Chiral Nonaromatic 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 nonaromatic 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: nonaromatic 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 nonaromatic 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 the increase of 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 are easily converted into chiral polysubstituted nonaromatic 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 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 haloamination 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 nonaromatic 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].

\[
\text{\begin{align*}
\text{i.} & \quad \text{I}_2 \ (1.6 \text{ equiv}), \text{NaHCO}_3 \ (6.0 \text{ equiv}), \text{DME}:\text{H}_2\text{O} \ 2:1, \ 0 \ ^\circ\text{C}, \\
\text{ii.} & \quad \text{NaOH} \ (42 \text{ equiv}), \text{Bu}_4\text{N}^+\text{I}^- \ (0.5 \text{ equiv}), \text{THF}, \ 45\% \ \text{overall yield}
\end{align*}}
\]

Scheme 1. Iodocyclization leading to 1,4-dideoxy-1,4-manno-D-lyxitol, LAB, 5.

Again exploiting the 2,3-cis-directing effect of a 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].
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 C-2 was 

\[
\text{cis}
\]


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 iodonium 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 \(\beta\)-amino acid derivative 13 (Scheme 3) [40, 41].

Scheme 3. Iodo cyclization leading to polyhydroxylated pyrrolidine \(\beta\)-amino acid derivative 13.

The iodoamination of the \textit{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-\textit{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 iodonium 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].
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 preferentially give 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 lying 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 4](image)

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

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 5](image)

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

![Scheme 6](image)

Scheme 6. Iodocyclization 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].

![Diagram](image)

i. I$_2$ (3.0 equiv), NaHCO$_3$ (3.0 equiv), MeCN, rt, 20%, >99:1 d.r.

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

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

![Diagram](image)

i. I$_2$ (3.0 equiv), NaHCO$_3$ (3.0 equiv), MeCN, rt, 48% from two steps, >99:1 d.r. ii. TsNCO (4.5 equiv), rt, K$_2$CO$_3$ (10 equiv), MeOH, rt, 83%, >99:1 d.r.

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 aminoalkenediol 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].
Another matching/mismatching effect was observed when polyfunctionalized diastereomeric alkenols displayed different configuration at the carbon atom bearing the amino group. Thus, diastereomeric alkenamines 39 and 42, displaying the same configuration at C-2 and C-4, underwent cyclization in the presence of NaHCO₃ 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 unfavorable configuration—with respect to the 2,5-trans-one—and the overwhelming cis-2,3-directing effect exerted by the oxygenated functionality lying at the chiral allylic carbon (Scheme 11) [32–37,53].

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

Scheme 10. Synthesis of bicyclic oxazolidin-2-ones 41 and 44 with matching 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 compound 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 the obtaining of the chiral bicyclic compound 55, whose structure is present in azinocine antibiotics (Scheme 12) [55].
Scheme 11. Synthesis of mixtures of bicyclic oxazolidin-2-ones 47, 48 and 50, 51 owing to mismatching effects directing stereochemistry.

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 NsNH₂ 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].

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 (NsNH₂) starting from chiral t-Boc aziridines 60 bearing a homoallylic substituent, and the corresponding azepanes 62 displaying three chiral centers were obtained through the bicyclic intermediate 61 with excellent yield and nearly total regio- and stereoselectivity (Scheme 14) [57].

\[
\begin{align*}
\text{i. } \text{NBS (1.5 equiv), NsNH}_2 \text{(1.5 equiv), AcOEt, } & -30 \, ^\circ \text{C.} \\
R^\prime = 4\text{-Br-C}_6\text{H}_4, 82\%, 99\% \text{ e.e., }>99\% \text{ d.r;} \\
R^\prime = 3\text{-CH}_3\text{-C}_6\text{H}_4, 80\%, 99\% \text{ e.e., }>99\% \text{ d.r.;} \\
R^\prime = 4\text{-Cl-C}_6\text{H}_4, 83\%, 99\% \text{ e.e., }>99\% \text{ d.r;} \\
R^\prime = 4\text{-C}_6\text{H}_5\text{H}_4, 92\%, 99\% \text{ e.e., }>99\% \text{ d.r.}
\end{align*}
\]

