidines **152** bearing a chiral quaternary center at C-2 only when the substituent of the double bond was an electron-deficient aryl group. On the contrary, when the substituent was hydrogen or an alkyl group, the reaction proceeded with low asymmetric induction (Scheme 40) [116].



i. NBS (1.2 equiv), catalyst **153** (10 mol %), $CHCl_3$, -62 °C.
R^1 = 4-Cl-C_6H_4, 98%, 98% e.e.; R^1 = CH_3, 96%, 40% e.e.;
R^1 = 4-CF_3-C_6H_4, 91%, 99% e.e.;R^1 = 3-Cl-C_6H_4, 87%, 97% e.e.;

Scheme 40. Synthesis of 2-bromomethylpyrrolidine derivatives **152** bearing a chiral quaternary center at C-2.

Under the same conditions, the nosyl derivative **154** afforded the *N*-nosyl isoindoline **155** [116] in very high yield, with total regio- and good enantioselectivity, subsequently oxidized to isoindolinone **156** whose framework occurs as a valuable pharmacophore in a wide range of natural compounds displaying different biological activities and therapeutic potential (Scheme 41) [117-119].

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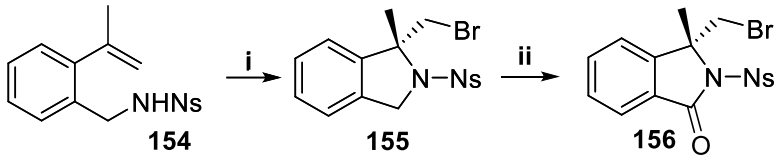
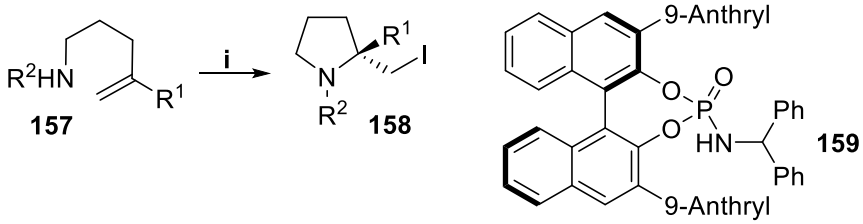


i. NBS (1.2 equiv), catalyst **133** (10 mol %), $CHCl_3$, -62 °C, 99%, 88% e.e.
ii. $KMnO_4$ (6.0 equiv), $CuSO_4$ $5H_2O$ (4.0 equiv), refluxing DCM, 95%, 88% e.e.

Scheme 41. Synthesis of chiral isoindolinone **156**.

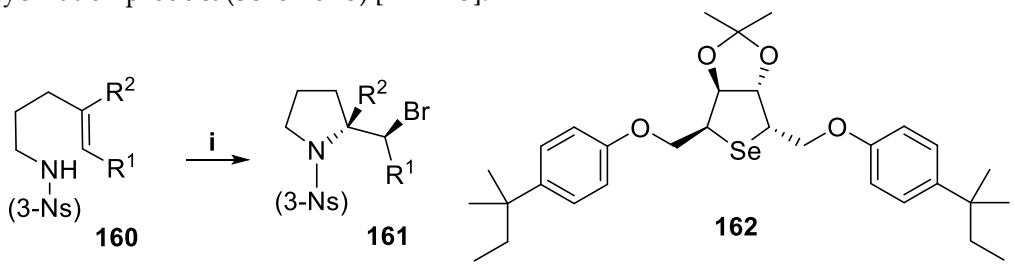
The chiral Lewis basic amidophosphate catalyst **159**, derived from BINOL, was effective for iodocyclization of *N*-sulfonyl amides **157** bearing a *gem*-disubstituted double bond, when iodine was used in the presence of Lewis acid *N*-chlorosuccinimide (NCS) in order to generate a highly reactive iodinating species [120]. In fact, the reaction proceeded in good yield and with excellent enantioselectivity to give *N*-sulfonyl 2-iodomethyl pyrrolidine derivatives 2**6** displaying at the quaternary center the configuration opposite to compounds **18** and **20** (Scheme 42) [121].



i. NCS (1.1 equiv), I_2 (0.5 equiv), catalyst **159** (5 mol %), toluene, -60 °C.
R^1 = cyclohexyl, R^2 = Ts, (- 78 °C) 95%, 99% e.e.;
R^1 = CH_2-cyclohexyl, R^2 = Ns, 89%, 90% 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.

Scheme 42. Synthesis of 2-iodomethyl pyrrolidine derivatives **158** bearing a chiral quaternary center at C-2.

The (*Z*)-nosylamides **160** were treated with *N*-bromopthalimide (NBPhth) as the bromenium ions source, in the presence of the chiral C_2-symmetric selenide Lewis base **162**. The reaction proceeded in a 5-*exo*-trig mode exclusively, leading to (3-nosyl) pyrrolidine derivatives **161** in excellent yield and high enantioselectivity. Concerning the reaction mechanism, at first coordination of the Lewis basic selenium of catalyst to NBP was proposed, followed by formation of an electrophilic brominating species whose interaction with the double bond gives a tightly selenium coordinated bromiranium intermediate that, by eventual S_N2 attack of the sulfonamide group, leads to the cyclization product (Scheme 43) [122-123].



i. NBPhth (1.1 equiv), catalyst **162** (20 mol %), DCM:toluene 1:1, -78 °C.
R^1 = C_2H_5, R^2 = C_6H_5, 93%, 91% e.e.; R^1 = n-C_3H_7, R^2 = C_6H_5, 82%, 91% e.e.;
R^1 = CH_3, R^2 = 3-Cl-C_6H_4, 85%, 83% e.e.; R^1 = CH_3, R^2 = C_6H_5, 90%, 92% e.e.

Scheme 43. Bromocyclization of (*Z*)-alkenylamides **160** mediated by catalyst **162**.

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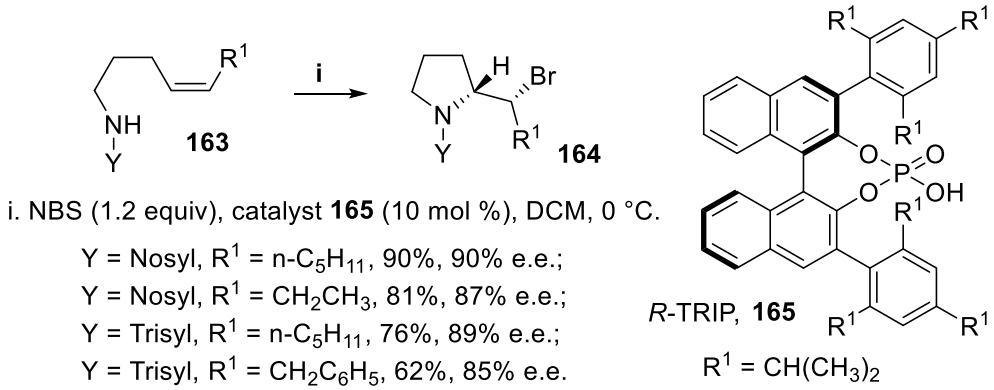
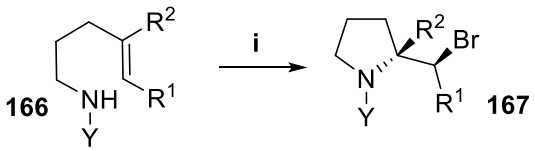
N-Sulfonyl amides bearing a disubstituted double bond underwent halocyclization mediated by NBS in the presence of the catalyst *R*-TRIP **165** [(3,3′-*bis*(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl) hydrogenphosphate] using a chiral phase-transfer catalysis (PTC) methodology [124], since exploiting H-bonding interactions it is able to transfer the poorly soluble NBS halogenating reagent into the organic solvent. When the reaction was carried out starting from compounds **163** displaying a (*Z*)-double bond, the 2-substituted pyrrolidine derivatives **164** were isolated in good yield with high enantioselectivity (Scheme 44) whereas under the same conditions (*E*)-sulfonamides **166** were converted into pyrrolidine derivatives **167** in moderate yield and stereoselectivity, the configuration of their quaternary center being the same as observed for compounds **161** (Scheme 45) [125].



Scheme 44. Bromocyclization of (*Z*)-alkenylamides **163** mediated by *R*-TRIP, **165**.



i. NBS (1.2 equiv), catalyst **165** (10 mol %), DCM, 0 °C.
Y = Trisyl, R^1 = n-C_5H_{11}, R^2 = H, 81%, 70% e.e.;
Y = Trisyl, R^1 = $CH_2CH_2C_6H_5$, R^2 = H, 62%, 85% e.e.;
Y = Nosyl, R^1 = n-C_5H_{11}, R^2 = CH_3, 59%, 74% e.e.

Scheme 45. Bromocyclization of (*E*)-alkenylamides **166** mediated by *R*-TRIP, **165**.

For this cyclization were proposed transition states where the catalyst **165** activates NBS through a hydrogen bond, whereas the nucleophilic amido group is in turn blocked to the P=O functionality by a hydrogen bond. Since (*Z*)-alkenes **163** underwent cyclization with higher stereoselectivity with respect to (*E*)-alkenes **166**, the most favored transition states were examined and this outcome was ascribed to unfavourable interactions occurring between the isopropyl groups of the catalyst and the substituent of the (*E*)-double bond with respect to the (*Z*)-one [125].

