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Enantioselective construction of the 8-azabicyclo[3.2.1]octane scaffold: application in the synthesis of tropane alkaloids

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The 8-azabicyclo[3.2.1]octane scaffold is the central core of the family of tropane alkaloids, which display a wide array of interesting biological activities . As a consequence, research directed towards the preparation of this basic structure in a stereoselective manner has gathered the attention of many research groups worlwide across the years. Despite this, most of the approaches relay on the enantioselective construction of an acyclic starting material that contains all the required stereochemical information to allow the stereocontrolled formation ot the bicyclic scaffold. As an alternative, there is an important number of methodologies reported in which the stereochemical control is achieved directly on the same transformation that generates the 8-oxabicyclo[3.2.1]octane architecture. This review compiles the most relevant achievements in this area.

1. Introduction

Tropane alkaloids[1] constitute a group of secondary metabolites produced by numerous plant species and is formed by more than 300 compounds that are characterized by containing the 8-azabicyclo[3.2.1]octane core in their structure (See some selected examples in Fig. 1). The interesting array of biological activities displayed by several members of this family is documented through multiple cases in which either natural or synthetic tropanes have been tested as potential therapeuticals, mainly related to the treatment of neurological and psychiatric diseases such as Parkinson, depression, schizophrenia or panic disorder.[2] Traditionally, these compounds have been obtained by isolation from plants of the *Solanaceae, Convolvulaceae*, *Moraceae*, *Erythroxylaceae*, *Proteaceae*, *Rhizophoraceae* or *Euphorbiaceae* families. However, research focussed on the development of efficient methodologies for the stereocontrolled synthesis of tropanes or related scaffolds has become an area of increasing interest in both academia and industry.

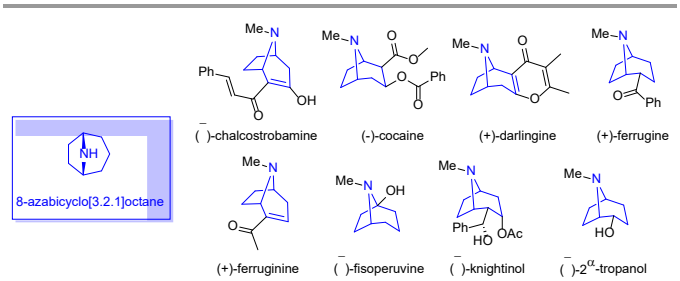

Fig. 1. Some selected examples of naturally occurring tropane alkaloids

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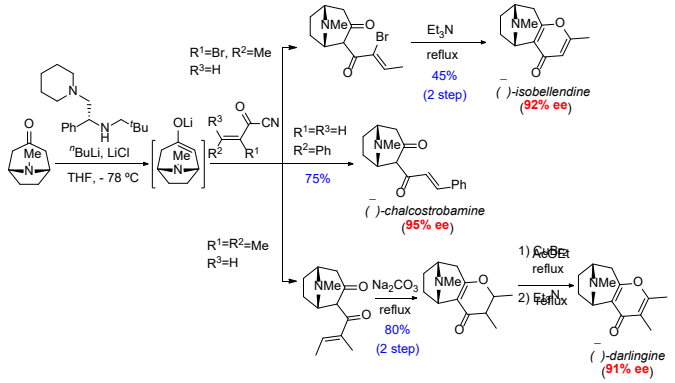
The synthetic efforts directed towards the stereoselective preparation of tropanes has been intense, with many examples of successful approaches to different members of this family of products. In particular, there is a remarkable prevalence in the chemical literature of methodologies for the stereoselective generation of the tropane scaffold from chiral enantioenriched starting materials, specially making use of the chiral pool approach.[3] As an alternative, enantioselective approaches directed to obtain the 8-azabicyclo[3.2.1]octane scaffold from achiral starting materials has experience an important increase in terms of new methodology development and applications. This review wishes to present the current state of the art on the different methodologies for the enantioselective synthesis of tropanes, strictly focussed on those approaches in which stereochemical control is achieved concomitant to the formation of the 8-azabicyclo[3.2.1]octane scaffold.

In general, the different methods described in the literature can be classified into two general categories: (1) the enantioselective desymmetrization of achiral tropinone derivatives or (2) the enantioselective *de novo* construction of the basic tropane scaffold, the latter involving either chiral auxiliary methodology or the utilization of enantioselective catalysis. The most relevant examples reported up to date will be disclosed in the following sections according to this classification.

