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2-Azanorbornane – a versatile chiral aza-Diels-Alder cycloadduct: preparation, applications in stereoselective synthesis and biological activity

Elżbieta Wojaczyńska,*[1] Jacek Wojaczyński,[2] Karolina Kleniewska,[1] Mateusz Dorsz[1] and Tomasz K. Olszewski[1]

[1]Department of Organic Chemistry, Faculty of Chemistry, Wrocław University of Technology, Wybrzeże Wyspiańskiego 27, 50 370 Wrocław, Poland

[2]Department of Chemistry, University of Wrocław, 14 F. Joliot-Curie St., 50 383 Wrocław, Poland

*Corresponding author. E-mail: elzbieta.wojaczynska@pwr.edu.pl

Abstract

The review presents the achievements in the field of preparation of chiral 2-azanorbornyl derivatives and their application in various stereoselective reactions as well as in biomimetic studies.

1. Introduction

Of three isomers of azanorbornane (azabicyclo[2.2.1]heptane), differing by the position of nitrogen atom (Figure 1), 2-aza-derivative is of special importance due to the intrinsic chirality of the molecule (Figure 2). This relatively simple bicyclic system possesses a rigid skeleton which can serve as a versatile platform for the synthesis of various enantiopure derivatives which have already found a number of applications.

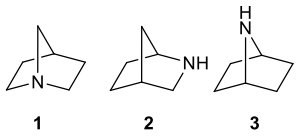


Figure 1. 1-azanorbornane (**1**), 2-azanorbornane (**2**, one of enantiomers shown) and 7-azanorbornane (**3**)

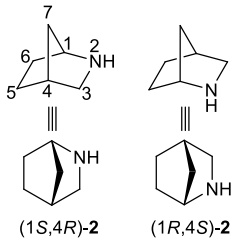


Figure 2. Two enantiomers of 2-azanorbornane (numbering scheme shown for one of isomers). Of two typical depictions of the bicyclic skeleton shown in the Figure, the first one is used throughout the review. Note that for 2-azanorbonene, due to Cahn-Ingold-Prelog priority rules, configurations of stereocenters are opposite in comparison with its reduced counterpart.

2-Azanorbornane (or its unsaturated analogue, 2-azanorbornene) is easily synthetically available and can be prepared in the both enantiomeric forms from inexpensive starting materials, also on a gram or even kilogram scale. The synthetic routes to this bicyclic system will be described in part 2 of this review. The basic structure offers wide possibilities of various modifications, from simple alteration of peripheral substituents to more elaborated transformations, in many cases utilizing the possible chiral induction. Typically, 3-substituted derivatives are used which are isolated from the synthesis of the bicyclic system as *exo* (a major product in most preparations) or *endo* isomers (Figure 3). This opens additional routes for adjusting the modified compounds for particular transformations.

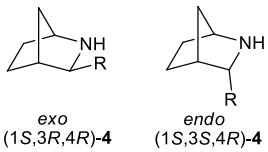


Figure 3. The two epimers of 3-substituted (1*S*,4*R*)-2-azanorbornane **4**

The applications of 2-azanorbornane derivatives as versatile chiral building blocks in asymmetric synthesis are presented in Part 3. The unlimited possibilities of modifications of the bicyclic scaffold include introduction of various donor groups and thus formation of catalytically active complexes. In consequence, they have been employed in numerous asymmetric processes as chiral ligands, and also as catalysts in metal-free transformations. This practical aspect of applications of 2-azanorbornanes is discussed in Section 4. Additionally, these compounds have been identified as valuable rigid analogues of various biologically active molecules, like piperidine or pyrrolidine alkaloids and proline. 2-Azabicyclo[2.2.1]heptane derivatives have been also applied as convenient precursors in the

stereoselective synthesis of monocyclic systems useful in medicinal chemistry. These biomedical applications of the title system are comprised in Part 5.

2. Preparation of 2-azanorbornyl derivatives

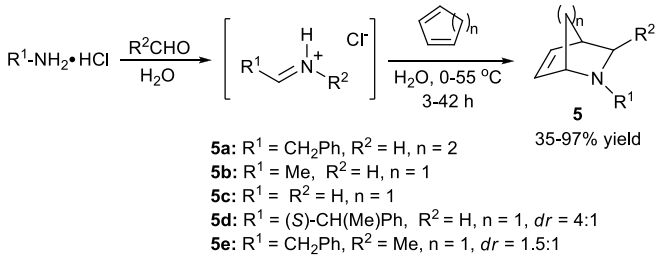
2.1. Synthesis of 2-azanorbornyl derivatives via the aza-Diels-Alder reaction

The Diels-Alder reaction (DA) is one of the most popular transformations for organic chemists to efficiently create complex molecules. Since its discovery in 1928 by Diels and Alder[1], this pericyclic reaction involving a conjugated diene and a dienophile has been used for the diastereo- and regioselective generation of six-membered rings with up to four stereogenic centres in a single step.[2-4] It is universally acknowledged for the rapid, atom-economical build-up of complex structures of defined geometry with minimal waste. These criteria fulfil the requirements of a scalable chemical process; thus application of this transformation in chemical industry is a feasible enterprise.[5-7] The aza-DA, a variant of Diels-Alder reaction where the dienophile contains the nitrogen atom,[8-10] was applied with great success for the synthesis of 2-azanorbonyl derivatives. Reaction of cyclopentadiene with imines, oximes and other aza-dienophiles leads to variously substituted 2-azabicyclo[2.2.1]heptenes which can be hydrogenated to their saturated counterparts. Facial diastereoselectivity of cycloaddition limits the number of possible isomeric products. Moreover, use of chiral dienophiles or catalysts allows obtaining of particular enantiomer of 2-azanorbornene, which is especially important for applications of its various derivatives in stereoselective synthesis and for biomimetic studies.

The review by Blondet and Morin published in 1982 presented the early achievements in the synthesis of 2-azabicyclo[2.2.1]heptanes, heptenes and heptadienes.[11] In this part, we focus on further developments in the field, in particular on the enantioselective preparative routes.

2.1.1. The aza-DA reaction between cyclic dienes and imines

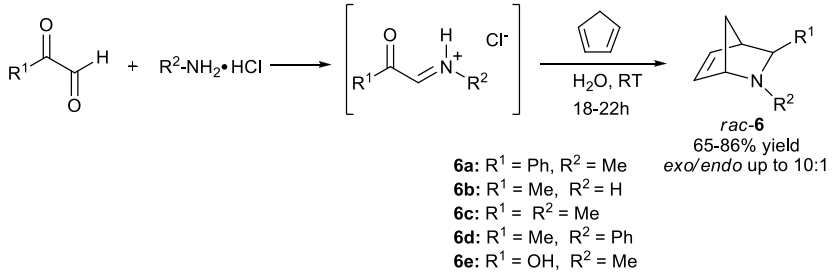
In 1985 Larsen and Grieco reported for the first time that simple inactivated iminium salts, generated in a Mannich-like protocol, can combine with dienes in aza-DA reaction under mild conditions and in aqueous media.[12] Using this protocol, 2-azabicyclo[2.2.1]octene **5a** and 2-azabicyclo[2.2.1]heptanes **5b-e** were obtained when cyclopenta- and cyclohexadiene were reacted with various imines generated from simple aldehydes and amine hydrochlorides (Scheme 1).



Scheme 1. Reaction of iminium ions with dienes[12]

In an asymmetric variant of this reaction employing (1*S*)-1-phenylethylamine hydrochloride as the source of chirality, aqueous formaldehyde and cyclopentadiene a 4:1 mixture of separable diastereoisomers **5d** was isolated in 86% yield. This protocol could also be performed in the presence of catalytic amount of lanthanide(III) triflates as reported later by Wang and co-workers, extending the scope of that reaction to include higher aldehydes.[13]

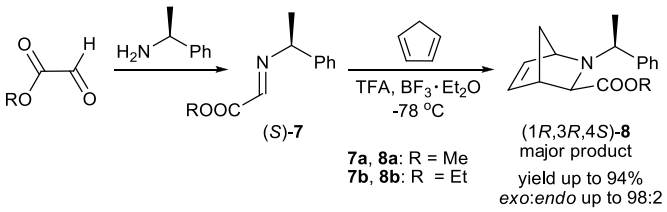
In continuation of their previous work, Grieco *et al.* showed that also iminium ions derived from activated aldehydes such as phenyl- and methylglyoxal and amine hydrochlorides react with cyclopentadiene in water at room temperature yielding the 2-azanorbornene derivatives **6a-e** (Scheme 2).[14]



Scheme 2. Reaction of cyclopentadiene with iminium ions derived from activated aldehydes[14]

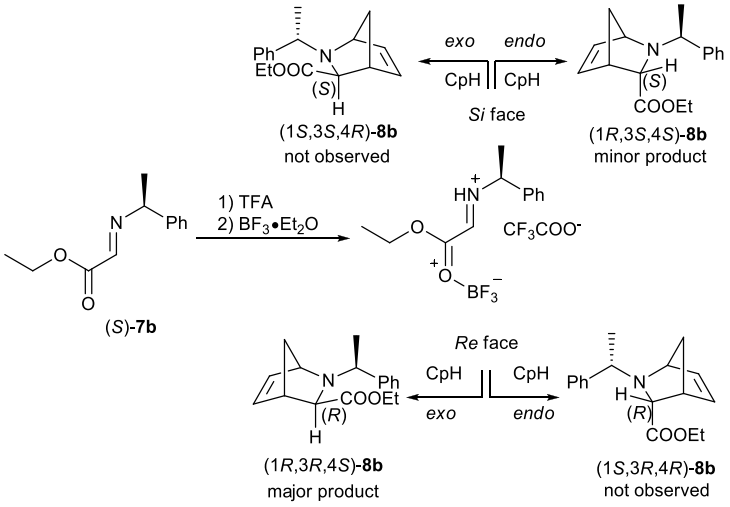
The best yield (86%) was obtained for the reaction of cyclopentadiene with imine derived from phenylglyoxal and methylamine, whereas the best *exo/endo* ratio (10:1) was observed for the product **6d** issued from the reaction of cyclopentadiene with imine obtained from methylglyoxal and benzylamine hydrochloride.[14]

After the seminal works of Grieco,[12,14] in 1990 and 1991 the groups of Stella,[15] Bailey[16] and Waldmann[17] independently reported an efficient stereoselective synthesis of 2-azabicyclo[2.2.1]heptene derivatives **8** employing the aza-DA reaction of chiral imines **7**, derived from the condensation of enantiopure 1-phenylethylamine and alkyl glyoxylate, with cyclopentadiene and catalyzed by TFA/$BF_3 \cdot OEt_2$ (Scheme 3).



Scheme 3. Synthesis of azabicyclo[2.2.1]heptene derivatives **8** via the TFA/$BF_3 \cdot OEt_2$ catalyzed aza-DA reaction of chiral imine **7** with cyclopentadiene[15-17]

The mechanism of the reaction between chiral imine (aza-dienophile) and cyclopentadiene was proposed by Stella and Abraham (Scheme 4).[15] The role of the catalyst is significant due to the activation of the imine and also has an impact on the diastereoselectivity (*exo/endo* ratio) of the aza-DA reaction. The complete diastereoface selectivity was suggested by the authors, with only products of *Re* addition observed. However, further investigations by Hashimoto *et al.* who isolated all the four isomers and assigned the configuration of all stereocenters, showed that under original Stella conditions the two epimers differing only by the configuration on 3-C were obtained (Scheme 4), and the modification of reaction conditions can lead to change of the ratio of minor products, with the *exo*-diastereomer with the configuration on 3-C opposite to the configuration of imine used remaining the major cycloadduct (constituting *ca.* 80%).[18] In most preparations, only this product is isolated from the reaction and the remaining isomers are discarded.



Scheme 4. Mechanism of the aza-DA reaction of an imine derived from (1*S*)-1-phenylethylamine and ethyl glyoxylate with cyclopentadiene (CpH)[15,18]

The advantage of the approach proposed by Stella, Bailey and Waldmann lies in the use of inexpensive starting materials in combination with the high selectivity observed when

utilizing (1*S*)- or (1*R*)-1-phenylethylamine as the chiral auxiliary. The reaction is highly *exo*-selective, the *exo*/*endo* ratio reported varied from 86:14 to 98:2.[15-17] Bailey and coworkers have extensively studied the asymmetric synthesis of 2-azanorbornene derivatives (including **8b**) using the aza-DA [4+2] cycloaddition between imines of the type Ph(R)CH-N=CHCOOEt and dienes.[19] The reaction showed extremely high regio- and diastereoselectivity, moreover, the use of (*S*)-1-phenylethyl group as a chiral auxiliary led to high asymmetric induction. A significant preference for the *exo* adducts was observed, which can be explained by directing the bulkier auxiliary away from bridging $(CH_2)_n$ group into the axial *endo* position and forcing the ester into the considerably less hindered *exo* stereochemistry.

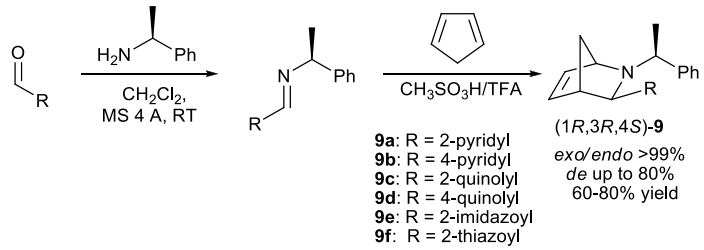
The aza-DA reactions between cyclopentadiene and iminium ions derived from glyoxylates have been a subject of theoretical studies performed in 2005 by Rodríguez-Borges *et al.* using density functional theory (DFT).[20] The obtained results suggested a highly asynchronous concerted mechanism, which in turn may explain the preferred *exo* stereoselectivity of the reaction and the significant effect of the solvent used in the reaction. The *exo/endo* ratio increased with the solvent polarity in good agreement with the experimental findings. Further theoretical studies carried out by the same authors in 2009, revealed that the *exo/endo* selectivity was predicted to decrease with increasing temperature with accordance with the experimental observations.[21] Additionally, DFT was used by Teixeira *et al.* to elucidate the role of the ester group of the dienophile. The theoretical calculations confirmed that the *exo* cycloadducts (sterically less hindered) are always favored relative to the *endo* analogues, both by kinetic and thermodynamic reasons. The influence of ester group was shown much more noticeable when solvent effect was considered.[22]

In 2002 using the methodology depicted in Scheme 3, Andersson *et al.* reported the synthesis of (1*R*,3*R*,4*S*)-**8a** on 111.5 g scale with 56% overall yield.[23] Later on, Hashimoto and co-workers reported on the preparation of (1*S*,3*S*,4*R*)-**8a** on an industrial scale (103 kg, 32% overall yield) by replacing fluorinated chemicals with a biphasic system TMSCl-CH_3OH/toluene.[18]

Due to the low reactivity (or poor electrophilicity) of the imine functionality, [4+2] cycloaddition is possible only with highly reactive dienes under Lewis acid catalysis. A new route based on the use of non-activated imine dienophiles would broaden the scope of this reaction considerably. Therefore several attempts to use different imines were described in the

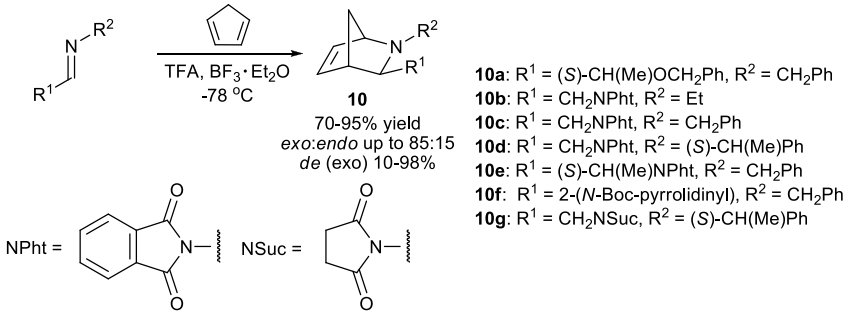
literature.

Andersson *et al.* reported on the use of nitrogen containing heterocyclic aldehydes in the synthesis of heterocyclic imine dienophiles and their reaction with cyclopentadiene affording a palette of heterocyclic azanorbornene derivatives **9a-f** (Scheme 5).[24] A second nitrogen atom placed in conjugation with the imine fulfilled the role as an electron-withdrawing group under the acidic reaction conditions and hence activated the imine. The use of a Lewis acid such as boron trifluoride (BF_3), which was beneficial in the earlier mentioned cycloaddition of glyoxylate-derived imines, resulted only in a fast polymerization of the aldehyde. In turn, strong Brønsted acids such as methanesulfonic acid and trifluoroacetic acid proved to be very effective, and the use of either alone or a 1:1 combination of those two reagents resulted in good conversions and stereoselectivities. In all cases the *exo* product was formed almost exclusively and the diastereoselectivities varied from 75:25 in the case of **9e** to 90:10 for **9c**, **9d** and **9f**.[24]



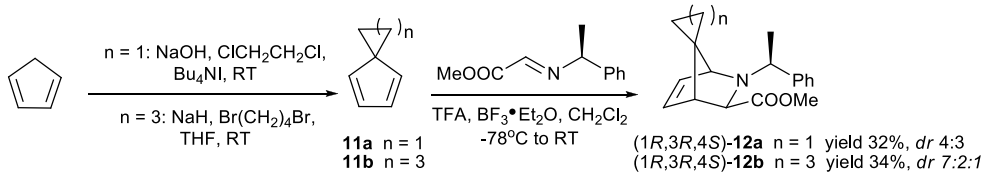
Scheme 5. Synthesis of heterocyclic azanorbornene derivatives **9**[24]

Later on the same group reported on the synthesis of 2-azanorbornene derivatives **10a-g** (Scheme 6).[25] The non-activated iminodienophiles having protecting groups such as benzyl, benzyloxycarbonyl, and tosyl did not undergo the cycloaddition reaction, most likely due to the steric hindrance. In turn the iminodienophiles prepared from less bulky phthalimide and succinimide aldehyde derivatives reacted smoothly with cyclopentadiene to give cycloadducts **10** (Scheme 6). The yields varied from 70% in the case of **10g** to 95% for **10c**. The best *exo/endo* selectivity (85:15) was observed for **10c** and **10d**. The use of chiral aldehydes for the preparation of imines applied in the synthesis of the two derivatives, **10a** and **10e** is worth noting since in most enantioselective routes leading to 2-azanorbornenes various enantiopure amines have been applied as the source of chirality.[26]



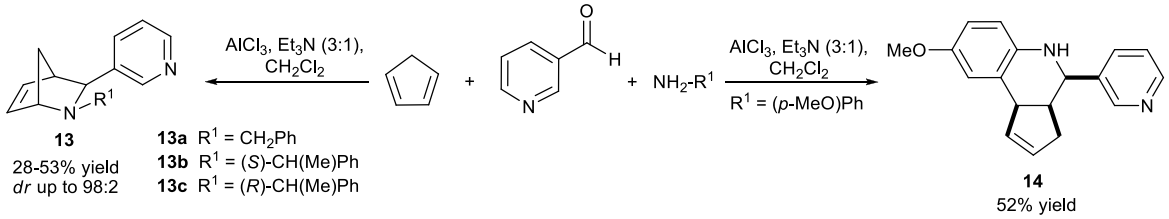
Scheme 6. The aza-DA reaction of non-activated imine derivatives with cyclopentadiene and the formation of bicyclic products **10**[25]

It is noteworthy, that apart from the possibility of using different iminodienophiles also modification of the diene moiety is feasible. As reported by Andersson's group the use of spirodienes **11a-b**, prepared by the addition of dihaloalkane to cyclopentadiene, led to spirocyclic 2-azanorbornene derivatives **12a-b** (Scheme 7).[27] The low yields were attributed to the high tendency of diene polymerization under acidic reaction conditions.



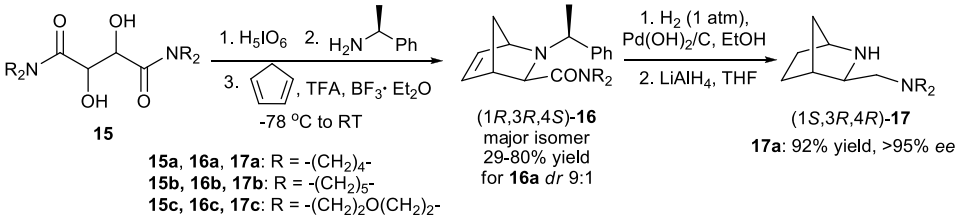
Scheme 7. Synthesis of spirocyclic 2-azanorbornene derivatives **11**[27]

Loh and co-workers reported a Lewis acid-mediated aza-DA reaction of cyclopentadiene and 3-pyridinecarboxaldehyde-derived imines as a new route for the preparation 2-azabicyclo[2.2.1]heptane derivatives **13a-c** (Scheme 8). The best results of aza-DA reaction between deactivated imines and cyclopentadiene were obtained using $AlCl_3/Et_3N$ mixture in 3:1 ratio under anhydrous conditions at 0 ^{0}C. Interestingly, when an imine derived from *p*-anisidine was used, the Povarov reaction product was formed resulting from the reversal of roles: the *N*-aryl-substituted, electron-poor imine acted as an azadiene and a cyclopentadiene as a dienophile to afford the quinoline derivative **14**.[28]



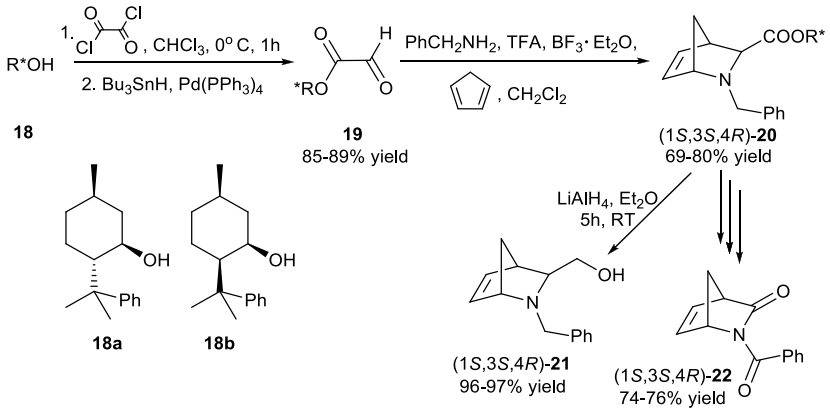
Scheme 8. Preparation of heterocyclic derivatives of 2-azanorbornene **13a-c**[28]

In 2000, in the search for alternative substrates for imine formation, Andersson's group reported on the use of bisamido tartrates **15**.[29] The oxidative cleavage of **15a-c** with periodic acid furnished the corresponding aminoaldehydes subsequently reacted with (*S*)-phenylethylamine to form the desired imines used in the aza-DA reaction with cyclopentadiene and yielding the 2-azanorbornene derivatives **16**. Compounds **16a-c** were further used as building blocks in the improved synthesis of enantiomerically pure diamines **17a-c**[30] by first deprotection of the amine by hydrogenolysis with $Pd(OH)_2$, and subsequent reduction of the amide by means of $LiAlH_4$ (Scheme 9).



