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Review

Ephedrine derivatives, extraordinary tools for the study of stereogenic centers in tetra- to heptacoordinated complexes☆

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Contents

Abstract

We have been investigating the synthesis of diverse ephedrine derivatives, as polyfunctional ligands, heterocyclic compounds, and metal and metalloid complexes. In this review, we present a brief discussion of our experience and from other research groups concerning the creation of stereogenic centers, different from carbon, in diverse ephedrine based molecules.

Keywords: Stereochemistry; Stereogenic centers; Ephedrine derivatives; Phosphorous; Boron; Transition metals; Coordination compounds

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1. Introduction

Much effort has been dedicated to investigate the stereochemistry at carbon atoms, even though many other elements can be stable stereogenic centers. The carbon stereochemistry is based on tetrahedral geometry, which has been studied intensively by many research groups, whereas other tetracoordinated elements have been much less studied. Other coordination numbers in different geometries are stable stereogenic centers, for example in penta-, hexa-, or hepta-coordination, but they have not been widely studied from the stereochemistry point of view. Stable configurations for certain elements can be acquired if an appropriate organic ligand is used. In this context, ephedrine and its isomers have played an important role in the preparation of optically active molecules, where the stable stereogenic center is an element different from carbon. One of the reasons is that the molecules afford bidentate structures forming very stable five membered rings. In addition, the ephedrine substituents and their arrangement can favor certain configurations or conformations in the new compounds.

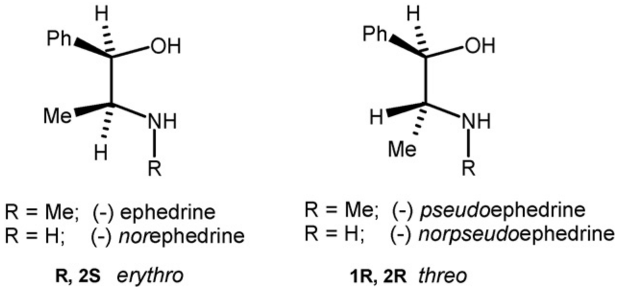


Fig. 1. Stereoisomers of ephedrine, *pseudo*ephedrine and *nor*ephedrine.

Ephedrine, its isomers and derivatives (Fig. 1) are important coordination ligands for many elements, such as transition and main group metals, and metalloids. The ligands and their complexes have relevant roles as catalytic agents, chiral auxiliaries or inductors in asymmetric organic synthesis [1–8].

2. Ephedrine

2.1. Metal, boron and phosphorus compounds

One of the first molecules to be reported derived from ephedrine and a metal atom, was the bis-(−)-ephedrine copper(II); this optically active coordination compound contains a copper(II) atom in a distorted square planar geometry, which

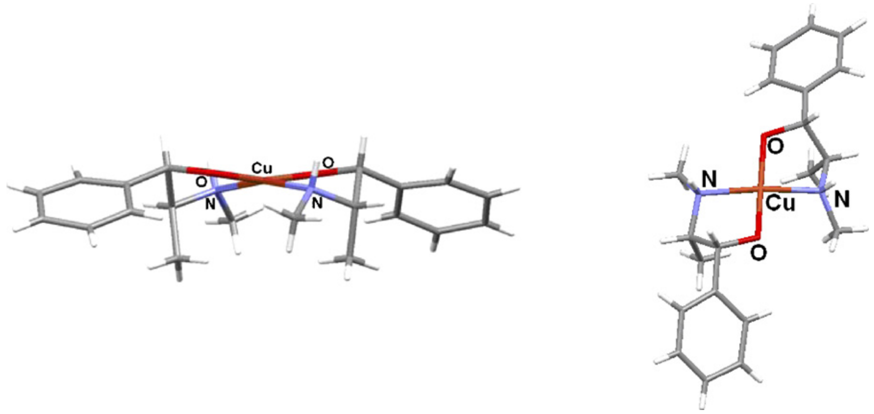


Fig. 2. Two perspectives of the X-ray diffraction structure of the copper(II) bis ephedrine complex [10].

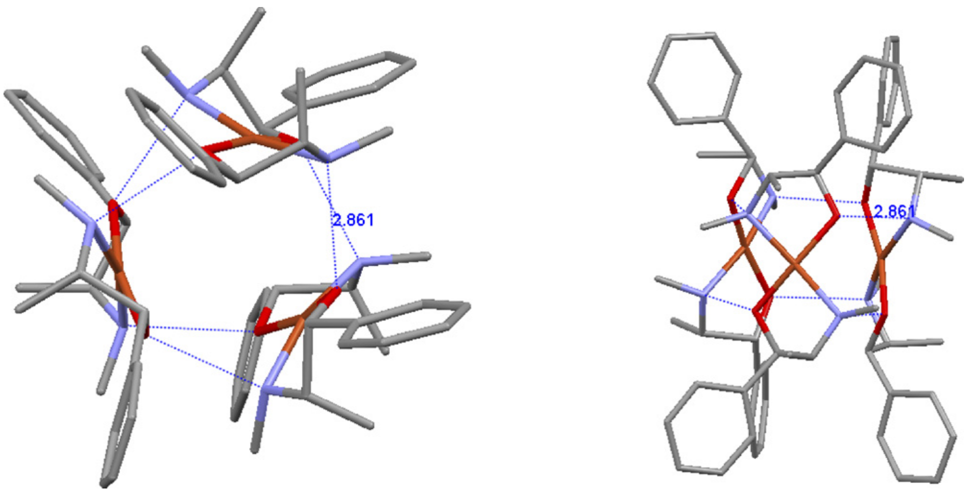


Fig. 3. Different views of the trimer formed in the crystal structure of bis-(−)-ephedrine copper(II) [10].

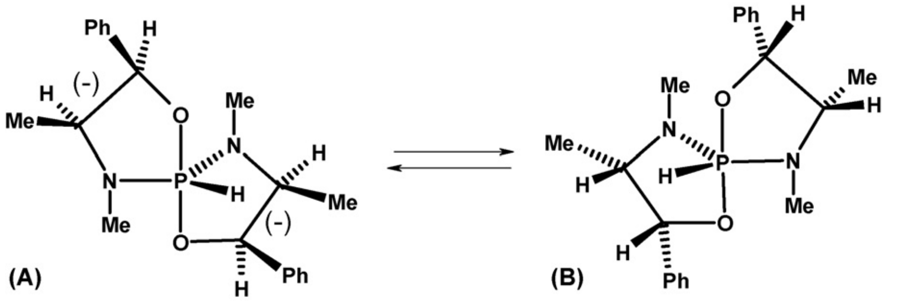


Fig. 4. Stereochemistry of the two helicoidal phosphoranes obtained from (−)-ephedrine and $P[NMe_2]_3$, the major isomer A was studied by X-ray diffraction [15].

is a new stereogenic center, together with two chiral nitrogen atoms (Fig. 2). The optically active molecule belongs to a C_2 symmetry group [9,10].

The bis-(−)-ephedrine copper(II) molecule forms a trimer via N–H···O intermolecular hydrogen bonds, the distance O···N is 2.86 Å (Fig. 3).

Another seminal contribution to this field was the syntheses of optically active PH *spiro*phosphoranes derived from ephedrine [11–13]. The ligand permits the synthesis of only two helicoidal isomers from 20 possible, the two isomers are in equilibrium in solution, one of them was isolated by crystallization (Fig. 4). The mechanism of the inversion of the configuration in the pentacoordinated *spiro*phosphoranes derived from aminoalcohols was reviewed [14].

A detailed stereochemical study of the phosphorus chirality in the pentacoordination (BPT geometry) was analyzed; the absolute configuration of the phosphorus atoms in the isomers prepared, was deduced based on NMR and optical rotation and was confirmed later by X-ray diffraction of bis-(−)-ephedrine *spiro*phosphorane [15] (Fig. 5a). Another example of a stereoselective synthesis of one active phosphorane derived from ephedrine and an aminoacid was reported by the same research group [16] (Fig. 5b).

Zinc(II) and palladium(II) compounds combined with ephedrines have important roles as catalytic auxiliary agents in organic synthesis, some examples for the zinc(II) compounds are discussed by several authors [1,2,8].

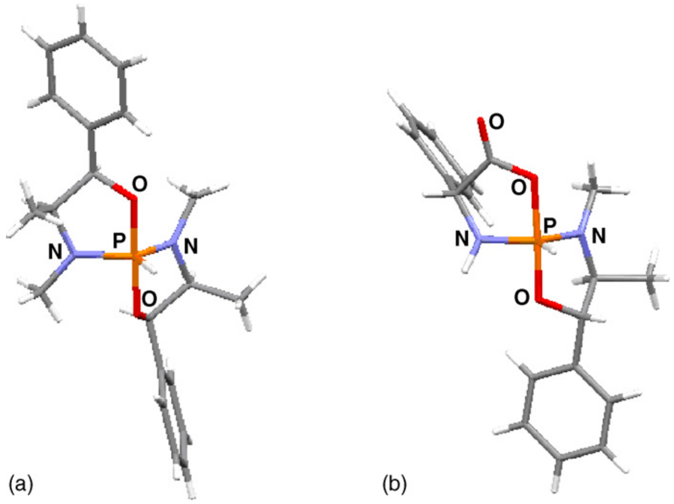


Fig. 5. Solid state structures of optically active *spiro*phosphoranes derived from ephedrines [11–16].

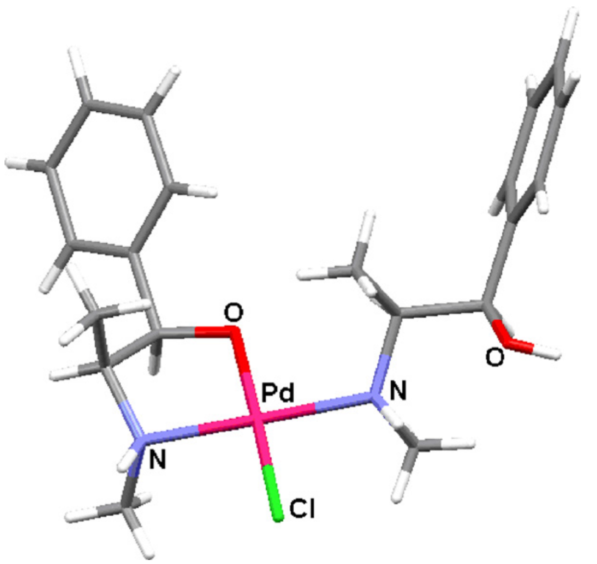


Fig. 6. X-ray diffraction structure of (−)-ephedrine palladium(II) complex [17].