2. Desymmetrization of tropinone derivatives

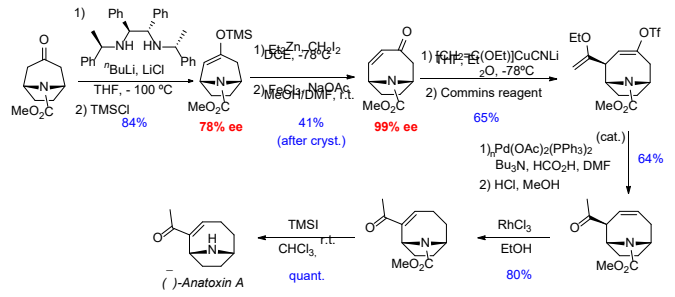
The desymmetrization[4] of tropinone, as well as other related derivatives, has been a widely used strategy to access different alkaloids of the tropane family, the most common approach being the use of chiral lithium amides[5] to promote the enantioselective deprotonation of the α-position to the carbonyl group to generate an enantioenriched enolate intermediate. For instance, Majewsky and coworkers demonstrated that the chiral lithium amide derived from phenylglycinol shown in Scheme 1 was able to differentiate the two enantiotopic groups of protons of tropinone in a very effective manner, being the enolate intermediate subsequently quenched with a variety of electrophiles (Scheme 1).[6] Remarkably, the incorporation of LiCl as additive to the reaction

resulted to be crucial for obtaining high enantiocontrol, obtaining the best results when 0.5 equiv. were added. In particular, acylation of this enolate with alkenoyl cyanides provided a highly versatile family of synthetic scaffolds that could be converted into the enantiomers of the naturally occurring tropane alkaloids such as (–)-chalcostrobamine, (–)-isobellendin or (–)-darlingine (Scheme 1).



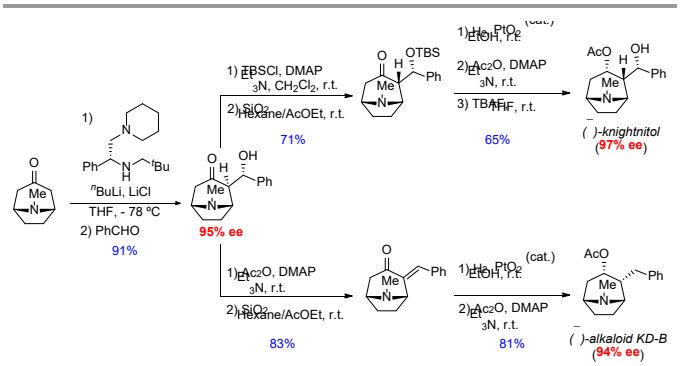
Scheme 1 The synthesis of the enantiomers of several naturally occurring tropane alkaloids through enantioselective deprotonation using a phenylglycinol-derived chiral lithium amide base.

The bis-amide base derived from (*S,S*)-diphenylethylenediamine shown in Scheme 2 has also been found to perform excellently in the same enantioselective deprotonation reaction. In this case, the enantioenriched lithium enolate was isolated as the corresponding silyl enol ether and this compound was employed as the starting material in the total synthesis of (–)-anatoxin-A,[7] which is the enantiomer of the naturally occurring alkaloid. The synthesis involved the homologation of the silyl enol ether through cyclopropanation/ring expansion to generate an homotropone derivative. Next, conjugate addition of a conveniently functionalized alkenyl heterocuprate followed by quenching of the enolate intermediate with Commins reagent proceeded with good yield and diastereoselectivity and further elaboration of this adduct through Pd-mediated reductive removal of triflate followed by hydrolysis of the enol ether, $RhCl_3$-mediated alkene isomerization and final *N*-deprotection provided the target (–)-anatoxin-A alkaloid.



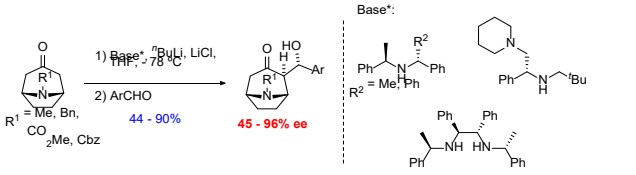
Scheme 2 The enantioselective synthesis of (–)-anatoxin-A using the enantioselective deprotonation of tropinone as key step.