Scheme 9. Synthesis of 2-azanorbornene derivatives **16**, **17**[29]

In order to improve the diastereoselectivity of the aza-DA reaction, chiral glyoxyloyl derived-iminodienophiles obtained with the use of various enantiopure auxiliaries have been applied, as reported in the literature. García-Mera, Rodríguez-Borges and co-workers described the effective and highly enantioselective synthesis of 3-functionalized 2-azabicyclo[2.2.1]heptene derivatives **21** and **22** via aza-DA reaction between cyclopentadiene and the protonated imines prepared from *N*-benzylamine and glyoxylates of the two diastereomers of (-)-8-phenylmenthol **18a** and **18b**, as easily recoverable stereo controlling chiral auxiliaries (Scheme 10).[31-33]

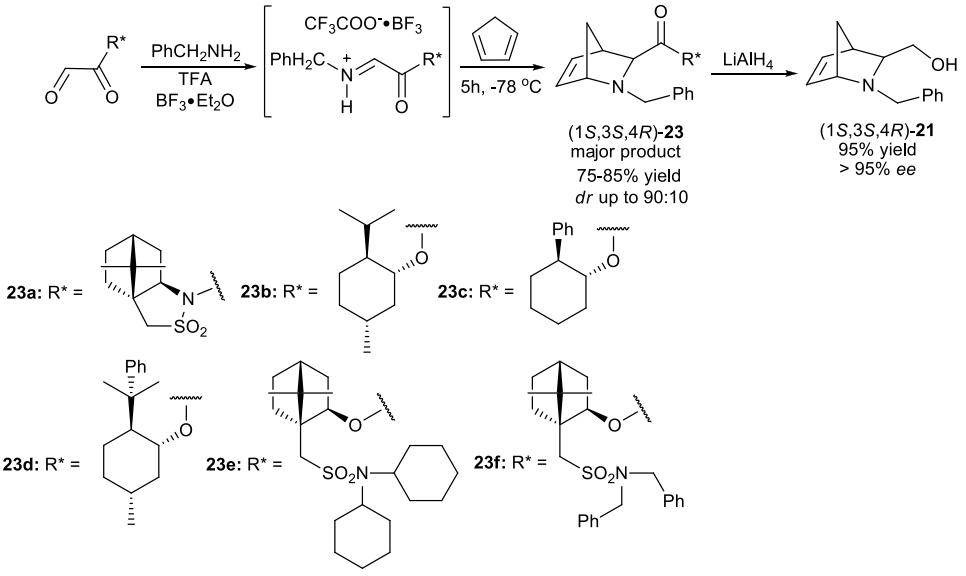


Scheme 10. Use of diastereomers of (-)-8-phenylmenthol **18a** and **18b** in the synthesis of 2-azanorbornene derivatives **21** and **22**[31-33]

High asymmetric (1*S*,3-*exo*) induction observed was explained considering two important factors: firstly, dienophile in the reaction should have an *E* configuration, more stable for stereochemical and polar reason, secondly in the close vicinity of the C=N bond, the benzyl group exerts a larger steric hindrance than the ester group. Additionally, to minimize stereochemical interactions between the methylene moiety of the diene and the bulky substituent of the iminium ion the approach diene–dienophile must occur in an *exo* manner.

The same authors described also the double diastereoselection in the aza-DA cycloaddition between a chiral imine derived from glyoxylates bearing chiral auxiliaries, (-)-8-phenylmenthyl or (+)-8-phenylneomenthyl and (1*S*)- or (1*R*)-1-phenylethylamines, with cyclopentadiene in the presence of $BF_3 \cdot OEt_2$/TFA.[34] The presence of two chiral auxiliaries and the stereochemistry of the phenylethylamine auxiliary played an important role in obtaining the single adduct since the need for coplanarity of the benzene rings and for maximum distance of bulky substituents turned one of the diastereotopic faces much less hindered than the other.

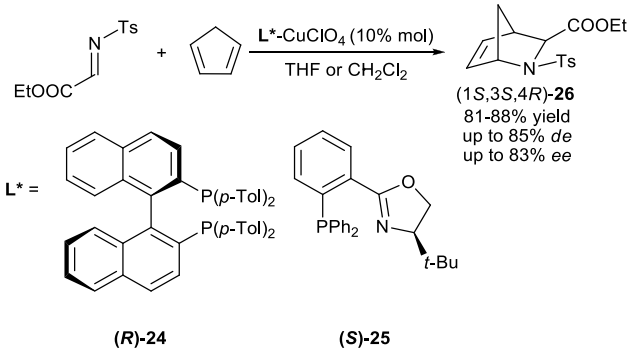
Another example of the use of chiral auxiliaries was reported by Jurczak's group who prepared a series of 2-azanorbornene derivatives **23** by aza-DA cycloaddition reaction between cyclopentadiene and *N*-benzyliminoacetyl derivatives of (2*R*)-bornane-10,2-sultam and chiral secondary alcohols as chiral auxiliaries reaching *de* up to 80% (Scheme 11).[35]



Scheme 11. Preparation of 2-azanorbornene derivatives **23** with the use of chiral auxiliaries

An interesting approach utilizing an enantiopure catalyst as a source of chiral induction in the aza-Diels-Alder reaction was proposed by Jørgensen and coworkers.[36] Bis-

phosphine (BINAP derivative (*R*)-**24**) and phosphine-oxazoline (*S*)-**25** and copper(I) perchlorate as the metal source were chosen in the catalyst screening using Danishefsky's diene and *N*-tosyl imino ester. Their application in the aza-DA reaction of this dienophile with cyclopentadiene led mainly to *exo* (1*S*,3*S*,4*R*)-2-azanorbornene derivative in 81-88% yield and *ee* up to 83% (Scheme 12); *endo* diastereomer was also formed in minor quantities (7-9%).

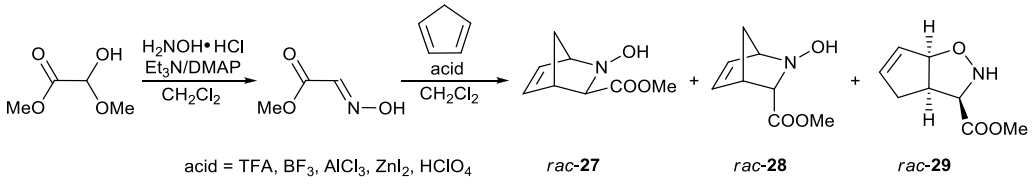


Scheme 12. Synthesis of 2-azanorbornane derivative catalyzed by a chiral copper(I) complex

A similar approach was used by Maison and co-workers for the synthesis of *N*-protected 2-azanorbornyl derivatives using (*R*)-**24** as a source of chirality.[37,38] The obtained 2-azabicycloalkane scaffolds were used as synthetic intermediates for conformationally constrained glutamate analogues,[37] potential ligands for glutamate receptors, known to play important role in several neurological disorders.[39]

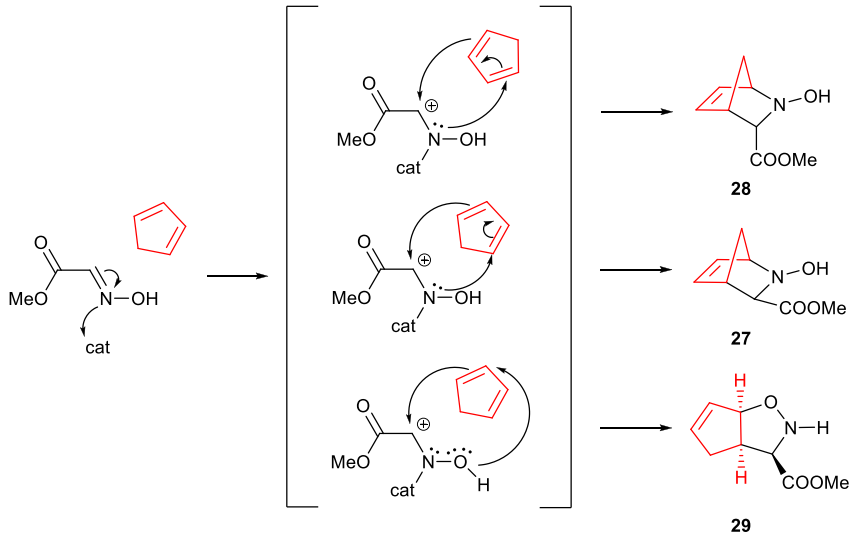
2.1.2. The aza-DA reaction between cyclic dienes and oximes or other aza-dienophiles

N-Hydroxylimines (oximes) can also be considered as imino dienophiles in the aza-DA reaction leading to *N*-hydroxyl-2-azanorbornene derivatives. In 2008, Sousa and co-workers reported the first aza-DA reaction with non-*O*-functionalized oximes as the azadienophiles (Scheme 13).[40] The influence of several Lewis and/or Brønsted acids such as TFA, BF_3, $AlCl_3$, ZnI_2 or $HClO_4$ on the [4+2] heterocycloaddition between cyclopentadiene and methyl glyoxylate oxime leading to a mixture of corresponding *exo/endo* adducts was investigated. Additionally, the influence of temperature on product ratio and yield was examined.



Scheme 13. Products of cycloaddition between oxime glyoxylate and cyclopentadiene[40]

Reaction yielded a mixture of the *exo*/*endo* formally [4+2] aza-DA azanorbornene cycloadducts **27** and **28**, together with the product of [3+2] dipolar cycloaddition **29** which was found the major product regardless of the conditions. The relative yields and diastereoselectivity were found to be more dependent on the catalyst rather than on the temperature. Later on, further investigations concerning the influence of various parameters of the mechanism for the formation of both 1,3- and 1,4-cycloadducts were performed by the same authors (Scheme 14).[41] The major impact on the course of the reaction and ratio of the *exo*/*endo* products had the type of catalyst, which may coordinate to the oxygen or the nitrogen atoms in oxime and should allow a competition between 1,3- and 1,4-cycloadditions. The best overall yields of 2-azanorbornenes **27** and **28** were obtained with TFA as catalyst, while the use of $BF_3 \cdot OEt_2$ yielded selectively the isoxazolidine **29**.



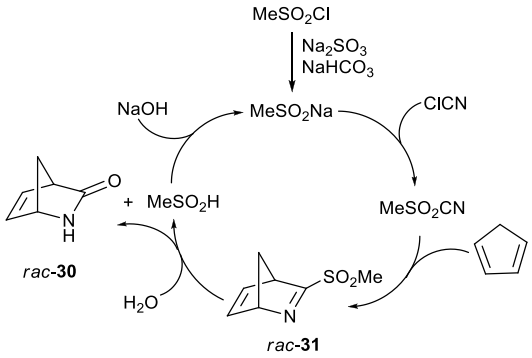
Scheme 14. Proposed mechanism for the cycloaddition of cyclopentadiene to oxime glyoxylate.[41]

The same authors also studied the use of chiral auxiliaries in the cycloaddition reaction between stereoisomeric of 8-phenylmenthyl and 8-phenylneomenthyl glyoxylate oximes and cyclopentadiene.[42] The results revealed that the 1,3-cycloaddition is preferred over the 1,4-process. Since the overall yields were moderate (32-40%), the stereoselectivity of the formation of the minor Diels-Alder cycloadducts was not established.

In a quest for an efficient route to 2-azabicyclo[2.2.1]hepten-3-one (Vince lactam **30**, a versatile synthetic building block for carbocyclic nucleoside analogues[43]), alternatives to the classical method based on cycloaddition of tosyl cyanide with cyclopentadiene[44] have been developed. An interesting aza-DA reaction was reported by Griffiths and co-workers who used methanesulfonyl cyanide as an aza-dienophile in the reaction with 20% excess of

cyclopentadiene at room temperature forming *in situ* the cycloaddition product **31**. Subsequent treatment with water resulted in formation of the desired 2-azanorbornene derivative **30** in up to 90% yield (Scheme 15).[45] One-pot procedure, involving regeneration of cyanide, was scaled up to give ca. 100 g/L of reactor volume of **30**.

Also chlorosulfonyl isocyanate was used as aza-dienophile in aza-DA reaction as described by Malpass and Tweedle; the procedure was improved in Vince's group by changing the reaction conditions to suppress the formation of β-lactam in favor of the desired γ-lactam **30**.[46] Attempts to obtain Vince lactam in enantiomerically pure form using menthylsulfonyl cyanides or chiral catalysts were moderately efficient; the highest *ee* reported (25.6%) was obtained for a reaction catalyzed by a chiral aluminum complex; instead, resolution of racemic compound **30** and its derivatives *via* enzymatic kinetic resolution with various biocatalysts was found as the most convenient method.[43]

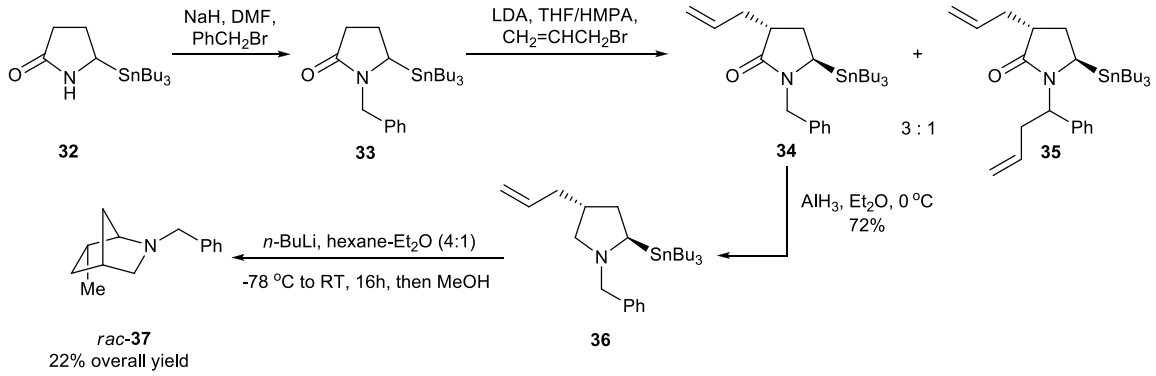


Scheme 15. Synthesis of Vince lactam **30**[45]

2.2. Synthesis of 2-azanorbornyl derivatives using multistep protocols

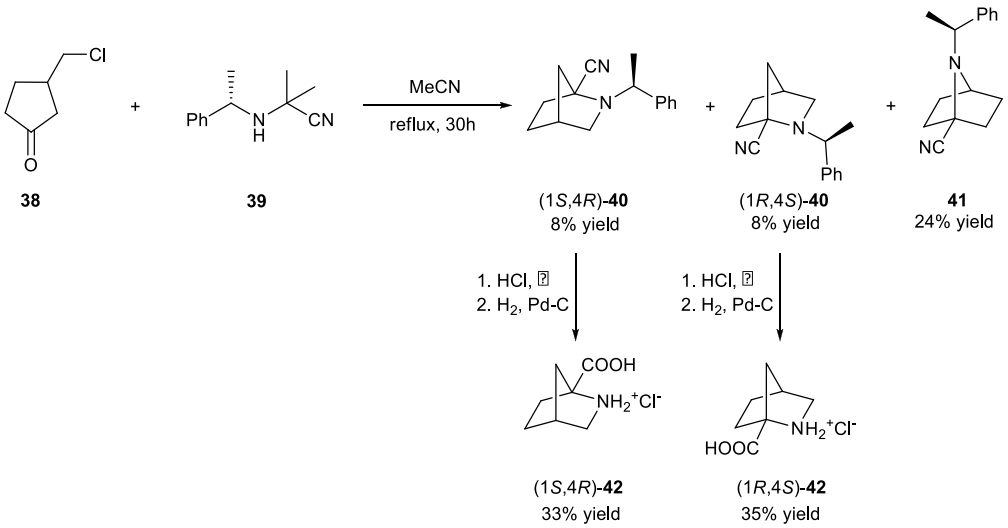
Apart from the very efficient aza-DA protocols leading to 2-azanorbornyl derivatives also other methods for the synthesis of these compounds have been reported in the literature. These procedures usually rely on a multistep reaction sequences. Coldham *et al.* reported on a synthesis of 2-azanorbornane derivative **37** (Scheme 16) using a tin-lithium exchange and anionic cyclization (carbolithiation) as the final step.[47] The lactam **32**, used as the starting material, was first *N*-alkylated and then allylated to yield a 3:1 mixture of products **34** and **35** separable by column chromatography. Subsequently, the isolated *trans*-**34** was decarbonylated to give intermediate **36** that was further reacted with *n*BuLi at -78°C to form the 2-azanorbornane derivative **37** in 22% overall yield. The diastereoselectivity of cyclization (only *endo* isomer was observed) was explained by a favored formation of boat-

shaped transition state. The intramolecular carbolithiation was also applied to the synthesis of 1- and 7-azanorbornane systems.



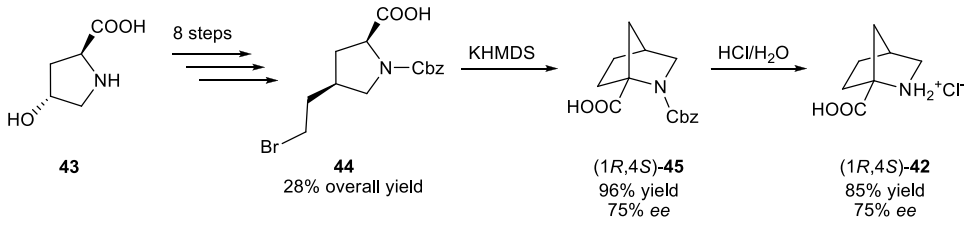
Scheme 16. Preparation of 2-azanorbornane derivative *endo*-**37**[47]

The synthesis of racemic derivatives of 2-azanorbornane starting from 1,2-substituted pyrrole was described by Zanardi *et al.*, with aldol carbocyclization as a decisive step for the diastereoselective formation of a bicyclic skeleton.[48] Enantioselective preparation of 2-azanorbornanes made use of enantiopure starting materials. Grygorenko and co-workers proposed a novel synthetic route to both enantiomers of 2-azabicyclo[2.2.1]heptane-1-carboxylic acid **42**, a rigid bicyclic proline analogue, based on a tandem cyanide addition-intramolecular cyclization.[49] In their approach chloromethylcyclopentanone **38** and nitrile **39** were reacted in refluxing acetonitrile for 30 h and led to a mixture of bicyclic products **40**, **41** in 40% overall yield (Scheme 17). Subsequent transformations of isomers of **40** led to the desired products **42** (in the form of hydrochlorides) in only 2% overall yield.



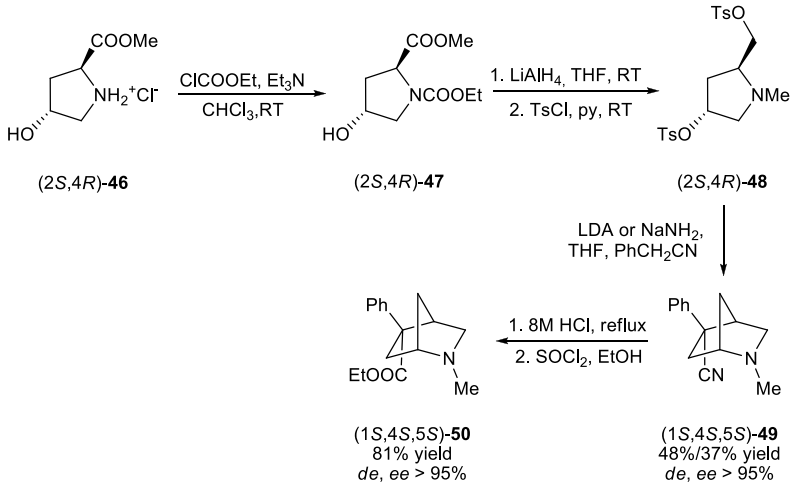
Scheme 17. Synthesis of azanorbornane derivatives **42**[49]

Later on Grygorenko *et al.* reported on an improved approach to 2-azabicyclo[2.2.1]heptane-1-carboxylic acid **42** involving a multistep reaction sequence starting from the optically pure *trans*-4-hydroxy-L-proline **43** and yielding the desired compound **42** in 22% total yield and 75% *ee* (Scheme 18). In a key step, cyclization of **44** derivative promoted by KHMDS allowed obtaining the azanorbornane derivative **45** which was hydrolyzed to give hydrochloride **42**.[50]



Scheme 18. Synthesis of bicyclic proline derivative **42**[50]

Another application of proline derivative for the stereoselective preparation of 2-azanorbornane system was reported by Husbands an co-workers who prepared the compound **50** (Scheme 19),[51] new analogue of meperidine, μ-opioid agonist that displays psychostimulant effect.[52] *trans*-L-Hydroxyproline methyl ester **46**, easily prepared from commercially available *trans*-L-hydroxyproline, was converted to ethyl carbamate **47** which was than subjected to reduction with lithium aluminum hydride followed by tosylation of the formed diol, yielding compound **48** (18% overall yield).



Scheme 19. Multistep preparation of 2-azanorbornane derivative **50**[51]

The key step in the synthesis was the alkylation of **48** with phenylacetonitrile anion using LDA (48% yield) or $NaNH_2$ (37% yield) as a base. Interestingly, alkylations resulted in

selective formation of a single diastereomer. Finally, hydrolysis of **49** followed by esterification, gave the desired conformationally restricted *exo*-phenyl derivative **50**.

2.3. Summary

Aza-Diels-Alder reaction of cyclopentadiene and chiral imines, presented in part 2.1.1, followed by double bond hydrogenation, remains the most convenient route to enantiomerically pure 2-azanorbornanes. The success of this approach is connected with the high optical purity of the product (with both enantiomers available) connected with a considerable diastereoselectivity (the major *exo* diastereomer can be easily isolated from the minor cycloadducts), and possibility to scale up. However, for derivatives with the unique substitution pattern (for example, those substituted in 1- or/and 4-position) protocols utilizing bridge formation in the respective 5-membered pyrrolidine or cyclopentane ring (to the best of our knowledge, six-membered piperidine ring has not been used as the synthetic precursor), though in general associated with lower overall yields, should be also taken into account. Interestingly, 2-azabicyclo[2.2.1]heptanes were identified as attractive substrates in the stereoselective syntheses of these monocyclic systems exhibiting substantial biological activity, as described in sections 3 and 5 of this review.

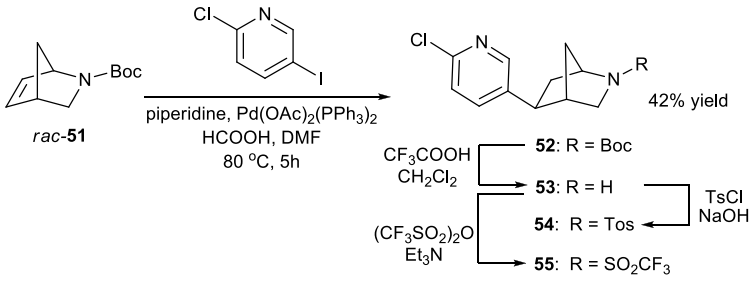
3. 2-Azanorbornyl derivatives as building blocks in the synthesis

As it was shown in previous part, the 2-azabicyclo[2.2.1]heptanes are generally easily synthetically available and can be prepared in both enantiomeric forms from inexpensive starting materials, even at a kilogram scale. This in combination with the fact that these simple bicyclic systems offer a wide range of possible modifications, including those in which additional stereogenic centers are created, made the 2-azanorbornyl derivatives a versatile platform for the synthesis of various compounds, which have already found a number of applications in medicinal chemistry and catalysis.