Reaction of palladium(II) chloride with (−)-ephedrine can lead to coordination of the ligand in different ways to the metal ion, only through the nitrogen, or in a bidentate mode if OH mono- or di-deprotonation occurs. In the cyclic compounds the palladium and the nitrogen atoms are stereogenic centers [3,17]. The X-ray diffraction structure of one of these complexes is shown in Fig. 6.

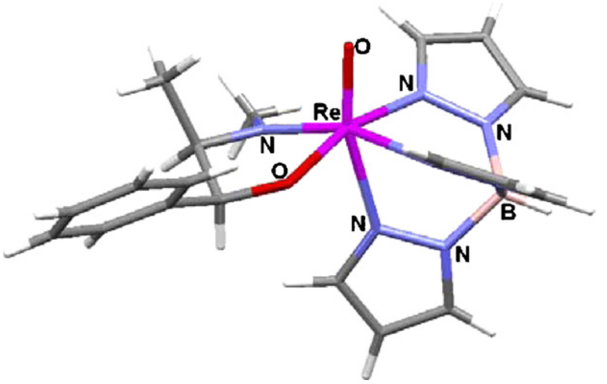


Fig. 7. X-ray diffraction structure of the optically active rhenium(V) compound, derived from (+)-ephedrine [18].

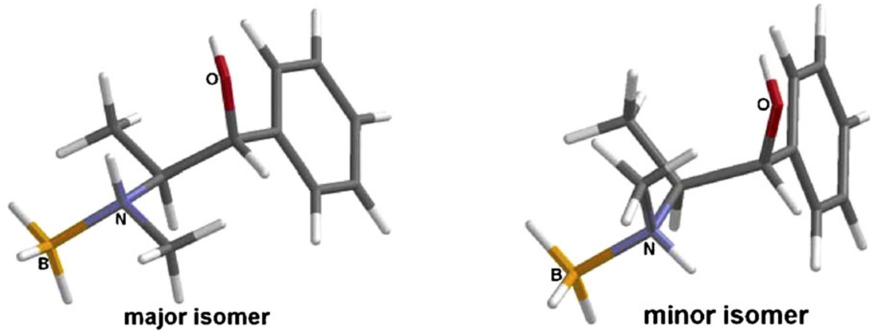


Fig. 8. Preferred conformation of the two N-epimers of N—BH_3 adducts of (−)-ephedrine [19].

Faller and Lavoie obtained a compound derived from (+)ephedrine, rhenium(V) and hydrotris(1-pyrazolylborate), where the rhenium(V) atom is a chiral center and the synthesis is diastereoselective [18], a view of the X-ray structure is shown in Fig. 7.

Borane coordination to the nitrogen in ephedrines generates a chiral nitrogen atom in a stable configuration. The reaction is stereoselective, since, from the two expected N-epimers, one is obtained as the major compound. A detailed stereochemical study for the assignment of the nitrogen configuration was performed. The modeled preferred conformation of both N-epimers is shown in Fig. 8, [19].

Reaction of trimethylgallium or trimethylindium and ephedrines afforded tricyclic dimetallic compounds with the structure shown in Fig. 9, where the nitrogen and the pentacoordinated metal atoms are chiral centers [6].

3. Other ligands based on ephedrine

Other examples of optically active derivatives of ligands, based on ephedrine, are included in the following discussion.

3.1. *N,N′-Ethylene-bis-ephedrines*

3.1.1. *Copper(II) compound*

N,*N*′-Ethylene-bis-(−)-ephedrine, was used by the Amano group in 1967, to prepare a copper(II) tricyclic compound, the geometry of the metal atom is similar to that found in the bis-(−)-ephedrine copper(II) compound (vide supra), the metal and the nitrogen atoms are stereogenic centers [20] (Fig. 10).

3.1.2. *Phosphorus tricyclic compounds*

Optically active tricyclic P—H phosphoranes, similar to that of the latter copper(II) tricyclic compound, were reported. The phosphoranes were prepared from reaction of the ligand *N*,*N*′-bis-[(−)-*nor*ephedrine]ethylene with P[NMe_2]$_3$. Only one isomer of the P—H tricyclic phosphorane was obtained. The pentacoordinated (TBP) phosphorus (helix Δ) and the apical nitrogen atoms became stereogenic centers with a stable configuration, which was determined by X-ray diffraction (Fig. 11). NMR studies did not detect any equilibrium between the two possible TBP isomers. The nitrogen and the oxygen placed in equatorial positions are planar, due to lone pair electronic delocalization towards the phosphorus atom, whereas the oxygen and nitrogen atoms in apical position are sp^3. Borane addition to the less hindered equatorial nitrogen atom gives a N-borane complex and, at the same time, changes the phosphorus configuration (helix Λ) by exchanging the oxygen and nitrogen atoms, placed in equatorial, to the apical positions (Fig. 12). The reason for this isomerization is that the N—BH_3 group is more electrophilic and suitable to be in the apical position [21].

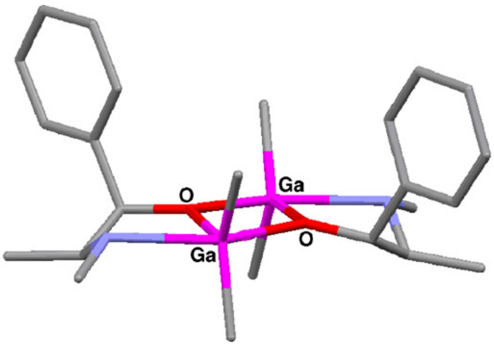


Fig. 9. Solid state structure of an optically active bis-[dimethyl-gallium-(−)-ephedrine] compound [6].

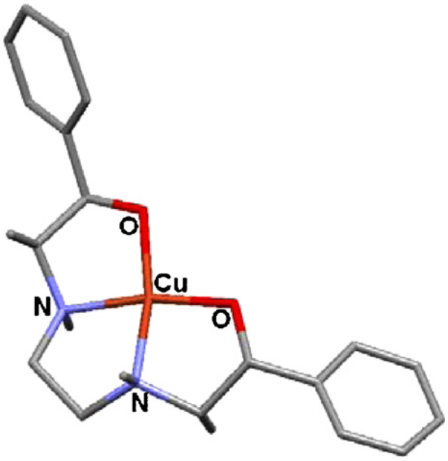


Fig. 10. X-ray diffraction structure of an optically active tricyclic copper(II) compound derived from *N*,*N*′-bis-[(−)-ephedrine]ethylene, the hydrogen atoms are omitted [20].

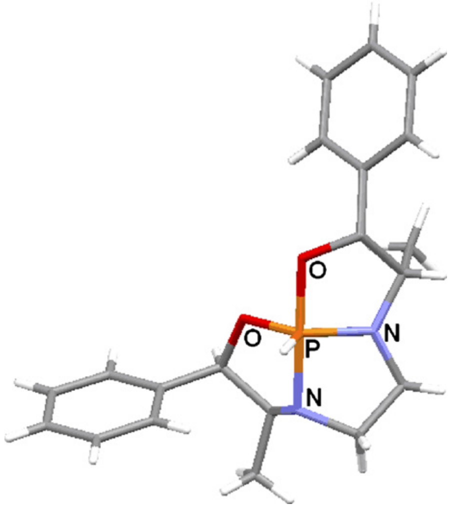


Fig. 11. X-ray diffraction structure of the PH tricyclic chiral phosphorane obtained from bis-[(−)-ephedrine]ethylene [21].

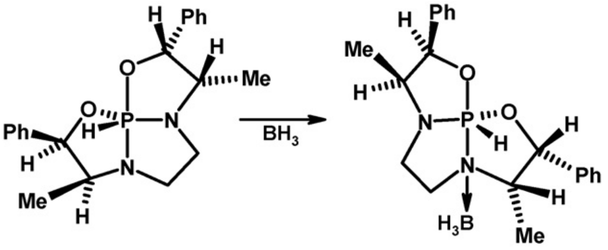


Fig. 12. Borane addition to the isolated [helix Δ] P-epimer gives a product where the P configuration [helix Λ] is changed [21].

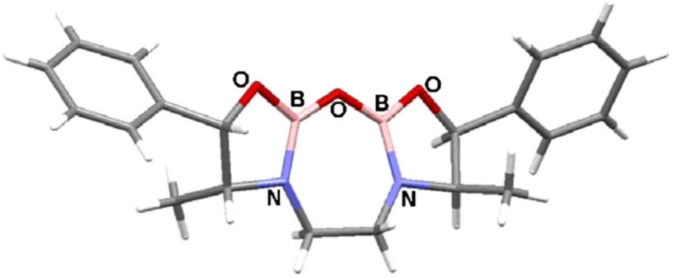
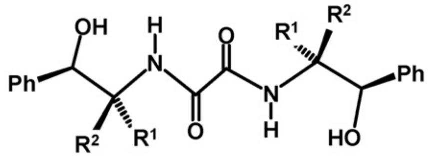


Fig. 13. X-ray structure of the bis-borate derived from *N*,*N*′-ethylene bis-(+)-*nor*ephedrine [22].



R^1 = Me, R^2 = H (-)*pseudonor*ephedrine oxalyl
R^1 = H, R^2 = Me (-)*nor*ephedrine oxalyl

Fig. 14. Ligands prepared from oxalic acid and ephedrines [23].

3.1.3. Boron heterocycle

On the other side, the direct reaction of *N*,*N*′-bis-[(+)-norephedrine]oxalyl (vide supra) with BH_3·THF affords 2,2′-oxy-bis-1,3,2-oxazaborolidine (Fig. 13). The tricyclic compound (C_2 group symmetry), with a delocalized planar system ONB-OBNO, was identified by X-ray diffraction analysis. The hydrolysis of this bis-borate gives the reduced ligand bis-ethylene-(−)-*nor*ephedrine [22].

3.2. Oxalyl ephedrines

Other interesting ligands were the bis-ephedrine oxalyl derivatives that gave place to, phosphorus, boron and tin heterocycles, as discussed below (Fig. 14). The synthesis and the structural study of the ligand are reported [23].