In alternative to BINOL derivatives, the chiral Brønsted acids tethered on Co(III)-complexes Δ-**168** and Λ-**169** were excellent catalysts able to transfer a slightly soluble brominating reagent to reaction solution generating at the same time a chiral environment with control of the stereochemical outcome. Thus, on treatment of the unsaturated benzenesulfonylamides **170** with NBS in the presence of the chiral Co(III) complex Δ-(*S*,*S*)-**169**, the 2-substituted pyrrolidine derivatives **171** were obtained in excellent yield and enantioselectivity (Scheme 46) [126].

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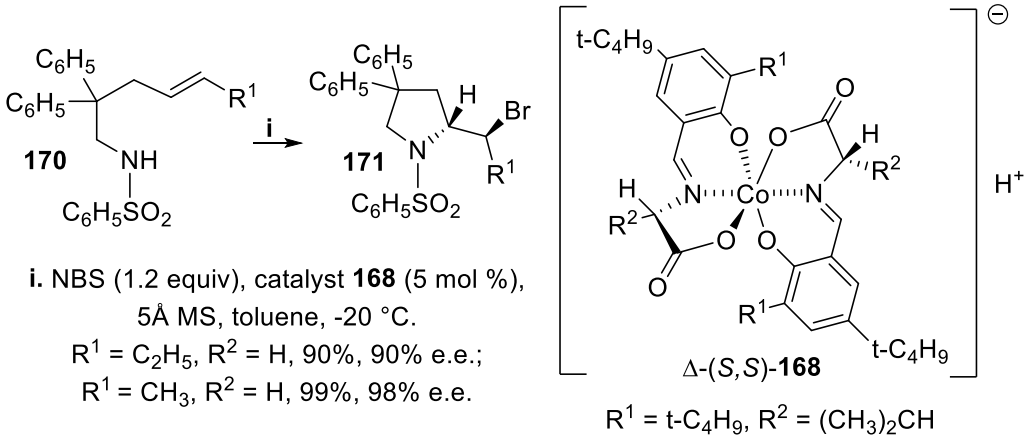
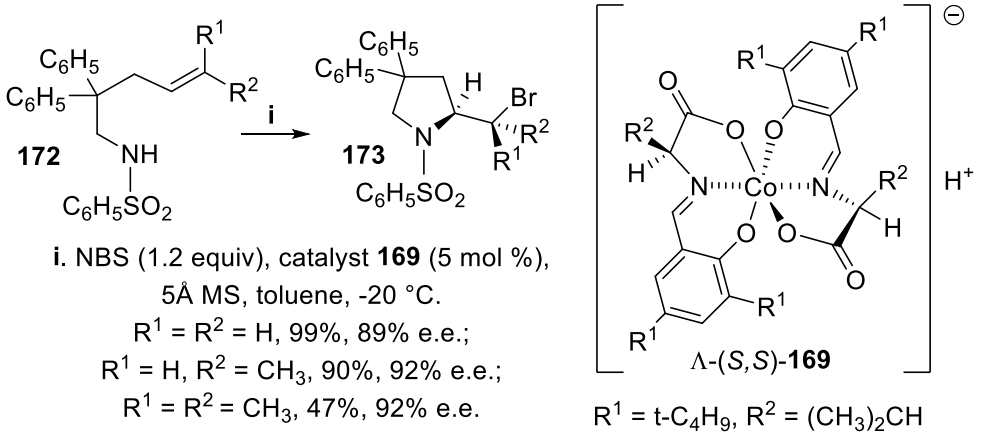


Scheme 46. Bromocyclization of (*E*)-alkenylamides **170** mediated by Co(III) complex Δ-(*S*,*S*)-**168.**

On the contrary, when the reaction was carried out under the same conditions but in the presence of the chiral Co(III) complex Λ-(*S*,*S*)-**169**, diastereomeric with Δ-**168**, the benzenesulfonamides **172** gave in good yield and with high stereoselectivity the pyrrolidine derivatives **173**, that displayed at C-2 the opposite configuration with respect to compounds **171** (Scheme 47) [126].



Scheme 47. Bromocyclization of (*Z*)-alkenylamides **172** mediated by Co(III) complex Λ-(*S*,*S*)-**169**.

The asymmetric halocyclization of tryptamine derivatives involved dearomatization of the electron-rich ring [127] leading to derivatives containing the 3-halohexahydropyrrolo [2,3,-b]indole (HPI) framework, a useful and versatile building block for preparation of cyclotryptamine alkaloids that display cytotoxic, neuroprotective and cholinesterase inhibitory activity [128]. Thus, compounds **174** underwent bromoamidation mediated by *N*-bromoacetamide in the presence of catalyst (DHQD)$_2$PHAL, **176**, to give in good yield and moderate enantioselectivity the tricyclic HPI derivatives **175** with the bromine atom suitable for a further substitution (Scheme 48) [129].

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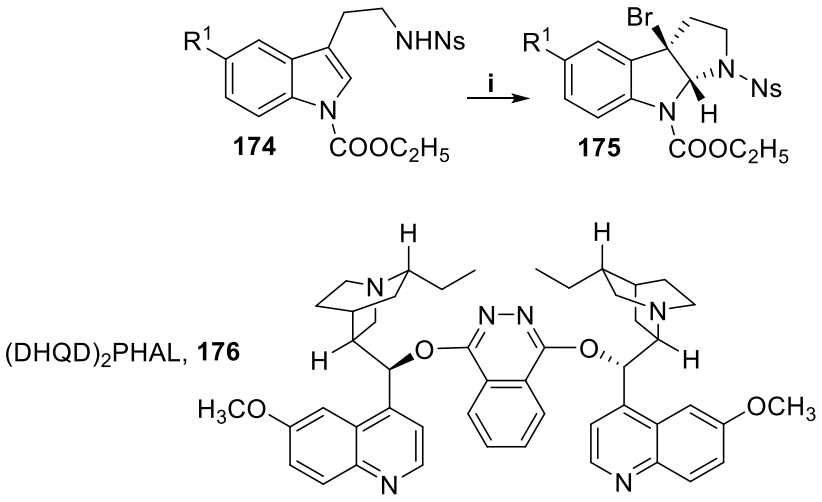


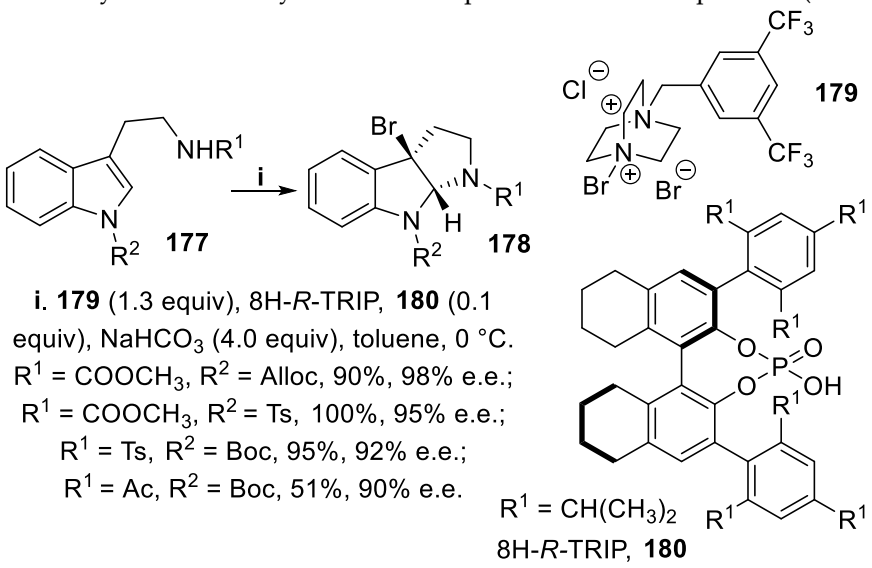
i. $CH_3CONHBr$ (1.2 equiv), L-CSA (20 mol %), $(DHQD)_2PHAL$, **176** (20 mol %), $CHCl_3$, -20 °C. R^1 = F, 98%, 68% e.e.; R^1 = Cl, 97%, 69% e.e.; R^1 = CH_3, 96%, 73% e.e.

Scheme 48. Dearomatization by bromoamidation of **174** leading to tricyclic HPI derivatives **175.**

Among the available sulfonyl groups, the nosyl substituent was preferred for this cyclization owing to high acidity of the proton on nitrogen [129], and a carbamate was found to be the best protecting group for the indolic nitrogen, with respect to acyl or alkyl substituents (Scheme 48) [129].

The haloamidation of tryptamine derivatives exploited also a chiral anion phase-transfer catalysis (PTC) methodology, where a BINOL-derived phosphate was associated with DABCO-derived poorly soluble cationic halogenating reagents whose solubility in the organic solvent was due to ion-pairing, rather than to H-bonding interactions with the catalyst [130], as it occurred for complexes **168** and **169** and NBS [126]. Thus, compounds **177** were treated with salt **179**, that gave the best results among other similar salts, together with Brønsted acid 8H-*R*-TRIP **180**, that with respect to *R*-TRIP **165** required shorter reaction times coupled with better stereoselectivity, and tricyclic products **178** were isolated in high yield with excellent enantioselectivity (Scheme 49) [131].

Following this methodology, the triptamine derivative **181** afforded on a multigram scale the bromo derivative **182** that through a multistep synthesis gave the C_2-symmetric bispyrrolidinoindoline-derived alkaloid (-)-chimonantine **183** [126], component of *Chimonanthus praecox*, that inhibits tyrosinase and tyrosine-related protein-1 mRNA expression (Scheme 50) [132].



i. **179** (1.3 equiv), 8H-*R*-TRIP, **180** (0.1 equiv), $NaHCO_3$ (4.0 equiv), toluene, 0 °C. 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 = $CH(CH_3)_2$

8H-*R*-TRIP, **180**

Scheme 49. Synthesis of tricyclic HPI derivatives **178** mediated by 8H-*R*-TRIP **180**.