Through the combination of a chiral amide base together with other electrophiles, Majewsky and coworkers have been able to synthesize a variety of other interesting scaffolds. For instance, reaction between the desymmetrized lithium enolate of tropinone with benzaldehyde provided the corresponding aldol with excellent yield and enantioselectivity, being this adduct an appropriate precursor for the enantioselective synthesis of (–)-knightinol, the enantiomer of the naturally occurring tropane (+)-knightinol and also the synthesis of (–)-KD-B alkaloid (Scheme 3).[8]



Scheme 3 The synthesis of several tropane alkaloids from tropinone using enantioselective deprotonation/aldol reaction as key step.

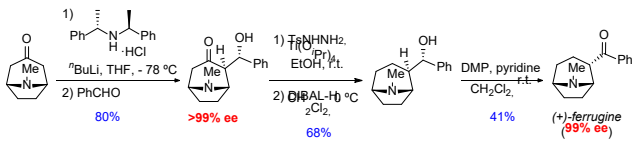
Later on, this enantioselective deprotonation/aldol strategy has been employed by several other authors, who evaluated diverse chiral lithium amides to promote this transformation directed to expand the scope of this procedure to the preparation of other tropinone-derived precursors, specially, with diverse substitution at nitrogen. As it can be seen in Scheme 4, several amides or bis-amides have been identified as excellent chiral bases to promote this aldol reaction providing moderate to excellent yields and enantiomeric excesses.[9] As it was found in all the preceding examples, the incorporation of LiCl as additive was found to be crucial in all cases for obtaining high enantiocontrol, observing significantly poorer enantiomeric excesses when each reaction was carried out in the absence of this salt.



Scheme 4 Desymmetrization of tropinone derivatives by enantioselective deprotonation/aldol reaction

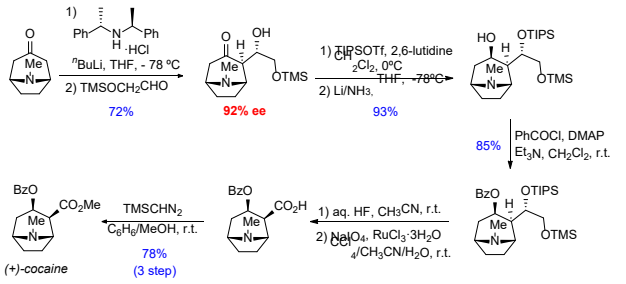
This methodology has been employed by Lazny *et al*. as the key step in the synthesis of (+)-ferrugine, this case using lithium (S,*S*)-*N*,*N* bis(1-phenylethyl)amide as chiral base (Scheme 5).[10] Thus, deprotonation of tropinone and the subsequent aldol reaction with benzaldehyde took place with complete enantiocontrol and this key synthetic intermediate was subjected to reductive deoxygenation through hydrazone formation followed by oxidation of the secondary alcohol moiety with Dess-Martin periodinane (DMP). The 2-benzoyltropinone oxidation product also underwent epimerization of the labile stereocentre at the α position with

respect to the ketone moiety to provide (+)-ferrugine, which is the thermodynamically favoured diastereoisomer.



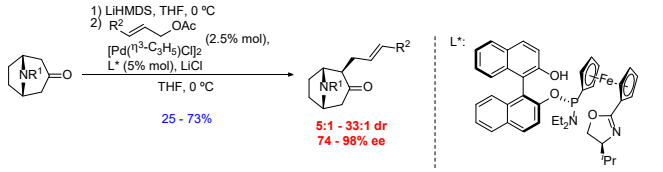
Scheme 5 Synthesis of (+)-ferrugine

Another example that shows the utility of this reaction design is shown in Scheme 6 with the total synthesis of the unnatural enantiomer of cocaine. In this case, the aldol reaction was carried out under the same reaction conditions as shown in the previous scheme, but using trimethylsilyloxyacetaldehyde as the electrophile. The aldol product was obtained with good yield and enantiocontrol and as a single diastereoisomer. Next, protection of the secondary alcohol as triisopropylsilyl (TIPS) ether followed by diastereoselective reduction of the ketone using lithium in ammonia provided the most stable equatorial alcohol diastereoisomer. Finally, benzoyl ester formation and deprotection of the diol followed by oxidative cleavage with $NaIO_4$ under ruthenium catalysis and final esterification provided (+)-cocaine in excellent overall yield.[11]