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 have found potential therapeutic applications as antidiabetic, antiviral, anticancer, antimitostatic, 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 the conversion of 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].

\[
\begin{align*}
\text{i. NIS (1.2 equiv), DCM, } & 0 \, ^\circ \text{C.} \\
\text{ii. AgOAc (5.0 equiv), toluene, rt,} & 46\% \text{ overall yield, }>99:1 \text{ d.r.} \\
\text{iii. Na, liq. NH}_3, & -78 \, ^\circ \text{C, 49%.
}\end{align*}
\]

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].
Exploiting a tertiary amino group tethered on a chiral center lying in a polycyclic compound, chiral bicyclic derivatives were prepared by transannular halocyclization. Thus, within a synthesis of (+)-lyconadine A, the bicyclic product was isolated in good yield and total stereoselectivity (Scheme 17) [62].

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

Exploiting a tertiary amino group tethered on a chiral center lying in a seven-membered cycloalkene, chiral bicyclic derivatives were prepared by transannular halocyclization. Thus, within a synthesis of (+)-pseudococaine, the bicyclic product was isolated in very high yield and nearly total enantioselectivity starting from the tertiary amine after reaction with iodine (Scheme 18) [63].

In a similar approach, the compound, containing a secondary amino group embedded in an eight-membered ring containing a double bond, was treated with iodine in methanol, to afford, in good yield and with nearly total stereoselectivity, the polynuclearized bicyclic derivative, key intermediate for the synthesis of the alkaloid (-)-hyacinthacine A, containing a secondary amino group embedded in an eight-membered ring containing a double bond, was treated with iodine in methanol, to afford, in good yield and with nearly total stereoselectivity, the polyfunctionalized bicyclic derivative, key intermediate for the synthesis of the alkaloid (-)-hyacinthacine A, (Scheme 18) [64]. However, when under the same conditions the structurally similar chiral tertiary amine 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].


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].

2.3. Piperidine, Morpholine and Piperazine Derivatives

In analogy with aminoalkenols 14 [42,43], 18 [44], 22 [48], and 26 [49], 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 iodonium 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].

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].
Substituted Guanidines


In addition to 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, which is missing in the lower transition state leading to the trans-isomer [76].

Scheme 24. Stereoselective iodocyclization leading to chiral piperazine derivatives 100.

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 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].

A guanidinium group is present also in saxitoxin (STX) 106 and its analogs, a family of naturally occurring tricyclic guanidinium 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\textsubscript{s}), so that these compounds became interesting pharmacological targets [80]. 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].
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, which 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].

\[
\begin{align*}
107 & \xrightarrow{i. \text{ NBS (1.1 equiv), MeCN, rt. ii. CH}_3\text{COCl-Nal, MeCN, 75\%}.} 108 \\
108 & \xrightarrow{i. \text{ Br, MeCN, 75\%}.} 109 \\
\end{align*}
\]

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].

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 the isolation, with excellent diastereoselectivity, of 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].

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

Eventually, within a synthesis of indolizidine dipeptide mimetics, the macrocyclic unsaturated amides 115a,b underwent transannular stereodivergent halocyclization with total regio- and stereoselectivity, depending on the reagents, the solvent employed, and the substituent of the nitrogen atom. In fact, treatment of 115a 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].

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].

![Scheme 31. Intramolecular cyclization leading to 121, key intermediate to alkaloid (−)-dysiherbaine, 122.](image)

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].

![Scheme 32. Synthesis of (+)-polyoxamic acid 125 and lactone 126 starting from imidate 123.](image)

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].

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 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 hypothesized between the quinuclidine nitrogen of the catalyst and bromonium ion, together with binding of the nosyl amide and bromonium ion stabilized by Lewis basic sulfur, 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].

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].
Enantiomerically pure substituted pyrrolidines and their derivatives are 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 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 iodoamination was ascribed to this interaction, but the real mechanistic changes leading to switch of the regiochemistry remained unclear (Scheme 36) [110].