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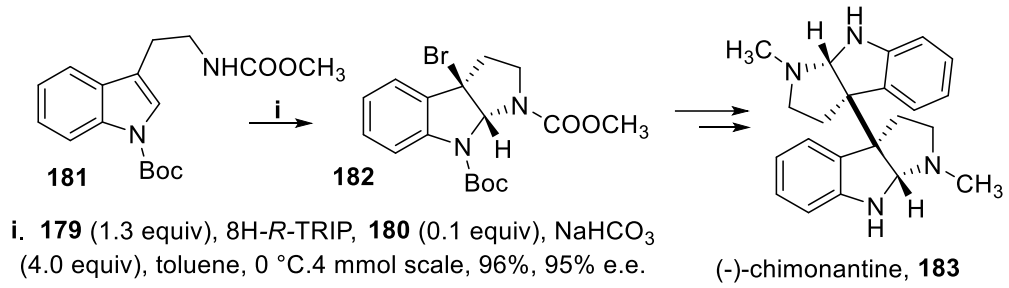
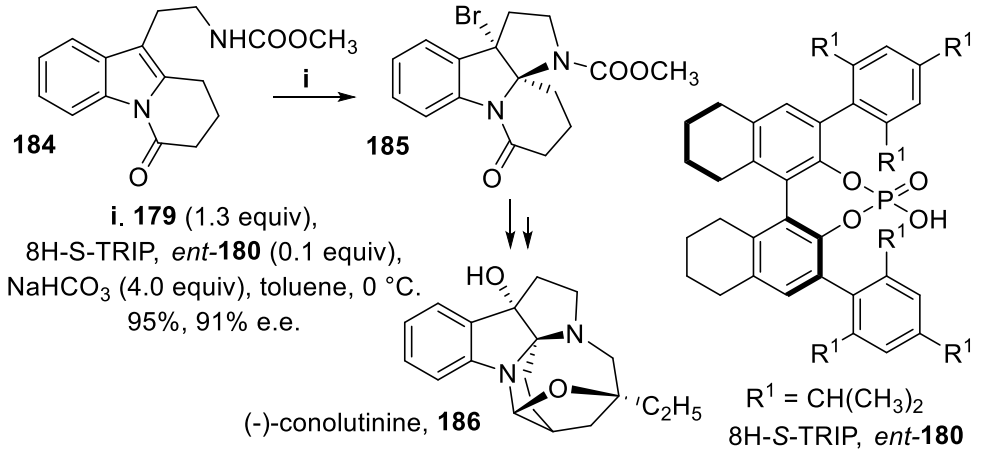


Scheme 50. Synthesis of tricyclic HPI derivative 182, key intermediate to (-)-chimonantine 183.

On the other hand, a HPI core displaying the opposite configuration at the chiral center was obtained on treating the compound **184** with the salt **179** and the Brønsted acid 8H-*S*-TRIP, *ent*-**180**. The tetracyclic structure **185** was isolated in excellent yield and stereoselectivity and eventually converted into (-)-conolutinine, **186**, an indole terpenoid alkaloid effective to reverse multidrug resistance in vincristine-resistant KB cells (Scheme 51) [133].



Scheme 51. Synthesis of tetracyclic HPI derivative **185**, intermediate to (-)-conolutinine **186**.

It is worth noting that this methodology was changed into an environmentally friendly process that avoided external chemical oxidants and harsh conditions. In fact by oxidation of bromide anion to bromine, that occurred in an undivided electrolytic cell in the presence of the salt **189,** allowed to generate in situ the brominating species **178**. From its interaction with the Brønsted acid **190** a weak ion pair soluble in the organic solvent arose, which reacted with tryptamine derivatives **187**, and the tricyclic compounds **188** were isolated in very good yield and excellent stereoselectivity (Scheme 52) [134]. It is worth mentioning that this metodology was successfully applied also on a multigram scale. In fact, using a reduced amount of **190** (1 mol %) compound **187e** was converted into **188e** in 99.5% yield and 90% e.e., suitable to be converted into alkaloids (-)-chimonantine **183** [130] and (-)-hodgkinsine [135].

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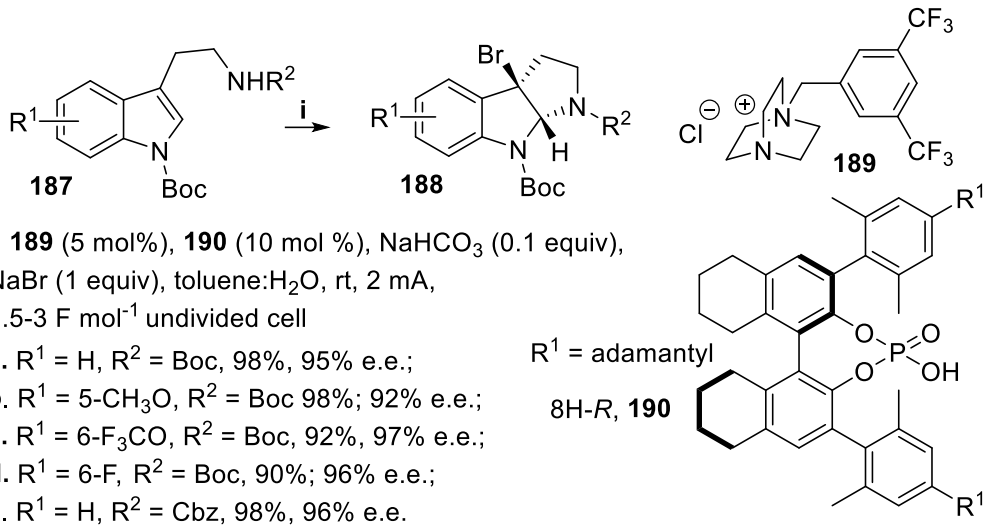
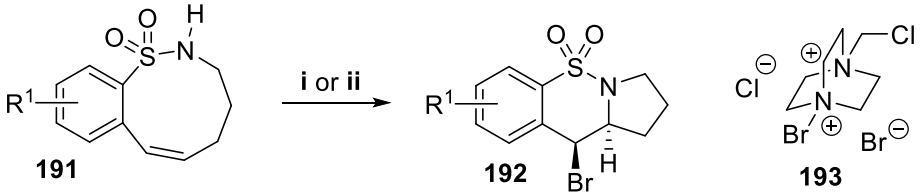


i. **189** (5 mol%), **190** (10 mol %), $NaHCO_3$ (0.1 equiv), NaBr (1 equiv), toluene:H_2O, rt, 2 mA, 2.5-3 F mol^{-1} undivided cell

a. R^1 = H, R^2 = Boc, 98%, 95% e.e.;
b. R^1 = 5-CH_3O, R^2 = Boc 98%; 92% e.e.;
c. R^1 = 6-F_3CO, R^2 = Boc, 92%, 97% e.e.;
d. R^1 = 6-F, R^2 = Boc, 90%; 96% e.e.;
e. R^1 = H, R^2 = Cbz, 98%, 96% e.e.

Scheme 52. Synthesis of tricyclic HPI derivatives **188** in an undivided electrolytic cell.

Eventually, exploiting again a chiral phase-transfer catalysis (PTC) methodology, sulfonamides **191** underwent transannular cyclization when the Brønsted acid TRIP **165** was employed together with NBS that was transferred into the organic solvent exploiting H-bonding interactions, to give the tricyclic derivatives **192** in good yield with high stereoselectivity. On the other hand, again exploiting the chiral phase-transfer catalysis methodology, the same compounds **192** were isolated in good yield but with better streoselectivity, when the cationic brominating reagent **193** was used in place of NBS together with TRIP **165** (Scheme 53). The ion-pairing with the catalyst allowed transfer of the poorly soluble salt **193** into the organic solvent and deep insight about the reaction mechanism was obtained by using computational methods [136].



i. NBS (1.0 equiv), **165** (5 mol %), succinimide (5 mol %), mesitylene, rt.
R^1 = H, 92%, 84% e.e.; R^1 = 8-CF_3, 80%, 90% e.e.; R^1 = 7-CH_3, 87%, 60% e.e.
ii. **193** (1.3 equiv), **165** (10 mol %), Na_2CO_3 (4 equiv), mesitylene:C_6H_{12} 1:1, 0 °C.
R^1 = H, 95%, 92% e.e.; R^1 = 7-CF_3, 95%, 74% e.e.; R^1 = 7-CH_3, 97%, 76% e.e.

Scheme 53. Transannular cyclization of sulphonamides **191**.

Diprotected tryptamines **194** were easily cyclized with NBS under phase-transfer conditions when the reaction was carried out by using as the catalyst the Brønsted acid chiral Co(III) complex Λ-**168** and the corresponding tricyclic derivatives **195a** were isolated in good yield and high enantioselectivity [137]. However, when NBS was changed for 1,3-diiodo-5,5-dimethylhydantoin (DIDMH), again in the presence of Λ-**168,** the conversion of compounds **194** into iododerivatives **195b** proceeded with lower yields but with comparable enantioselectivity (Scheme 54) [138].