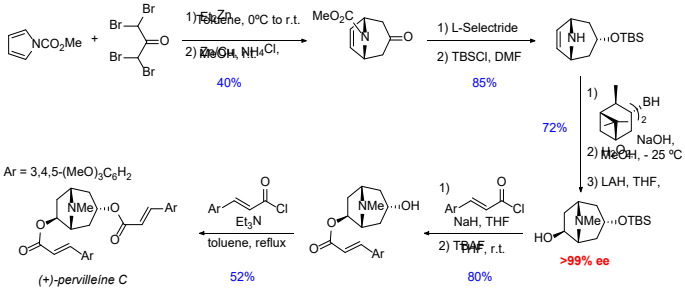
Scheme 6 Synthesis of (+)-cocaine using the enantioselective deprotonation/aldol reaction of tropinone as key step

A different strategy was presented by Ding, Hou and coworkers, who used the asymmetric allylic alkylation in the presence of a chiral palladium catalyst to promote the desymmetrization of differently *N*-protected tropinone derivatives (Scheme 7).[12] The reaction was carried out in a two-step sequence, initially adding a strong base such as LiHMDS to form the enolate species from tropinone and next, incorporating the alkylating agent and 2.5 mol% of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ together with 5 mol% of an enantiopure ferrocenyl-type ligand. Under these conditions, equilibration between the two enantiomers of the lithium enolate of the tropinone reagent had to take place, one of them undergoing allylic alkylation faster than the other. The authors do not clarify whether the chiral catalyst is involved in the racemization process, therefore not being able to discriminate between the possibility of a DKR or a DYKAT process operating in this reaction.



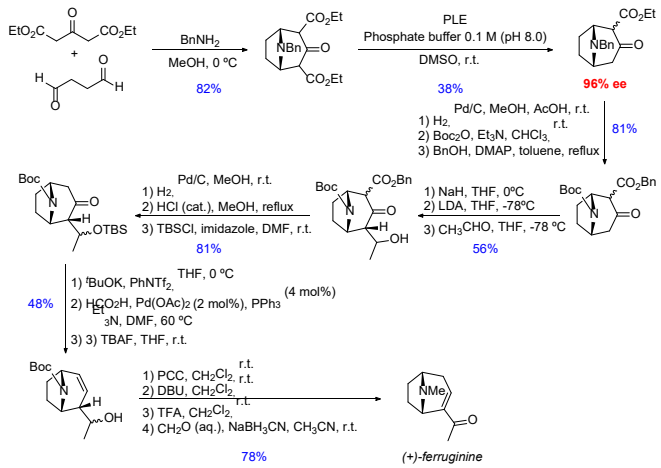
Scheme 7 Synthesis of tropane derivatives through desymmetrization of tropinone derivatives *via* Pd-catalyzed asymmetric allylic alkylation.

Other achiral azabicyclo[3.2.1]octane compounds that incorporate other functionalities different than the ketone moiety present at the tropinone core have also been successfully employed in desymmetrization reactions, using these other functional groups as a handle for chemical modification. A good example is shown in Scheme 8, in which enantioselective hydroboration of an *O*-protected 3-hydroxy-8-azabicyclo[3.2.1]oct-6-ene derivative was employed to promote the desymmetrization process and the obtained product was applied to the total synthesis of the natural product (+)-pervilleine C (Scheme 8).[13] The synthesis of the achiral bicyclo[3.2.1]octane precursor was carried out from commercially available reagents through (4+3) cycloaddition between *N*-methoxycarbonylpyrrole and 1,1,3,3 tetrabromoacetone, followed by dehalogenation, diastereoselective reduction and *O*-silylation. The enantioselective hydroboration/oxidation sequence involved the stoichiometric use of chiral (–)-diisopinocampheylborane as the hydroboration agent, obtaining the desymetrized product in excellent enantioselectivity after reduction of the carbamate moiety. Two successive acylation processes of the chemically differentiated secondary alcohols furnished the target natural product.



Scheme 8 Total synthesis of (+)-pervilleine C through enantioselective desymmetrizative hydroboration.