3.2.1. Phosphorus heterocycles

Reaction of the *N*,*N*′-bis[(−)-*norpseudo*ephedrine] oxalyl with $P[NMe_2]_3$ gave exclusively the epimer helix Λ of the

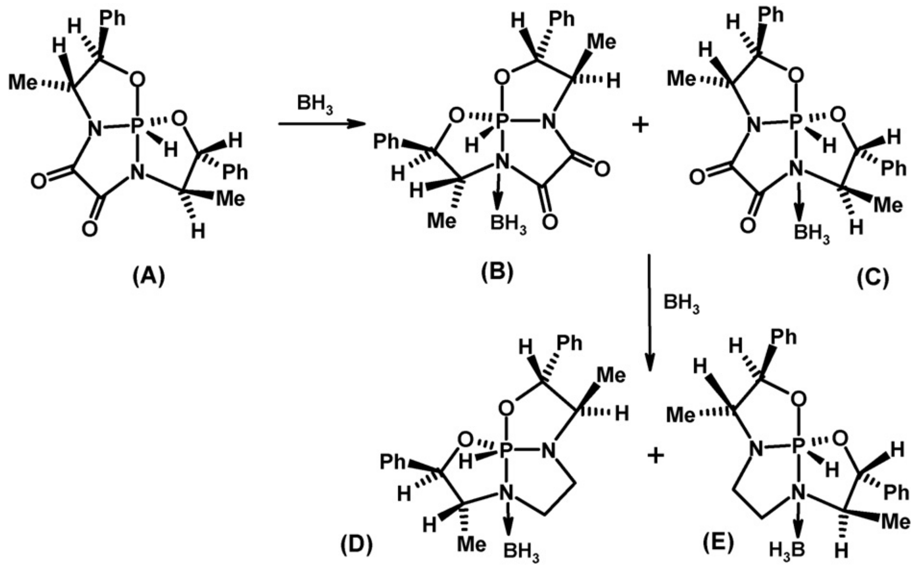


Fig. 15. Reaction of the *N*,*N*′-bis-[(−)-*norpseudo*ephedrine]oxalyl with $P(NMe_2)_3$ afforded isomer A. Its reaction with BH_3 gives B and C whereas in an excess of BH_3, D and E. Heterocycles B and D are the major isomers [21].

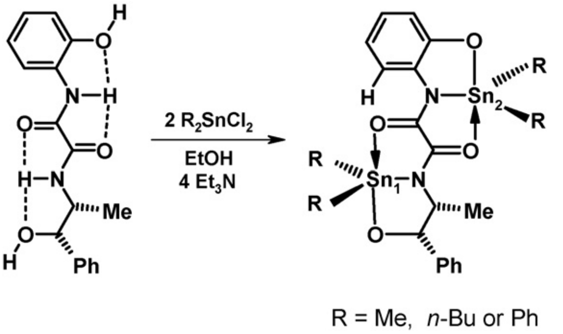


Fig. 16. The non-symmetric ligand was used to prepare chiral bis-tin compounds [24].

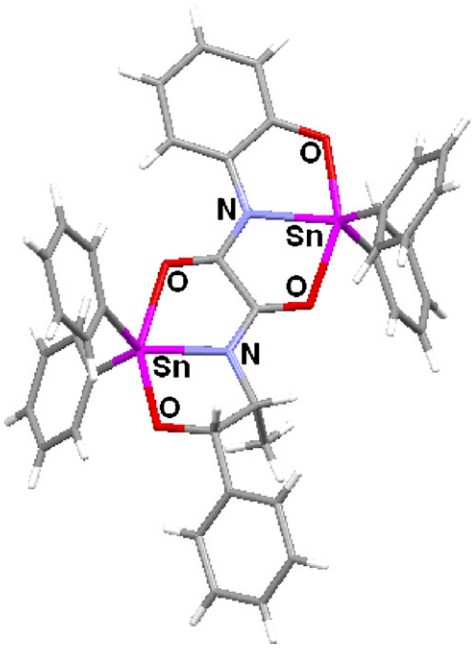


Fig. 17. X-ray diffraction structure of a pentaheterocyclic compound with two different chiral pentacooordinated TBP tin atoms [24].

tricyclic phosphorane P–H, compound A [21] (Fig. 15). The reaction of the phosphorane A with borane produces the two isomeric phosphoranes N–BH$_3$: B and C, both compounds in an excess of borane, afforded the two reduced isomers D and E.

3.2.2. *Tin heterocycles*

The non-symmetrical optically active oxalyl derivative bearing a phenolamine and a (+)-*nor*ephedrine was reacted with dialkyldichlorotin compounds providing optically active binuclear diorganotin compounds, with a delocalized pentacyclic framework and two non-equivalent pentacoordinated (TBP) tin atoms [24]. The metallic atoms are tightly coordinated by the amide oxygen atoms; the relevance is due to their stable rigid structures, suitable models for NMR and X-ray diffraction studies of hypervalent metallic atoms. The two pentacoordinated tin atoms are stereogenic centers and therefore an isomeric mixture should be expected; however, the reactions gave only one isomer in each case, which implies stereoselective reactions (Fig. 16).

Crystals of diphenyltin derivative were suitable for its X-ray diffraction analysis (Fig. 17). The phenolamide fragment is almost planar, whereas the cyclic aliphatic part of the molecule has an envelop conformation with the benzylic carbon atom being out of the ring plane, the C–Ph group is in equatorial and the C–Me group in a *pseudo*axial position.

Compounds were submitted to a detailed NMR study in order to assign their resonances (^{1}H, ^{13}C and ^{119}Sn). As a consequence of the lack of symmetry both tin atoms are not equivalent, as shown by ^{119}Sn NMR. The presence of four stereogenic centers (two carbon and two tin atoms) complicated the assignment of the ^{1}H and ^{13}C signals, due to the diastereotopic nature of the Sn-organyl groups. The unequivocal assignment of the ^{119}Sn resonance has been made by a [^{1}H,^{119}Sn] Heteronuclear Multiple Quantum Coherence (HMQC) experiment [24].

3.3. *Diaminohydroquinone ephedrines*

The reaction of quinone with two molecules of (+)-*nor*ephedrine, followed by a reduction reaction, afforded 2,5-diaminohydroquinone (+)-ephedrine ligand. This compound with phenylboronic acid, in ethyl acetate, gave a pentacyclic compound (Fig. 18). The optically active compound has a C_2 symmetry and four new chiral centers are introduced: two nitrogen and two boron atoms but only one isomer, of the 16 possible isomers, was obtained [25].

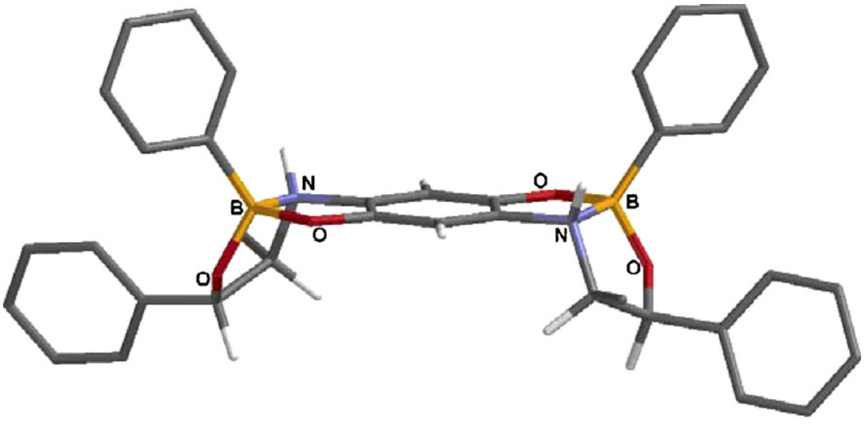


Fig. 18. Calculated preferred conformation of the bisphenyl borate derived from di[2,5-(+)-*nor*ephedrine hydroquinone] [25].

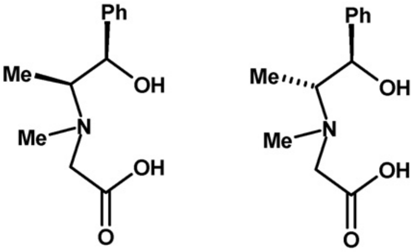


Fig. 19. Stereochemistry of *N*-acetyl ephedrine and *pseudo*ephedrine ligands [26].

3.4. N-acetyl-ephedrines

Another series of ligands were synthesized from glyoxal and ephedrine compounds, the *N*-acetyl-ephedrines (Fig. 19). The ligands were employed in the preparation of boron and transition metal coordination compounds, which will be briefly discussed [26].

3.4.1. Boron compounds

The *N*-acetyl ephedrine and *pseudo*ephedrine ligands stereoselectively form bicyclic phenylboronic esters containing configurationally stable chiral nitrogen and boron atoms. In Fig. 20, the two isomers obtained from (−)-ephedrine are shown. From the two possible isomers, A is the major product and was isolated by crystallization [27].

When a similar reaction was performed with the *pseudo*ephedrine ligand, the major compound crystallized (Fig. 21). The product of the reaction between the 1,4-diboronic-benzene and *N*-acetyl (+)-*pseudo*ephedrine was also reported [28] (Fig. 21).

3.4.2. Cobalt(II) and nickel(II) mononuclear coordination compounds

Reactions of the two diasteromeric ligands *N*-acetyl (−)-*pseudo*ephedrine and *N*-acetyl (−)-ephedrine with cobalt(II) and nickel(II) acetates, gave the corresponding optically active octahedral coordination compounds $[ML_2]\cdot 2H_2O$. X-ray crys-

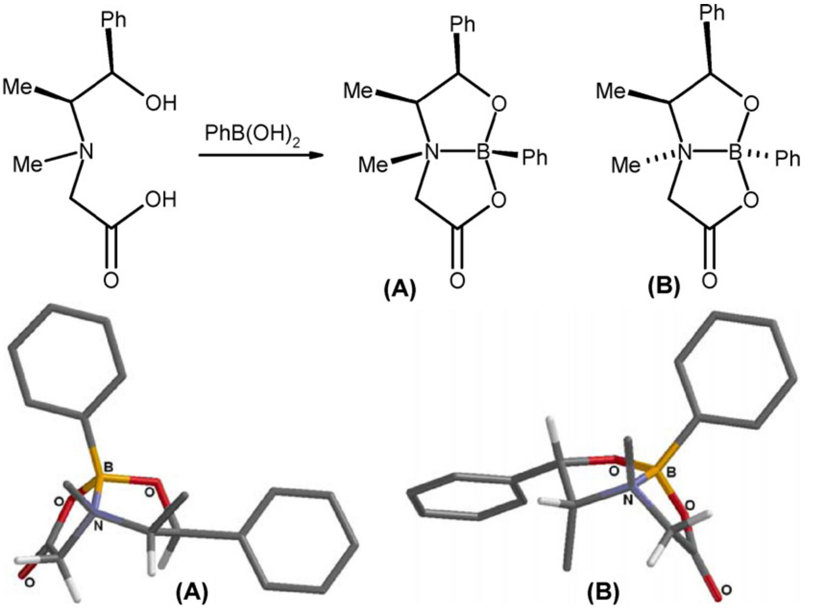


Fig. 20. The reaction of $PhB(OH)_2$ and *N*-acetyl (−)-ephedrine is shown. A is the main product, the modeled isomers are included [27].