From the variety of transformations of 2-azabicyclo[2.2.1]heptanes we have selected examples of stereoselective reactions in which high asymmetric induction from the bicyclic system have been observed: substitution or modification of existing substituents, and ring opening (leading to valuable monocyclic products) or its expansion. Thus, the numerous, sometimes very sophisticated changes in substitution pattern will not be discussed if they are not associated with alteration of stereochemistry of the substrate.

3.1. Reactions retaining the 2-azanorbornyl scaffold

Several research groups concentrated on the selective introduction of various substituents into the 2-azanobornane skeleton. The presence of a double bond in the product of aza-DA reaction, 2-azabicyclo[2.2.1]heptene, allows additions which typically lead mainly to *exo* stereoisomers. In particular, arylation procedures of 5- or 6-position were described. Kasyan and co-workers prepared analogues of alkaloid epibatidine modified in the bicyclic ring.[53] The Boc-protected substrate **51** was subjected to the reductive Heck coupling reaction with aryl iodide under typical conditions, which allowed obtaining the corresponding 5-aryl-2-azabicyclo[2.2.1]heptane derivatives in a regio- and stereospecific manner (Scheme 20). The Boc group was removed under acidic conditions to provide the amine **53**, followed by treatment with tosyl chloride in the presence of sodium hydroxide, or trifluoromethanesulfonic anhydride and triethylamine which furnished the corresponding crystalline derivatives **54** and **55** as single 5-*exo* isomers. In contrast, Pd-catalyzed hydroarylation reaction of Vince lactam **30** with a series of electron rich and electron poor aryl/heteroaryl iodides afforded mixtures of 5- and 6-substituted isomers in moderate to good yields (59-98%).[54] Also rhodium-catalyzed arylation of Vince lactam derivatives using arylboronic acids under microwave radiation yielded a mixture of 5-*exo*- and 6-*exo*-regioisomers,[55] while *N*-substitution of **30** was achieved with copper catalyst,[56] as described by Ishikura and coworkers.

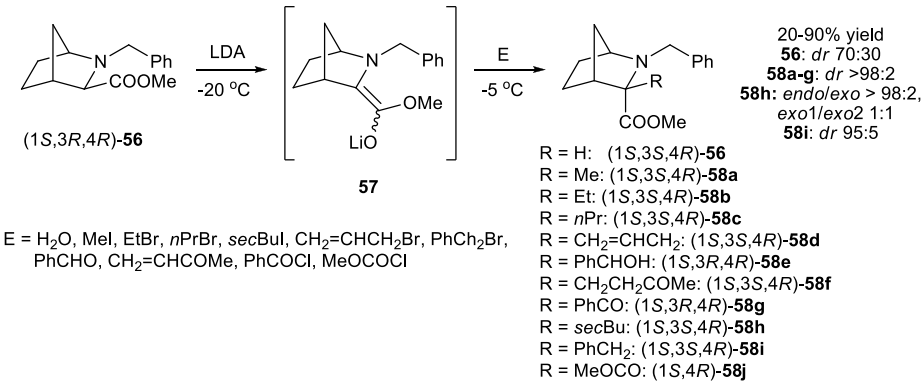


Scheme 20. 2-Azanorbornene derivative **51** as a building block in the synthesis of epibatidine analogues[53]

Oxidations of double bond of 2-azanorbonene leading to 5,6-disubstituted derivatives were also described. Dihydroxylation with osmium tetroxide and *N*-methylmorpholine *N*-oxide, $K_2OsO_2(OH)_4/K_2CO_3/K_3[Fe(CN)_6]$ system or $KMnO_4$ in aqueous KOH led to *exo* vicinal diols.[57] An efficient epoxidation of Vince lactam **30** was performed with oxone in water at pH = 6, and *exo* isomer of epoxide was selectively obtained in 80% yield.[58] Dioxalane-appended derivatives, which were obtained via the protection of diols with a

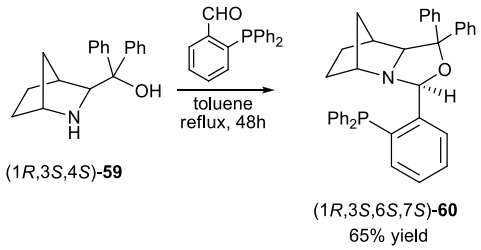
ketone or a corresponding dimethyl ketal, were found effective as chiral ligands in the ruthenium-catalyzed transfer hydrogenation of ketones (see part 4.4).[57a,59]

Andersson's group reported on a diastereoselective synthesis of various 3,3-disubstituted 2-azanorbornane derivatives *via* the reaction of exocyclic enolate **57** with various electrophiles (Scheme 21).[60] In the case of treatment of enolate **57** with water as electrophile a 70:30 mixture of *endo/exo* diastereoisomers was obtained due to the protonation from the less hindered *exo* face of the enolate, yielding epimer of starting compound **56**. However, enolate reacted with high diastereoselectivity with other electrophiles to afford the bicyclic products **58**. For all cases the obtained regio- and chemoselectivity were high (95->98%) albeit reactions with both secondary halides and *α,β*-unsaturated ketone led to much lower yields, 40 and 20% respectively.



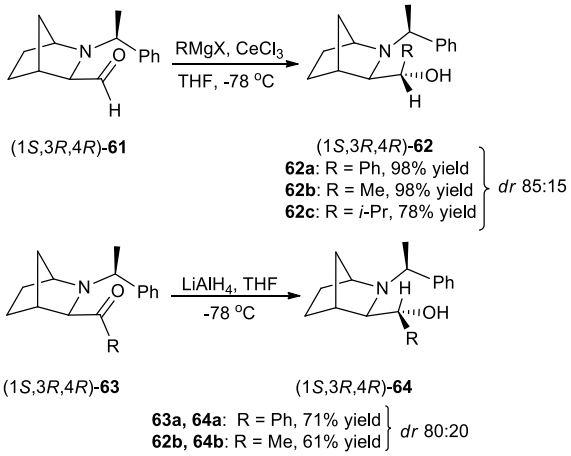
Scheme 21. Reaction of enolate **57** with electrophiles[60]

In a different approach to introduce additional donor atoms to the structure of 2-azabicyclo[2.2.1]heptane, the derivative **59** was used by Okuyama and co-workers to prepare a new 2-azanorbornane-based phosphinooxazolidine chiral ligand **60**, as an analogue of the known chiral phosphinooxazolidine, very effective in palladium-catalyzed asymmetric allylation reaction.[61] The reaction of **59** with 2-(diphenylphosphino)benzaldehyde in refluxing toluene furnishing the desired compound **60** as a single diastereomer in 65% yield (Scheme 22). Other oxazolidine-fused enantiopure 2-azanorbornanes prepared by the same research group were used as chiral ligands in the enantioselective diethylzinc addition to aldehydes.[62]



Scheme 22. Preparation of 2-azanorbornane-based phosphinooxazolidine chiral ligand **60**[61]

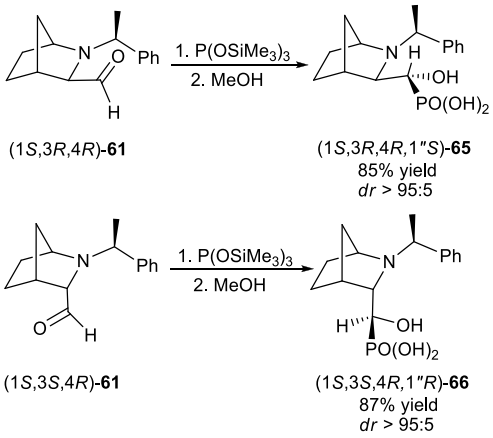
Stereoselective conversions of substituents attached to the chiral 2-azanorbornane scaffold have been also reported. Andersson's group described a preparation of secondary alcohols containing additional stereocenters, useful in the enantioselective addition of dialkylzinc to imines.[63,64] (*S*)-Epimers were obtained from aldehyde **61** (prepared by Swern oxidation of the respective primary alcohol) in the reaction with Grignard reagents in the presence of cerium(III) chloride (Scheme 23). Two products were formed in 85:15 ratio, and the major isomer was isolated by flash chromatography. The selectivity of the reaction was explained by the preferential approach of the nucleophile from the less hindered side of the substrate.[63] (*R*)-Epimers were prepared in the diastereoselective reduction of ketone **63** with lithium aluminum hydride, with slightly lower yields and selectivity (*dr* = 80:20).[63] Pfaltz and coworkers described an analogous reaction of two enantiomers of aldehyde **61** with 1-naphthylmagnesium bromide which provided the corresponding alcohols as single diastereomers.[65]



Scheme 23. Preparation of secondary alcohols based on 2-azanorbornane scaffold[63]

Higher asymmetric induction was observed in our laboratory in the hydrophosphonylation of aldehyde **61** with silylated phosphorus esters leading to α-hydroxyphosphonic acid derivatives of 2-azanorbornane.[66] When *exo*-aldehyde furnished

exclusively the (*S*)-α-hydroxyphosphonic acid **65**, the use of aldehyde *endo*-**61** epimer yielded the isomer with the opposite configuration of the newly created stereogenic center **66**. (Scheme 24).

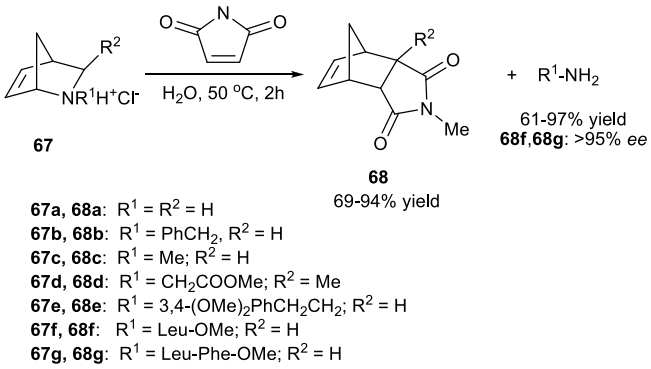


Scheme 24. Synthesis of α-hydroxyphosphonic acids attached to a 2-azanorbornane[66]

3.2. Modification of the 2-azanorbornyl skeleton

Another group of transformations of the 2-azanorbornene and 2-azanorbornane derivatives include the alteration of the bicyclic skeleton: ring opening leading to derivatives of cyclopentane or pyrrolidine and conversion to other bicyclic scaffolds. Many of these products, often obtained with high enantioselectivity, found various applications in asymmetric synthesis as chiral ligands or precursors of biologically active compounds.[38,43] Part of target compounds will be shown in Section 5 of this review. In this part, selected examples of above mentioned transformations will be presented.

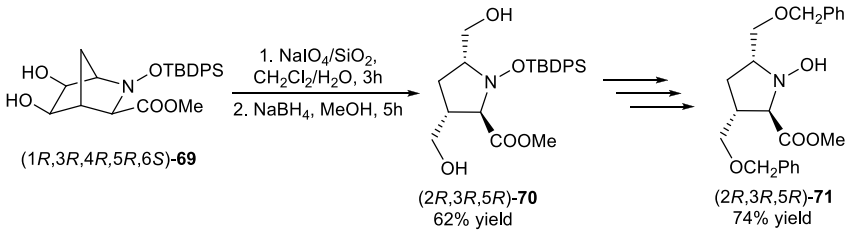
In the earliest works on this topic and inspired by previously performed studies on reaction of cyclopentadiene with *C*–acyl iminium ions,[14] Grieco *et al.* observed that the 2-azanorbonene hydrochloride and its *N*-alkyl derivatives **67** underwent a retro-DA reaction at 50 ^{o}C or even at room temperature in the presence of *N*-methylmaleimide (used as a trapping agent for cyclopentadiene), affording the chiral primary amines without any racemization (Scheme 25).[67] High conversion rates and yields were observed when the process was carried out in aqueous solution; quaternary ammonium salts were suggested as intermediates in the reaction.



Scheme 25. Retro-DA reaction as a tool in the synthesis of chiral primary amines from 2-azanorbornenes[67]

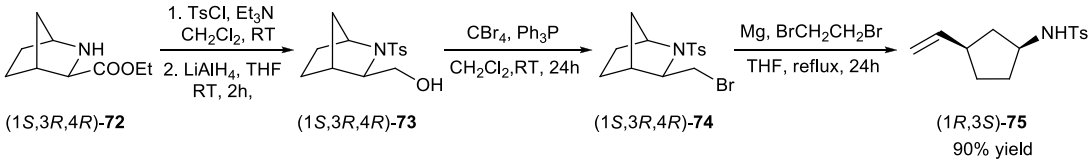
Other reagents such as copper sulfate ($CuSO_4$) or sulfonic acid based ion exchange resins were also tested with success in this reaction.[68] The methodology was used for preparation of N-methylated amino acids, di- and tripeptides: the iminium ion species generated during the retro-DA reaction of the appropriate 2-substituted-2-azanorbornene derivative in 1:1 chloroform/trifluoroacetic acid mixture, treated with triethylsilane at room temperature yielded the desired enantiopure products in just 0.5-2 h reaction time in good yields.[51]

Synthesis of pyrrolidine derivatives is typically achieved by C_5-C_6 bond cleavage of the appropriately substituted bicyclic system. As a continuation of previously performed work,[40] Rodríguez-Borges and coworkers used the 2-azanorbornene derivatives including **27** and **56** as the starting materials in the synthesis of polyhydroxypyrrolidines and their selective functionalization.[70,71] The dihydroxylated bicyclic compounds were converted to monocyclic products using the oxidative cleavage with sodium periodate and *in* situ reduction of the obtained aldehydes, as exemplified in Scheme 26. The obtained results showed the efficiency of the applied methodology, allowing selective introduction of functional groups into polyhydroxypyrrolidine analogues.



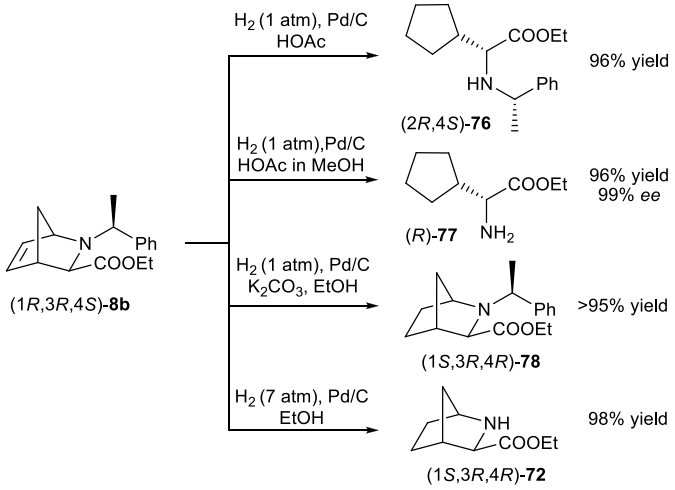
Scheme 26. Application of dihydroxylated 2-azanorbornene derivative **69** in the synthesis of functionalized pyrrolidines[70]

Formation of cyclopentane ring requires C-N (C_1-N or C_3-N) or (less probable) C_3-C_4 bond cleavage of the 2-azabicyclo[2.2.1]heptane. Andersson *et al.* used the 2-azanorbornane derivative **72** as the starting material in the synthesis of cyclopentylamine **75**, molecule of high importance for medicinal chemistry.[57a] After protection of the nitrogen atom with tosyl group, the ester moiety was reduced to form the alcohol **73** which was transformed to the bromide derivative **74**. Ring opening was achieved by treatment of **74** with magnesium in refluxing tetrahydrofuran. The reaction was facilitated by the presence of the electron-withdrawing tosyl group, and the desired amine **75** was formed in 90% yield (Scheme 27). The protocol was successfully applied to the synthesis of cyclopentylamine and cyclohexylamine bearing ketal functionality.[57a]



Scheme 27. Preparation of cyclopentylamine **75**[57a]

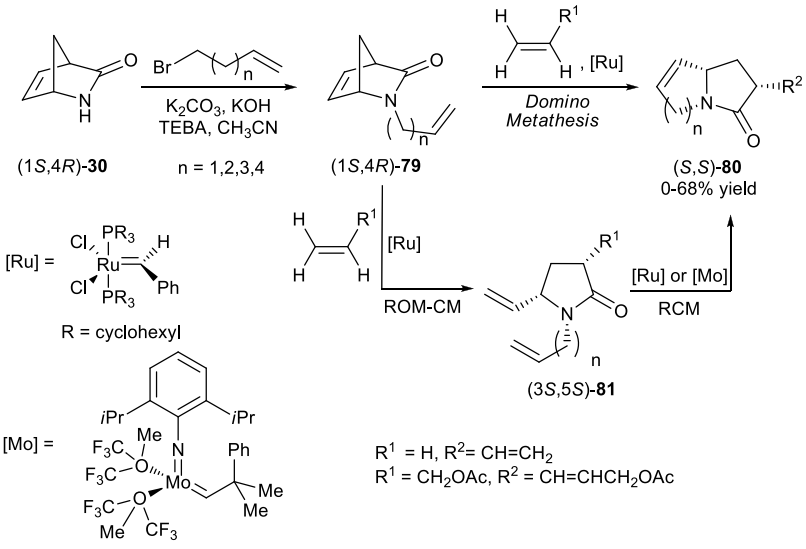
The same group reported also on the synthesis of four types of α-amino acid derivatives using one azabicyclic substrate **8b** as chiral building block under different reductive reaction conditions (Scheme 28).[72]



Scheme 28. Synthesis of α-amino acid derivatives from 2-azanorbornene substrate **8b** as chiral building block[72]

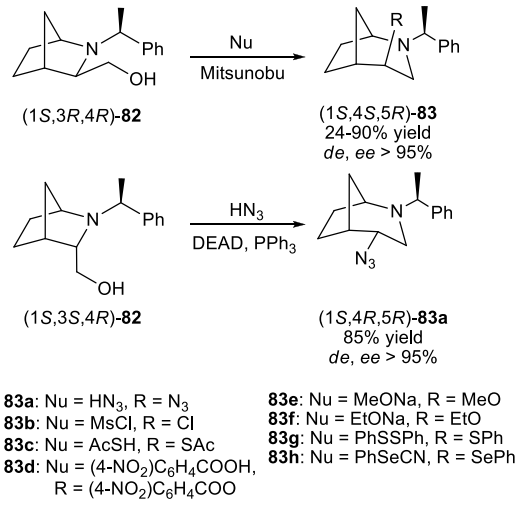
Additionally, authors demonstrated that the obtained optically pure amino ester (*R*)-**77** could be easily transformed into the corresponding amino alcohol, and further into valuable chiral auxiliaries with potential for use in asymmetric synthesis.

2-Azanorbornanes and 2-azanorbornenes can be also converted into other bicyclic compounds. Arjona *et al.* described an application of 2-azanorbornene derivative **30** in the enantioselective synthesis of the azabicyclic γ-lactams **80** (Scheme 29).[73] The synthetic pathway was based on the *N*-alkylation of **30** in the first step, and followed by a domino olefin metathesis. The procedure allowed the preparation of optically pure 1-azabicyclic alkaloids **80** with different ring size. Usually, derivatives **79** underwent the metathesis smoothly, but in some cases the 2-azanorbornene derivatives did not cyclize and the products of ring-opening – cross metathesis (ROM-CM) **81** were obtained, but they could be converted into the desired azabicyclic γ-lactams by the independent ring-closure metathesis (RCM).



Scheme 29. Synthesis of 1-azabicyclic alkaloids **80** with the use of Vince lactam **30** as a building block[73]

Bailey *et al.* demonstrated the formation of two isomeric oxaazabicyclooctanes as a result of the brief treatment of 2-azanorbornene derivative **8b** with *m*-chloroperbenzoic acid (*m*CPBA).[74] Ring expansion of 2-aza[2.2.1]heptane was also observed in our laboratory. A nucleophilic substitution of 2-azanorbornane-3-yl methanol **82** under Mitsunobu conditions or with the use of mesyl chloride resulted in conversion into derivatives containing a seven-membered ring.[75] The synthetic method was found versatile, and bridged chiral azepanes (2-azabicyclo[3.2.1]octanes) **83** bearing various functional groups could be prepared, including azide, sulfide, selenide, esters, ethers and chloride (Scheme 30).



Scheme 30. Synthesis of bridged azepanes **83** from 2-azanorbornane building block[75]

Ring expansion reaction was stereoselective: in each case alcohol (1*S*,3*R*,4*R*)-**82** (*exo*) was converted to a product with (1*S*,4*S*,5*R*) configuration. The process proceeds also in a stereospecific manner: when alcohol (1*S*,3*S*,4*R*)-**82** (*endo*) was used as substrate, azide **83a** with an opposite configuration on C-4 was formed as compared to the product obtained from *exo*-isomer (Scheme 30).

2-Azabicycloalkanes were also used as key intermediates in the synthesis of variously substituted diazabicycloalkanes with defined (and diverse) stereochemistry.[57b] A number of other target structures available from 2-azabicyclo[2.2.1]heptene illustrate the versatility of this unsaturated heterocyclic precursor.

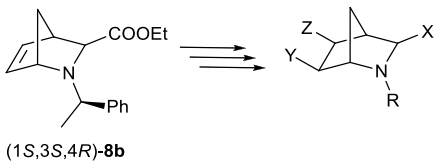
4. Catalytic applications of chiral 2-azanorbornane derivatives

4.1. Introduction

The successful stereoselective synthesis of 2-azabicyclo[2.2.1]heptene almost immediately arose an interest in possible application of this compound and its derivatives as ligands in asymmetric synthesis. A cycloadduct obtained in the course of aza-Diels-Alder reaction contains a rigid bicyclic skeleton bearing a nitrogen donor (a tertiary amine which can be converted to a secondary one by the reductive removal of the original substituent derived from aza-dienophile used), a substituent in the 3 position and a double bond which are three places of possible modifications (Scheme 31), as described in the previous chapter. All changes of the electronic or steric properties of chiral ligands allow the adjustment of their coordination properties, and, as a consequence, the activity and stereocontrol in the catalytic

reactions. The controlled tuning of basicity of donors and possibility of hydrogen bond formation are of special importance for the potential organocatalytic applications.

In addition, the basic bicyclic compound is easily synthetically available in both enantiomeric forms. The relatively underexplored possibility of application of the minor *endo* diastereomer formed in the aza-DA reaction is also worth mentioning. Modifications of the 2-azanorbornane scaffold may involve ring opening or ring expansion as well.