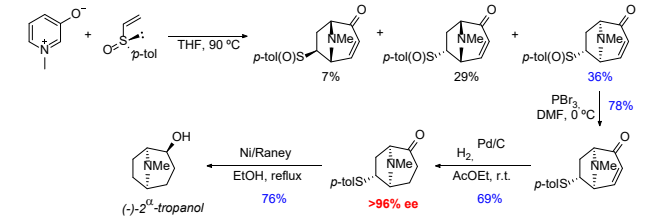
Finally the enantioselective enzymatic dealkoxycarbonylation of tropinone 1,5-diesters has also demonstrated to be an excellent approach to the enantioselective synthesis of tropane derivatives, in this case also applying this reaction as the key step in the total synthesis of (+)-ferruginine (Scheme 9).[14] The starting material was prepared by means of the classical Robinson synthesis,[15] which was submitted to enantioselective dealkoxycarbonylation in the presence of PLE esterase, thus generating the corresponding monoester as a mixture of epimers, both of them with excellent enantiomeric excesses. The synthesis of (+)-ferruginine was accomplished from this material in additional 14 steps and in an overall 4% yield.



Scheme 9 Total synthesis of (+)-ferruginine.

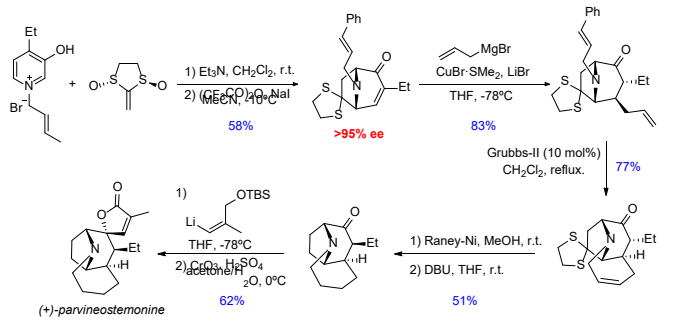
3. The use of chiral auxiliaries in the synthesis of tropane type alkaloids

Chiral auxiliaries have also been widely used as a general strategy for the enantioselective construction of the 8-azabicyclo[3.2.1]octane scaffold, in general focusing on cycloaddition chemistry between olefins and azomethine ylides.[16] A good example is shown in Scheme 10, in which a chiral sulfoxide was employed to achieve stereocontrol in the (3+2) cycloaddition with 3-oxidopyridinium ylides.[17] The reaction provided three diastereoisomers, with the major one holding the appropriate configuration for accessing natural (–)-2α-tropanol by means of sulfoxide reduction followed by reductive desulfuration through catalytic hydrogenation, that also involved the hydrogenation of the enone moiety. Final diastereoselective reduction of the ketone with Ni Raney provided (–)-2α-tropanol.



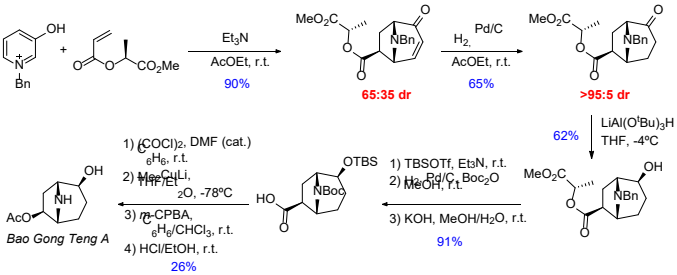
Scheme 10 Synthesis of (-)-2α-tropanol via (3+2) cycloaddition with oxidopyridinium ylides using sulfoxides as chiral auxiliaries.

In addition, Aggarwal has also described the use of enantioenriched *trans*-2-methylene-1,3-dithiolane 1,3-dioxide as useful chiral dipolarophile for the stereocontrolled (3+2) cycloaddition with these 3-oxidopyridinium ylides (See Scheme 11 for an example).[18] This chemistry has been afterwards applied to the synthesis of a highly functionalized tropane-like compound that has served as useful starting material for the enantioselective synthesis of other more complex alkaloids. Scheme 11 shows the application of this methodology towards the total synthesis of (+)-parvineostemonine, which was accomplished in only 5 steps and with an overall yield of 17% from this key synthetic intermediate.[19]



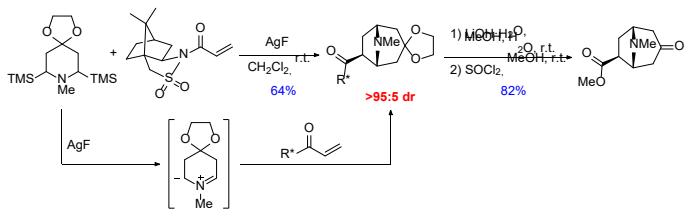
Scheme 11 Total synthesis of (+)-parvineostemonine.