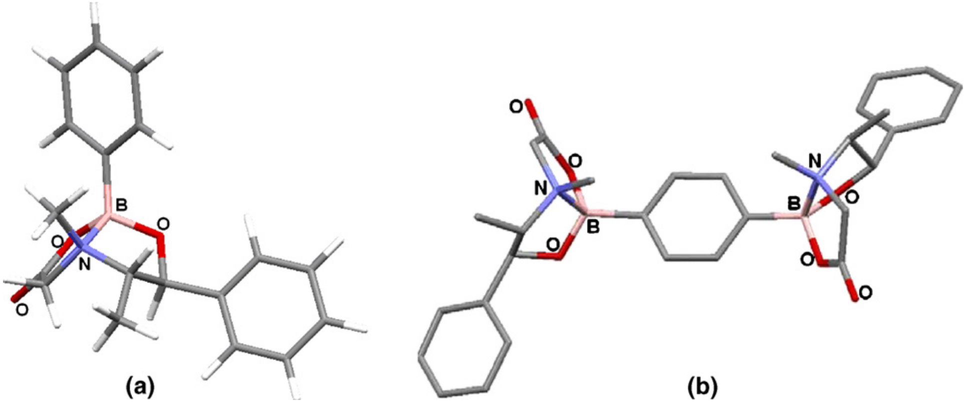


Fig. 21. Solid state structures of the major isomers derived from *N*-acetyl *pseudo*ephedrine and phenylboronic acid (a) and from 1,4-diboronic-benzene and *N*-acetyl (+)-*pseudo*ephedrine (b) [28].

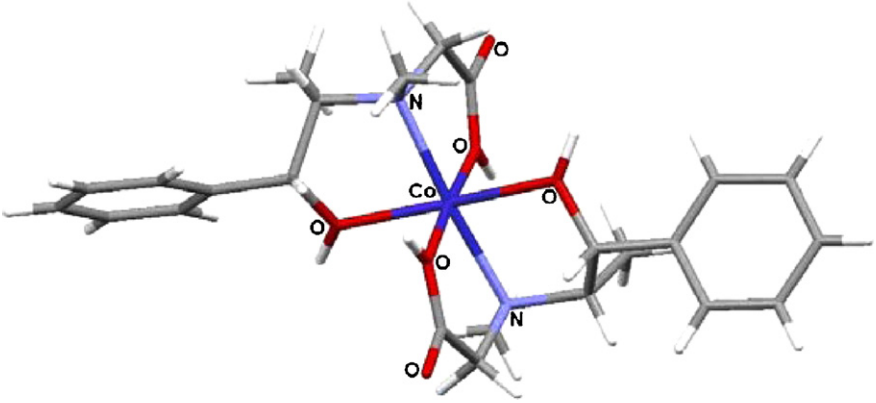


Fig. 22. X-ray crystal structure of the *trans*-octahedral cobalt(II) coordination compound derived from *N*-acetyl (−)-ephedrine [29,30].

tal structures showed that the two ligands are coordinated to the metal ion in a tridentate mode through the nitrogen atom, the OH group and the deprotonated carboxylic group, forming two five-membered rings in an all-*trans fac*-isomer, as shown for cobalt(II) compound derived from (−)-ephedrine [29,30] (Fig. 22).

The ligand coordination to the metal ion produces five new stereogenic centers, the metal atom, the two OH oxygen and the two nitrogen atoms, the syntheses are stereoeselective. The all-*trans* coordination of the ligands organizes the opposite configuration for the nitrogen and oxygen atoms (one *"S"* and the other "*R*", the oxygen presents a tetrahedral geometry, the lone pair being the fourth substituent).

Interestingly, however in a reaction with the ligand *N*-acetyl (+)-ephedrine and cobalt(II) acetate it was possible to isolate crystals of the *cis*-isomer, where the two nitrogen and the two OH oxygen atoms are *cis* to each other, in this configuration of the metal atom both nitrogen atoms appear with the "*S*" configuration, whereas both OH oxygen atoms are "*R*" (Fig. 23).

3.4.3. Copper(II) mononuclear compounds

When the two diastereomeric ligands *N*-acetyl (+)-*pseudo*ephedrine and *N*-acetyl (+)-ephedrine, react with copper(II) acetate, different optically active coordination compounds are obtained.

The *N*-acetyl (+)-*pseudo*ephedrine complex $[CuL_2]\cdot H_2O$ was stabilized in an octahedral geometry, all-*trans fac*-isomer, as observed for its analogous cobalt(II) and nickel(II) compounds. The longest bond lengths (2.37 and 2.48 Å) correspond to the Cu–OH, while the Cu–N (2.03 and 2.05 Å) and Cu–OCO (1.94 and 1.97 Å) are shorter due to Jahn Teller disotortion [31].

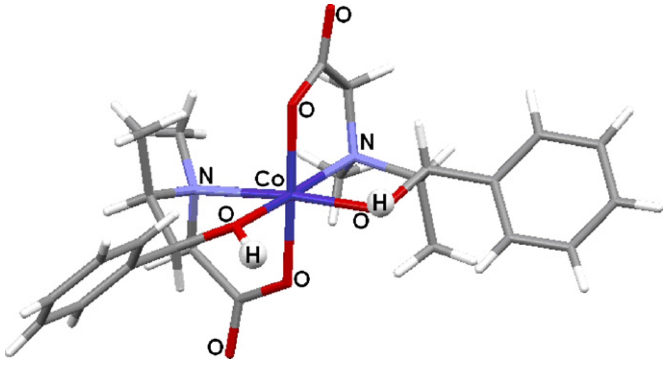


Fig. 23. X-ray crystal structure of *cis*-octahedral cobalt(II) coordination compound derived from *N*-acetyl (+)-ephedrine [29,30].

On the other hand, in the copper(II) compound prepared with *N*-acetyl (+)-ephedrine, the two ligands are coordinated in a different way, one is tridentate in a facial arrangement, while the second is bidentate, with the peculiarity that one OH group is not bonded. The reason for this behavior could be explained based on the more hindered *erythro* configuration of the ligand. In addition to that, the different configuration of the OH oxygen and nitrogen atoms in each ligand present different steric interactions, which weakens one of the oxygen copper(II) bonds, also favored by a dimeric association, via hydrogen bonding, through the uncoordinated OH proton (Fig. 24). From the X-ray crystal structure a C–hydrogen has a short distance to the copper(II) ion, occupying the sixth position, with a distance (2.44 Å) shorter than the van der Waals Cu–H distance (2.6 Å) (Fig. 24a). Evidently the hydrogen presents a weak bond to the copper(II) atom, as shown by a Cu–H HOMO bonding orbital between both atoms, indicated by theoretical calculation [32,33] (Fig. 24b).

3.4.4. Trinuclear copper(II) compound

An important difference in the behavior between the two coordination compounds, one derived from *N*-acetyl ephedrine and the other from *N*-acetyl *pseudo*ephedrine, is their response to deprotonation with NaOH. With the monomeric *pseudo*ephedrine derivative, the reaction yields a trinuclear copper(II) compound, with C_3 symmetry, where the nitrogen and copper(II) are stereogenic centers. In this molecule the ligand is coordinated in a meridional arrangement, with three planar bridging oxygen atoms and the copper(II) ions form a six membered ring, adopting a chair conformation. Each metal atom is in a square pyramidal geometry, with a water molecule in the apical position [32] (Fig. 25).

A complicated intermolecular hydrogen-bonding network and a two-dimensional arrangement of the trinuclear units stabilize the crystal. One layer of cyclic trinuclear units is connected to another through strong intermolecular hydrogen bonding. This occurs between the coordinated water molecules from a cyclic trinuclear unit of copper(II), and the O atom from the

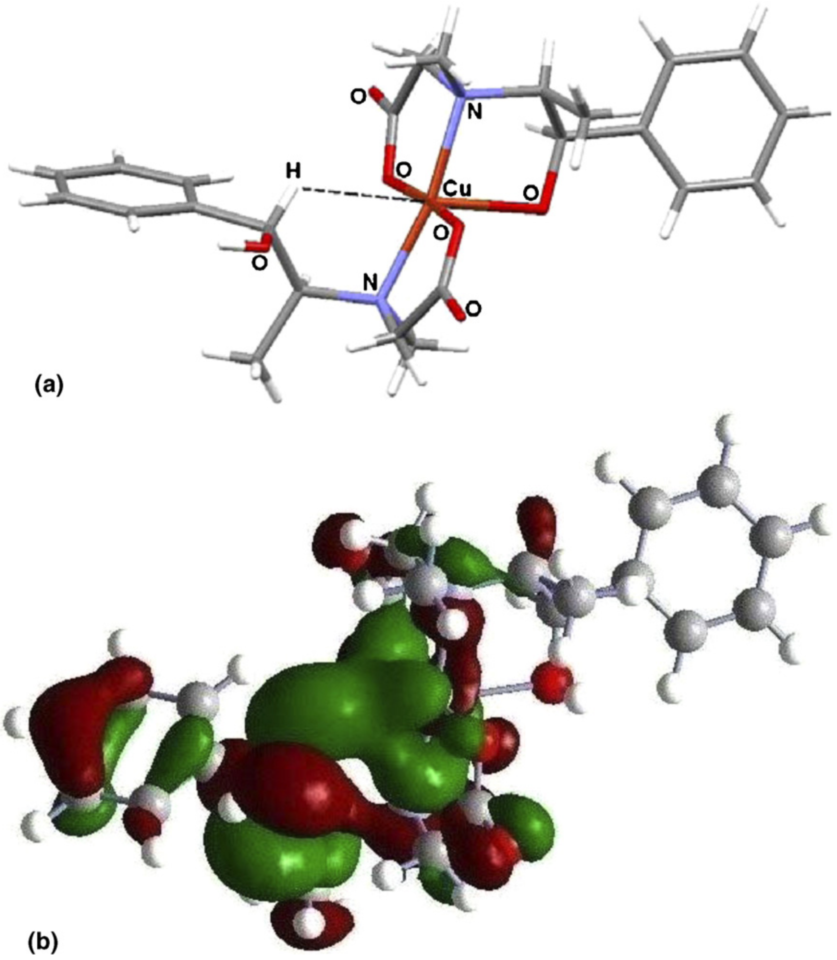


Fig. 24. (a) Copper(II) compound derived from *N*-acetyl (+)-ephedrine from the X-ray crystal structure. (b) Calculated Cu—H HOMO orbital, the green lobe links the hydrogen and the copper(II) atoms [32,33]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

carboxylate groups of another unit of the neighboring layer. This intermolecular hydrogen bonding has implications on the magnetic properties of this compound. The overall magnetic behavior corresponds to an antiferromagnetically coupled trinuclear system. The expected value for $\chi_M T$ at low temperature for a trinuclear $S = 1/2$ antiferromagnetically coupled system is 0.40 $cm^3 K mol^{-1}$ ($g = 2.1$). The experimental value of $\chi_M T$ at 2 K, 0.30 $cm^3 K mol^{-1}$, indicates an intercluster antiferromagnetic interaction (Fig. 26).