(1*S*,3*S*,4*R*)-**8b**

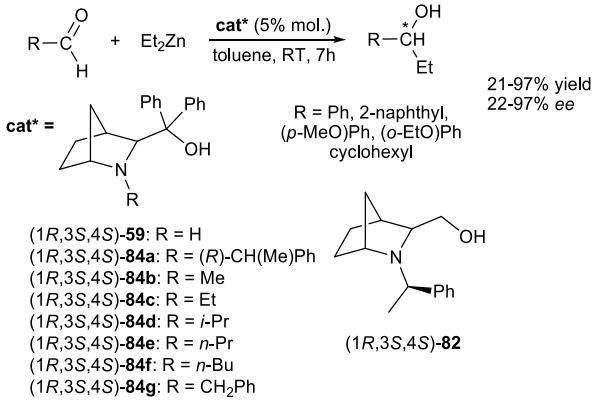
Scheme 31. A general scheme of possible transformations of aza-DA cycloadduct (exemplified by one of isomers of **8b**) as a route to the family of chiral ligands

A large family of chiral ligands based on 2-azabicyclo[2.2.1]heptane has been prepared and used with a success in diverse asymmetric transformations. The majority of contributions in the field come from the group led by Pher G. Andersson. A review by Brandt and Andersson published in 2000 showed the variety of possible catalytic applications of these bicyclic compounds.[76] Since that time, a substantial development has been observed, in particular 2-azanorbornane derivatives bearing phosphine and oxazoline or thiazole substituents were found efficient in the iridium-catalyzed hydrogenation of various substrates containing C=C or C=N bond. In this chapter, we shall focus on the new achievements though comparisons to the older results will be made as well.

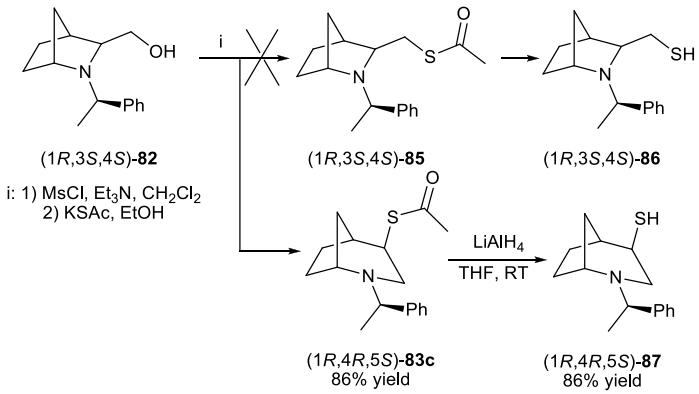
4.2. Enantioselective addition of diethylzinc to aldehydes and other organocatalytic transformations

2-Azanorbornanes have proved to be very potent catalysts for asymmetric addition of dialkylzinc to aldehydes. The importance of this reaction is connected with its synthetic utility since it yields chiral secondary alcohols, useful building blocks for asymmetric synthesis.[77] As β-amino alcohols were previously reported to be extremely efficient catalysts in this reaction,[78] Nakano *et al.* prepared a series of 2-azanorbornene derivatives containing a tertiary alcohol fragment in the desired position with respect to the nitrogen atom.[79,80] These derivatives **59**, **84a-g** and the primary alcohol **82** were used as catalysts in the enantioselective addition of diethylzinc to various aldehydes (Scheme 32). For most derivatives (*S*)-alcohols

were formed preferentially with *ee* values in the range of 28-92% and 20-97% yield; only **59** and **82** led mainly to (*R*) product, albeit with low stereoselectivity (36% and 22% *ee* for the addition to benzaldehyde, respectively). The *N*-methylated ligand **84b** was found the most effective (65-97% yield and 73-92% *ee* for aryl aldehydes). Even better results were obtained for the thiol derivative, but the analysis of the synthetic route reveals that in fact this compound has in fact a bridged azepane structure **87** instead of expected **86** (Scheme 33). Similar rearrangement upon formation a thioacetate (enantiomer of **83c**) was observed in our investigations on ring expansion 2-azanorbornane derivatives (chapter 3.2).[75]



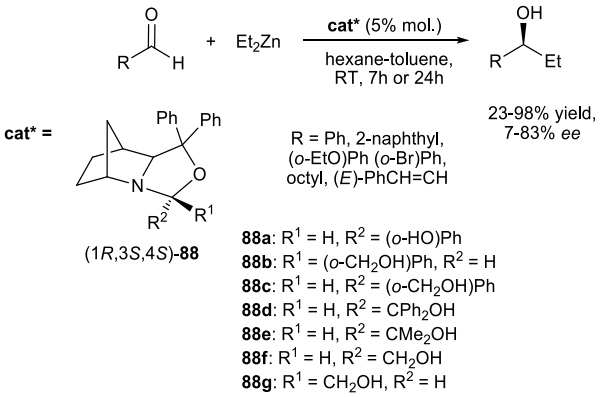
Scheme 32. Enantioselective diethylzinc addition to aldehydes catalyzed by 2-azanorbornyl-3-methanols[79,80]



Scheme 33. Ring expansion upon introduction of thioacetate moiety[75,80]

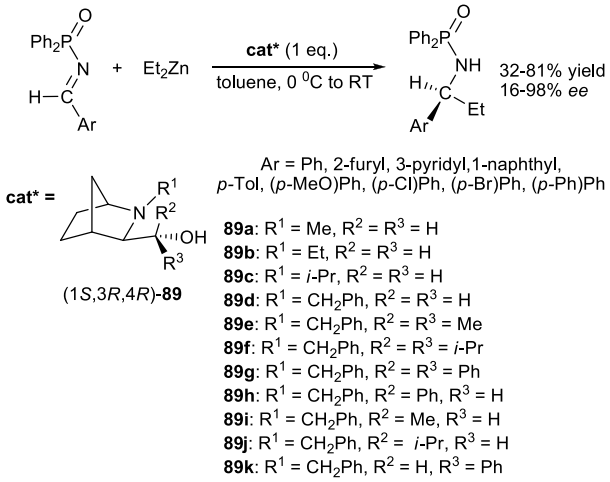
Nakano and coworkers published two articles on the application of oxazolidines fused to the chiral 2-azanorbornanyl scaffold in the enantioselective diethylzinc addition to aldehydes (Scheme 34).[62] Among chiral ligands **88a-g** tested in the conversion of benzaldehyde, the use of compound **88f** was accompanied with the highest yield (89%) and

enantiomeric excess (83%). For other substrates, the reported enantioselectivity was rather medium or low (24-63% *ee*).



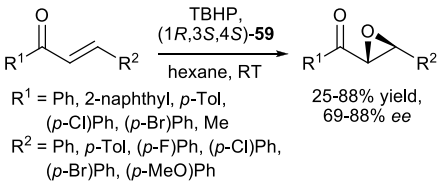
Scheme 34. Enantioselective addition of diethylzinc to aldehydes catalyzed by fused oxazoline derivatives[62]

Andersson's group concentrated on the application of alcohols derived from 2-azanorbornane in the enantioselective addition of dialkylzinc to imines.[63,64,81] The series of 2-azanorbornyl-3-methanols **89a-k**, including primary, secondary and tertiary alcohols were prepared bearing various substituents on the hydroxylated carbon atom. Using the addition of Et_2Zn to *N*-(diphenylphosphinoyl)benzaldimine as a model reaction, ligand **89h** bearing an additional stereogenic center was selected as an optimal inducer of chirality (Scheme 35).[81] The observed tendencies of the stereochemical outcome were substantiated by theoretical calculations.[63] Toluene and chlorobenzene were identified as the most suitable solvents for the reaction, allowing preparation of various phosphinoyl imines in 65-91% yield and 87-98% *ee*.[64] The high enantioselectivity was only noted when stoichiometric amounts of the chiral inducer were used. For example, when 10 mol% of ligand **89d** was applied, the *ee* dropped significantly (from 91% to 68%), and the yield lowered from 63% to 38%.[81] However, the catalyst could be recovered from the reaction and reused without significant loss of stereoselectivity.

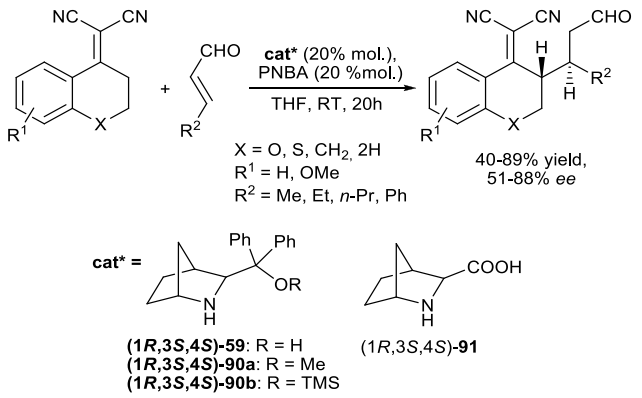


Scheme 35. Enantioselective addition of diethylzinc to imines.[63,64,81]

Chiral (1*R*,3*S*,4*S*)-2-azanorbornyl-3-methanol **59** was also used by Loh and coworkers as catalyst for enantioselective epoxidation of α,β-enones (Scheme 36).[82] For the optimal reaction conditions (20 mol% of catalyst, hexane used as solvent, room temperature, 6 days) results of *trans*-chalcone were found promising (81% yield and 88% *ee*), and for the most of substrates tested enantioselectivity was also high (*ee* for aryl-substituted ketones were in the range of 80-88%). The structure of catalyst was not optimized in that study. The same group applied alcohol **59** and its derivatives **84a**, **90a-b** as well as carboxylic acid **91** as chirality inducers for the stereoselective Michael addition of vinyl malononitriles to α,β-unsaturated aldehydes (Scheme 37).[83] *N*-Substituted alcohol **84a** was completely ineffective, while compound **59**, used in 20 mol% load, led to the highest yield and enantioselectivity. THF solvent and *p*-nitrobenzoic acid as an additive were found beneficial for the good reaction outcome. Various maleonitriles were reacted with crotonaldehyde in 41-86% isolated yield and 71-91% *ee* which was in several cases increased up to >99% by recrystallization from 2-propanol.



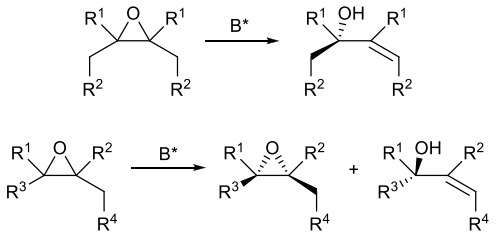
Scheme 36. Enantioselective epoxidation of enones[82]



Scheme 37. Organocatalytic stereoselective vinylogous Michael addition[83]

4.3. Rearrangement of epoxides to allylic alcohols

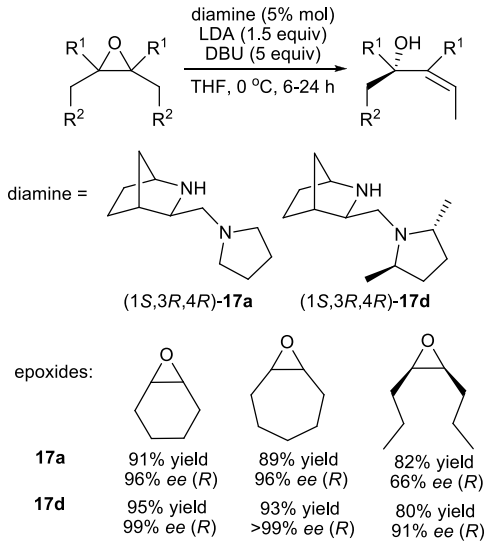
Andersson's group exhibited also an interest in the desymmetrization of *meso*-epoxides or chiral, racemic epoxides *via* their rearrangement to the isomeric allylic alcohols (Scheme 38). In the second case, also nonracemic chiral epoxides can be isolated due to the kinetic resolution if the reaction is stopped before complete conversion. The resulting chiral allylic alcohols are regarded as useful precursors in the synthesis of the number of biologically active compounds.[84]



Scheme 38. Base-mediated desymmetrization of epoxides

The enantioselective variant of the reaction has been developed in which the rearrangement has been mediated by a chiral base (typically a lithium amide), in many cases used in superstoichiometric amounts (1.5-3.0 equivalents), and the substrate scope has been rather limited.[85] In their quest for a versatile, stereoselective system allowing the use of much lower catalyst loadings, Andersson and coworkers developed a new protocol, based on 2-azanorbornyl diamines (2-azabicyclo[2.2.1]heptane derivatives bearing a cyclic amine substituent).[30,86-88] These compounds are available in both enantiomeric forms, which opened the possibility of preparation of the desired isomer of the chiral allylic alcohol.[29,30] Both the structure of the catalyst and reaction conditions were optimized. Evaluation of the chiral 2-azanorbornyl derivatives resulted in the identification of pyrrolidine derivatives: **17a**, and, in

particular, a dimethylated **17d** as the optimal chiral bases, prevailing the ones containing piperidine or benzopyrrolidine substituent. Tetrahydrofuran was recognized as the best solvent, and DBU additive showed the beneficial influence on the stereochemical outcome of the reaction by preventing aggregation of lithium amides. Only 5% of the chiral catalyst in the presence of 1.5-2 equivalents of LDA was found sufficient for the stereoselective conversion of various *meso*-epoxides with *ee* values in most cases ≥94% (**17a**) and even 98-99% (**17d**).[30,86] Several examples of substrates and the results of catalytic reaction are shown in Scheme 39, and the remaining tested diamines **17** are depicted in Figure 4.



Scheme 39. Comparison of the efficiency of two chiral diamines in the rearrangement of *meso*-epoxides[86]

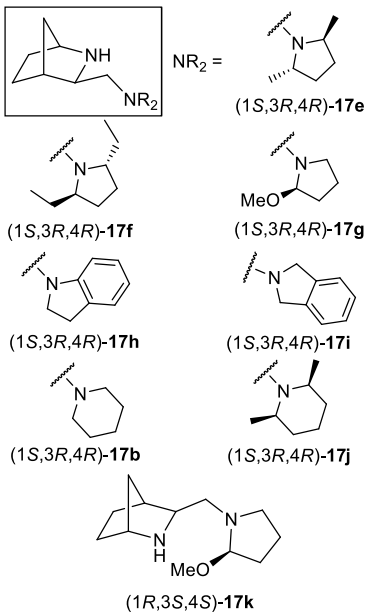
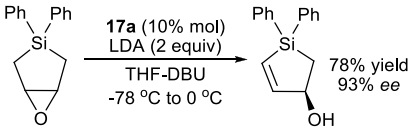


Figure 4. Structure of diamines tested in the desymmetrization of epoxides[30,86]

Since LDA-mediated background reaction can be responsible for the lowering of stereoselectivity of epoxide rearrangement, Bertilsson and Andersson tested other achiral bases in the catalytic process with diamine **17a** as the chirality source.[89] No satisfactory replacement for LDA was found, however, a great improvement of *ee*s was achieved by slow addition of the stoichiometric base and thus maintaining its low concentration during the reaction.

The proposed reaction mechanism was confirmed by theoretical calculations performed by Brandt *et al*.[90] A possible dimerization of lithium amides derived from pyrrolidine-substituted 2-azanorbornanes in the absence of DBU-cosolvent was taken into account. It was shown that dimers are likely to form and are inactive in the catalytic reaction. A correct prediction of the enantioselectivity was achieved and allowed explanation of differences between catalytic and stoichiometric mode for investigated ligands. The non-stereospecific background reaction was suggested to account for the observed variation of selectivity.

The methodology and catalysts developed by Andersson and co-workers were successfully used by Liu and Kozmin for desymmetrization of *meso*-silane oxide (Scheme 40).[91] A bicyclic amine **17a** was selected as an optimal chirality source, and 10 mol% loading and addition of 2 equivalents of LDA resulted in allylic alcohol obtained in 78% yield and 93% *ee*. This compound was further used for the synthesis of several polyols with a complete diastereoselectivity.[91] The silacyclic allylic alcohol and its enantiomer available from the enantioselective desymmetrization of epoxide were also applied as key precursors in the synthesis of (-)-pinolidoxin, a potent modulator of plant pathogenesis.[92]



Scheme 40. Desymmetrization of silacyclopentene oxide[91]

Pyrrolidine derivatives of 2-azanorbornane were also found effective in the kinetic resolution of racemic epoxides by a selective rearrangement of one of the enantiomers to an allylic alcohol.[30a,87,88] When the reaction was stopped shortly before or after reaching 50% conversion, both chiral epoxides and alcohols were isolated in up to 99% *ee*. Reactions were performed in THF at 0 °C using an excess of LDA (1.2-2 equivalents) and DBU (5 equivalents). Amine **17a** (10 mol%) exhibited a limited substrate scope, yielding high

stereoselectivity for *cis*-β-methylstyrene oxide, and 1-alkyl- or 2,2-disubstituted cyclohexene oxides, while epoxides having other substitution patterns either did not react nor led to racemates.[87] An improvement of the stereochemical outcomes and extending of the reaction scope was made possible when **17a** was replaced by its dimethylated derivative **17d** (used in 5 mol%), though in most cases *ee* was rarely high for both the epoxide and allylic alcohol.[88]

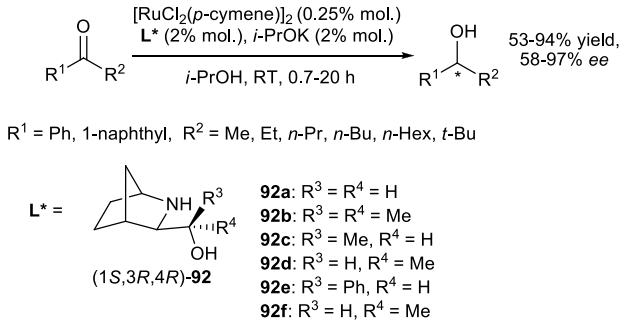
4.4. Asymmetric reduction of ketones

Enantioselective reduction of asymmetrical ketones yielding chiral secondary alcohols belongs to the most exploited methods of creation of a new stereogenic center in the molecule. Catalytic transfer hydrogenation offers a cheap and operationally simple protocol for this transformation utilizing various convenient sources of hydrogen, like secondary alcohols or formic acid.[93]

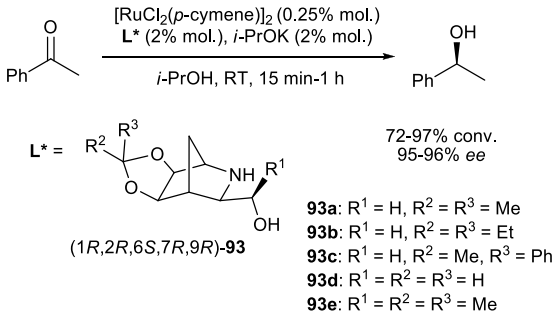
Various chiral ligands based on 2-azanorbornane skeleton were applied by Andersson's group to the enantioselective transfer hydrogenation of ketones using isopropanol as the reducing agent (Schemes 41-43).[59,94-99] Among chiral promoters: sulfur-containing ligands[97] and oxazoline derivatives,[99] combined with iridium(I), and alcohols,[94-96,98] including those bearing an additional ketal functionality at the remote end,[59,98,100] the latter complexed with ruthenium(II) were found the most efficient. Promising results (83-97% ee) were also obtained in Ru-catalyzed reaction (Scheme 41) of various ketones with the addition of 2% mol of 2-azanorbornylmethanol **92a** (racemic product was obtained when a tertiary alcohol **92b** was used).[94] Also secondary alcohols **92c-f** yielded the addition product in relatively high *ee* and reasonable conversions in the most cases (also for aryl-substituted acetophenones).[95,96] However, introduction of dioxolane ring (ligands **93a-e**, Scheme 42) increased the turnover frequency, and for **93e** acetophenone was reduced within 30 minutes (97% conversion) to (*S*)-alcohol of 96% *ee*, and for other tested aromatic ketones the results were comparable (with the optimum for 1-acetonaphthone: 100% conversion after 4 minutes and >99% *ee*).[59,98] Dioxalane-appended ligand (enantiomer of **93e**) was also found efficient in the ruthenium-catalyzed asymmetric transfer hydrogenation of various azirines to aziridines (72-92% yield, up to 70% *ee*).[100]

Moderate enantioselectivities (up to 79% *ee*) and yields were observed in the transfer hydrogenation of acetophenone catalyzed by metal-complexed 2-azanorbornanes substituted with oxazoline fragment (**94a-k**, Scheme 43).[99] A test with ligand **94a** showed that, in contrast to previously studied alcohols **92**, **93**, it was inactive in combination with ruthenium(II) precatalysts, better results were obtained with rhodium(I) (up to 18% conversion after 16 hours and 71% *ee*), but iridium(I) was found to be most efficient (32% conversion and 79% *ee*). Ten of the 11 newly synthesized derivatives bore an additional stereogenic center, constituting five epimeric pairs. For isopropyl, *tert*-butyl and phenyl-substituted compounds an isomer with (*S*) configuration of oxazoline carbon atom led mainly to 1-(*R*)-phenylethanol, while for (*R*) diastereomers (*S*)-product predominated. Though the outcome of ligands **94a-k** was not excellent, further investigations conducted in Andersson's group on oxazoline derivatives based on a 2-azanorbornane scaffold, containing phosphine substituent, revealed their high efficiency in the iridium-catalyzed hydrogenation of alkenes (*vide infra*).

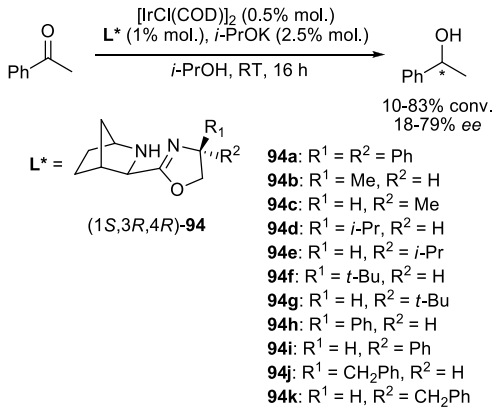
Comparable results as for compounds **94a-k** were obtained for N,S-donating ligands containing sulfide or sulfoxide moiety (up to 80% for one of diastereomeric sulfoxides).[97] However, as sulfanyl derivative was prepared from *N*-protected 2-azanorbornanemethanol *via* a route involving nucleophilic substitution, one should take into account the possible ring-expanded structures for these ligands (see chapter 3.2).



Scheme 41. Transfer hydrogenation of ketones with 2-azanorbonane-derived alcohols[59,98,100]

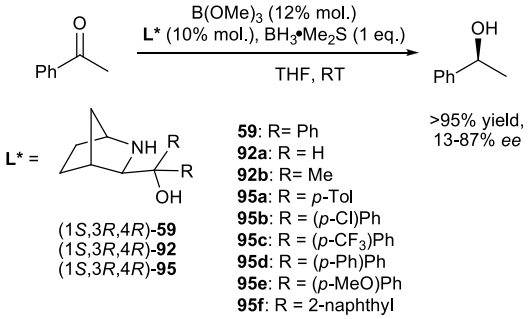


Scheme 42. Transfer hydrogenation of ketones with dioxolane-appended ligands[59,98]



Scheme 43. Transfer hydrogenation with iridium complexes of oxazoline-derived ligands[99]

2-Azanorbornylmethanols **59**, **92a**, **92b** and newly prepared **95a-f** were also applied by Pinho *et al.* in the enantioselective borane reduction of ketones (Scheme 44).[101] Screening of potential catalysts in the reaction of acetophenone allowed the choice of **59** as the best ligand for this purpose (>95% yield and 87% *ee*), though similar values were noted for the di-naphthyl-substituted derivative. Compound **59** was then tested in the reduction of the series of aromatic ketones; again, the yields were excellent (>95%), and enantiomeric excess fell into the 47-89% range.