Alternatively, lactic acid esters have also demonstrated their efficacy as chiral auxiliaries in this type of cycloadditions. In particular, the total synthesis of Bao Gong Teng A was accomplished starting with the (3+2) cycloaddition involving the same type of oxidopyridinium ylide and the acrylate of (S)-methyl lactate as the key step for the stereoselective construction of the 8-azabicyclo[3.2.1]octane scaffold (Scheme 12).[20] The cycloaddition took place with high yield and moderate diastereoselectivity, but the minor diastereoisomer could be removed after hydrogenation of the mixture of cycloadducts followed by crystallization. Next, diastereoselective reduction of the ketone provided the required *endo* alcohol with acceptable yield, although together with some amount of the undesired *exo* diastereoisomer that was removed after column chromatography purification. A series of additional transformations delivered the target natural alkaloid with a 10% overall yield from the starting materials.



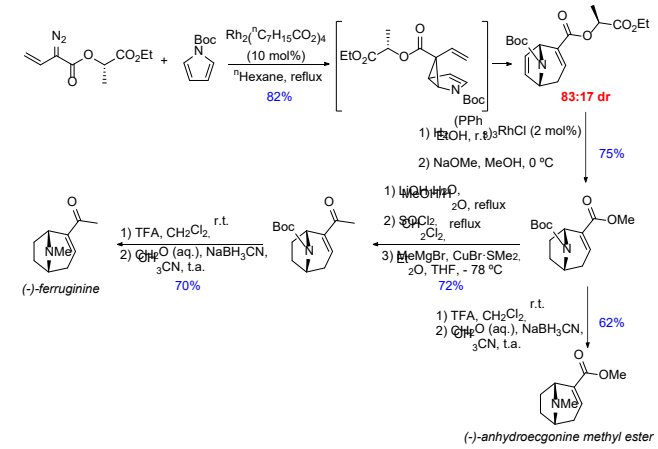
Scheme 12 Use of Oppolzer chiral auxiliary in (3+2) cycloaddition for the synthesis of the tropane scaffold.

The (3+2) cycloaddition involving azomethine ylides has also been carried out efficiently using the Oppolzer sultam as a chiral auxiliary, as shown in Scheme 13.[21] In this case, the ylide was generated from a 2,6-bis(trimethylsilyl)piperidine in the presence of AgF as the oxidizing agent, as it underwent diastereoselective 1,3-dipolar cycloaddition with the corresponding α,β-unsaturated amide derived from Oppolzer camphorsultam. This reaction took place in moderate yield but with an excellent diastereoselectivity, obtaining the final tropane derivative after hydrolysis of the chiral auxiliary and subsequent esterification.



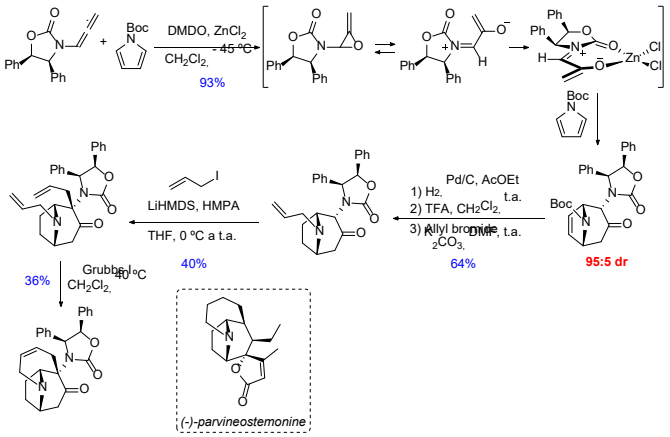
Scheme 13 Use of Oppolzer chiral auxiliary in (3+2) cycloaddition for the synthesis of the tropane scaffold.

The formal (4+3) cycloaddition[22] between *N*-Boc-pyrroles and vinyldiazomethanes is another alternative to build up the tropane scaffold, as described by Davies and coworkers in the total synthesis of (–)-ferruginine and (–)-anhydroecgonine methyl ester (Scheme 14).[23] This key transformation involved a cascade process that started with the cyclopropanation of the pyrrole by the vinyldiazomethane reagent under Rh-catalysis and was followed by Cope rearrangement and it was carried out employing enantiopure (*S*)-ethyl lactate as chiral auxiliary, providing the 8-azabicyclo[3.2.1]octane adduct with good yield and a 66% diastereomeric excess. Completion of the synthesis of (–)-ferruginine involved hydrogenation of the unconjugated olefin, hydrolysis of the ester that also enabled the recovery of the chiral auxiliary, conversion of the carboxylate moiety into an acetyl group and final removal of the *N*-Boc protecting group followed by *N*-methylation. The synthesis of (–)-anhydroecgonine methyl ester was carried out by carbamate hydrolysis/*N*-methylation after the chiral auxiliary was removed.