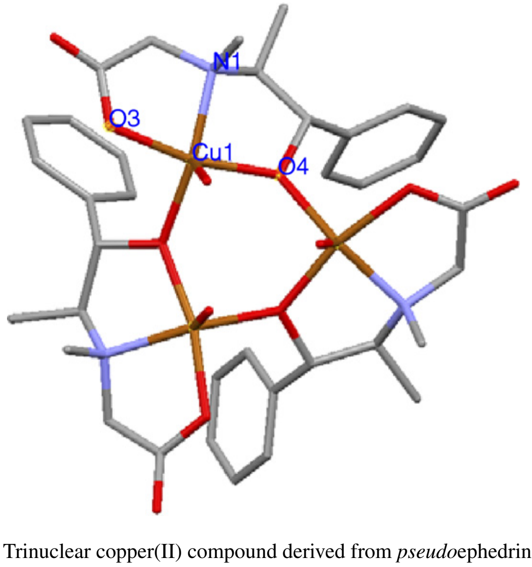


Fig. 25. Trinuclear copper(II) compound derived from *pseudo*ephedrine [32].

Changing the configuration of the ligand from *threo* to *erythro* prevents the formation of the analogous trinuclear compound. Clearly, the stereochemistry of the ligand is a significant factor in the rearrangement of the initial mononuclear compound on deprotonation.

3.4.5. Heptacoordinated cadmium(II) compounds

The reaction of *N*-acetyl *pseudo*ephedrine and cadmium(II) acetate gives a monomer in the solid state. The cadmium(II) atom has a distorted pentagonal bipyramidal geometry, with one *N*-acetyl *pseudo*ephedrine ligand tricoordinated in a similar facial arrangement to that found in the octahedral compounds of cobalt(II), nickel(II) and copper(II), the second ligand is tridentate in the equatorial plane, an unusual coordination mode for this ligand, while the seventh position is occupied by a water molecule. Both stereogenic nitrogen atoms acquire the "*S*" configuration [31] (Fig. 27). We have not found other reported examples of stereogenic centers in heptacoordinate metal atoms.

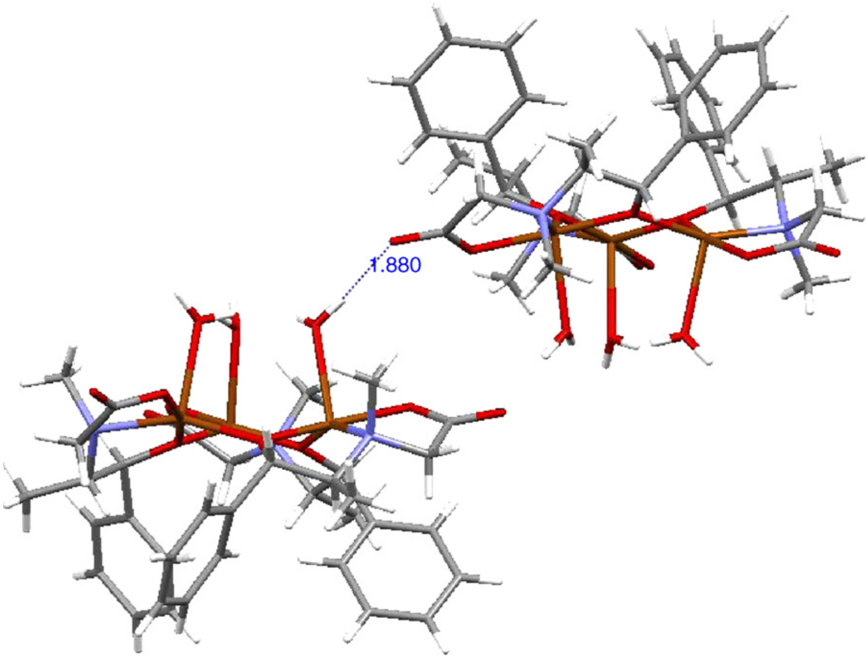


Fig. 26. Intermolecular hydrogen bonding of the trinuclear copper(II) compound derived from *pseudo*ephedrine [32].

A polymeric compound was obtained from the reaction of *N*-acetyl *pseudo*ephedrine with cadmium(II) chloride. The metal center has a distorted pentagonal bipyramidal geometry, where the apical positions are occupied by a water molecule and a chloride ion. The tridentate ligand lies in the equatorial plane and the coordination sphere is completed by a chelating carboxylic group from another ligand. Each carboxylate group is bridging two different cadmium atoms, forming a zigzag chain in a polymeric structure, as depicted in Fig. 28, [31].

4. 1,3-Heteroazolidines and boroxazolidines

Another way to develop two new stereogenic centers in oxazaborolines was adding a water molecule (Fig. 29a). The reaction gives the saturated borolidine heterocycle, where the boron and nitrogen atoms become chiral. X-ray diffraction structure of the optically active oxazaliborolidine derived from *pseudo*ephedrine was determined [34] (Fig. 29b).

Some other heterocycles derived from ephedrine are known, a dithiazine derivative was synthesized from the reaction of

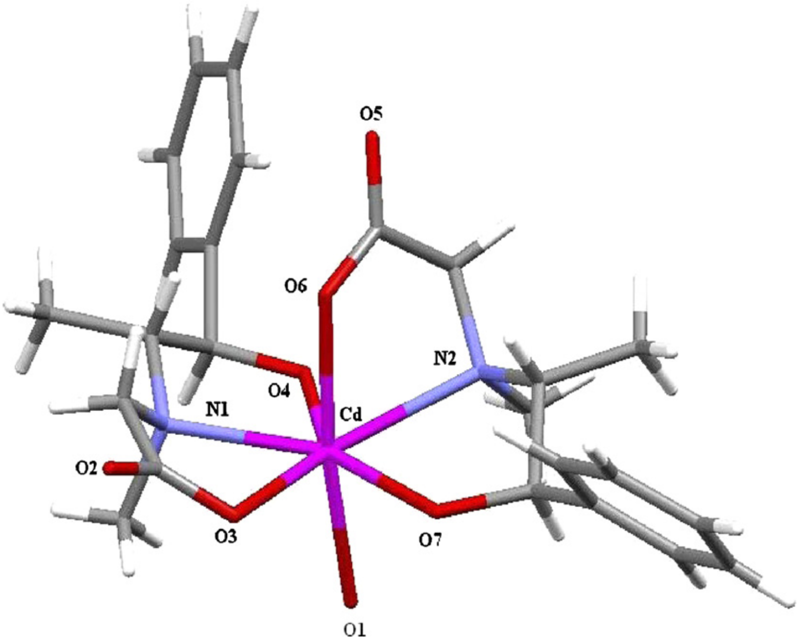


Fig. 27. X-ray diffraction structure of the cadmium compound derived from the *N*-acetyl (−)-*pseudo*ephedrine, the cadmium(II) has a pentagonal bipyramidal geometry [31].

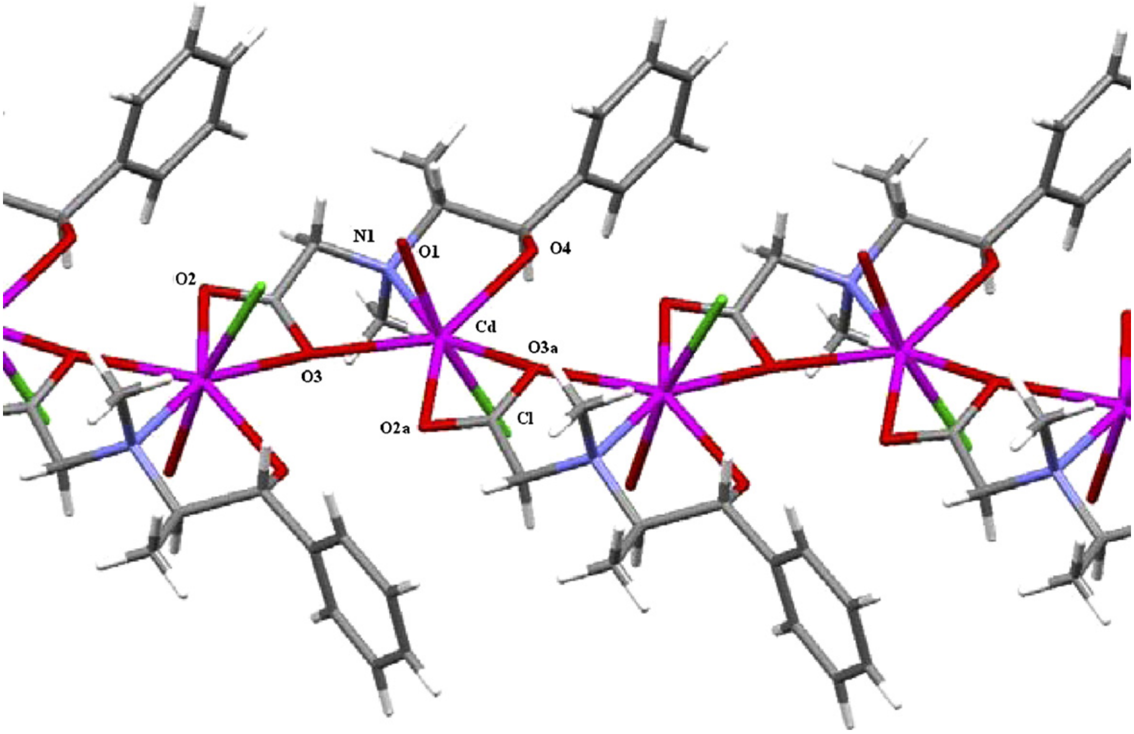


Fig. 28. Polymeric heptacoordinate cadmium compound derived from *N*-acetyl *pseudo*ephedrine [31].