Tosylamides 143a,b, prepared starting from 2-allylanilines, underwent stereoselective iodoamination according to the preceding protocol to give indolines (2,3-dihydro-1H-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 (R1 = 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 indole 144, although a better yield was obtained upon adding iodine [114]. On the contrary, the tosylamide 143b (R1 = 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].

\[
\begin{align*}
\text{i. NIS (1.2 equiv), catalyst 142 (10 mol%), KI (2 mol%), DCM, -78 °C, 99%, 78% e.e.} \\
\text{ii. NIS (1.2 equiv), catalyst 142 (10 mol%), KBr (2 mol%), DCM, -78 °C, 77%}
\end{align*}
\]

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

\[
\begin{align*}
\text{i. NIS (1.2 equiv), catalyst 142 (10%) DCM, -78 °C.} \\
\text{a. R^1 = H: no additive, 57%, 87% e.e.; KBr (2 mol%), 58%, 87% e.e.; I_2 (2 mol %), 89%, 80% e.e.} \\
\text{b. R^1 = Cl: no additive, 86%, 88% e.e.; KBr (2 mol %), 14%, 89% e.e.}
\end{align*}
\]

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

NBS was also 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].

\[
\begin{align*}
\text{i. NBS (1.2 equiv), catalyst 148 (10 mol %), toluene:DCM 10:1, -78 °C.} \\
R^1 = H, 90%, 85% e.e.; R^1 = 4-OC_2H_5, 82%, 86% e.e.; R^1 = 5-OC_2H_5, 84%, 34% e.e.; \\
R^1 = 4-F, 80%, 74% e.e.; R^1 = 5-F, 78%, 82% e.e.; R^1 = 4-t-Bu, 91%, 80% e.e.
\end{align*}
\]

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

Homoallylic tosylamides 149 containing a gem-disubstituted double bond underwent iodoamination 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].
Scheme 40. Synthesis of 2-bromomethylpyrrolidine derivatives 152 bearing a chiral quaternary center at C-2.

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].

Scheme 41. Synthesis of chiral isoindolinone 156.

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].

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

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 158 displaying at the quaternary center the configuration opposite to compounds 18 and 20 (Scheme 42) [121].
The (Z)-nosylamides \( \text{160} \) were treated with \( N \)-bromopthalimide (NBPhth) as the bromonium ions source, in the presence of the chiral \( C_2 \)-symmetric selenide Lewis base \( \text{162} \). The reaction proceeded in a 5-exo-trig mode exclusively, leading to (3-nosyl) pyrrolidine derivatives \( \text{161} \) 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 \( S_N 2 \) attack of the sulfonamide group, leads to the cyclization product (Scheme 43) [122,123].

\[
\text{Scheme 42. Synthesis of 2-iodomethyl pyrrolidine derivatives \( \text{158} \) bearing a chiral quaternary center at C-2.}
\]

\[
\text{NCS (1.1 equiv), } I_2 (0.5 \text{ equiv}), \text{catalyst } \text{159 (5 mol %), toluene, -60 °C.}
\]
\[
R^1 = \text{cyclohexyl, } R^2 = \text{Ts, (-78 °C) 95%, 99% e.e.;}
\]
\[
R^1 = \text{CH}_2\text{-cyclohexyl, } R^2 = \text{Ns, 89%, 90% e.e.;}
\]
\[
R^1 = \text{C}_8\text{H}_{15}, R^2 = \text{Ns, 98%, 90% e.e.; } R^1 = \text{n-C}_8\text{H}_{17}, R^2 = \text{Ns, 96%, 96% e.e.}
\]

\[
\text{Scheme 43. Bromocyclization of (Z)-alkenylamides \( \text{160} \) mediated by catalyst \( \text{162} \).}
\]