Scheme 44. Borane reduction of ketones catalyzed by 2-azanorbornylmethanols[101]

3.5. Enantioselective hydrogenation

Andersson *et al.* undertook asymmetric hydrogenation of various, often demanding, substrates containing double C=C or C=N bonds as a means of introduction of chirality into compounds bearing a variety of functional groups, useful in the synthesis of more complex chiral molecules.[102-118] They selected several chiral ligands which complexed with iridium(I)

led to the optimal results of the catalytic reaction. Among them, (N,P) and (S,P)-donating 2-azanorbornyl derivatives substituted with phosphine and oxazoline or thiazole ring **96**, **97** (Figure 5) were found particularly effective (Scheme 45), though their performance was found dependent on the structure of substrates studied. The idea of such a modification of a bicyclic skeleton was substantiated by the success of Pfaltz's chiral phosphinooxazoline-based iridium catalyst with a tetrakis[3,5-bis(trifluoromethyl)phenyl]borate anion ($[BArF]^-$)[119] and the performance of chiral thiazole-based ligands designed in Andersson's group.[120] Iridium complexes were prepared as microcrystalline, stable solids and characterized.[103,108]

The performance of 2-azarnorbornyl derivatives was compared to other chiral ligands; comprehensive reviews on iridium-catalyzed hydrogenations offer a wider perspective of the field.[121-124] DFT calculations were undertaken to probe relatively poorly understood mechanism of iridium-catalyzed olefin hydrogenation using various chiral ligands (including **96a**).[107] The study revealed the utility of simple model system which could be used, in most cases with a success, the configuration of the major product of the reaction.

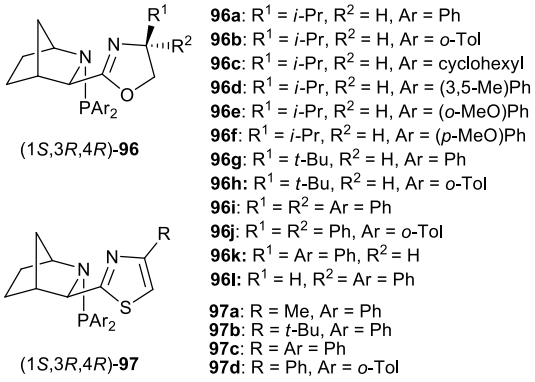
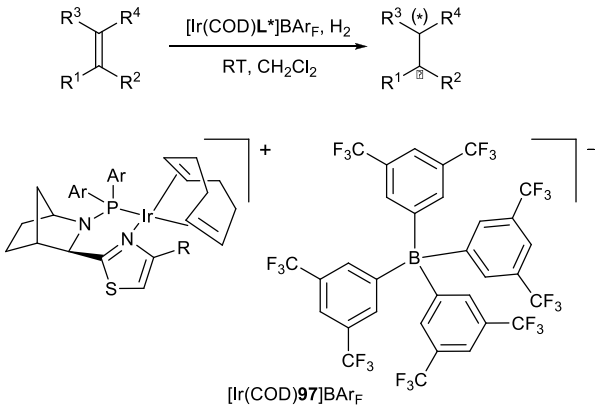
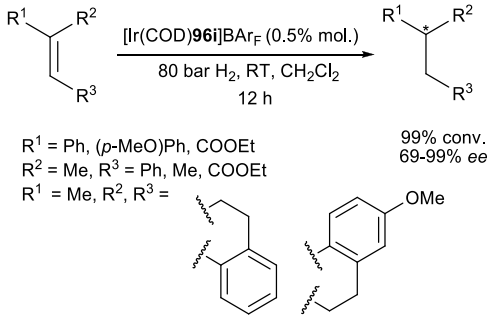


Figure 5. Phosphine-oxazoline and phosphine-thiazole ligands based on a 2-azanorbornane skeleton[102-118]



Scheme 45. Asymmetric hydrogenation of olefins catalyzed by iridium(I) complex with ligands **96**, **97**. The structure of the complex shown for the thiazole derivative

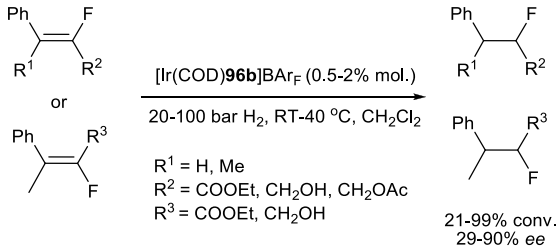
Series of ten oxazoline-phosphine (N,P)-donating ligands based on the chiral 2-azanorbornane scaffold **96** were prepared by Andersson *et al.* and their performance in the iridium-catalyzed hydrogenation of various alkenes was investigated.[103] Part of them were found effective in the stereoselective reduction of trans-α-methylstilbene: 99% conversion within 0.5 h with *ee* = 73-92% was noted for **96a-d**, **96f**, **96g**, and **96k**. On the other hand, a hindered derivative with two phenyl substituents on oxazoline ring (**96i**) led to the highest *ee* value of 96%, albeit accompanied by lower conversion (81%; it could be increased by application of higher pressure of H_2). This compound was chosen for tests of the possible substrate scope and resulted in high yields and *ee* up to 99% for the part of examined alkenes (Scheme 46) – the notable exceptions were a terminal alkene and several hindered cycloalkenes which were unreactive.



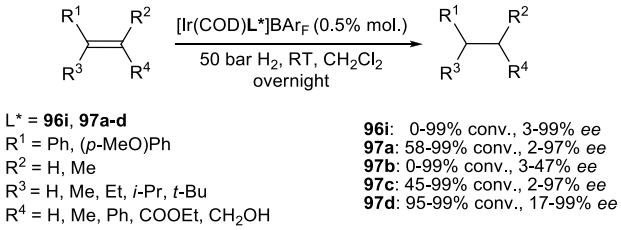
Scheme 46. Asymmetric hydrogenation of alkenes catalyzed by iridium complex[103]

In case of olefins bearing fluorine substituent in the vinyl position, among three 2-azanorbornane-derived ligands (**96a**, **96b** and **96i**) derivative **96b** complexed with iridium was recognized as the best catalyst resulting in the highest conversion and chemoselectivity (low extent of C-F bond cleavage).[104] However, the stereoselectivity was low for the part of substrates (Scheme 47). Similarly, trifluoromethyl-substituted alkene was hydrogenated using ligands **96b** and **96i** with the outcome (27% *ee* and 79% conversion for **96b**, 47% *ee* and only 8% conversion for **96i**) much worse than observed for other chiral inducers containing thiazole or imidazole moiety.[105] 2-Azanorbornyl derivatives **96a** and **96b** were also inferior to these ligands in the screening of catalysts for the asymmetric hydrogenation of 1,1-diarylsubstituted olefins (up to 80% *ee* was noted for **96b**).[106] A progress was achieved when thiazole derivatives **97** were introduced (Scheme 48); in particular, compounds **97c** and **97d** performed significantly better for certain substrates as compared to **96i**, though terminal

alkenes bearing isopropyl or ethyl group remained a challenge (up to 50% and 17% *ee*, respectively).[108]

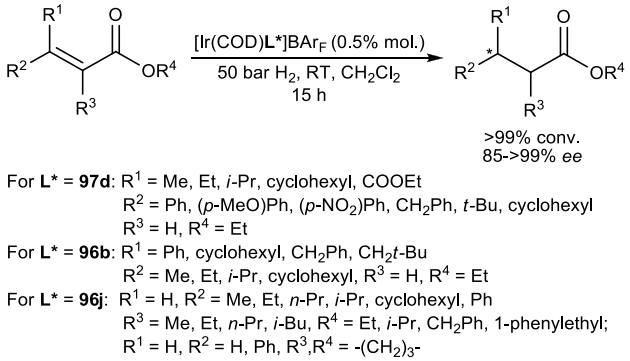


Scheme 47. Asymmetric hydrogenation of fluoroalkenes[104]



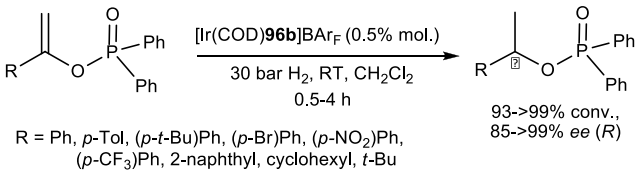
Scheme 48. Asymmetric hydrogenation of alkenes catalyzed by iridium(I) complexes with oxazoline and thiazole-based ligands[108]

Both oxazoline- (**96b**, **96j**) and thiazole-based (**97d**) 2-azaznorbornane derivatives were found efficient in the iridium-catalyzed hydrogenation of α,β-unsaturated carboxylic esters.[112] These ligands appeared to complement each other for the substrates of particular structure: in case of (*E*)-β,β-disubstituted esters compound **97d** gave optimal results, while **96b** was found the most effective for (*Z*) isomers, and **96j** was chosen as the best ligand for reduction of α,β-disubstituted unsaturated carboxylates (Scheme 49). In all cases quantitative conversion and very high enantioselectivities (*ee* was in the range of 85 to >99%) were observed. The utility of the described catalytic hydrogenation was demonstrated by the enantioselective preparation of several intermediates used previously in total syntheses of biologically active compounds.

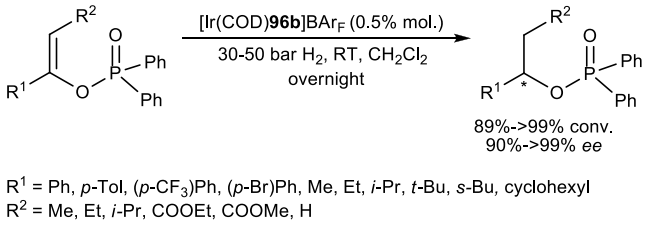


Scheme 49. Asymmetric hydrogenation of α,β-unsaturated carboxylic esters[112]

Iridium complex of oxazoline derivative **96b** appeared to be an optimal catalyst for hydrogenation of enol phosphinates (Schemes 50, 51).[113,114] For substrates with a terminal double bond, high conversions (in most cases in the range from 93 to >99%) and enantioselectivities (*ee* between 85 and >99%) were observed.[113] The obtained products were transformed to the corresponding secondary alcohols or phosphines without loss of enantioselectivity. Most of the di- and trisubstituted enol phosphinates, including those bearing two alkyl groups at the double bond were also hydrogenated with high stereoeselectivity.[114] However, catalyst screening showed that **96b** led to unsatisfactory results of hydrogenation of diphenylvinylphospine oxide (>99% conversion, but 78% *ee*) as compared to other, thiazole-based ligands which were than used for conversion of various phosphine oxides and vinyl phosphonates.[115]

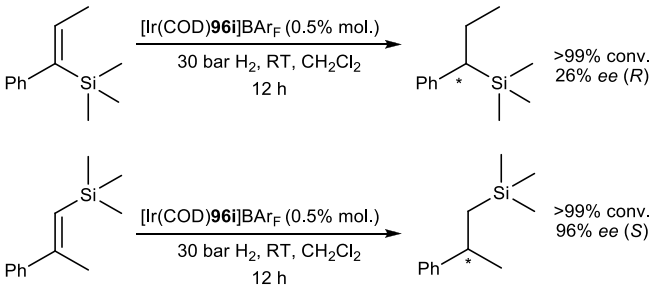


Scheme 50. Asymmetric hydrogenation of phosphinates containing a terminal C=C bond[113]



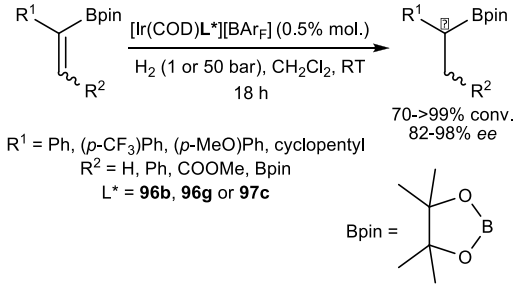
Scheme 51. Asymmetric hydrogenation of unsaturated phosphinates[113,114]

In their studies on expanding the possible substrate classes, Andersson's group investigated iridium-catalyzed hydrogenation of vinylsilanes.[116] Only one of two silanes tested with oxazoline ligand **96i** was transformed with high stereoselectivity (Scheme 22); slightly better results were noted for thiazole-derived ligand (not based on the 2-azanorbornane skeleton; compounds of type **97a-d** were introduced two years later) and further evaluation with various substrates was performed with this compound.



Scheme 52. Asymmetric hydrogenation of vinylsilanes[116]

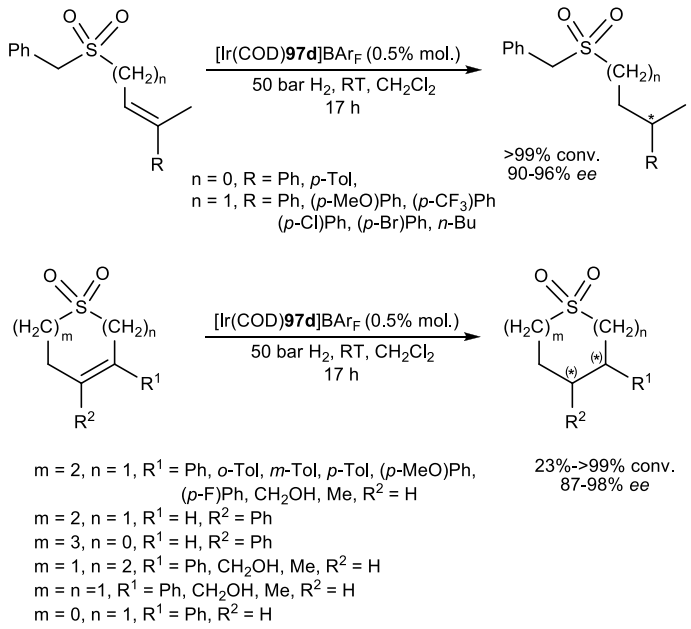
Satisfactory enantioselectivity (72-98% *ee*) and yield were observed when vinyl boronates bearing aryl or cyclopentyl substituent were hydrogenated using iridium complexes of ligands **96b**, **96g**, or **97c** as catalysts (Scheme 53).[117] These derivatives were found to complement one another for various substrates. For most boronates, the decrease of pressure of hydrogen resulted in lowering or even reversal of stereoselectivity.



Scheme 53 Asymmetric hydrogenation of unsaturated boronates[117]

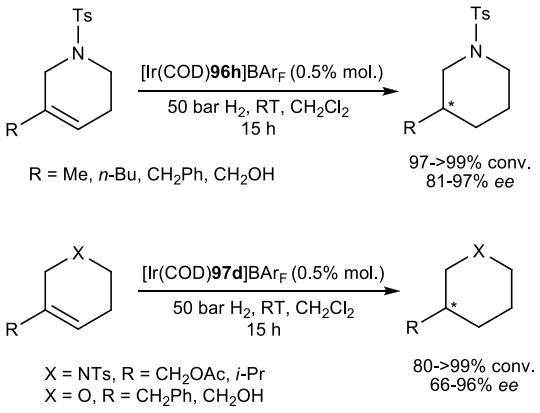
2-Azanorbornane-based thiazole-phosphine ligand **97d** was chosen by the preliminary screening as the best ligand for the iridium-catalyzed hydrogenation of cyclic and linear unsaturated sulfones (Scheme 54).[118] Enantioselectivity was high in all cases, and yield were in most cases high with exception of *ortho*-tolyl seven-membered and phenyl-substituted six-

membered derivatives (23% and 43% conversion, respectively). Hydrogenation products were further converted to chiral allylic and homoallylic compounds using the Ramberg-Bäcklund rearrangement.



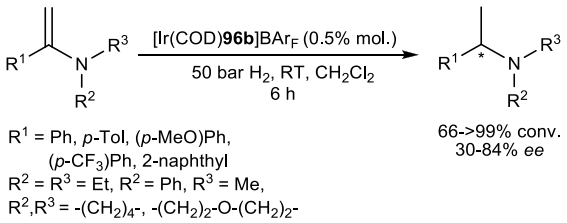
Scheme 54. Asymmetric hydrogenation of unsaturated sulfones[118]

Among ligands tested in hydrogenation of *N*-heterocyclic olefins, compound **96h** was most efficient for alkyl-substituted substrate with six-membered ring.[109] For particular 3,4-unsaturated heterocycles, also the use of derivatives **96b** and **97d** led to optimal results, as exemplified in Scheme 55.[111]



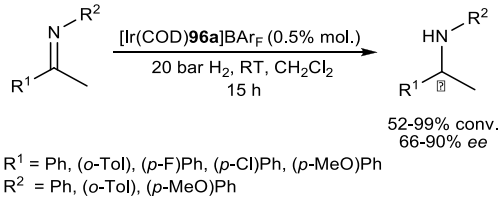
Scheme 55. Asymmetric hydrogenation of heterocyclic olefins[109,111]

Asymmetric hydrogenation of enamines leading to chiral tertiary amines was also performed by Andersson's group.[110] Preliminary screening which included, among others, 2-azanorbonane derivatives **96a**, **96b**, **96i** and **97c**, selected *o*-tolyl-substituted ligand **96b** which was used in further studies on the possible substrate scope (Scheme 56). For most enamines, moderate to high enantioselectivity (*ee* = 64-87%) and quantitative conversion after 6 hours were noted, however, in case of certain pyrrolidine or morpholine derivatives yields and *ee*s were significantly lower which was attributed to the catalyst poisoning by basic amines formed in the course of reaction.



Scheme 56. Asymmetric hydrogenation of enamines[110]

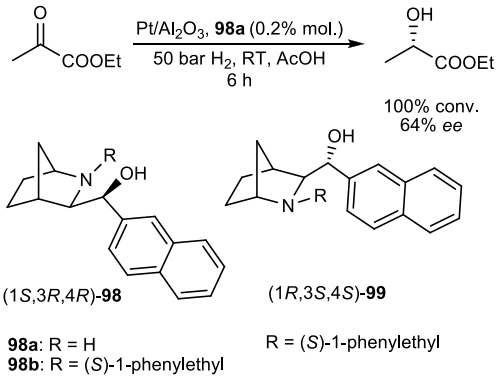
Chiral secondary amines were efficiently produced by iridium-catalyzed hydrogenation of imines with oxazoline-phosphine ligands based on the 2-azanorbornane scaffold.[102,103] Ligand **96a** was tested for the series of acyclic *N*-arylimines, yielding in most cases high conversions (98-99%, with an exception of *N*-benzyl and *ortho*-tolyl derivatives) and enantioselectivities (80-98%; Scheme 57). For more complex imines the results were less satisfactory which was explained by the conformational strain upon coordination to iridium in the transition state. Studies on the modification on the structure of catalyst revealed that while the change of substituents on oxazoline ring resulted in the decrease of both yield and stereoselectivity of the catalytic reaction (ligands **96g**, **96i**, **96k**, **96l**), an appropriate substitution of phosphine aryls retained or slightly improved the outcome as compared to **96a** (ligands **96b**, **96d**, **96f** as well as cyclohexyl-substituted **96c**); only for **96e** conversion dropped down to 61%.



Scheme 57. Asymmetric hydrogenation of imines[102,103]

The presented examples strongly confirm the statement from 2006 paper by Andersson and coworkers that „iridium-catalyzed asymmetric hydrogenation is still highly substrate dependent and the development of efficient chiral ligands that tolerate a broader range of substrates remains a challenge".[116] Since that time a significant progress have been made, mainly thanks to introduction of thiazole-derived bicyclic ligands which have been found complementary to oxazoline-based ones. It is thus possible that previous results obtained for certain substrates could be not optimal. Still, very high conversions and enantioselectivities observed for a large variety of substrates bearing functional groups should be underlined.

Besides the wide use of iridium-based systems, also platinum was tried as the catalyst for the hydrogenation of ethyl pyruvate in acetic acid with 2-azanorbornane-based naphthyl-substituted aminoalcohols as chiral modifiers.[65] Pfaltz and coworkers obtained the best result (quantitative yield and 64% *ee*) for **98a** compound with no substituent in the position 2 of the 2-azanorbornyl system, while **98b** and **99** gave less than 30% *ee* and low conversion (Scheme 58).

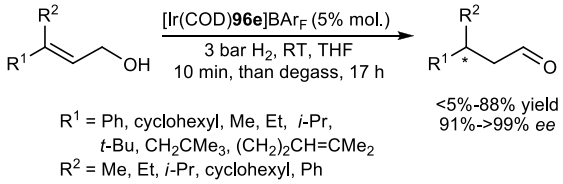


Scheme 58. Platinum-catalyzed asymmetric hydrogenation of ethyl pyruvate[65]

4.6. Other catalytic reactions

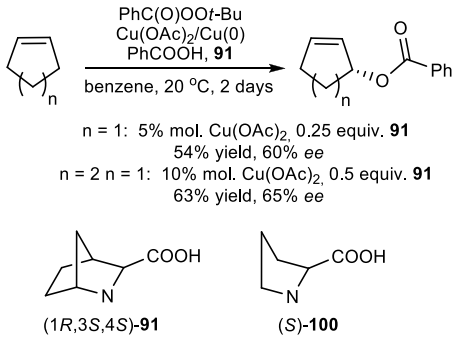
Several articles have been published in which the authors studied other catalytic reactions, often focusing on the possibility of replacement of pyrrolidine or proline derivative by their more rigid 2-azanorbornane counterpart and the effect of such a modification on the yield and stereochemical outcome.

Interestingly, catalytic system [Ir(COD)**L***]BAr$_F$ efficient in hydrogenation of various unsaturated compounds, was found useful in the enantioselective isomerization of primary allylic alcohols.[125] Of three ligands tested in the conversion of (*E*)-4-methyl-3-phenylpent-2-en-1-ol, compound **97a** was almost inactive, while other thiazole derivative **97c** and oxazoline **96e** led to the desired (*S*)-aldehyde with >99% *ee* (Scheme 59). Since the yield for **96e** was significantly higher (88% *vs* 43% for **97c**), this derivative was applied for the series of (*E*)- and (*Z*)-trisubstituted substrates; the stereoselectivity was excellent (91 to >99% *ee*), and the yields were strongly substitution-dependent.



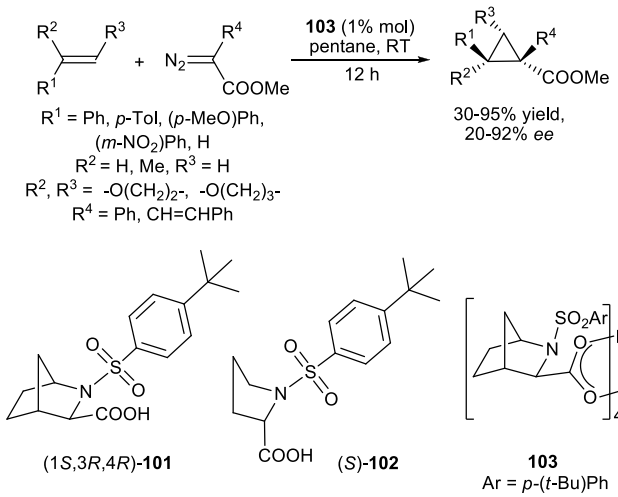
Scheme 59. Enantioselective isomerization of allylic alcohols[125]

Södergren and Andersson described the attempted use of chiral 2-azanorbornyl derivative in the allylic oxidation of olefins with a peroxy ester to give the corresponding allylic alcohol derivative, catalyzed by copper salt (Kharasch-Sosnovsky reaction[126]). Compound **91** was tested in this reaction as a rigid analogue of proline (**100**).[127] Cyclopentene was converted into (*R*)-2-benzoate in yields up to 54% and *ee* up to 60%, while maximum values for the 2-cyclohexene derivative were Y = 63% and *ee* = 65%. These results were found superior to proline itself, however, high catalyst loadings and long reaction time were necessary (Scheme 60).