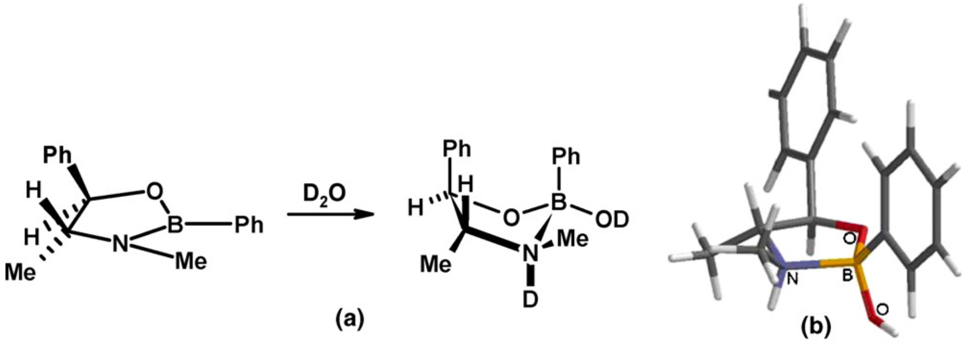


Fig. 29. (a) Addition of water to the oxazaboroline, derived from (−)-*pseudo*ephedrine, is stereoselective, it gives only one pure isomer of the borolidine, whose X-ray diffraction structure is shown in b [34].

formaldehyde, NaSH and *nor*ephedrine [35]. The reaction of the dithiazine ephedrine with tosyl chloride affords a *N*-tosyl-oxazolidine (Fig. 30). Their solid state structure is shown in Fig. 31, [35].

Some boron derivatives have been prepared from the ephedrine dithiazines [36,37] (Fig. 32).

A *bis*(oxazolidine)methane derived from (−)-*nor*ephedrine was obtained (X-ray crystal structure, Fig. 33). An interesting behavior of this molecule was observed; in the presence of a Grignard compound an equilibrium with dioxabicyclo[4,4,1]undecane is established and the Grignard reagent is eliminated, the equilibrium is completely returned to the bis(oxazolidine) methane as shown in Fig. 34 [38].

A series of polyfunctional ligands derived from 2-aminobenzothiazole and ephedrine derivatives was reported. The compounds, shown in Fig. 35, are suitable ligands for the

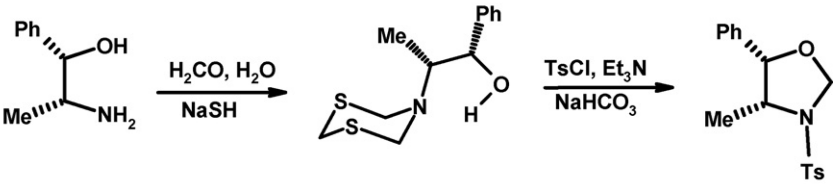


Fig. 30. Synthesis of dithiazine and *N*-tosyl-oxazolidine derived from (+)-ephedrine [35].

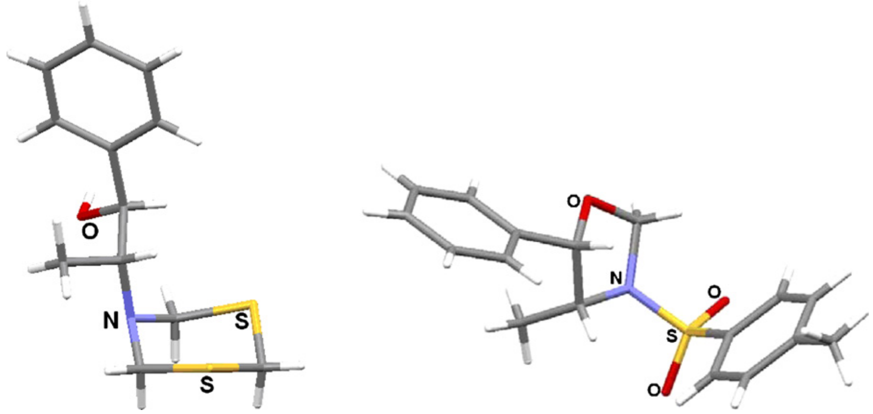


Fig. 31. Solid state structures of dithiazine and *N*-tosyl-oxazolidine derived from (+)-ephedrine [35].

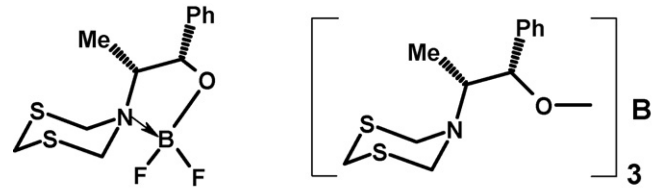


Fig. 32. Boron compounds of a dithiazine derived from (+)-ephedrine ligand [36,37].

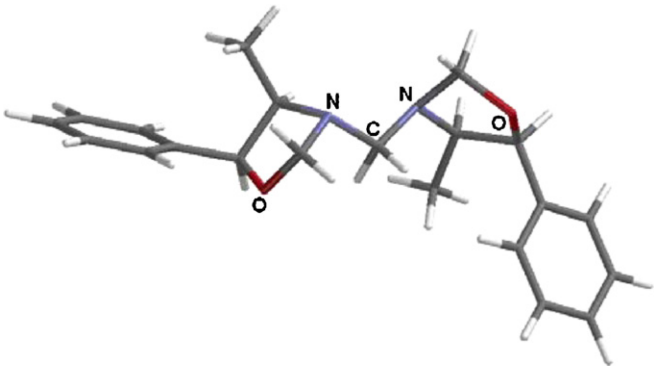


Fig. 33. Solid state structure of the bis(oxazolidine)methane derived from (−)-*nor*ephedrine [38].

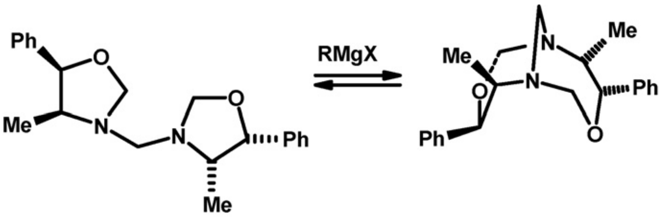


Fig. 34. Equilibrium between bis(oxazolidine) methane and dioxabicyclo[4,4,1]undecane in the presence of a Grignard reagent [38].

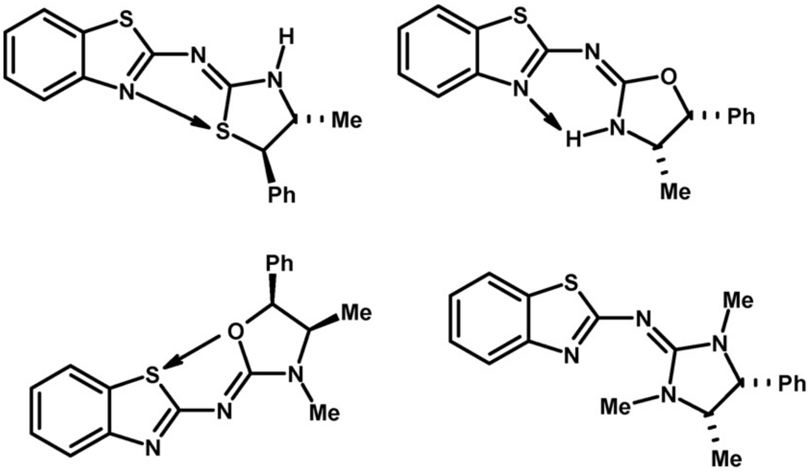


Fig. 35. Some 2-aminobenzothiazole heterocycles derived from ephedrines [39].

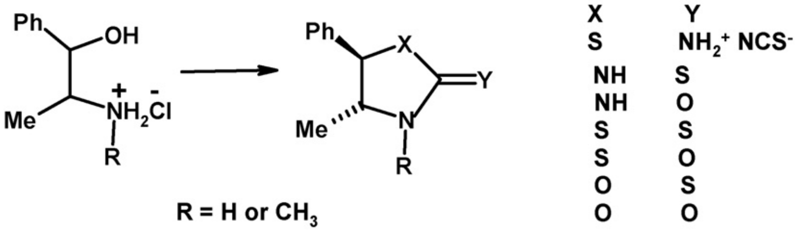


Fig. 36. 1,3-heterazolidines-2-heterounsaturated [40].

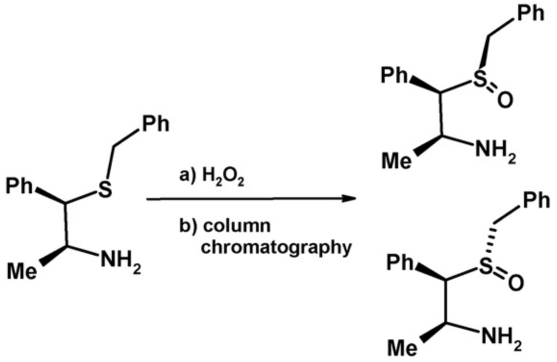


Fig. 37. *S*-diastereomers of benzylsulfoxide of deoxy*nor*ephedrine [41].

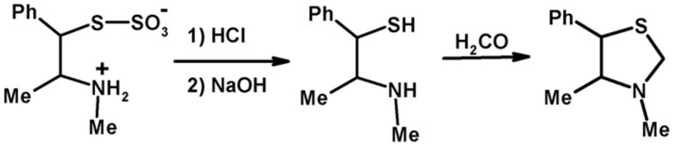


Fig. 38. Thiosulfate-deoxyephedrine is a starting material for the synthesis of thioephedrine and thiazolidines [42,43].

preparation of metallic derivatives. Intramolecular short contacts between the N and S, as between O and S, were found, which together with a N–H· · ·N hydrogen bond, determined the preferred conformation of the compounds [39].