\[
\text{N-Sulfonyl amides bearing a dissubstituted double bond underwent halocyclization mediated by NBS in the presence of the catalyst R-TRIP \( \text{165} \) [(3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl) hydrogenphosphate] using a chiral phase-transfer catalysis (PTC) methodology [124], since by exploiting H-bonding interactions it is possible to transfer the poorly soluble NBS halogenating reagent into the organic solvent. When the reaction was carried out starting from compounds \( \text{163} \) displaying a (Z)-double bond, the 2-substituted pyrrolidine derivatives \( \text{164} \) were isolated in good yield with high enantioselectivity (Scheme 44), whereas under the same conditions, (E)-sulfonamides \( \text{166} \) were converted into pyrrolidine derivatives \( \text{167} \) in moderate yield and stereoselectivity, with the configuration of their quaternary center being the same as observed for compounds \( \text{161} \) (Scheme 45) [125].}
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 unfavorable 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 Bronsted acids tethered on Co(III)-complexes \( \Delta-168 \) and \( \Lambda-169 \) 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 \( \Delta-(S,S)-168 \), the 2-substituted pyrrolidine derivatives 171 were obtained in excellent yield and enantioselectivity (Scheme 46) [126].
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.](image)

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)₂PHAL, 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].

![Scheme 48. Dearomatization by bromoamidation of 174 leading to tricyclic HPI derivatives 175.](image)

Among the available sulfonyl groups, the nosyl substituent was preferred for this cyclization owing to high acidity of the proton on nitrogen, 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 also exploited 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].

![Scheme 49. Synthesis of tricyclic HPI derivatives 178 mediated by 8H-R-TRIP 180.](image)

Following this methodology, the triptamine derivative 181 afforded, on a multigram scale, the bromo derivative 182 that through a multistep synthesis gave the C2-symmetric bispyrrolidinoindoline-derived alkaloid (−)-chimonantine 183 [126], component of Chimonanthus praecox, that inhibits tyrosinase and tyrosine-related protein-1 mRNA expression (Scheme 50) [132].

![Scheme 50. Synthesis of tricyclic HPI derivative 182, key intermediate to (−)-chimonantine 183.](image)

On the other hand, an 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, oxidation of bromide anion to bromine, that occurred in an undivided electrolytic cell in the presence of the salt 189, allowed the generation, in situ, of 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 methodology was successfully applied also on a multigram scale. In fact, using a reduced amount of 190 (1 mol%), compound 188e was converted into 188e in 99.5% yield and 90% e.e., suitable to be converted into alkaloids (−)-chimonantine 183 [130] and (−)-hodgkinsine [135].

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 stereoselectivity, 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 into the reaction mechanism was obtained by using computational methods [156].

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-169, 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-169, the conversion of compounds 194 into iododerivatives 195b proceeded with lower yields but with comparable enantioselectivity (Scheme 54) [138].

Scheme 54. Synthesis of HPI derivatives 195a,b mediated by Co(III) complex Λ-(S,S)-169.

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].

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].

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 to 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].

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 compound 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 negligible e.e., the \( \text{trans}-2,3\)-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 bromonium ions source (Scheme 58) [151].

![Scheme 58. Synthesis of 3-bromo piperidine 207 exploiting NBS in the presence of catalyst 208.](image)

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 the isolation of 2,3-trans-disubstituted piperidines 210 in high yield and with good stereoselectivity. It is worth mentioning that these compounds displayed the chiral centers, a configuration opposite to 207, but the reason for this outcome remained unclear (Scheme 59) [151].

![Scheme 59. Synthesis of 3-bromo piperidines derivatives 210 exploiting DBDMH and the catalyst 208.](image)

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.](image)

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 214 being isolated as the major products in good yield and high enantios-
electivity (Scheme 61). On the contrary, when the compounds 213 were treated with TsNCl₂
as the donor of halonium 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].

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 that the reaction of compound 213 was carried out with BsNBr₂ in the
presence of ligand 219 and Lu(OTf)₃, followed by treatment with Et₃N, the initial
bromoamination reaction afforded, in good yield, diastereomeric mixtures of derivatives

\[
\text{Scheme 62. Synthesis of anti- and syn-[1,2,3]oxathiazines 2,2-dioxides, 217 and 218.}
\]

\[
\text{Scheme 61. Synthesis of syn- and anti-[1,2,3]oxathiazines 2,2-dioxides, 214 and 215.}
\]
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].