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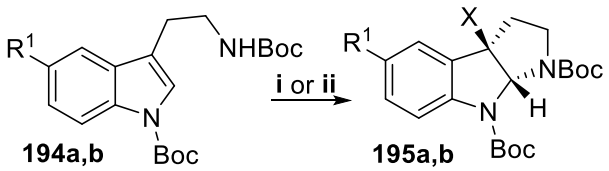
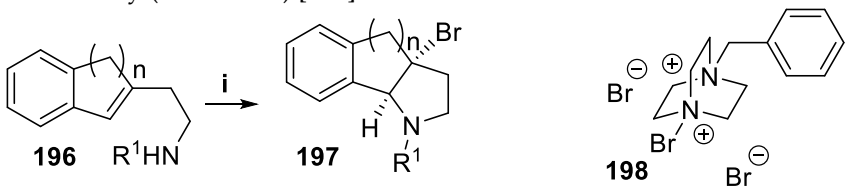


i. X = Br. NBS (1.2 equiv), catalyst Λ-**168** (10 mol %), toluene, air, -30 °C;
a.: R^1 = H, 89%, 88% e.e.; R^1 = CH_3, 95%, 82% e.e.; R^1 = F, 78%, 80% e.e.

ii. X = I. DIDMH (1.0 equiv), catalyst Λ-**168** (10 mol %), CCl_4, MS 4Å, -20 °C;
b.: R^1 = H, 53%, 81% e.e.; R^1 = CH_3, 44%, 89% e.e.; R^1 = CH_3O, 40%, 85% e.e.

Scheme 54. Synthesis of HPI derivatives **195a,b** mediated by Co(III) complex Λ-(*S,S*)-**168**.

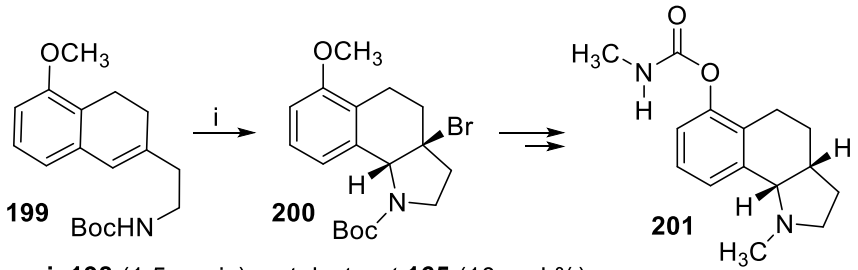
In addition, for the cyclization of indene (n=1) and 1,2-dihydronaphthalene (n=2) derivatives **196**, a chiral anionic phase-transfer methodology exploiting the DABCO-derived cation **198** together with Brønsted acid TRIP **165** was employed, and the corresponding tricyclic products **197**, key building blocks for the synthesis of bioactive molecules, were obtained in very good yield and with excellent enantioselectivity (Scheme 55) [139].



i. **198** (1.5 equiv), catalyst **165** (10 mol %), Na_2CO_3 (4.0 equiv), *p*-xylene, rt.
R^1 = Ts, n = 1, 98%, 95% e.e.; R^1 = Ts, n = 2, 96%, 93% e.e.;
R^1 = 4-Brosyl, n = 1, 98%, 93% e.e.; R^1 = 4-Brosyl, n = 2, 95%, 92% e.e.

Scheme 55. Amidocyclization of indene and 1,2-dihydronaphthalene derivatives **196** mediated by TRIP, **165**.

Moreover, within the synthesis of the tricyclic compound **201**, a potent acetyl cholinesterase (AChE) inhibitor displaying the opposite configuration at the chiral centers with respect to **197** [134], compound **199** was treated under the same conditions but using *ent*-**165** as the catalyst, and the tricyclic derivative **200** was isolated in high yield and enantioselectivity (Scheme 56) [140].



i. **198** (1.5 equiv), catalyst *ent*-**165** (10 mol %),
Na_2CO_3 (4.0 equiv), *p*-xylene, rt, 88%, 95% e.e.

Scheme 56. Bromocyclization leading to acetyl cholinesterase inhibitor **201** mediated by *ent*-**165**.

Eventually, a desymmetrization with enantiotopic group discrimination [97] [99] [141-147] was carried out starting from prochiral cyclohexa-1,4-dienes **202** exploiting the bromoamidocyclization mediated by TRIP **165** and the salt **204** under PTC conditions. According this methodology *cis*-3a-arylhydroindoles **203** were obtained in moderate to good yield but always with excellent stereoselectivity [148], and the usefulness of this methodology was confirmed by the synthesis of (+)-mesembrane, **205,** found in plants of the *Amaryllidaceae* family (Scheme 57) [149-150].

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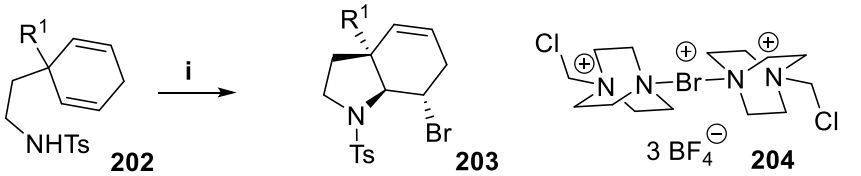
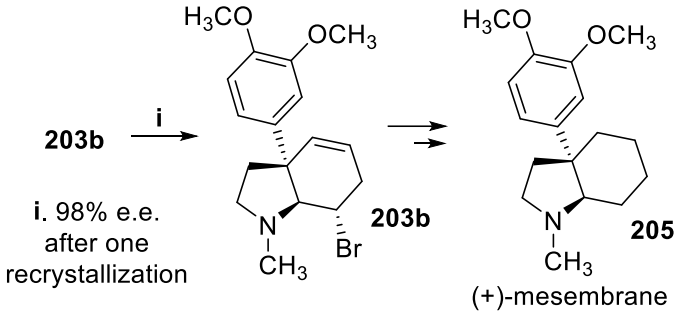


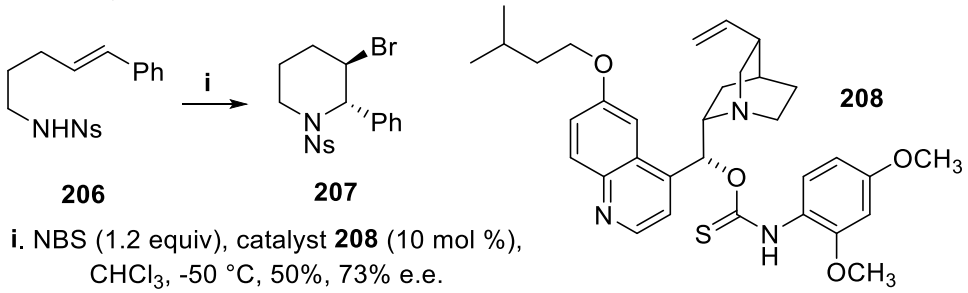
i. **204** (1.5 equiv), **165** (10 mol%), Na_2CO_3 (4.0 equiv) CCl_4, 0 °C.
a. $R^1 = C_6H_5$, 78%, 97% e.e.; b. R^1 = 3,4-$(CH_3O)_2$-C_6H_3, 68%, 86% e.e.;
c. $R^1 = CH_2OTBS$, 59%, 95% e.e.; d. R^1 = 3-CH_3-C_6H_4, 67%, 97% e.e.



Scheme 57. Desymmetrization of prochiral cyclohexa-1,4-dienes **202** leading to (+)-mesembrane, **205**.

3.2. N-Sulfonyl Piperidines

In the presence of the catalyst **136** the bromoamidation of compounds **134**, mediated by *N*-bromopyrrolidinone (NBP) and proceeding in a 5-*endo*-trig mode, led to the enantioenriched *trans*-2-substituted 3-bromopyrrolidine derivatives **135** with total regioselectivity and high stereoselectivity (Scheme 34) [106]. However, under the same conditions, the homolog (*E*)-substrate **206**, biased to cyclize in a 6-*exo*-mode by electronic factors, afforded in very low yield and neglectable e.e. the *trans*-2,3-disubstituted *N*-sulfonyl piperidine **207** that was however isolated with moderate yield and enantioselectivity when the catalyst **136** was changed for **208** and NBS was the bromenium ions source (Scheme 58) [151].



i. NBS (1.2 equiv), catalyst **208** (10 mol %),
$CHCl_3$, -50 °C, 50%, 73% e.e.

Scheme 58. Synthesis of 3-bromo piperidine **207** exploiting NBS in the presence of catalyst **208**.

However, a further, significant improvement was obtained using 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) in place of NBS in the presence of catalyst **208**, since the cyclization of (*E*)-sulfonylamino derivatives **209**, proceeding in a 6-*endo*-trig mode, exclusively, allowed to isolate 2,3-*trans*-disubstituted piperidines **210** in high yield and with good stereoselectivity. It is worth mentioning that these compounds displayed at the chiral centers the configuration opposite to **207**, but the reason of this outcome remained unclear (Scheme 59) [151].