Recently, an easy and direct method for the preparation of 2-oxo, 2-thione and 2-imine 1,3-heterazolidine derived from ephedrines and norephedrines by reaction of solvent free ephedrine hydrochlorides and oxocyanates or thiocyanate salts was reported [40] (Fig. 36).

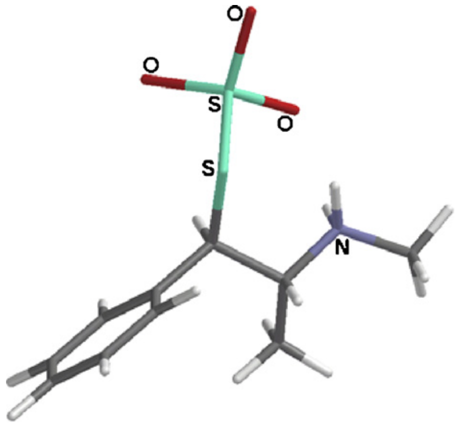


Fig. 40. X-ray solid state structure of the thiosulfate *pseudo*ephedrine [45].

5. Sulfur and selenium derivatives of ephedrine

Thioephedrines and sulfoxide-ephedrines also have relevance as optically active ligands combined with iridium(I) for hydrogen transfer hydrogenation reactions, in these compounds the sulfoxide is a chiral center, and the authors claim to have isolated both *S*-diastereomers [41] (Fig. 37).

The thiosulfonic deoxyephedrine derivatives are precursors of thioephedrines and 1,3-thiazolidines [42,43] (Fig. 38).

The configuration of thiosulfate ephedrine can be changed depending on the solvent used in its reaction synthesis [44] (Fig. 39).

The X-ray diffraction structure of the thiosulfate *pseudo*ephedrine appears in Fig. 40 [45].

The thiosulfonic deoxy-*pseudo* ephedrine has been used for the preparation of a trinuclear nickel(II) cluster $Ni_3S_4N_3$,

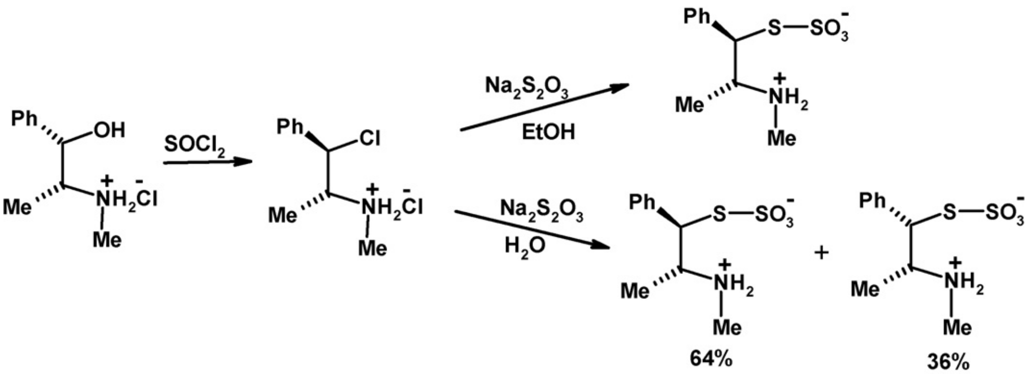


Fig. 39. Stereochemistry of the synthesis of thiosulfate ephedrines [44].

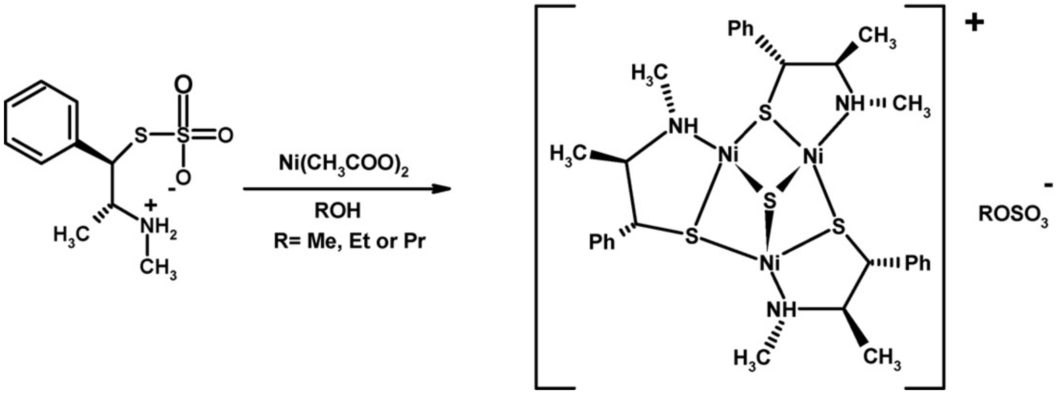


Fig. 41. Reaction syntheses of trinuclear $Ni_3S_4N_3$ clusters derived from (−)-*pseudo*thioephedrine [46].

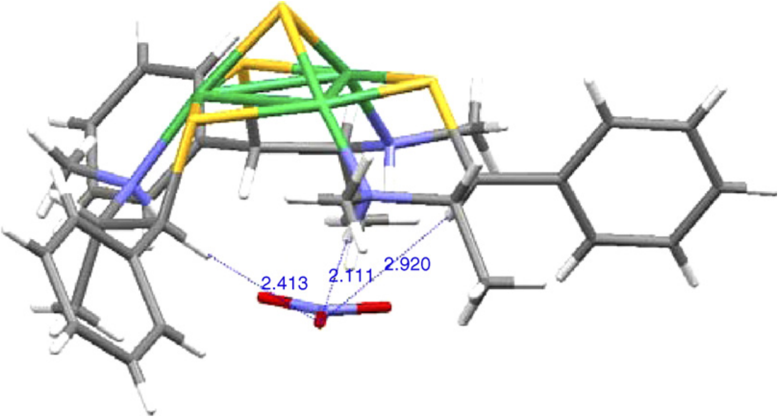


Fig. 42. Trinuclear nickel(II) compound derived from (−)-*pseudo*thioephedrine. There are nine cooperative hydrogen bonds to the nitrate oxygen atoms. For clarity only three are shown [46].

by reaction of the (−)-*pseudo*ephedrine thiosulfonic acid and nickel(II) acetate [46] (Fig. 41).

The cluster has C_3 symmetry and nine new stereogenic centres, three nickel, three sulfur and three nitrogen atoms. The molecule is a coned-shaped cluster topped by a μ_3-sulfide ion, each triangular edge is also bridged by a sulfide ion, each nickel(II) is in a distorted planar geometry and the three phenyl groups form a calyx which contains $R{-}OSO_3^-$ ($R = C_2H_5$, C_3H_7). The alkyl sulfates were generated during the synthesis. The methyl sulfate counterion ($MeOSO_3^-$) was exchanged by a nitrate, to form a similar compound in which the nitrate anion occupies the cavity. In this cavity there are several hydrogen atoms, which allow cooperative hydrogen bonding with the different anions, as ethyl or propyl sulfate, and nitrate, as shown in Fig. 42.

An optically active diborane tricyclic compound was prepared from seleno-deoxy-(+)-*pseudo*ephedrine, its X-ray diffraction structure showed that the two boron atoms are bonded to selenium and coordinated to the nitrogen atoms [47] (Fig. 43).

A series of 2-imino-1,3-selenazolidines or 1,3-thiazolidines and some 2-iminophosphanes and 2-iminotrimethylsilane derived from ephedrine are interesting optically active ligands bearing atoms with lone pairs, useful for coordination bonds [48,49] (Fig. 44). The solid state structure of a tris iminophosphanes is shown in Fig. 45 [49].

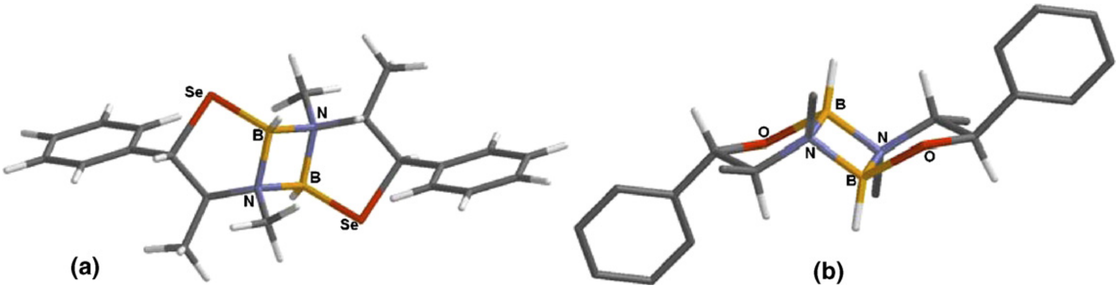


Fig. 43. Two views of solid state structure of a bis-[borane seleno-deoxy-(+)-*pseudo*ephedrine], for clarity in b the phenyl hydrogen atoms are omitted [47].

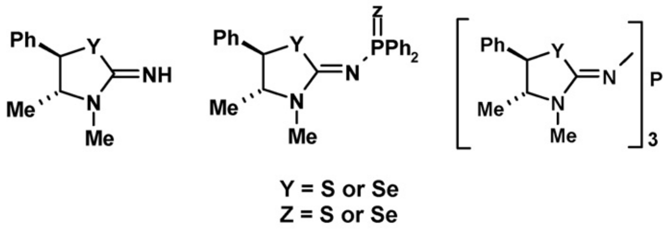


Fig. 44. 2-Imino-1,3-selenazolidines or -1,3-thiazolidines and 2-iminophosphanes [48,49].

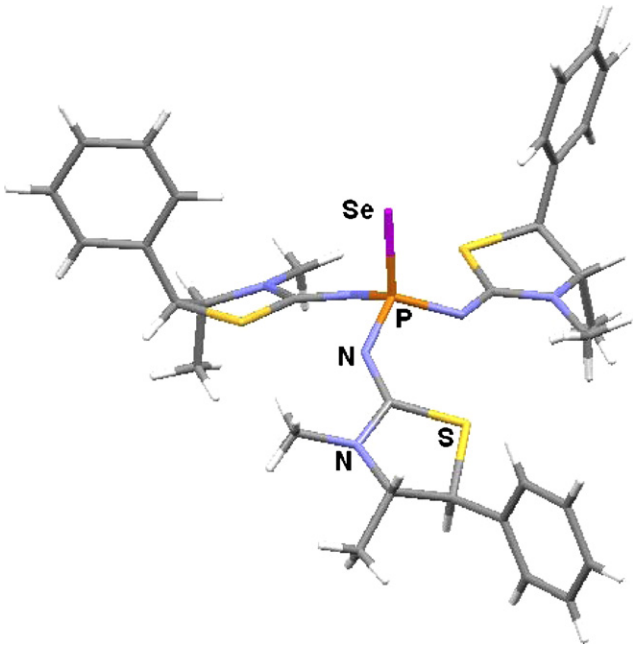


Fig. 45. X-ray diffraction structure of a tris iminophosphane derived from *pseudo*ephedrine [49].