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 have 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].

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

Alternatively, Co-complex Λ-(S,S)-169 was also highly effective for iodoamidation of unsaturated hydrazones 226 carried out with DIDMH, and the corresponding 5-iodomethyl
4,5-dihydro-1H-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].

\[
\text{\[154\]. Thus, starting from hydrazones 223, the chiral bromomethyl derivatives 228 were obtained in high yield and with good enantioselectivity (Scheme 66) [158].}
\]

was less effective in generating chirality, and the corresponding 1-nosyl-4,5-dihydro-1H-pyrazoles bearing a quaternary center were isolated in moderate yield but with good enantioselectivity (Scheme 67) [159].

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 or a iodomethyl functionality suitable for further transformations. At first, starting from nosyl hydrazones 228, the source of iodonium ion was N-iodopyrrolidin-2-one (NIPyr) employed together with the chiral amino thiourea 230. This bifunctional catalyst was able to coordinate both the iodonium ion and the nucleophilic nitrogen, thus generating a chiral environment, and the chiral 3,5-disubstituted 5-iodomethyl-1-nosyl-4,5-dihydro-1H-pyrazoles 229 were obtained in high yield and with good enantioselectivity (Scheme 66) [158].

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-1H-pyrazole derivatives 232 were isolated in moderate yield but with good enantioselectivity (Scheme 67) [159].

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-1H-pyrazole 234, having structure similar to that of a potent kinesin spindle protein (KSP) inhibitor (Scheme 68) [160].
The tosylamides 235 and 238, bearing a sulfonyl functionality at the amic 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(2H)-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 H3 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 small 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 CHCl₃/toluene 2:1, -78 °C. 
R¹ = CH₃, 72%, 91% e.e.; R¹ = C₂H₅, 97%, 92% e.e.; R¹ = n-C₃H₇, 88%, 90% e.e.

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 bromonium ions donor. The reaction proceeded with total regioselectivity and excellent enantioselectivity, and ³¹P NMR spectroscopy evidenced interactions between the ligand 242 and Sc, leading to a chiral reaction environment followed by activation of NBS (Scheme 71) [163].

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].

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 of 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].

![Scheme 73. Bromocyclization of tosylcarbamates 246 and 249 mediated by ligand 248.](image)

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].

![Scheme 74. Bromocyclization of dienyl carbamates 251 mediated by ligand 248.](image)

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 bromonium 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].
Eventually, in the presence of an even larger amount of the complex arising from phosphine oxide 248 and Sc triflate, compound 255 were converted in good yield and with excellent enantioselectivity into the spiro derivatives 256, exploiting dearomatization initiated by attack of a bromonium ion to the electron-rich benzofuran ring (Scheme 76) [168].

Scheme 75. Bromocyclization 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, compound 255 were converted in good yield and with excellent enantioselectivity into the spiro derivatives 256, exploiting dearomatization initiated by attack of a bromonium ion to the electron-rich benzofuran ring (Scheme 76) [168].

Scheme 76. Dearomatization of an electron-rich benzofuran ring leading to chiral spiro compound 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 Bronsted catalyst 260, gave the chiral N-tosylimidazolidin-2-ones 259 in good yield with high enantioselectivity (Scheme 77) [169].

Scheme 77. Synthesis of N-tosylimidazolidin-2-ones 259 mediated by chiral catalyst 260.
With the aim of demonstrating the usefulness of this methodology, the amine 261 was converted in good yield and high enantioselectivity into the iodomethyl derivative 262, precursor of the product SCH 388714, 263, a potent and selective NK₁ receptor antagonist that is orally active and displays good CNS penetration (Scheme 78) [170].

Scheme 78. Synthesis of SCH 388714, 263, potent and selective NK₁ receptor antagonist.

Moreover, starting from the (Z)-allylamine 264, the cyclization proceeded in a 5-exo-mode leading to imidazolidin-2-one 265 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 266a led to tetrahydropyrimidin-2(1H)-ones 267a in high yield and stereoselectivity, whereas amine 266b, displaying a trisubstituted double bond, gave the corresponding tetrahydropyrimidin-2(1H)-one 267b with high enantioselectivity but in low yield, probably due to the formation of a quaternary chiral center (Scheme 79) [169].