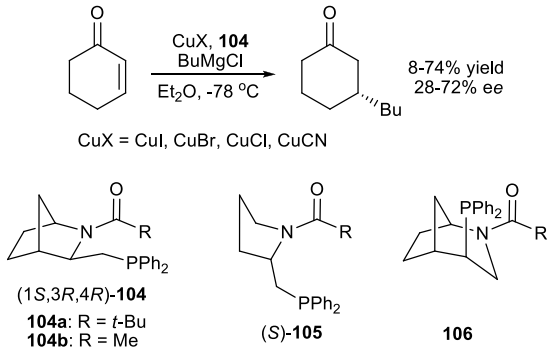
Scheme 60. Allylic oxidation of alkenes catalyzed by copper complexes[127]

Bertilsson and Andersson synthesized and characterized a dinuclear rhodium complex of the sulfonylated carboxylate ligand **101**, a bicyclic analogue of proline derivative **102**.[128] The obtained compound (**103**, Scheme 61) was applied as a catalyst in the asymmetric cyclopropanation of various olefins with vinyl- and phenyl-diazoesters.[129] *Trans* diastereomers were formed almost exclusively (*dr* > 20:1), enantioselectivities were rather satisfactory (*ee* was generally in the range of 65-92%, with exception of *p*-nitrophenyl derivatives), and yields in most cases exceeded 50%. However, the expected increase of the stereoselectivity in comparison with the complex of the less rigid proline derivative was not observed.



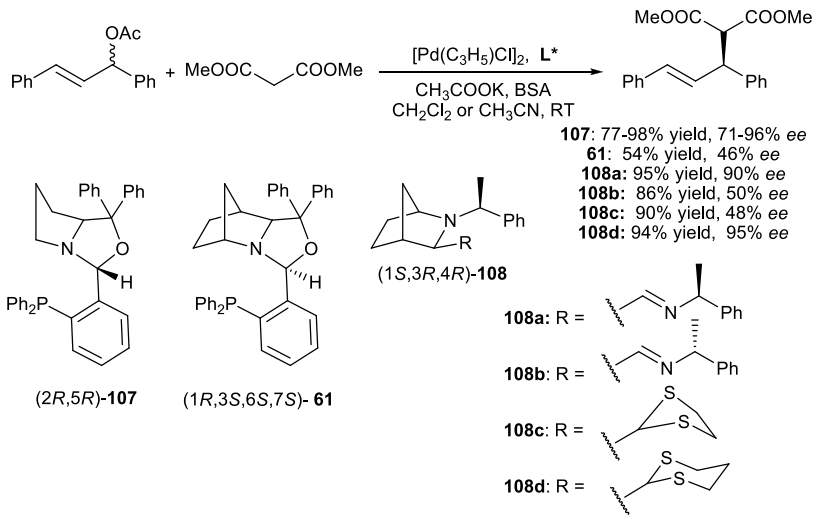
Scheme 61. Cyclopropanation of alkenes catalyzed by dirhodium complex **103**.[128]

Modin *et al.* described the synthetic approach to phosphines **104a-b**, the bicyclic analogues of pyrrolidine derivative **105**, and their application as (O,P)-donating ligands in the copper(I)-catalyzed enantioselective 1,4-addition of a Grignard reagent to 2-cyclohexenone (Scheme 62).[130] The performance of the obtained chiral inducers was much worse than **105** at high catalyst loadings (34% mol and 17% mol), while the best results were noted for only 4.7% mol of the bicyclic *t*-butyl derivative **104a** (73% yield, 71% *ee* and less than 10% of the 1,2 addition). The methylated ligand **104b** led to the desired product with a comparable stereoselectivity, albeit with lower yield. The simple comparison with pyrrolidine-derived phosphine **`06** is hampered by the fact that bicyclic compounds presumably contained a significant amount of ring-expanded isomers **106**, formed under conditions of nucleophilic substitution applied to the synthesis of **104** (see chapter 3.2).



Scheme 62. 1,4-addition of a Grignard reagent to 2-cyclohexenone[130]

2-Azanorbornane-derived ligands were also applied in palladium-catalyzed asymmetric allylic alkylation (Trost-Tsuji reaction).[131] Okuyama, Nakano and Hongo prepared a bicyclic pyrrolidynyl-phosphinooxazolidine ligand **107** and its tricyclic analogue **60** and examined their effectiveness as chiral inducers in the AAA reaction of 1,3diphenyl-2-propenyl acetate and dimethyl malonate (Scheme 63).[61] The low yield and stereoselectivity obtained for ligand **60** containing the 2-azanorbornane fragment was attributed to the hindered formation of the catalytically active palladium complex. Much better results were obtained by our group for (N,S)-coordinating ligands, prepared in one step from the 2-azanorbornane-3-carbaldehyde **61**.[132] A striking difference between the two Schiff bases tested (**108a** and **108b**) shows that the change of configuration of only one of the five stereogenic centers can be responsible for the observed stereoselectivity. The increase of size of dithioacetal ring had the beneficial influence on the stereochemical outcome of the reaction; 94% yield and 95% *ee* for the dithiane derivative **108d** were the best values in the series (Scheme 63). Other (N,S) ligands investigated in that study performed significantly worse which may be connected with the fact that they were actually bridged azepane derivatives.[132]



Scheme 63. Application of 2-azanorbornyl derivatives in palladium catalyzed AAA reaction.[61,132] Results for ligands **108** are given for 10% mol. of chiral ligand used.

Application of 2-azanorbornyl derivatives in the variety of asymmetric catalytic reactions proves the utility of this bicyclic skeleton as a versatile basis for the synthesis of the effective chiral ligands or organocatalysts. A significant progress has been made, in particular, in the field of asymmetric hydrogenation, while other catalytic processes received relatively less attention which opens the area for further explorations.

5. Biological activity of 2-azanorbornyl derivatives

A relative ease of preparation of chiral 2-azanorbornyl derivatives arose an interest in possible biomedical applications of these bicyclic compounds. They were recognized as valuable rigid analogues of various piperidine alkaloids, and 2-azabicyclo[2.2.1]heptane-3-carboxylic acid was used as a proline surrogate in a powerful approach to conformationally constrained oligopeptides with possible therapeutic utility. On the other hand, the bicyclic chiral 2-azanorbornane or 2-azanorbornene system was found useful in enantioselective construction of cyclopentanoids. In this approach, the rigid skeleton is constructed and appropriately modified with a complete control of stereochemistry, and stereoselective ring opening leads to the desired monocyclic derivative. In particular, 2-azabicyclo[2.2.1]hept-5-en-3-one (Vince lactam **30**) appeared to be an attractive precursor of carbocyclic nucleoside analogues, many of which exhibited significant antibiotic, antitumor and, first of all, antiviral activity (Carbovir derivatives).

5.1. Bicyclic analogs of biologically active compounds

2-Azanorbornane derivatives found use as precursors of bridged, bicyclic analogues of various natural compounds containing appropriately substituted cyclopentane fragment (in particular, cyclopentylamine derivatives), piperidine or pyrrolidine heterocycle, including mimetics of proline (Figure 6). The studies were focused on their synthesis and determination of the impact of the modification on the exhibited biological activity, *e.g.* affinity for specific receptors.

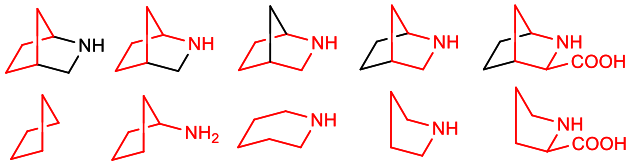


Figure 6. 2-Azanorbornane as a bridged analogue of cyclopentane, cyclopentylamine, piperidine, pyrrolidine and proline

Both piperidine and pyrrolidine structural motives can be found in the number of natural alkaloids, including piperine **109**, lobeline **110**, coniine **111**, nicotine **112** or hygrine **113** (Figure 7), to name a few. Their synthetic analogs are therefore of great interest of pharmaceutical industry. Most of these compounds are chiral and their biological activity is strongly dependent on the absolute stereochemistry. Thus, synthetic methods leading to piperidine or pyrrolidine derivatives with the defined configurations of stereogenic centers are of special importance.[133] The aza-Diels-Alder reaction offering the desirable stereocontrol was thus recognized as an interesting synthetic pathway which was utilized in the synthesis of bridged pyrrolidine or piperidine derivatives.

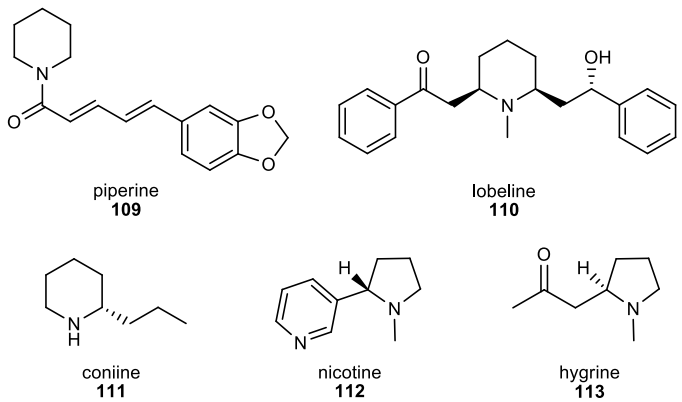
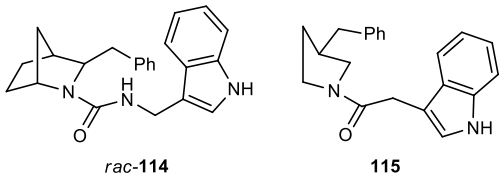


Figure 7. Examples of alkaloids bearing piperidine or pyrrolidine ring

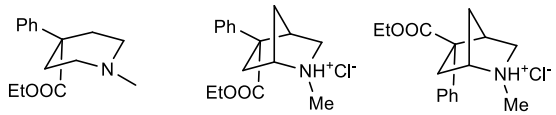
In a search for nonpeptide drug candidates for neuropeptide receptors, Horwell *et al.* used molecular modeling to design a compound with a desired conformation and dipole moment to mimic a bicyclic hexapeptide exhibiting high tachykine affinity.[134] Racemic 2-azanorbornane derivative **114** was prepared which was found to fulfill the criteria and compared to the previously synthesised[135] pyrrolidine-based β-turn mimetic **115** of the peptide (Figure 8). An additional constrain did not improve the performance of these compounds which showed only moderate affinity for neurokine-1 (NK-1) receptor and lack of NK-2 affinity.



rac-**114** **115**

Figure 8. Polar β-turn mimetics containing 2-azanorbornane (**114**) or pyrrolidine (**115**) fragment[134]

As an example of construction of constrained piperidine derivatives, Portoghese *et al.* investigated the bridged analogs of the synthetic analgesic meperidine (pethidine **116**).[136] Two epimers of **117** (Figure 9) were obtained to study the effect of conformation on analgetic potency. *Endo* (5*S*) isomer was found more active (but also more toxic) than *exo* form (5*R*) and meperidine itself, which was in part connected with better brain penetration due to higher lipid solubility.



meperidine **116** (1*S*,4*R*,5*S*)-**117** (1*S*,4*R*,5*R*)-**117**

Figure 9. Meperidine and its bicyclic mimetics[136]

Also bicyclic rigid analogues of a nicotinic acid-derived alkaloid arecoline **118** were prepared by Pombo-Villar *et al.*[137] Two enantiomeric pairs **119a** and **119b** (Figure 10) were obtained to test their cholinergic activity as muscarinic agonists.

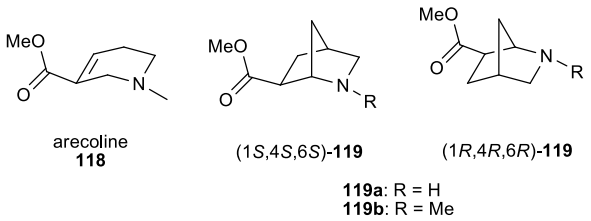


Figure 10. Arecoline and its bicyclic analogues[137]

Raubo *et al.* prepared enantiopure 1-phenyl-2-azabicyclo[2.2.1]heptane derivatives **120** bearing 6-*exo* or *endo* substituent as 2-phenylpiperidine mimics in neurokin NK_1 receptor modulators (Figure 11).[138] Ring-closing metathesis and regio- and stereoselective oxirane opening were applied as key steps in the reaction sequence in which Diels-Alder cycloaddition was not utilized. Only *endo* (6*S*) epimer exhibited binding to NK_1 receptor comparable to the known *cis*-substituted piperidine analog **121**.

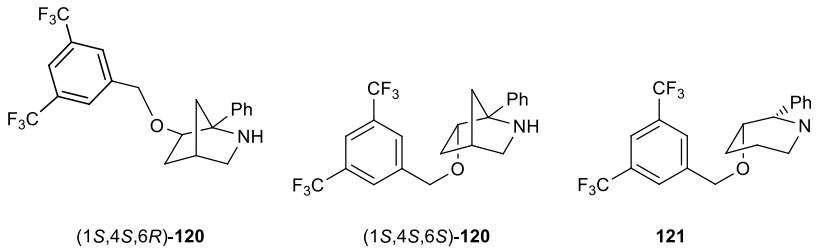


Figure 11. NK_1 receptor ligands[138]

The synthesis of ledipasvir **122** (Figure 12, a clinical drug candidate for oral treatment of hepatitis C virus infection was elaborated).[139] The compound contains 2-azanorbornane fragment as a terminal heterocycle which was found a key feature for pharmacokinetic properties of the drug, surpassing the piperidine analog.

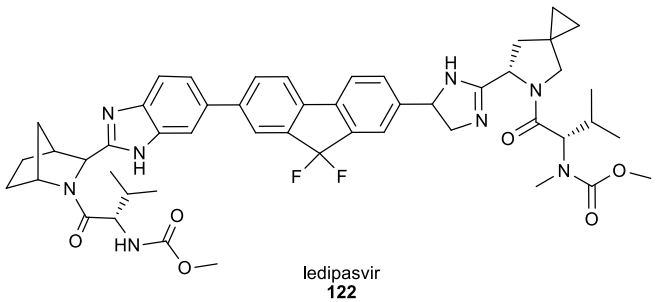
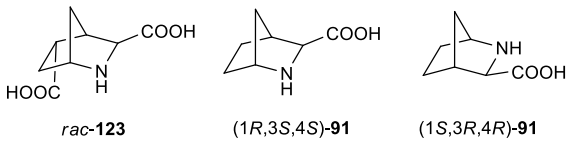


Figure 12. The structure of ledipasvir[139]

Bicyclic mimetics of natural amino acids, especially proline, also received a considerable attention. A racemic, dicarboxylic 2-azanorbornyl derivative **123** (Figure 13) was prepared by Bunch and coworkers as a conformationally restricted analogue of (*S*)-

glutamic acid.[140] The Authors intended to mimic the folded conformation of this amino acid which plays an important role as neurotransmitter in the central nervous system. However, compound **123** did not show affinities at the native ionotropic Glu receptors.

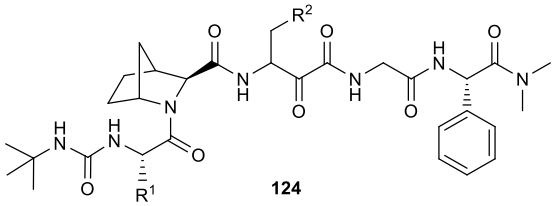
Two enantiomers of *exo*-2-azabicyclo[2.2.1]heptane-3-carboxylic acid **91** (Figure 13) were used by Mellor *et al.* as a means for construction of conformationally constrained oligopeptides, analogues of fragments of transforming growth factor (TGFα).[141] Eight peptides (four linear, and four with a disulfide bridge) were successfully synthesized containing either prolyl (L- or D-enantiomer) or **91** (one of enantiomers) residue. The conformational studies showed that the bridged amino acids behaved similarly to their proline counterparts. Only the two peptides containing both the cystyl fragment and the bicyclic proline analogues were effective in the tests of induction of DNA synthesis.[142]



rac-**123** (1*R*,3*S*,4*S*)-**91** (1*S*,3*R*,4*R*)-**91**

Figure 13. 2-Azanorbornane derivatives used as rigid analogues of natural amino acids

Compound **91** was also used as a proline mimetic and appeared a convenient building block to develop new tetrapeptides as inhibitors of the X-linked inhibitor of apoptosis protein (XIAP), which exhibited activity similar to natural ligands.[143] Venkatraman and coworkers tested peptides containing **91**-derived residue in their search for the effective inhibitors of hepatitis C NS3-NS4A serine protease essential for viral replication, which could be used for the treatment of chronic HCV infections.[144] They assumed that the conformation of the rigid proline surrogate could ensure the maximum contact with the surface of the enzyme. Optimization of the remaining residues, supported by the X-ray structure of one of inhibitors bound to the target enzyme, led to identification of four most potent derivatives **124a-d** (Figure 14). The general idea of using bicyclic proline analogs in the construction of new agents for treatment of hepatitis was later successfully applied for the design of boceprevir, telaprevir and narlaprevir.[145]



124a: R^1 = cyclohexyl, R^2 = cyclopropyl
124b: R^1 = *t*-butyl, R^2 = cyclopropyl
124c: R^1 = cyclohexyl, R^2 = cyclobutyl
124d: R^1 = *t*-butyl, R^2 = cyclobutyl

Figure 14. 2-Azanorbornane derivatives exhibiting activity against hepatitis C serine protease[144]

2-Azanorbornane, perhydroindole and 2-azabicyclo[2.2.2]octane fragment were used as skeletons of the series of compounds tested as inhibitors of prolyl endopeptidase.[146] Carboxylic acid **91** served as a starting point for the preparation of five derivatives **125a-e** (Figure 15); **125a** showed activity comparable with the reference proline analog and **125b** was among the most promising. However, authors decided to perform *in vivo* tests with other derivatives among which perhydroindole-containing compounds provided the most potent inhibition and oral availability.

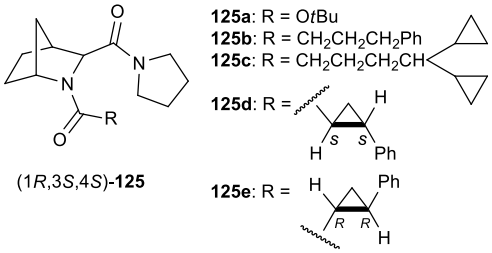


Figure 15. 2-Azanorbornyl derivatives tested as inhibitors of prolyl endopeptidase.[146]

In a continuation of their study of proline derivatives as effective ligands for the peptidyl-prolyl isomerase FKBP12 which could be used for treatment of neurodegenerative diseases, Wu and coworkers prepared a series of *exo* and *endo* 2-azanorbornyl-based *N*-glyoxyl or sulfonamide esters and thioesters **126a-e**, **127a-d** (Figure 16).[147] They observed that *exo* isomers, showing more structural similarity to L-proline, exhibited significant FKBP12 inhibitory activity. This was in line with the molecular modeling studies showed less effective binding modes of *endo* isomers to the active site of isomerase. *In vivo* tests, in which compounds *exo*-**126a** and **127a** were used in a mouse model of Parkinson's disease, proved their efficiency in neuroregeneration.

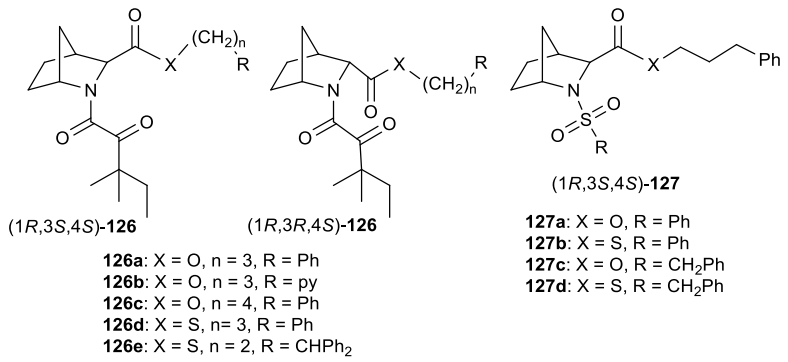
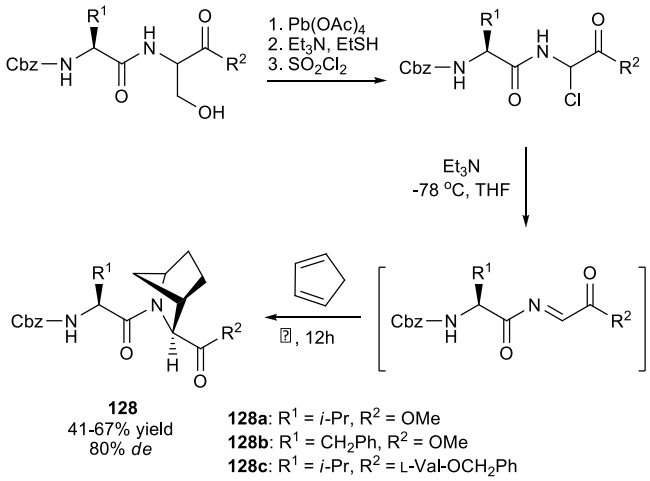


Figure 16. 2-Azanorbornane derivatives tested as ligands for the peptidyl-prolyl isomerase[147]

Another approach to the stereoselective synthesis of peptides **128a-c** containing *exo*-2-azabicyclo[2.2.1]hept-5-ene-3-carbonyl subunit as a bicyclic proline mimetic was described by Jäger *et al.*[148] Instead of incorporation of a preformed 2-azanorbornene-derived residue, it was synthesized by the aza-Diels-Alder cycloaddition of cyclopentadiene to dehydroglycyl-containing peptides, which were prepared in two steps from the corresponding seryl derivatives (Scheme 64). *Exo* diastereomers were preferentially formed, which was substantiated by the diene approach from the less sterically hindered face opposite to valine or phenylalanine residue. The presence of the double bond in the resulting peptide allowed further on-site modifications.