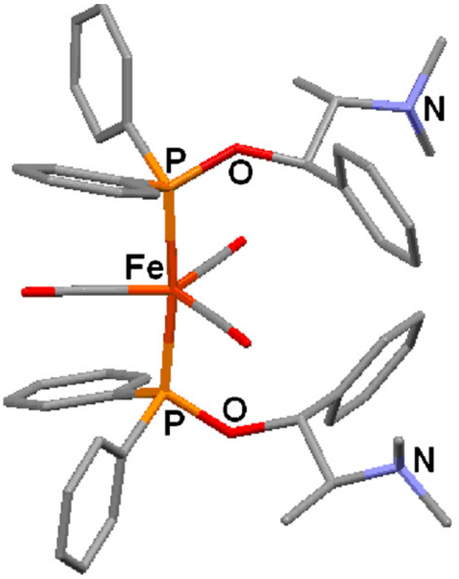


Fig. 46. X ray diffraction structure of bis(*N*-methyl-ephedrinediphenylphosphine)tricarbonyliron [7], hydrogen atoms have been omitted for clarity.

Aminophosphanes derived from (−)-*N*-methylephedrine were used as ligands for tricarbonyliron, where the metal atom is a stereogenic center (Fig. 46) [7].

6. Concluding remarks

This brief review, presents some interesting compounds derived from the family of ephedrines. These ligands have been used for the preparation of linear and cyclic organic derivatives, heterocycles and metal complexes, all having enormous potential as optically active compounds. The combination of ligands derived from ephedrine and elements different from carbon produces new compounds where the elements become stereogenic centers in optically active molecules. Their use as fine reagents for asymmetric synthesis or optically active catalytic agents in industry is a motivation for the study of these simple but relevant molecules. Much investigation is still needed in order to better understand the stereochemistry and the dynamic behavior in the molecules resulting from chiral organic ligands and other elements different from carbon.

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References

[1] M. Li, C. Zou, C. Duhayon, R. Chauvin, Tetrahedron Lett. 47 (2006) 1047.
[2] Y. Nakamura, S. Takeuchi, K. Okumura, Y. Ohgo, Tetrahedron 57 (2001) 5565.
[3] S. Bouquillon, S. Humbel, U. Létinois-Halbes, F. Henin, J. Muzart, J. Organomet. Chem. 687 (2003) 377.
[4] A.G. Myers, H. Bryant, H.C. Yang, L. McKinstry, D.J. Kopecky, J.L. Gleason, J. Am. Chem. Soc. 119 (1997) 6496.
[5] S.R. Hitchcock, D.M. Casper, J.F. Vaughn, J.M. Finefield, G.M. Ferrence, J.M. Esken, J. Org. Chem. 69 (2004) 714.
[6] F. Yuan, C. Zhu, J. Sun, Y. Liu, Y. Pan, J. Organomet. Chem. 682 (2003) 102.
[7] J. Brunet, R. Chauvin, J. Chiffre, B. Donnadieu, S. Huguet, P. Leglaye, E. Mothes, Inorg. Chim. Acta 291 (1999) 300.
[8] S. Abramson, M. Lasperás, D. Brunel, Tetrahedron Asymm. 13 (2002) 357.
[9] Z. Foldi, T. Toldi, A. Foldi, Chem. Ind. (1955) 1297.
[10] Y. Amano, K. Osaki, T. Watanabé, Bull. Chem. Soc. Jpn. 37 (1964) 1363.
[11] J.F. Brazier, J. Ferekh, A. Munoz, R. Wolf, C.R. Acad. Sci., Paris (C) (1971) 1521.
[12] J. Ferekh, J.F. Brazier, A. Munoz, R. Wolf, C.R. Acad. Sci., Paris (C) (1970) 865.
[13] M. Sanchez, J. Ferekh, J.F. Brazier, A. Munoz, R. Wolf, R. Chimii, Ann. Soc. Chim. Polorum 45 (1971) 131.
[14] A. Klaebe, J.F. Brazier, A. Cachapuz Carrelhas, B. Garrigues, M.R. Marre, R. Contreras, Tetrahedron 38 (1982) 2111.
[15] M.G. Newton, J.E. Collier, R. Wolf, J. Am. Chem. Soc. 96 (1974) 6888.
[16] J. Devillers, B. Garrigues, R. Wolf, J.J. Bonnet, Acta Cryst. B35 (1979) 2153.
[17] S. Bouquillon, A. Du Moulinet d'Hardemare, M.-T. Averbuch-Pouchot, F. Henin, J. Muzart, A. Durif, Acta Crystallogr. Sect. C 55 (1999) 2028.
[18] J.W. Faller, A.R. Lavoie, Organometallics 19 (2000) 3957.
[19] H. Tlahuext, F. Santiesteban, E. García-Báez, R. Contreras, Tetrahedron Asymm. 5 (1994) 1579, and references cited therein.

[20] M. Motohashi, Y. Amano, T. Uno, Bull. Chem. Soc. Jpn. 41 (1967) 2007.
[21] M. Tlahuextl, F.J. Martínez-Martínez, M.J. Rosales-Hoz, R. Contreras, Phosphorus, Sulfur Silicon 123 (1997) 5.
[22] M. Tlahuextl, A.R. Tapia-Benavides, A. Flores-Parra, R. Contreras, H. Tlahuextl, E.M. Cruz, Heteroatom Chem. 16 (2005) 513.
[23] F.J. Martínez-Martínez, A. Ariza-Castolo, H. Tlahuext, M. Tlahuext, R. Contreras, J. Chem. Soc. Perkin Trans. (II) (1993) 1481.
[24] V.M. Jiménez-Pérez, H. Nöth, A. Ariza-Castolo, A. Flores-Parra, R. Contreras, J. Organometal. Chem. 691 (2006) 1584.
[25] N. Farfán, R. Contreras, Heterocycles 23 (1985) 2989.
[26] N. Farfán, L. Cuellar, J.M. Aceves, R. Contreras, Synthesis (1987) 927.
[27] T. Mancilla, R. Contreras, J. Organometal. Chem. 321 (1987) 191.
[28] N. Farfán, T. Mancilla, D. Castillo, G. Uribe, L. Carrilo, P. Joseph-Nathan, R. Contreras, J. Organometal. Chem. 381 (1990) 1.
[29] G. Vargas-Díaz, H.C. López-Sandoval, A. Peña-Hueso, A. Flores-Parra, R. Contreras, M. Flores-Alamo, M. Castro, L. Feria, N. Barba-Behrens, in review.
[30] G. Vargas-Díaz, A.B. Vázquez-Palma, H.C. López-Sandoval, A. Peña-Hueso, A. Flores-Parra, R. Contreras, N. Barba-Behrens, in review.
[31] H.C. López-Sandoval, N. Barba-Behrens, S. Bernès, N. Farfán-García, H. Höpfl, J. Chem. Soc. Dalton Trans. (1997) 3415.
[32] H. López-Sandoval, R. Contreras, A. Escuer, R. Vicente, S. Bernès, H. Nöth, G.J. Leigh, N. Barba-Behrens, J. Chem. Soc. Dalton Trans. (2002) 2648.
[33] M. Castro, J. Cruz, H. López-Sandoval, N. Barba-Behrens, Chem. Commun. (2005) 3779.
[34] A. Rosendo Rico, M. Tlahuextl, A. Flores-Parra, R. Contreras, J. Organometal. Chem. 581 (1999) 122.
[35] J.C. Gálvez-Ruíz, J.C. Jaen-Gaspar, I.G. Castellanos-Arzola, R. Contreras, A. Flores-Parra, Heterocycles 63 (2004) 2269.
[36] J.C. Gálvez-Ruíz, Ph.D. Thesis, 4169, Cinvestav México, 2003.
[37] J.C. Gálvez-Ruíz, R. Contreras, A. Flores-Parra, in review.
[38] R. Salas-Coronado, J.C. Gálvez-Ruíz, C. Guadarrama-Pérez, A. Flores-Parra, Heterocycles (2003) 1123.
[39] A. Cruz, M. Gayosso, R. Contreras, Heteroatom Chem. 12 (2001) 586.
[40] A. Cruz, R. Contreras, I.I. Padilla-Martínez, M. Juárez-Juárez, Tetrahedron Asymm. 17 (2006) 1499.
[41] D.G.I. Petra, T.C.J. Kamer, A.L. Spek, H.E. Schoemaker, P.W.N. van Leeuwen, J. Org. Chem. 65 (2000) 3011.
[42] B. Kone, M. Gelbcke, Spectrochim. Acta 39 (1983) 409.
[43] B. Kone, M. Gelbcke, Bull. Soc. Chim. Belg. 92 (1983) 139.
[44] A. Cruz, A. Vásquez-Badillo, I. Ramos-García, R. Contreras, Tetrahedron Asymm. 12 (2001) 711.
[45] A. Cruz, A. Flores-Parra, H. Tlahuext, R. Contreras, Tetrahedron Asymm. 6 (1995) 1933.
[46] H. López-Sandoval, A. Richaud, R. Contreras, G.J. Leigh, P.B. Hitchcock, A. Flores-Parra, J.C. Gálvez-Ruíz, A. Cruz, H. Nöth, N. Barba-Behrens, Polyhedron 23 (2004) 1837.
[47] A. Cruz, D. Macias-Mendoza, E. Barragán-Rodríguez, H. Tlahuext, H. Nöth, R. Contreras, Tetrahedron Asymm. 28 (1997) 3903.
[48] E.V. Bakhmutova, A. Cruz, R. Ramírez-Trejo, R. Contreras, B. Wrackmeyer, Magn. Reson. Chem. 39 (2001) 739.
[49] E.V. Bakhmutova, H. Noth, R. Contreras, B. Wrackmeyer, Z. Anorg. Allg. Chem. 627 (2001) 1846.