Scheme 79. Synthesis of imidazolidin-2-one 265 and tetrahydropyrimidin-2(1H)-ones 267a,b.

4. Conclusions
A lot of asymmetric syntheses of nonaromatic 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 a multigram scale, within total synthesis of compounds with high medicinal potential, as 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, the introduction of enzymes in a cascade process, which 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 nonaromatic 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].

Author Contributions: Conceptualization, M.O.; writing—review and editing, S.R. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflicts of interest.

References
3. Lyubchuk, T.V.; Hordiyenko, O.V. The use of N-halosuccinimides for cyclization with the formation of five-membered heterocyclic compounds. Chem. Heterocycl. Comp. 2020, 56, 1–29. [CrossRef]


22. Tripathi, C.B.; Mukherjee, S. Catalytic enantioselective halocyclizations beyond lactones: Emerging routes to enantioenriched nitrogenous heterocycles. *Synlett* 2014, 25, 163–169. [CrossRef]


27. Yao, C.-Z.; Tu, X.-Q.; Jiang, H.-J.; Li, Q.; Yu, J. Recent advances in catalytic asymmetric haloamination and haloetherification of alkenes. *Tetrahedron Lett.* 2023, 126, 154639. [CrossRef]


46. Welter, A.; Jadot, J.; Dardenne, G.; Marlier, M.; Casimir, J. 2,5-Dihydroxymethyl 3,4-dihydroxy-pyrrolidine dans les feuilles de *Derris elliptica*. *Phytochemistry* 1976, 15, 747–749. [CrossRef]
76. Bera, S.; Pandai, G. I2-Mediated diversity oriented diastereoselective synthesis of amino acid derived trans-2,5-disubstituted morpholines, piperazines, and thiomorpholines. ACS Comb. Sci. 2012, 14, 1–4. [CrossRef]


90. Schulte, A.; Siti, X.; Saito, S.; Wünsch, B. Bromolactamization: Key step in the stereoselective synthesis of enantiomerically pure, cis-configured perhydroxyproloquinoloxalines. Chirality 2014, 26, 793–800. [CrossRef] [PubMed]


97. Studer, A.; Schleth, F. Desymmetrization and diastereotropic group selection in 1,4-cyclohexadienes. Synlett 2005, 2005, 3033–3041. [CrossRef]


136. Tan, X.; Wang, Q.; Sun, J. Electricity-driven asymmetric bromocyclization enabled by chiral phosphate anion phase-transfer catalysis. Nat. Commun. 2023, 14, 357. [CrossRef]


141. R. S. Non-enzymatic asymmetric transformations involving symmetrical bifunctional compounds. Chem. Soc. Rev. 1990, 19, 1–19. [CrossRef]


143. Tan, X.; Wang, Q.; Sun, J. Electricity-driven asymmetric bromocyclization enabled by chiral phosphate anion phase-transfer catalysis. Org. Lett. 2015, 17, 4428–4431. [CrossRef]


151. R. S. Non-enzymatic asymmetric transformations involving symmetrical bifunctional compounds. Chem. Soc. Rev. 1990, 19, 1–19. [CrossRef]


168. Li, Z.; Shi, Y. Chiral phosphine oxide–Sc(OTf)3 complex catalyzed enantioselective bromoaminocyclization of 2-benzofuranmethyl N-tosylcarbamates. Approach to a novel class of optically active spiro compounds. Org. Lett. 2015, 17, 5752–5755. [CrossRef]


175. Jiang, Y.; Mondal, D.; Lewis, J.C. Expanding the reactivity of flavin-dependent halogenases toward olefins via enantioselective intramolecular haloetherification and chemoenzymatic oxidative rearrangements. ACS Catal. 2022, 12, 13501–13505. [CrossRef]

176. Jiang, Y.; Lewis, J.C. Asymmetric catalysis by flavin-dependent halogenases. Chirality 2023, 35, 452–460. [CrossRef]


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