Scheme 64. Synthesis of peptides containing *exo*-2-azabicyclo[2.2.1]hept-5-ene-3-carbonyl subunit[148]

2-Azanorbornyl derivatives were also used to mimic other bicyclic systems exhibiting biological activity. Malpass and coworkers studied the analogues of epibatidine (**129**, Figure 17), the alkaloid isolated from the skin of the Equadorian poison tree frog, *Epipedobates Tricolor*.[53,149-153] This compound exhibits high analgesic activity as an agonist at the nicotinic acetylcholine receptors of the nervous system; however, its therapeutic application is hindered

by the extreme toxicity. This fact stimulated work on analogues and isomers devoid of drawbacks of the original alkaloid while preserving its antinociceptive activity. In this line, four (6-chloro-3-pyridyl)-substituted 2-azarbornane derivatives **53**, **130** (Figure 17) preserving the rigid bicyclic structure, were prepared by treatment of *N*-protected 2-azanorbornene with 2-chloro-4-iodopyridine.[53,149-151] Also 7-substituted isomers, *syn*- and *anti*-isoepibatidine (**131**) in which the positions of the heterocycle and the amine were reversed as compared to epibatidine itself, and their methylisoaxolyl analogs (isoepiboxidines **132**) were obtained.[152-154] Studies on structure-activity relationships showed that compounds *endo*-**53**, *endo*-**130**, *syn*-**131** and *syn*-**132** with similar N-N distances to **129** (4.3-4.8 Å) retain its high affinity at nicotinic receptors, while *exo*- and *anti*-derivatives were inactive.[151,154] However, the new compounds did not exhibit the desired receptor subtype selectivity which is regarded as a key factor of lower toxicity and fewer undesirable side effects.[154]

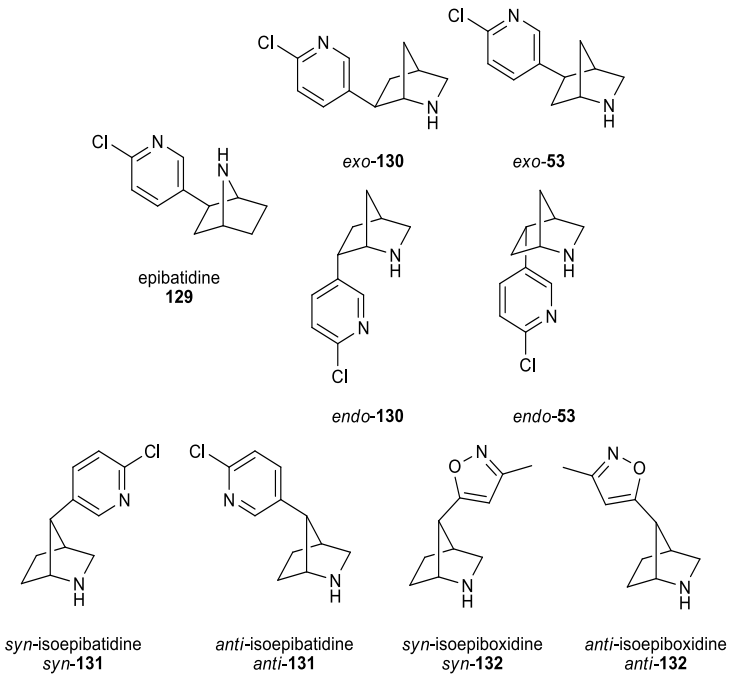


Figure 17. Epibatidine and its analogues

Various bicyclic systems were also used to mimic the properties of atropine, a potent tropane alkaloid based on a 8-azabicyclo[3.2.1]octane skeleton. Azaprophen **133**, a highly potent antimuscarinic agent with nitrogen atom in 2-position of bicyclooctane fragment was synthesized by Carroll and coworkers (Figure 18).[155] Its 2-azanorbornyl analogs, bearing one carbon atom less in the bicyclic system, were tested as muscarinic antagonists (2,2-diphenylpropionate derivatives **134a**, **135a**) or agonists (acetoxy-substituted compounds **119b**, **134b**, **135b-c**), with highest efficiency observed for endo-**134a** and *exo*-**119b**,

respectively.[156] The investigated compounds did not show the selectivity for subtypes of muscarinic receptors.

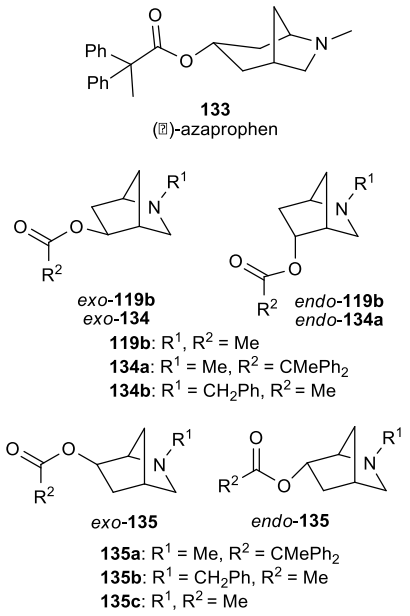
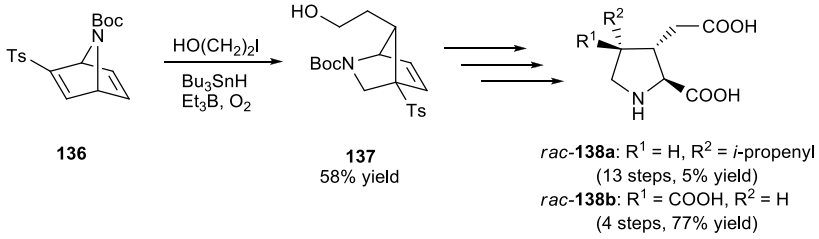


Figure 18. Azaprophen and its 2-azanorbornyl analogues[155,156]

5.2. Precursors of chiral monocyclic systems

Derivatives of 2-azanorbornane or 2-azanorbornene have been utilized as useful synthetic precursors of monocyclic systems exhibiting biological activity. Some of these compounds contain an appropriately substituted pyrrolidine ring. For example, neuroexcitants, α-kainic acid **138a** and 3-(carboxymethyl)pyrrolidine-2,4-carboxylic acid **138b** were obtained from a 7-azabicyclo[2.2.1]heptadiene (**136**) through its rearrangement to 2-azabicyclo derivative (**137**) and stereoselective ring opening (Scheme 65).[157]



Scheme 65. 2-Azanorbornene as a precursor of kainic acid derivatives[157]

More frequently, various cyclopentane or cyclopentene derivatives, including carbocyclic nucleosides exemplified by entecavir and carbovir (Figure 19) were prepared from 2-azanorbornene precursors. In a typical approach, a functionalized five-membered ring is obtained in two stages, starting with [4+2] cycloaddition of cyclopentadiene with aza-

dienophiles, followed by the ring opening; additional steps involve modifications either of cycloadduct or the monocyclic product. Numerous synthetic procedures have been developed, and most of them make use of 2-azabicyclo[2.2.1]hepten-3-one (Vince lactam **30**, Scheme 66). Its chiral rigid skeleton and the presence of lactam function and a double bond which reactivity can be utilized, make it an ideal precursor for organic and pharmaceutical chemistry. Vince lactam is now commercially available, both as a racemate and in the enantiomerically pure form. The synthetic versatility of this compound has been thoroughly reviewed.[43] As one of the recent examples, a racemic Vince lactam was used as a precursor in the synthesis of potential inhibitors (**143**, **144**; Scheme 66) of aminotransferase BioA involved in biotin biosynthesis.[158] Stereoselective synthesis of 2′-fluoro-6′-methylene carbocyclic adenosine **146** starting from *rac*-**30** (in one of initial steps, its *N*-protected derivative **145** was resolved into enantiomers) was also reported (Scheme 67).[159]

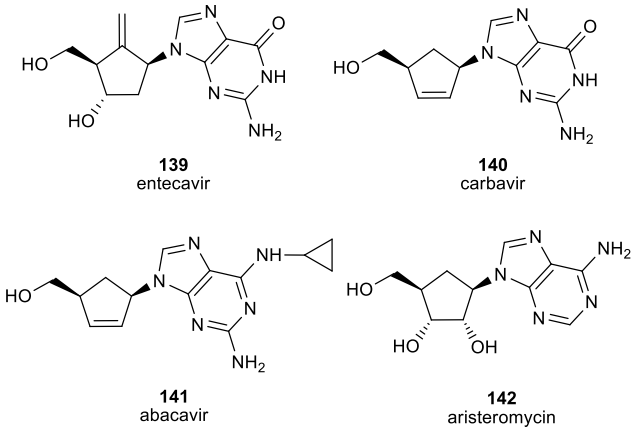
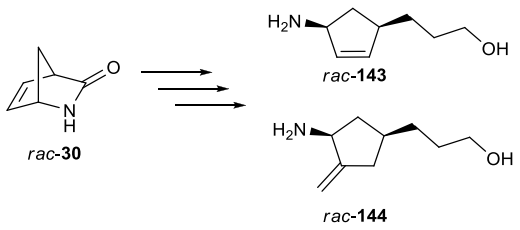
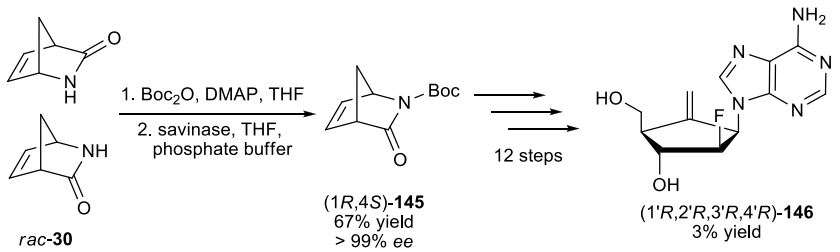


Figure 19. Examples of carbocyclic nucleosides of antiviral or antibiotic activity

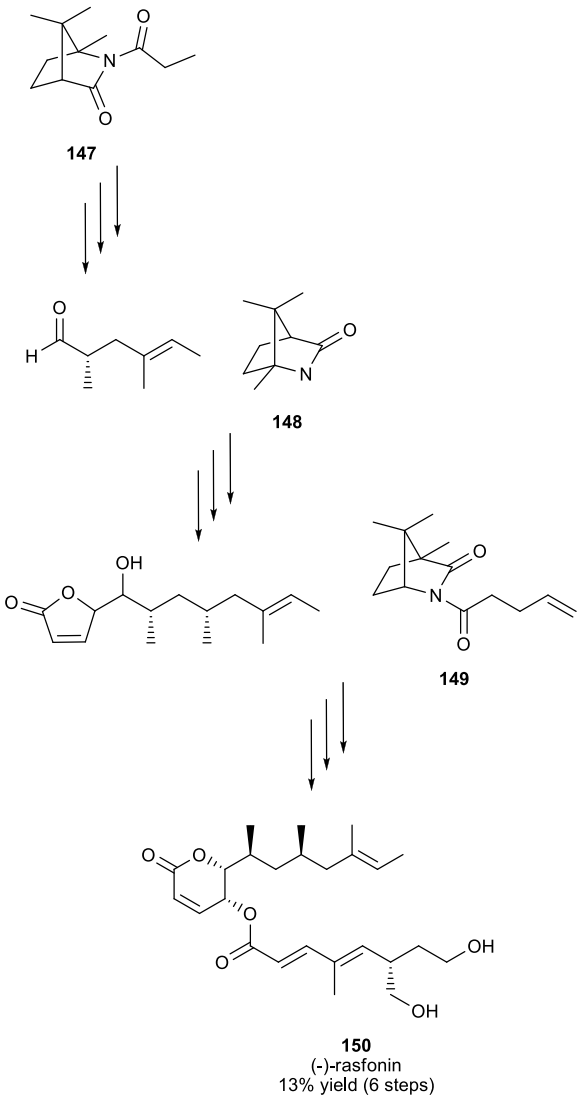


Scheme 66. The use of Vince lactam for the synthesis of inhibitors of aminotransferase BioA[158]



Scheme 67. The use of Vince lactam for the synthesis of carbocyclic adenosine derivative[159]

Derivatives of Vince lactam **147-149** were applied in the total synthesis of (−)-rasfonin **150**, a possible selective inducer of apoptosis (Scheme 68).[160] After diastereoselective side chain modifications, the bicyclic chiral auxiliaries were removed from the reaction intermediate.

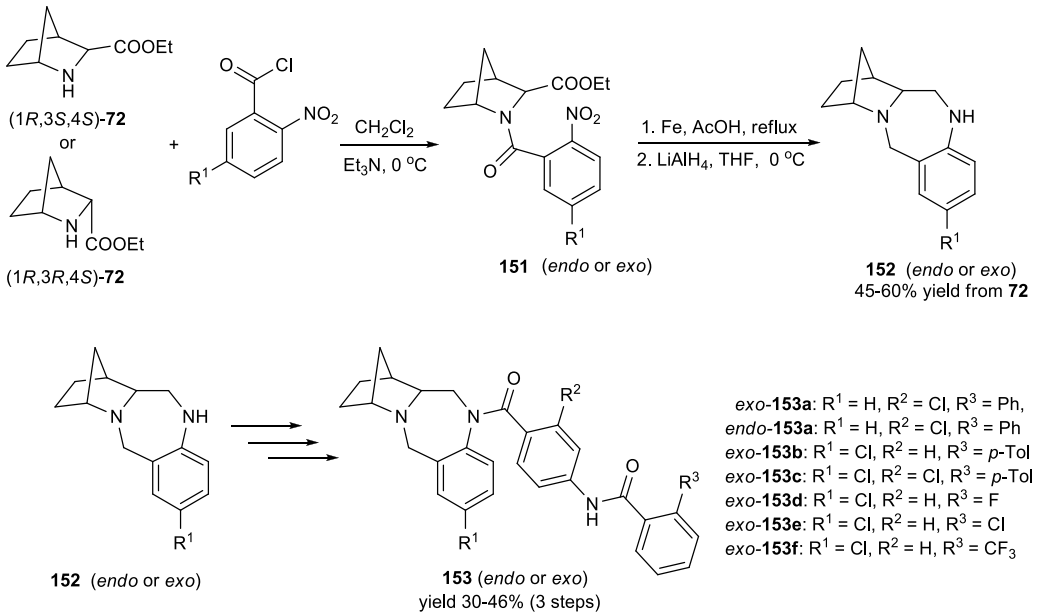


Scheme 68. Synthesis of (−)-rasfonin[160]

5.3. Elements of various systems exhibiting biological activity

In a quest for selective vasopressin receptor antagonists, which could be used for treatment of congestive heart failure, hypertension, renal disease, edema, and hyponatremia Dyatkin *et al.* prepared a series of benzodiazepines fused to a chiral 2-azanorbornane **153a-f**

(Scheme 69).[161] While *exo* derivatives showed significant *in vitro* affinity to both human V_{1a} *vs* V_2 receptors, isomer *endo*-**153a** was V_2-selective. *In vivo* tests on rats revealed modest bioavailability and plasma clearance rates, and good efficacy as diuretics (compounds **153a**, **153b**) and ability to reverse vasopresin-induced hypertension (derivatives **153a**, **153b**, **153f**).



Scheme 69. Synthesis of benzodiazepines fused to a chiral 2-azanorbornane backbone[161]

Three polysulfones based on 2-azanorbornenes **154a-c** were prepared by Gorbunova and Anikina to test their antioxidant properties in lipid peroxidation (Figure 20).[162] *N*-Benzyl derivative **154a** exhibited significant activity in mice liver homogenate oxidation by iron(II) chloride/ascorbate and inhibited mice erythrocyte hemolysis by H_2O_2 which, together with lack of cytotoxicity made it a good candidate for further investigations.

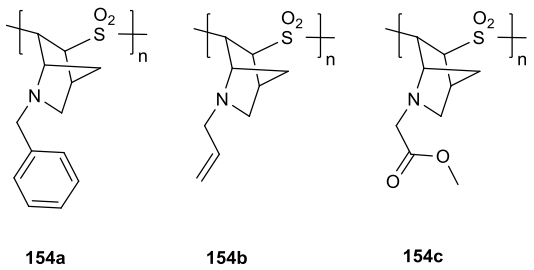


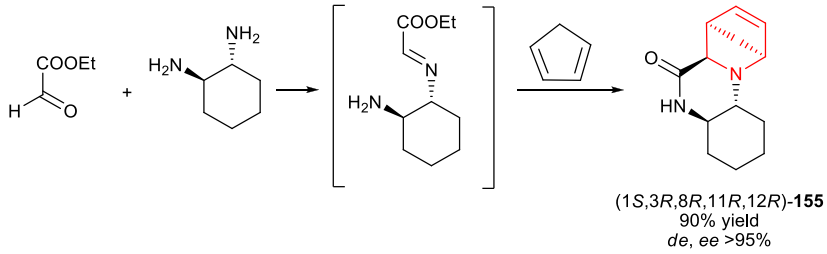
Figure 20. Polysulfones based on 2-azanorbornene scaffold[162]

6. Summary

The chiral 2-azabicyclo[2.2.1]heptane (or 2-azabicyclo[2.2.1]heptene) system can be attained by several synthetic routes, with aza-Diels-Alder cycloaddition of enantiomerically

pure imines to cyclopentadiene being the most important and convenient method. Chirality multiplication due to high stereoselectivity of cycloaddition is particularly worth emphasizing. The examples presented in chapters 3-5 showed the versatility of 2-azanorbornyl derivatives as chiral building blocks, their utility in the stereoselective catalysis and applications in biomedical studies. The investigations are now facilitated by the fact that these bicyclic compounds are now commercially available.

Still, there is room for further exploration. Novel, modified systems can be obtained by using various substrates at the cycloaddition stage as exemplified by our stereoselective synthesis of enantiopure tri- and tetracyclic compounds bearing up to 5 stereogenic centers (example is shown in Scheme 70).[163]



Scheme 70. Synthesis of the enantiopure tetracyclic compound using 1,2-diaminocyclohexane as a chirality source.[163] 2-Azanorbornene fragment in the tetracyclic product **155** indicated.

The known modifications of the 2-azabicyclo[2.2.1]heptane derivatives include transformations of the bicyclic skeleton, stereoselective ring opening, and alteration of substituents. The synthesis of bisfunctional ligands with a possible control of the mutual position and character of donor groups remains the most important since 2-azanorbornane serves as a rigid chiral scaffold and as an additional source of discrimination in the course of catalytic reaction. Certain possibilities remain relatively underexplored, like preparation of systems containing two or more bicyclic fragments. Also catalytic (in particular, organocatalytic) applications have been limited to several reactions. Thus, intrinsic chirality, the ease of synthesis and various possible ways of modifications make 2-azanorbornane an attractive compound for diverse and yet not completely explored applications.

Abbreviation list

aza-DA – aza-Diels-Alder reaction

BINAP - 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

Boc - *tert*-butoxycarbonyl

Bpin - pinacolatoboron

BSA – (N,O)-bis(trimethylsilyl)acetamide

Cbz – carboxybenzyl

COD – cyclooctadiene

CpH - cyclopentadiene

DBU – 1,8-diazabicyclo[5.4.0]undec-7-ene

DEAD - diethyl azodicarboxylate

DMAP – 4-dimethylaminopiridine

HCV - hepatitis C virus

KHMDS - potassium bis(trimethylsilyl)amide

LDA – lithium diisopopylamide

NK-1 – neurokine-1

NPht – phthalimide

NSuc - succinimide

PNBA – *para*-nitrobenzoic acid

RCM – ring-closure metathesis

ROM-CM – ring-opening metathesis-cross metathesis

TBDPS - *tert*-butyldiphenylsilyl

TBHP – *tert*-butyl hydoperoxide

TEBACl - benzyl trimethylammonium chloride

TGFα – transforming growth factor

TMSCl – trimethylsilyl chloride

Ts – tosyl, *para*-toluenesulfonyl

XIAP – X-linked inhibitor of apoptosis protein

References

1. O. Diels and K. Alder, *Justus Liebigs Ann. Chem.*, 1928, **460**, 98-122.
2. M. Juhl and D. Tanner, *Chem. Soc. Rev*., 2009, **38**, 2983-2992.
3. E. J. Corey, *Angew. Chem. Int*. *Ed.,* 2002, **41**, 1650-1667.
4. K. C. Nicolaou, S. A. Snyder, T. Montagnon and G. E. Vassilikogiannakis, *Angew. Chem. Int. Ed.*, 2002, **41**, 1668-1698.
5. A. A. Desai, *Angew. Chem. Int. Ed.,* 2011, **50**, 1974-1976.
6. M. F. Lipton and A. G. M. Barrett, *Chem. Rev.,* 2006, **106**, 2581-2582.
7. J.-A. Funel and S. Abele, *Angew. Chem. Int. Ed.*, 2013, **52**, 3822-3863.
8. S. Kobayashi, *Catalytic Enantioselective* Aza-*Diels-Alder Reactions.* In *Cycloaddition Reactions in Organic Synthesis* (Kobayashi, S.; Jørgensen, K. A., Eds.); Wiley-VCH Verlag GmbH, Weinheim, Germany, 2001**,** Chapter 5, pp. 187-209.
9. H. Sundén, I. Ibrahem, L. Eriksson and A.Córdova, *Angew. Chem. Int. Ed.* 2005, **44**, 4877-4880
10. M. G. Memeo and P. Quadrelli, *Chem. Eur. J.*, 2012, **18**, 12554-12582.
11. D. Blondet and C. Morin, *Heterocycles*, 1982, **19**, 2155-2182.
12. (a) S. D. Larsen and P. A. Grieco, *J. Am. Chem. Soc.* 1985, **107,** 1768-1769; (b) For and improved and optimized procedure see: P. A. Grieco and S. D. Larsen, *Org. Synth.*, 1990, **68**, 206-208.
13. L. Yu, D. Chen and P. G. Wang, *Tetrahedron Lett.*, 1996, **37**, 2169-2172.
14. A. P. Grieco, S. D. Larsen and W. F. Fobare, *Tetrahedron Lett*., 1986, **27**, 1975-1978.
15. (a) L. Stella, H. Abraham, J. Feneau-Dupont, B. Tinant and J. P. Declercq, *Tetrahedron Lett*., 1990, **31**, 2603–2606; (b) H. Abraham and L. Stella, *Tetrahedron,* 1992, **48**, 9707-9718.
16. (a) P. D. Bailey, R. D. Wilson and G. R. Brown, *Tetrahedron Lett*., 1989, **30**, 6781–6784; (b) P. D. Bailey, R. D. Wilson and G. R. Brown, *J. Chem*. *Soc*., *Perkin Trans*. 1, 1991, 1337-1340.
17. H. Waldmann and M. Braun, *Liebigs Ann*. *Chem*., 1991, 1045-1048.
18. N. Hashimoto, H. Yasuda, M. Hayashi and Y. Tanabe, *Org. Process Res. Dev.,* 2005,

9, 105-109.