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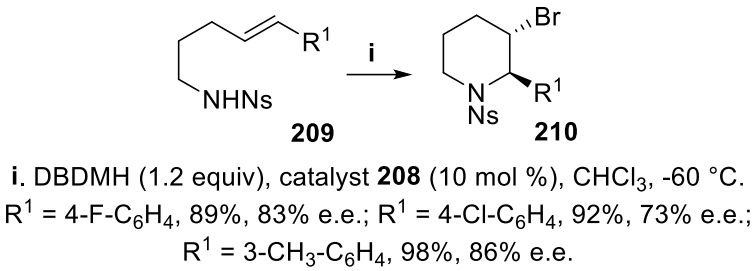
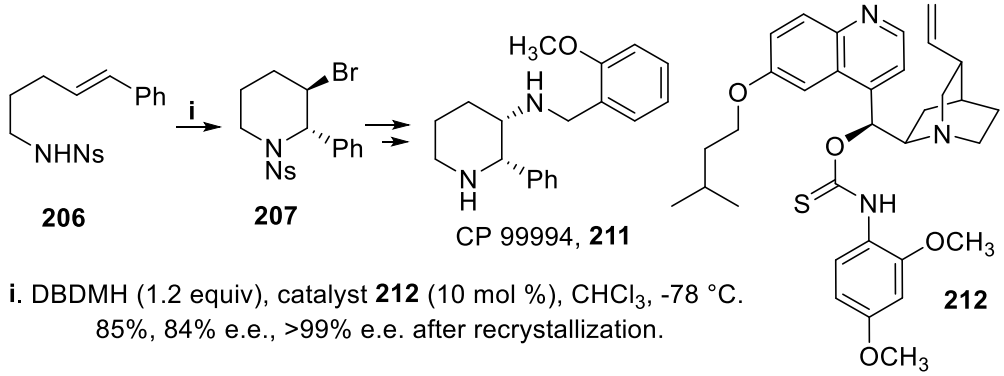


Scheme 59. Synthesis of 3-bromo piperidines derivatives **210** exploiting DBDMH and the catalyst **208**.

Eventually, starting from **206** but using DBDMH in the presence of catalyst **212**, pseudoenantiomeric with **208**, the piperidine derivative **207** was obtained in the pure enantiomeric form after recrystallization [139], suitable to be converted into bioactive products such as CP 99994, **211**, a high affinity NK1 antagonist (Scheme 60) [152].



Scheme 60. Stereoselective synthesis of 3-bromo piperidine **207**, key intermediate to NK1 antagonist **211**.

3.3. [1,2,3] Oxathiazine 2,2-dioxides

The outcome of halofunctionalization of unsaturated sulfamate ester derivatives **213** relied on both the halogen source and the catalyst employed. In fact, when the reaction was carried out with NBS in the presence of ligand **216** and $Sc(OTf)_3$ a diastereomeric mixture of [1,2,3]oxathiazine 2,2-dioxides *syn*-**214** and *anti*-**215** was obtained, the *syn*-bromoderivatives **83** being isolated as the major products in good yield and high enantioselectivity (Scheme 61). On the contrary, when the compounds **213** were treated with $TsNCl_2$ as the donor of halenium ions, together with the ligand **219** and $Lu(OTf)_3$, diastereomeric mixtures of *anti*-**217** and *syn*-**218** were isolated in good yield, and the major *anti*-isomers 217 were obtained with excellent enantioselectivity (Scheme 62) [153].

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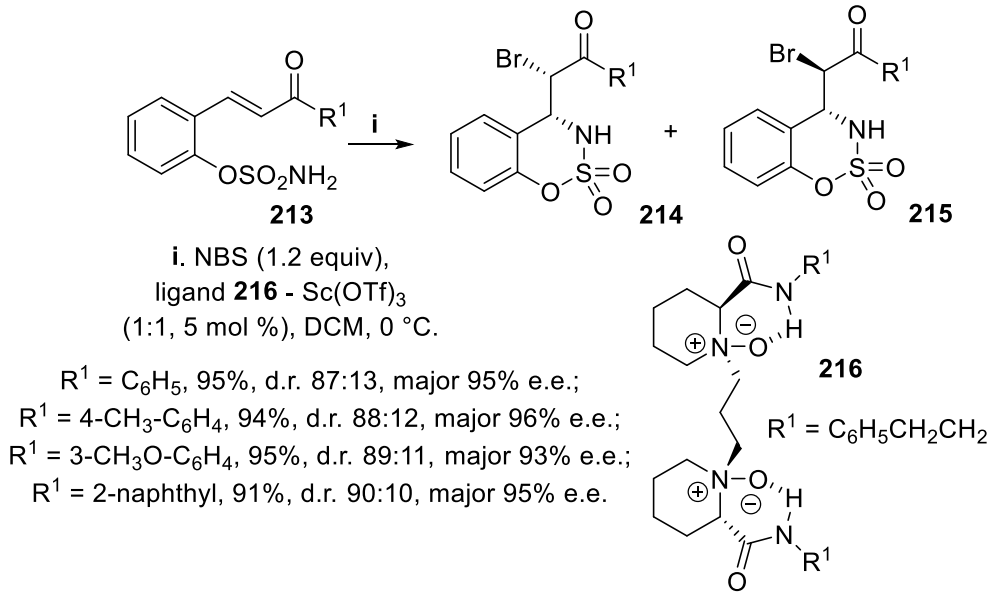
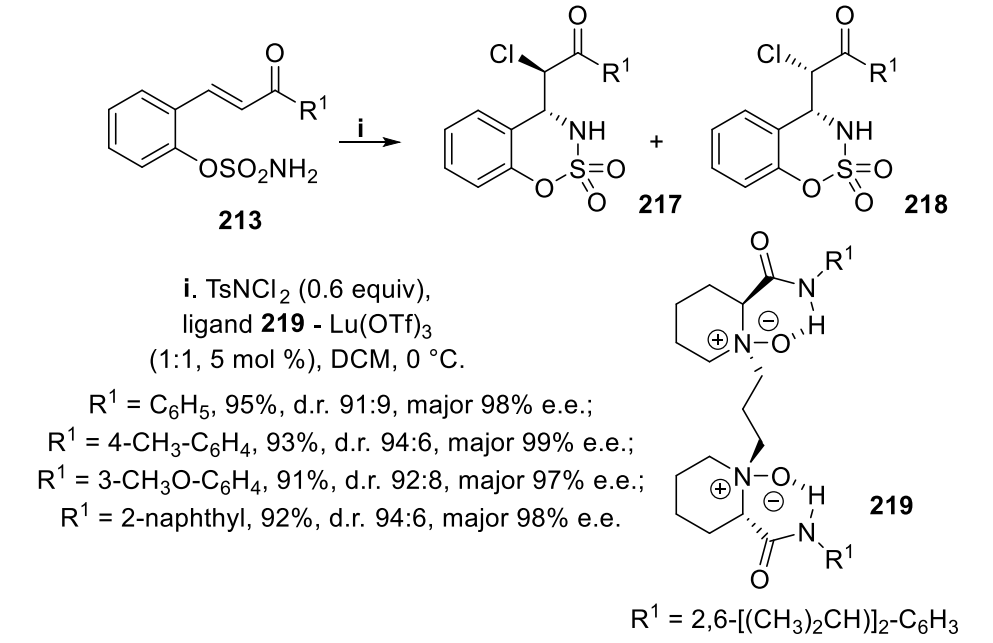


Scheme 61. Synthesis of *syn*- and *anti*-[1,2,3]oxathiazines 2,2-dioxides, **214** and **215**.



Scheme 62. Synthesis of *anti*- and *syn*-[1,2,3]oxathiazines 2,2-dioxides, **217** and **218**.

In the event, when the reaction of compounds **213** was carried out with $BsNBr_2$ in the presence of ligand **219** and $Lu(OTf)_3$, followed by treatment with Et_3N, the initial bromoamination reaction afforded in good yield diastereomeric mixtures of derivatives *anti*-**220** and *syn*-**221**. However, under the basic reaction conditions the minor *syn*-isomers **221** remained unchanged, whereas the major *anti*-isomers **220** were easily converted with excellent stereoselectivity into the corresponding (3,3-dioxido-1,8b-dihydroazirino [1,2-c]benzo[e][1,2,3] oxathiazin-1-yl) aryl ketones **222** (Scheme 63) [153].

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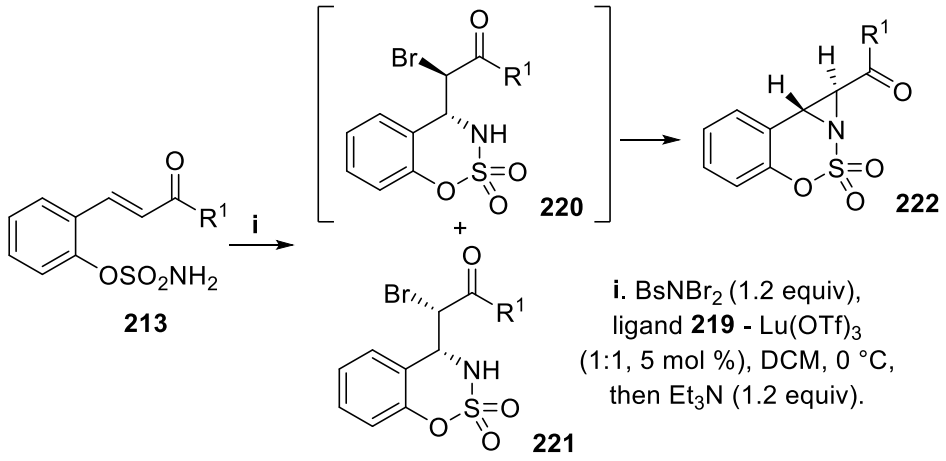
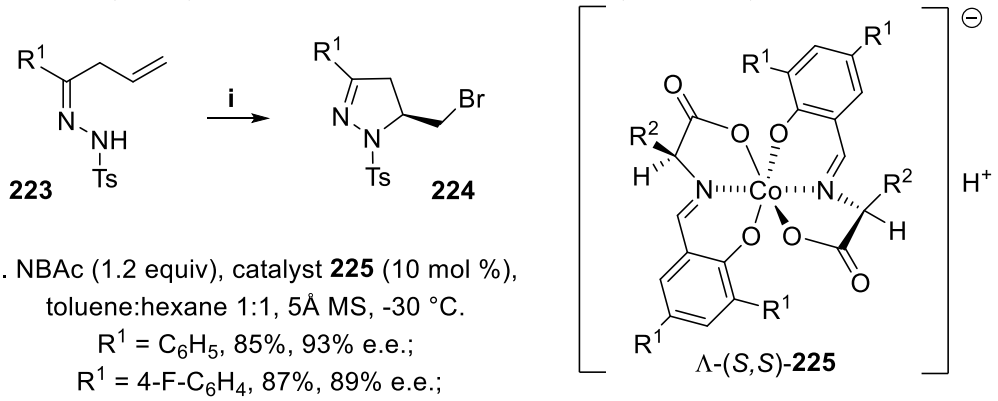


R^1 = C_6H_5, 88%, 9:1 ratio, major 99% e.e.;
R^1 = 4-Cl-C_6H_4, 84%, 9:1 ratio, major 96% e.e.;
R^1 = 3-CH_3O-C_6H_4, 85%, 9.5:1 ratio, major 96% e.e.;
R^1 = 2-naphthyl, 88%, 9.5:1 ratio, major 96% e.e.