19. P. D. Bailey, G. R. Brown, F. Korber, A. Reed and R. D. Wilson, *Tetrahedron: Asymmetry*, 1991**, 2**, 1263-1282.
20. J. E. Rodríguez-Borges, X. García-Mera, F. Fernández, V. H. C. Lopes, A. L. Magalhães and M. N. D. S. Cordeiro, *Tetrahedron*, 2005, **61**, 10951-10957.
21. F. Teixeira, J. E. Rodríguez-Borges, A. Melo and M. N. D. S. Cordeiro, *Chem. Phys. Lett.,* 2009, **477**, 60-64.
22. F. Teixeira, A. Melo and M. N. D. S. Cordeiro, *Comput. Theor. Chem.,* 2013, **1012**, 54-59.
23. J. K. Ekegren, S. A. Modin, D. A. Alonso and P. G. Andersson, *Tetrahedron: Asymmetry,* 2002, **13**, 447–449.
24. C. Hedberg, P. Pinho, P. Roth and P. G. Andersson, *J. Org. Chem.,* 2000, **65***,* 2810-2812.
25. A. Trifonova and P. G. Andersson, *Tetrahedron: Asymmetry,* 2004, **15**, 445-452.
26. The use of chiral (*S*)-lactate- or (*R*)-pantolactone-derived *N*-toluene-*p*-sulfonyliminoacetate in the aza-DA reaction was described by Haley *et al.*: P. Hamley, G. Helmchen, A. B. Holmes, D. R. Marshall, J. W. M. MacKinnon, D. F. Smith and J. W. Ziller, *J. Chem. Soc., Chem. Commun.*, 1992, 786-788.
27. S. K. Bertilsson, J. K. Ekegren, S. A. Modin and P. G. Andersson, *Tetrahedron*, 2011, **57**, 6399-6406.
28. T.-P. Loh, K. S.-V. Koh, K.-Y. Sim and W.-K. Leong, *Tetrahedron Lett.*, 1999, **40**, 8447-8451.
29. S. A. Modin and P. G. Andersson, *J. Org. Chem*., 2000, **65**, 6736-6738.
30. a) M. J. Södergren and P. G. Andersson, *J. Am. Chem. Soc.*, 1998, **120**, 10760-10761. b) M. J. Södergren, S. K. Bertilsson and P. G. Andersson, *J. Am. Chem. Soc.*, 2000, **122**, 6610-6618.
31. J. M. Blanco, O. Caamaño, F. Fernández, X. García-Mera, C. López, G. Rodríguez, J. E. Rodríguez-Borges and A. J. E. Rodríguez-Hergueta, *Tetrahedron Lett.* 1998, **39**, 5663-5666.
32. M. L. C. do Vale, J. E. Rodríguez-Borges, O. Caamaño, F. Fernández and X. García-Mera, *Tetrahedron,* 2006, **62**, 9475-9482.
33. (a) F. Fernández, X. García-Mera, M. L. C. do Vale and J. E. Rodríguez-Borges, *Synlett,* 2005, 319-321; (b) The use of menthol auxilaries in the aza-DA reaction was

also studied by Baliley's group: P. D. Bailey, D. J. Londesbrough, T. C. Hancox, J. D. Heffernan and A. B. Holmes, *J. Chem. Soc., Chem. Commun.*, 1994, 2543-2544.

34. X. García-Mera, J. E. Rodríguez-Borges, M. L. C. do Vale and M. J. Alves, *Tetrahedron,* 2011, **67**, 7162-7172.
35. a) T. Bauer, S. Szymański, A. Jeżewski, P. Gluziński and J. Jurczak, *Tetrahedron: Asymmetry*, 1997, **8**, 2619-2625; b) S. Szymański, C. Chapuis and J. Jurczak, *Tetrahedron: Asymmetry*, 2001, **12**, 1939-1945.
36. S. Yao, S. Saaby, R. G. Hazell and K. A. Jørgensen, *Chem. Eur. J.*, 2000, **6**, 2435-2448.
37. A. H. G. P. Prenzel, N. Deppermann and W. Maison, *Org. Lett.*, 2006, **8**, 1681-1684.
38. W. Maison, *Eur. J. Org. Chem.,* 2007, 2276-2284.
39. C. J. Swanson, M. Bures, M. P. Johnson, A.-M. Linden, J. A. Monn and D. D. Scheopp, *Nat. Rev. Drug Discovery,* 2005, **4**, 131-144.
40. C. A. D. Sousa, M. L. C. Vale, J. E. Rodríguez-Borges, X. García-Mera and J. Rodríguez -Otero, *Tetrahedron Lett.,* 2008, **49**, 5777-5781.
41. C. A. D. Sousa, M. L. C. Vale, J. E. Rodríguez-Borges and X. García-Mera, *Tetrahedron*, 2012, **68**, 1682-1687.
42. C. A. D. Sousa, C. F. R. A. C. Lima, M. Andrade, X. García-Mera and J. E. Rodríguez-Borges, *Tetrahedron,* 2013, **69**, 5048-5057.
43. R. Singh and R. Vince, *Chem. Rev*., 2012, **112**, 4642-4686.
44. J. C. Jagt and A. M. van Leusen, *J. Org. Chem.*, 1974, **39**, 564-566.
45. G. J. Griffiths and F. E. Previdoli, *J. Org. Chem.,* 1993, **58**, 6129-6131.
46. a) J. R. Malpass and N. J. Tweddle, *J. Chem. Soc., Perkin Trans 1*, 1977, 874-884; b) P.-T. Pham and R. T. Vince, *Phosphorus, Sulfur, Silicon Relat. Elem.*, 2007, **182**, 779-791.
47. I. Coldham, J. C. Fernàndez, K. N. Price and D. J. Snowden, *J. Org. Chem.,* 2000, **65**, 3788-3795.
48. F. Zanardi, C. Curti, A. Sartori, G. Rassu, A. Roggio, L. Battistini, P. Burreddu, L. Pinna, G. Pelosi and G. Casiraghi, *Eur. J. Org. Chem.*, 2008, 2273-2287.
49. O. O. Grygorenko, O. S. Artamonov, G. V. Palamarchuk, R. I. Zubatyuk, O. V. Shishkin and I. V. Komarov, *Tetrahedron: Asymmetry*, 2006, **17**, 252-258.
50. O. O. Grygorenko, I. V. Komarov and C. Cativiela, *Tetrahedron: Asymmetry*, 2009, **20**, 1433-1436.

51. S. M. Husbands, R. H. Kline, A. C. Allen and A. H. Newman, *J. Org. Chem.,* 1998, **63**, 418-419.
52. C. K. Himmelsbach, *J. Pharmacol. Exp. Ther.*, 1942, **75**, 64-68.
53. A. Kasyan, C. Wagner and M. E. Maier, *Tetrahedron*, 1998, **54**, 8047-8054.
54. D. W. Piotrowski and J. Polivkova, *Tetrahedron Lett.,* 2010, **51**, 17-19.
55. T. Abe, H. Takeda, Y. Takahashi, Y. Miwa, K. Yamada and M. Ishikura, *Heterocycles*, 2008, **75**, 2931-2936.
56. T. Abe, H. Takeda, K. Yamada and M. Ishikura, *Heterocycles,* 2008, **76**, 133-136.
57. a) P. Pinho and P. G. Andersson, *Chem. Commun.,* 1999, 597-598; b) W. Maison, D. C. Grohs and A. H. G. P. Prenzel, *Eur. J. Org. Chem.* 2004, 1527-1543.
58. M. Legraverend, E. Bisagni and C. Huel, *J. Heterocycl. Chem.*, 1989, **26**, 1881.
59. S. J. M. Nordin, P. Roth, T. Tarnai, D. A. Alonso, P. Brandt and P. G. Andersson, *Chem. Eur. J.*, 2001, **7**, 1431-1436.
60. D. A. Alonso, S. J. M. Nordin and P. G. Andersson, *Org. Lett.,* 1999, **1**, 1595-1597.
61. Y. Okuyama, H. Nakano and H. Hongo, *Tetrahedron*: *Asymmetry,* 2000, **11**, 1193-1198;
62. a) H. Nakano, Y. Okuyama, K. Iwasa, and H. Hongo, *Heterocycles*, 2001, **54**, 411-418; b) H. Nakano, Y. Okuyama, K. Fushimi, R. Yamakawa, D. Kayaoka and H. Hongo, *Heterocycles*, 2002, **56**, 457-466.
63. P. Brandt, C. Hedberg, K. Lawonn, P. Pinho and P. G. Andersson, *Chem. Eur. J.*, 1999, **5**, 1692-1699.
64. P. Pinho and P. G. Andersson, *Tetrahedron*, 2001, **57**, 1615-1618.
65. M. Genov, G. Scherer, M. Studer and A. Pfaltz, *Synthesis*, 2002, 2037-2042.
66. T. K. Olszewski, E. Wojaczyńska, R. Wieczorek and J. Bąkowicz *in press*.
67. P. A. Grieco, D. T. Parker, W. F. Fobare and R. Ruckle, *J. Am. Chem. Soc.* 1987, **109,** 5859-5861.
68. P. A. Grieco and J. D. Clark, *J. Org. Chem.,* 1990, **55**, 2271-2272.
69. (a) A. P. Grieco and A. Bahsas, *J. Org. Chem.*, 1987, **52**, 5746-5749. (b) In the case of the synthesis of 2-azanorbornene derivatives of simple aminoacid esters very similar procedure was described by Waldmann: H. Waldmann, *Liebigs Ann. Chem*., 1989, 231-238.
70. C. A. D. Sousa, F. Rizzo-Aguiar, M. L. C. Vale, X. García-Mera, O. Caamaño and J. E. Rodríguez-Borges, *Tetrahedron Lett.*, 2012, **53**, 1029-1032.

71. M. J. Alves, X. García-Mera, M. L. C. Vale, T. P. Santos, F. R. Aguiar and J. E. Rodríguez-Borges, *Tetrahedron Lett.,* 2006, **47**, 7595-7597.
72. D. A. Alonso, S. K. Bertisslon, S. Y. Johnsson, S. J. M. Nordin, M. J. Södergren and P. G. Andersson, *J. Org. Chem.,* 1999, **64**, 2276-2280.
73. O. Arjona, A. G. Csákÿ, R. Medel and J. Plumet, *J. Org. Chem.,* 2002, **67**, 1380-1383.
74. P. D. Bailey, I. M. McDonald, G. M. Rossair and D. Taylor, *Chem. Commun.* 2000, 2451-2452.
75. E. Wojaczyńska, I. Turowska-Tyrk and J. Skarżewski, *Tetrahedron* 2012, **68**, 7848-7854.
76. P. Brandt and P. G. Andersson, *Synlett*, 2000, 1092-1106.
77. L. Pu and H.-B. Yu, *Chem. Rev.*, 2001, **101**, 757-824.
78. R. Noyori and M. Kitamura, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 49-69.
79. H. Nakano, N. Kumagai, C. Kabuto, H. Matsuzaki and H. Hongo, *Tetrahedron: Asymmetry*, 1995, **6**, 1233-1236.
80. H. Nakano, N. Kumagai, H. Matsuzaki, C. Kabuto, and H. Hongo, *Tetrahedron: Asymmetry*, 1997, **8**, 1391-1401.
81. D. Guijarro, P. Pinho and P. G. Andersson, *J. Org. Chem.*, 1998, **63**, 2530-2535.
82. J. Lu, Y.-H. Xu and T.-P. Loh, *Tetrahedron Lett.*, 2008, **49**, 6007-6008.
83. J. Lu, F. Liu, W.-J. Zhou and T.-P. Loh, *Tetrahedron Lett.*, 2008, **49**, 5389-5392.
84. S. J. Oxenford, J. M. Wright, P. O'Brien, N. Panday and M. R. Shipton, *Tetrahedron Lett.*, 2005, **46**, 8315-8318.
85. A. Magnus, S. K. Bertilsson and P. G. Andersson, *Chem. Soc. Rev.*, 2002, **31**, 223-229.
86. S. K. Bertilsson, M. J. Södergren and P. G. Andersson, *J. Org. Chem.*, 2002, **67**, 1567-1573.
87. A. Gayet, S. K. Bertilsson and P. G. Andersson, *Org. Lett.*, 2002, **4**, 3777-3779.
88. A. Gayet and P. G. Andersson, *Tetrahedron Lett.*, 2005, **46**, 4805-4807.
89. S. K. Bertilsson and P. G. Andersson, *Tetrahedron* 2002, **58**, 4665-4668.
90. P. Brandt, P.-O. Norrby and P. G. Andersson, *Tetrahedron*, 2003, **59**, 9695-9700.
91. D. Liu and S. A. Kozmin, *Angew. Chem. Int. Ed.*, 2001, **40**, 4757-4759.
92. D. Liu and S. A. Kozmin, *Org. Lett.*, 2002, **4**, 3005-3007.
93. S. Gladiali and E. Alberico, *Chem. Soc. Rev.*, 2006, **35**, 226-236.
94. D. A. Alonso, D. Guijarro, P. Pinho, O. Temme and P. G. Andersson, *J. Org. Chem.*, 1998, **63**, 2749-2751.

95. D. A. Alonso, P. Brandt, S. J. M. Nordin and P. G. Andersson, *J. Am. Chem. Soc.*, 1999, **121**, 9580-9588.

96. D. A. Alonso, S. J. M. Nordin, P. Roth, T. Tarnai, P. G. Andersson, M. Thommen and U. Pittelkow, *J. Org. Chem.*, 2000, **65**, 3116-3122.

97. J. K. Ekegren, P. Roth, K. Källström, T. Tarnai and P. G. Andersson, *Org. Biomol. Chem.*, 2003, **1**, 358-366.

98. P. Brandt, P. Roth and P. G. Andersson, *J. Org. Chem.*, 2004, **69**, 4885-4890.

99. A. Trifonova, K. Källström and P. G. Andersson, *Tetrahedron*, 2004, **60**, 3393-3403.

100. P. Roth, P. G. Andersson and P. Somfai, *Chem. Commun.*, 2002, 1752-1753.

101. P. Pinho, D. Guijarro and P. G. Andersson, *Tetrahedron*, 1998, **54**, 7897-7906.

102. A. Trifonova, J. S. Diesen, C. J. Chapman and P. G. Andersson, *Org. Lett.*, 2004, **6**, 3825-3827.

103. A. Trifonova, J. S. Diesen and P. G. Andersson, *Chem. Eur. J.*, 2006, **12**, 2318-2328.

104. M. Engman, J. S. Diesen, A. Paptchikhine and P. G. Andersson, *J. Am. Chem. Soc.*, 2007, **129**, 4536-4537.

105. M. Engman, P. Cheruku, P. Tolstoy, J. Bergquist, S. F. Völker and P. G. Andersson, *Adv. Synth. Catal.*, 2009, **351**, 375-378.

106. P. Tolstoy, M. Engman, A. Paptchikhine, J. Bergquist, T. L. Church, A. W.-M. Leung and P. G. Andersson, *J. Am. Chem. Soc.*, 2009, **131**, 8855-8860.

107. T. L. Church, T. Rasmussen and P. G. Andersson, *Organometallics*, 2010, **29**, 6769-6781.

108. J.-Q. Li, A. Paptchikhine, T. Govender and P. G. Andersson, *Tetrahedron: Asymmetry*, 2010, **21**, 1328-1333.

109. J. J. Verendel, T. Zhou, J.-Q. Li, A. Paptchikhine, O. Lebedev and P. G. Andersson, *J. Am. Chem. Soc.*, 2010, **132**, 8880-8881.

110. P. Cheruku, T. L. Church, A. Trifonova, T. Wartmann and P. G. Andersson, *Tetrahedron Lett.*, 2008, **49**, 7290-7293.

111. J. J. Verendel, J.-Q. Li, X. Quan, B. Peters, T. Zhou, O. R. Gautun, T. Govender and P. G. Andersson, *Chem. Eur. J.*, 2012, **18**, 6507-6513.

112. J.-Q. Li, X. Quan and P. G. Andersson, *Chem. Eur. J.*, 2012, **18**, 10609-10616.

113. P. Cheruku, S. Gohil, and P. G. Andersson, *Org. Lett.*, 2007, **9**, 1659-1661.

114. P. Cheruku, J. S. Diesen and P. G. Andersson, *J. Am. Chem. Soc.* 2008, **130**, 5595-5599.

115. P. Cheruku, A. Paptchikhine, T. L. Church and P. G. Andersson, *J. Am. Chem. Soc.*, 2009, **131**, 8285-8289.

116. K. Källström, I. J. Munslow, C. Hedberg and P. G. Andersson, *Adv. Synth. Catal.*, 2006, **348**, 2575-2578.

117. A. Paptchikhine, P. Cheruku, M. Engman and P. G. Andersson, *Chem. Commun.*, 2009, 5996-5998.

118. T. Zhou, B. Peters, M. F. Maldonado, T. Govender and P. G. Andersson, *J. Am. Chem. Soc.*, 2012, **134**, 13592-13595.

119. A. Lightfoot, P. Schnider and A. Pfaltz, *Angew. Chem., Int. Ed.*, 1998, **37**, 2897-2905.

120. C. Hedberg, K. Källström, P. Brandt, L. K. Hansen and P. G. Andersson, *J. Am. Chem. Soc.*, 2006, **128,** 2995-3001.

121. T. L. Church and P. G. Andersson, *Coord. Chem. Rev.*, 2008, **252**, 513-531.

122. O. Pàmies, P. G. Andersson and M. Diéguez, *Chem. Eur. J.*, 2010, **16**, 14232-14240.

123. A. Cadu and P. G. Andersson, *J. Organometallic Chem.*, 2012, **714**, 3-11.

124. A. Cadu and P. G. Andersson, *Dalton Trans.*, 2013, **42**, 14345-14356.

125. J.-Q. Li, B. Peters, and P. G. Andersson, *Chem. Eur. J.*, 2011, **17**, 11143-11145.

126. M. B. Andrus and M. C. Lashley, *Tetrahedron*, 2002, **58**, 845-866.

127. M. J. Södergren and P. G. Andersson, *Tetrahedron Lett.*, 1996, **37**, 7577-7580.

128. S. K. Bertilsson and P. G. Andersson, *J. Organometallic Chem.*, 2000, **603**, 13-17.

129. H. Lebel, J.-F. Marcoux, C. Molinaro and A. B. Charette, *Chem. Rev.*, 2003**, 103***,*** 977-1050.

130. S. A. Modin, P. Pinho, P. G. Andersson, *Adv. Synth. Catal.*, 2004, **346**, 549-553.

131. B. M. Trost and M. L. Crawley, *Chem. Rev.*, 2003, **103**, 2921-2944.

132. E. Wojaczyńska and J. Skarżewski, *Tetrahedron: Asymmetry*, 2008, **19**, 2252-2257.

133. F.-X. Felpin, S. Girard, G. Vo-Thanh, R. J. Robins, J. Villiéras and J. Lebreton, *J. Org. Chem.*, 2001, **66**, 6305-6312.

134. D. C. Horwell, D. Naylor and H. M. G. Willems, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 31-36.

135. D. C. Horwell, W. Howson, D. Naylor and H. M. G. Wilems, *Bioorg. Med. Chem. Lett.*, 1995, **5**, 1445-1450.

136. P. S. Portoghese, A. A. Mikhail and H. J. Kupferberg, *J. Med. Chem.*, 1968, **11**, 219-225.

137. E. Pombo-Villar, P. Supavilai, H. P. Weber and H. W. G. M. Boddeke, *Bioorg. Med. Chem. Lett.*, 1992, **2**, 501-504.

138. P. Raubo, J. J. Kulagowski and G. G. Chicchi, *Synlett*, 2006, 271-274.

139. J. O. Link, J. G. Taylor, L. Xu, M. Mitchell, H. Guo, H. Liu, D. Kato, T. Kirschberg, J. Sun, N. Squires, J. Parrish, T. Keller, Z.-Y. Yang, C. Yang, M. Matles, Y. Wang, K. Wang, G. Cheng, Y. Tian, E. Mogalian, E. Mondou, M. Cornpropst, J. Perry and M. C. Desai, *J. Med. Chem.*, 2014, **57**, 2033-2046.

140. L. Bunch, T. Liljefors, J. R. Greenwood, K. Frydenvang, H. Bräuner-Osborne, P. Krogsgaard-Larsen and U. Madsen, *J. Org. Chem.*, 2003, **68**, 1489-1495.

141. J. M. Mellor, N. G. J. Richards, K. J. Sargood, S. G. Chamberlin and D. E. Davies, *Tetrahedron Lett.*, 1995, **36**, 6765-6768.

142. S. G. Chamberlin, K. J. Sargood, A. Richter, J. M. Mellor, D. W. Anderson, N. G. J. Richards, D. L. Turner, R. P. Sharma, P. Alexander and D. E. Davies, *J. Biol. Chem.*, 1995, **270**, 21062-21067.

143. Q. Hu, A. Nie, K. Welsh, F. R. Pinacho Cristósomo, X. Zhu, Z. Li, J. An, J. C. Reed, L. Zhang. and Z. Huang, *Exp. Biol. Med.*, 2011, **236**, 247-251.

144. S. Venkatraman, F. G. Njoroge, W. Wu, V. Girijavallabhan, A. J. Prongay, N. Butkiewicz and J. Pichardo, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 1628-1632.

145. S. Venkatraman, *Trends Pharmacol. Sci.*, 2012, **33**, 289-294.

146. B. Portevin, A. Benoist, G. Rémond, Y. Hervé, M. Vincent, J. Lepagnol and G. De Nanteuil, *J. Med. Chem.*, 1996, **39**, 2379-2391.

147. D. C. Limburg, B. E. Thomas, IV, J.-H. Li, M. Fuller, D. Spicer, Y. Chen, H. Guo, J. P. Steiner, G. S. Hamilton and Y.-Q. Wu, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3867-3870.

148. M. Jäger, K. Polborn and W. Steglich, *Tetrahedron Lett.*, 1995, **36**, 861-864.

149. J. R. Malpass and C. D. Cox, *Tetrahedron Lett.*, 1999, **40**, 1419-1422.

150. C. D. Cox and J. R. Malpass, *Tetrahedron*, 1999, **55**, 11879-11888.

151. C. D. Cox, J. R. Malpass, J. Gordon and A. Rosen, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2372-2379.

152. J. R. Malpass and R. White, R. *J. Org. Chem.*, 2004, **69**, 5328-5334.

153. J. R. Malpass, S. Handa and R. White, *Org. Lett.*, 2005, **7**, 2759-2762.

154. R. White, J. R. Malpass, S. Handa, S. R. Baker, L. M. Broad, L. Folly and A. Mogg, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 5493-5497.

155. F. I. Carroll, P. Abraham, K. Parham, R. C. Griffith, A. Ahmad, M. M. Richard, F. N. Padilla, J. M. Witkin and P. K. Chiang, *J. Med. Chem.*, 1987, **30**, 805-809.

156. F. I. Carroll, P. Abraham, S. Chemburkar, X.-C. He, S. W. Mascarella, Y. W. Kwon and D. J. Triggle, *J. Med. Chem.*, 1992, **35**, 2184-2191.

157. D. M. Hodgson, S. Hachisu and M. D. Andrews, *Org. Lett.*, 2005, **7**, 815-817.

158. C. Shi and C. C. Aldrich, *J. Org. Chem.*, 2012, **77**, 6057-6058.

159. U. S. Singh, R. C. Mishra, R. Shankar, and C. K. Chu, *J. Org. Chem.*, 2014, **79**, 3917-3923.

160. R. K. Boeckmann, Jr., J. E. Pero and D. J. Boehmler, *J. Am. Chem. Soc.*, 2006, **128**, 11032-11033.

161. A. B. Dyatkin, W. J. Hoekstra, D. J. Hlasta, P. Andrade-Gordon, L. de Garavilla, K. T. Demarest, J. W. Gunnet, W. Hageman, R. Look and B. E. Maryanoff, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 3081-3084. (corrigendum: *Bioorg. Med. Chem. Lett.*, 2004, **14**, 3363.)

162. M. Gorbunova and L. Anikina, *Eur. J. Med. Chem.*, 2013, **63**, 655-661.

163. E. Wojaczyńska, J. Bąkowicz, M. Dorsz and J. Skarżewski, *J. Org. Chem.* 2013, **78**, 2808-2811.