Scheme 63. Synthesis of [1,2,3]oxathiazin-1-yl) aryl ketones **222**.

3.4. N-Sulfonyl 4,5-dihydro-1H-pyrazoles

Recently, 5-halomethyl dihydropyrazoles deserved interest since 1,3-diamine derivatives used as precursors of analogs of anti-influenza agent Peramivir were prepared through cleavage of the N−N bond of polysubstituted pyrazolines bearing a tertiary chiral center [154]. Thus, starting from hydrazones **223**, the chiral bromomethyl derivatives **224** were obtained in good yield and excellent stereoselectivity via bromoamidation using the anionic chiral Co(III) complex Λ-(*S*,*S*)-**225** that, being highly soluble in apolar solvents, was proven to be an efficient phase-transfer catalyst when *N*-bromoacetamide (NBAc) was the source of bromenium ions (Scheme 64) [155].



i. NBAc (1.2 equiv), catalyst **225** (10 mol %), toluene:hexane 1:1, 5Å MS, -30 °C.
R^1 = C_6H_5, 85%, 93% e.e.;
R^1 = 4-F-C_6H_4, 87%, 89% e.e.;
R^1 = cyclohexyl, 60%, 92% e.e.

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

Scheme 64. Stereoselective synthesis of 5-bromomethyl dihydropyrazoles **224** mediated by Λ-(*S*,*S*)-**225**.

In alternative, also Co-complex Λ-(*S*,*S*)-**169** was highly effective for iodoamidation of unsaturated hydrazones **226** carried out with DIDMH, and the corresponding 5-iodomethyl 4,5-dihydro-1*H*-pyrazoles **227** displaying at the tertiary center the same configuration as the bromomethyl derivatives **224**, were isolated in good yield and high stereoselectivity (Scheme 65) [155].

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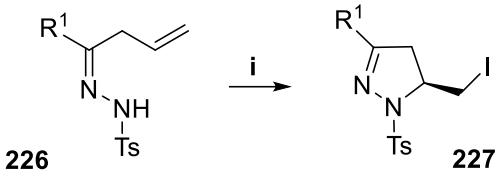
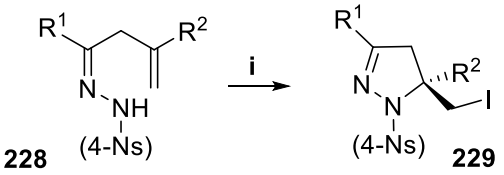
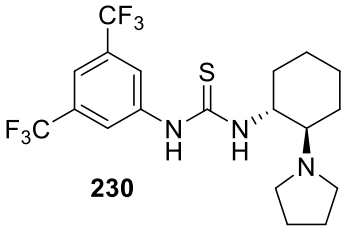


i. DIDMH (1.2 equiv), catalyst **169** (10 mol %),
toluene:hexane 1:1, 5Å MS, -30 °C.
R^1 = C_6H_5, 91%, 91% e.e.; R^1 = 4-F-C_6H_4, 99%, 86% e.e.;
R^1 = cyclohexyl, 73%, 81% e.e.

Scheme 65. Synthesis of 5-iodomethyl dihydropyrazoles **227** mediated by Λ-(*S,S*)-**169**.

It is worth noting that some dihydropyrazoles containing a quaternary chiral center were established as potent kinesin spindle protein (KSP) inhibitors, halting the cellular mitosis [156-157]. Thus, many efforts were directed towards asymmetric iodoamidation of unsaturated arenesulfonyl hydrazones directed towards preparation of dihydropyrazoles bearing either a quaternary center and a iodomethyl functionality suitable for further transformations. At first, starting from nosyl hydrazones **228**, the source of iodenium ion was *N*-iodopyrrolidin-2-one (NIPyr) employed together with the chiral amino thiourea **230**. This bifunctional catalyst was able to coordinate both the iodiranium ion and the nucleophilic nitrogen, thus generating a chiral environment and the chiral 3,5-disubstituted 5-iodomethyl-1-nosyl-4,5-dihydro-1*H*-pyrazoles **229** were obtained in high yield and good enantioselectivity (Scheme 66) [158].



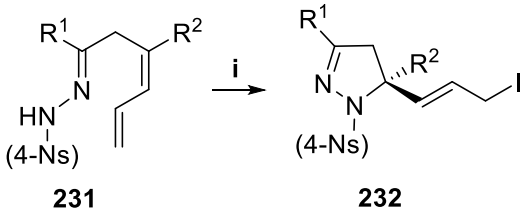


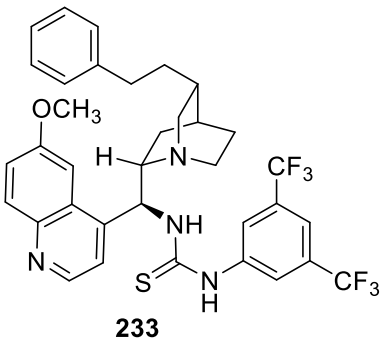
i. NIPyr (1.4 equiv), catalyst **230** (10 mol %),
toluene:DCM 1:1 4A MS, -80 °C.

R^1 = R^2 = C_6H_5, 95%, 85% e.e.;
R^1 = C_6H_5, R^2 = 4-F-C_6H_4, 88%, 83% e.e.;
R^1 = 3-Cl-C_6H_4, R^2 = 4-CH_3-C_6H_4, 78%, 88% e.e.

Scheme 66. Synthesis of 4,5-dihydro-1*H*-pyrazoles **229** mediated by catalyst **230**.

In addition, dienyl nosyl hydrazones **231** underwent cyclization mediated by NIS in the presence of difunctional catalyst **233**, since under these conditions catalyst **230** was less effective in generating chirality, and the corresponding 1-nosyl-4,5-dihydro-1*H*-pyrazole derivatives **232** were isolated in moderate yield but with good enantioselectivity (Scheme 67) [159].





i. NIS (1.2 equiv), catalyst **233** (10 mol %),
toluene:$CHCl_3$ 3:1.
a. R^1 = R^2 = C_6H_5, 54%, 97% e.e.;
b. R^1 = 4-F-C_6H_4, R^2 = C_6H_5, 61%, 82% e.e.
c. R^1 = 2-naphthyl, R^2 = C_6H_5, 74%, 94% e.e.

Scheme 67. Synthesis of 4,5-dihydro-1*H*-pyrazoles **232** mediated by catalyst **233**.

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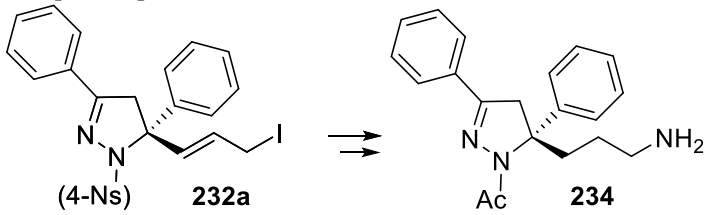
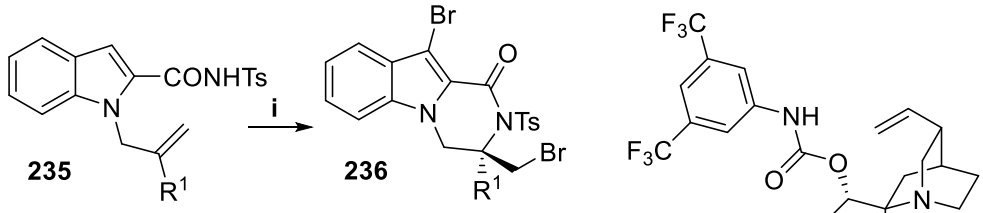
The usefulness of this methodology was proven by conversion through simple steps of the chiral product **232a** into the *N*-acetyl 3,5-diphenyl-4,5-dihydro-1*H*-pyrazole **234,** having structure similar to that of a potent kinesin spindle protein (KSP) inhibitor (Scheme 68) [160].



Scheme 68. Synthesis of compound **234**, analog of a kinesin spindle protein (KSP) inhibitor.

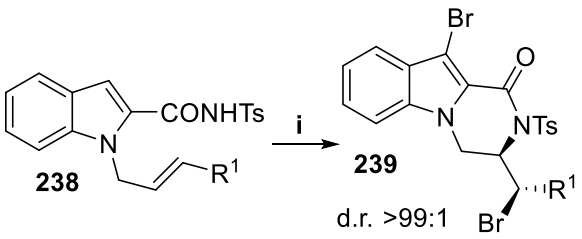
3.5. N-Tosyl Lactams

The tosylamides **235** and **238**, bearing a sulfonyl functionality at the amidic nitrogen, underwent cyclization mediated by NBS in the presence of the difunctional catalyst **237**, to give in excellent yield and enantioselectivity either 3-bromomethyl **236** (Scheme 69) or 3-bromoalkyl 10-bromo-2-tosyl-3,4-dihydropyrazino [1,2-a]indol-1(2*H*)-ones **239**, respectively (Scheme 70), and under the reaction conditions the process was completely regioselective, since products arising from attack of carbonyl oxygen to bromiranium ion were never observed and the tricyclic lactam core formed occurs in bioactive molecules, such as an histamine H_3 receptor agonist [161]. Two equivalents of bromenium ion were required for this cyclization, since eventually a bromine atom was transferred to C-3 of the indole ring, and the use of chloroform analytical reagent (AR) grade was compulsory for higher stereoselectivity, due to the presence of a little amount of ethanol, since the stereoselectivity clearly dropped when ethanol was totally removed, although its role in the process was not ascertained. Concerning the reaction mechanism, NMR experiments suggested the initial formation of an intermediate where bromine is directly bonded to the catalyst, unlike catalysts in which a thiocarbamate sulfur interact with the halenium ion as Lewis base, whereas the quinuclidinic nitrogen forces the amide in the enolic form, thus avoiding oxygen attack to the bromiranium ion [162].



i. NBS (2.4 equiv), catalyst **237** (10 mol %),
AR $CHCl_3$:toluene 2:1, -78 °C.
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.

Scheme 69. Synthesis of *N*-tosyl lactams **236** bearing a bromomethyl substituent.



i. NBS (2.4 equiv), catalyst **237** (10 mol %), AR $CHCl_3$:toluene 2:1, -78 °C.
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.

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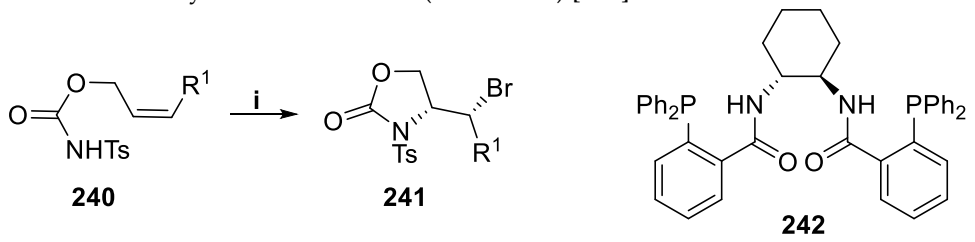
Scheme 70. Synthesis of *N*-tosyl lactams **239** bearing a bromoalkyl substituent.

3.6. N-Tosyl 1,3-oxazolidin-2-ones and 1,3-oxazin-2-ones

In the presence of the complex generated by chiral phosphine ligand **242** and Sc triflate, *N*-tosyl carbamates **240** containing a (*Z*)-double bond were converted in good yield into the corresponding *N*-tosyl oxazolidin-2-ones **241** through a 5-*exo*-mode cyclization exploiting NBS as bromenium ions donor. The reaction proceeded with total regioselectivity and excellent enantioselectivity, and ^{31}P NMR spectroscopy evidenced interactions between the ligand **242** and Sc, leading to a chiral reaction environment followed by activation of NBS (Scheme 71) [163].

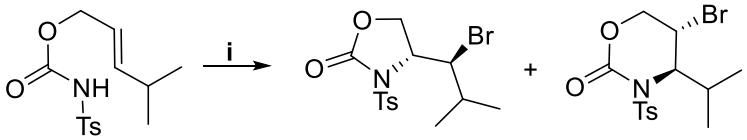


240 **241** **242**

i. NBS (1.2 equiv), ligand **242** - $Sc(OTf)_3$ (1:1, 10 mol %), toluene:DCM 3:1, -50 °C.
$R^1 = C_2H_5$, 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.

Scheme 71. Synthesis of chiral oxazolidin-2-ones **241** mediated by ligand **242**.

Both regio- and stereoselectivity of this cyclization strongly relied upon the configuration of the double bond. In fact, under the same reaction conditions, the reaction of (*E*)-carbamate **243** led to a regioisomeric mixture of 1,3-oxazolidin-2-one **244** and 1,3-oxazin-2-one **245**, but only this latter, displaying a six-membered ring, was isolated with good enantioselectivity (Scheme 72) [163].



243 **244** **245**
48%, 5% e.e. 20%, 90% e.e.

i. NBS (1.2 equiv), ligand **242** - $Sc(OTf)_3$ (1:1, 10 mol %), toluene:DCM 3:1, -50 °C.

Scheme 72. Non-regioselective bromocyclization of (*E*)-tosyl carbamate **243**.

However, exploiting the same complex arising from phosphine oxide **248** and Sc triflate, but changing dibromodimethylhydantoin (DBDMH) for NBS and using NaCl as an additive, the cyclization the (*E*)-carbamates **246** proceeded in a 6-*endo*-mode, exclusively, to afford *N*-tosyl oxazin-2-ones **247** in good yield, with total regioselectivity and excellent enantioselectivity. It is worth noting that the corresponding (*Z*)-carbamates under the same reaction conditions gave only oxazolidin-2-ones but in poor yield and low stereoselectivity [164], unlike the results observed with the ligand **242**. Furthermore, by addition of KBr in place of NaCl and increasing the amount of the complex, carbamates **249**, displaying a trisubstituted double bond, afforded in high yield and excellent stereoselectivity oxazin-2-ones **250** containing a quaternary chiral carbon (Scheme 73) [165].

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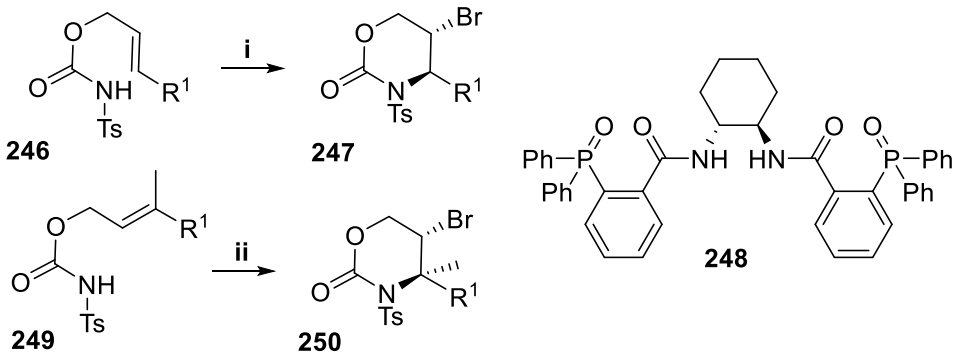
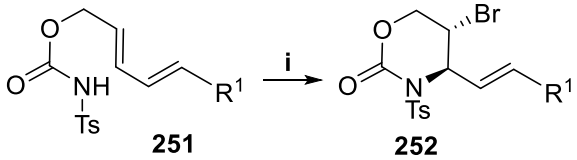


i. DBDMH (1.2 equiv), ligand **248** - $Sc(OTf)_3$ (2 mol %),
NaCl (1.2 equiv), $CHCl_3$, -50 °C.
$R^1 = C_6H_5$, 86%, 95% e.e.; R^1 = 2-CH_3-C_6H_4, 94%, 95% e.e.;
R^1 = 4-Cl-C_6H_4, 96%, 95% e.e.; R^1 = 1-naphthyl, 75%, 99% e.e.
i. DBDMH (1.2 equiv), ligand **248** - $Sc(OTf)_3$ (5 mol %),
KBr (1.2 equiv), $CHCl_3$, -50 °C.
$R^1 = C_6H_5$, 90%, 94% e.e.; R^1 = 3-CH_3-C_6H_4, 80%, 98% e.e.;
R^1 = 4-Br-C_6H_4, 67%, 88% e.e.; R^1 = 3-CH_3O-C_6H_4, 75%, 92% e.e.

Scheme 73. Bromoyclization of tosylcarbamates **246** and **249** mediated by ligand **248**.

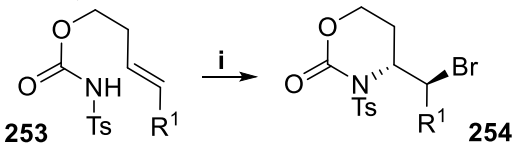
Accordingly, by reaction of dienyl carbamates **251** under the same conditions, the corresponding oxazin-2-ones **252** were isolated in good yield and high enantioselectivity (Scheme 74) [166].



i. DBDMH (1.2 equiv), ligand **248** - $Sc(OTf)_3$(1:1) (5 mol %),
NaCl (1.2 equiv), $CHCl_3$, -50 °C.
$R^1 = CH_3$, 91%, 97% e.e.; R^1 = n-C_4H_9, 79%, 93% e.e.;
$R^1 = C_6H_5$, 61%, 95% e.e.; R^1 = 4-Cl-C_6H_4, 68%, 97% e.e.

Scheme 74. Bromoyclization of dienyl carbamates **251** mediated by ligand **248**.

The cyclization of homoallyl *N*-tosyl carbamates **253** with (*E*)-configuration at the double bond required a larger amount of the complex between phosphine oxide **248** and Sc triflate, when *N*-bromoacetamide was used as bromenium ions source in the absence of halide ions, and the reaction proceeded according to a 6-*exo* mode, leading to oxazin-2-ones **254** in moderate yield but with nearly total enantioselectivity (Scheme 75) [167].



i. $CH_3CONHBr$ (1.2 equiv), ligand **248** - $Sc(OTf)_3$ (1:1, 10 mol %), DCM, -15 °C.
$R^1 = CH_3$, 58%, 99% e.e.; $R^1 = C_2H_5$, 57%, >99% e.e.; $R^1 = C_5H_{11}$, 57%, >99% e.e.;
$R^1 = CH_2CH_2Cl$, 45%, 99% e.e.

Scheme 75. Bromoyclization of homoallyl carbamates **253** mediated by ligand **248**.

Eventually, in the presence of an even larger amount of the complex arising from phosphine oxide **248** and Sc triflate, compounds **255** were converted in good yield and with excellent

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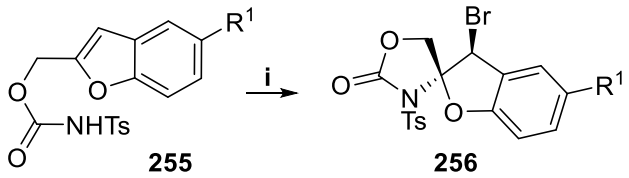
enantioselectivity into the spiro derivatives **256**, exploiting dearomatization initiated by attack of a bromenium ion to the electron-rich benzofuran ring (Scheme 76) [168].

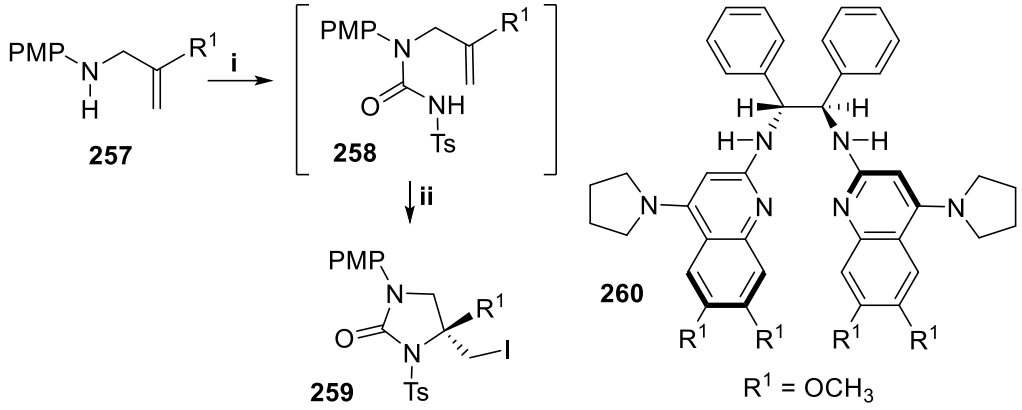


i. DBDMH (1.2 equiv), ligand **248** - $Sc(OTf)_3$(1:1) (20 mol %),
Na_2CO_3 (2.4 equiv), $CHCl_3$, -60 °C.
R^1 = H, 90%, 94% e.e.; R^1 = CH_3, 89%, 94% e.e.; R^1 = t-C_4H_9, 90%, 97% e.e.

Scheme 76. Dearomatization of an electron-rich benzofuran ring leading to chiral spiro compounds **256**.

3.7. 1,3-Imidazolidin-2-Ones and Tetrahydropyrimidin-2(1H)-Ones

Unsaturated *N*-tosyl urea intermediates **258** were prepared by reaction of *gem*-disubstituted allylamines **257** with tosyl isocyanate and the cyclization, carried out in situ using *N*-iodopyrrolidinone (NIPyr) in the presence of the basic Brønsted catalyst **260**, gave the chiral *N*-tosylimidazolidin-2-ones **259** in good yield with high enantioselectivity (Scheme 77) [157].



i. TsN=C=O (1.0 equiv), toluene -50 °C **ii**. NIPyr (1.2 equiv),
catalyst **260** (5 mol %), toluene, -50 °C.
R^1 = C_6H_5, 82%, 91% e.e.; R^1 = 4-CH_3-C_6H_4, 97%, 92% e.e.;
R^1 = 4-F-C_6H_4, 90%, 89% e.e.; R^1 = CH_3, 93%, 29% e.e.

Scheme 77. Synthesis of *N*-tosylimidazolidin-2-ones **259** mediated by chiral catalyst **260**.

Starting from the (*Z*)-allylamine **261**, the cyclization proceeded in a 5-*exo*-mode leading to imidazolidin-2-one **262** with excellent yield and stereoselectivity, and steric bias due to the double bond configuration overwhelmed electronic factors. On the contrary, proceeding through a 6-*endo*-mode cyclization directed by electronic factors, the (*E*)-allylamine **263a** led to tetrahydropyrimidin-2(1*H*)-ones **264a** in high yield and stereoselectivity, whereas amine **263b**, displaying a trisubstituted double bond, gave the corresponding tetrahydropyrimidin-2(1*H*)-one **264b** with high enantioselectivity but in low yield, probably due to the formation of a quaternary chiral center (Scheme 78) [169].

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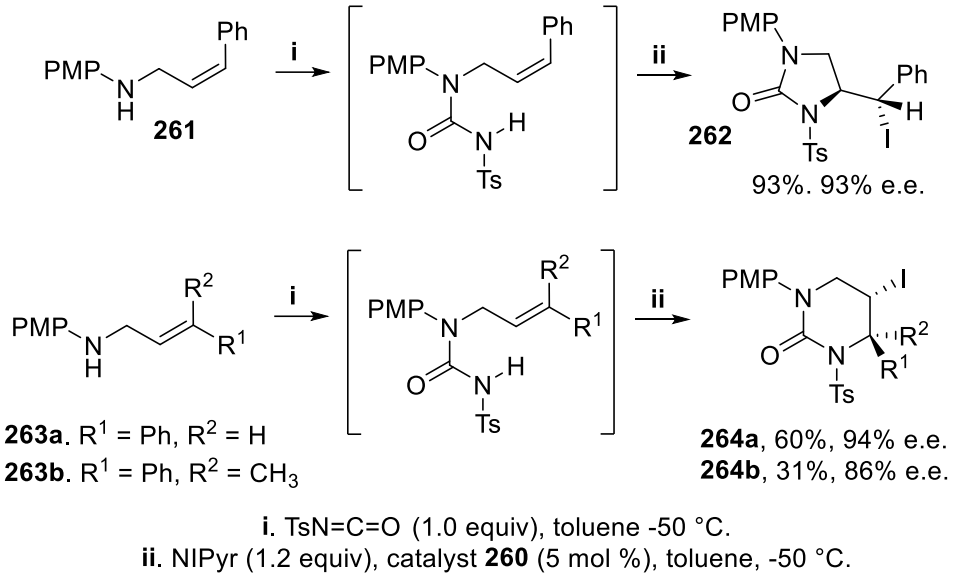
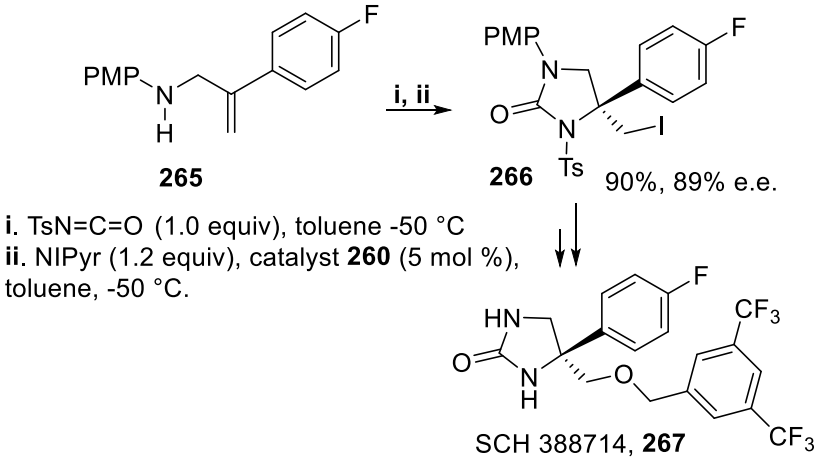


Scheme 78. Synthesis of imidazolidin-2-one **262** and tetrahydropyrimidin-2(1*H*)-ones **264a,b**.

With the aim of demonstrating the usefulness of this methodology [157], the amine **265** gave in good yield and high enantioselectivity the iodomethyl derivative **266**, precursor of the product SCH 388714, **267**, a potent and selective NK_1 receptor antagonist that is orally active and displays good CNS penetration (Scheme 79) [170].



Scheme 79. Synthesis of SCH 388714, **267**, potent and selective NK_1 receptor antagonist.

4. Conclusions

A lot of asymmetric syntheses of non-aromatic nitrogen containing heterocycles were recently developed, exploiting halenium ion initiated cyclofunctionalizations. Thus, starting from chiral intermediates, polyfunctionalized structures were obtained by internal chirality transfer, whereas expensive organocatalysts were very effective in transferring chirality information to achiral starting substrates and the final products were often obtained on multigram scale, within total synthesis of compounds with high medicinal potential, as it occurred for alkaloids or specific inhibitors of biological processes. Moreover, enzymes could provide unique possibilities for chiral induction in highly stereoselective C–N bond formation, but were employed only for C-O bond formation [171-177]. Thus, introduction of enzymes in a cascade process, that is becoming a very useful and versatile methodology for the synthesis of a broad number of chiral molecules, could lead to new methodologies in this area, and efficient and easy enzymatic approaches protocols for the stereoselective formation of C-N bonds directed towards synthesis of bioactive non aromatic

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heterocycles can be expected in the next few years [178-179], using green solvents and avoiding the pollution and waste problems arising from halogen containing reagents [134].

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