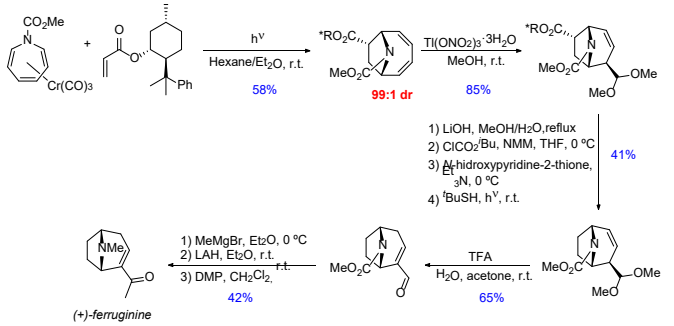
Scheme 14 Total synthesis of (–)-ferruginine and (–)-anhydroecgonine methyl ester through formal (4+3) cycloaddition between N-Boc pyrrole and 2-diazobut-3-enoates.

On the other hand, chiral oxazolidinones have also been effective as stereodirecting elements in an alternative type of (4+3) cycloaddition chemistry, in this case involving oxyallyl cations as the 1,3-dipolar reagent undergoing cycloaddition with the pyrrole reagent (Scheme 15).[24] The key oxyallyl cations had to be generated *in situ* from allenamides after regioselective oxidation of the more electron-rich alkene of the allenamide reagent using DMDO. The incorporation of $ZnCl_2$ as chelating Lewis acid was also necessary for the formation of a rigid 1,3-dipolar intermediate in which facial selectivity was controlled by the two substituents of the oxazolidinone auxiliary. This adduct was employed for the preparation of an advanced intermediate in the total synthesis of (-)-parvineostemonine through a series of subsequent transformations, which involved hydrogenation of the olefin, the substitution of the protecting group of the amine by an allyl residue, α-allylation of the ketone at the most substituted position and ring-closing metathesis.



Scheme 15. Stereoselective synthesis of the tricyclic core of (-)-parvineostemonine trough (4+3) cycloaddition using oxazolidinones as chiral auxiliaries

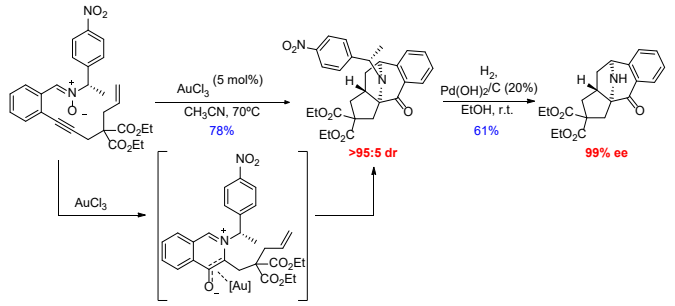
In a different context, (-)-8-phenylmenthol has been used as a chiral auxiliary in the (6+2) photocycloaddition reaction between an hexahapto azepine/chromium complex and acrylates directed towards the total synthesis of (+)-ferruginine (Scheme 16).[25] The reaction provided a direct access to the homotropane scaffold with excellent stereoselectivity, being this adduct converted into the required 8-oxa-bicyclo[3.2.1]octane derivative through McKillop-Taylor oxidative rearrangement in the presence of a Tl(III) complex.[26] Next, saponification, Barton decarboxylation, aldehyde deprotection followed by addition of methylmagnesium bromide and a final carbamate reduction and Dess-Martin oxidation of the alcohol provided the target compound in a 6% overall yield of a 8-step linear sequence.



Scheme 16 Total synthesis of (+)-ferruginine through (6+2) photocycloaddition using (-)-8-phenylmenthol as chiral auxiliary

Finally, the stereoselective synthesis of complex polycyclic systems containing the tropane subunit has been accomplished from acyclic nitrones derived from ortho-alkynyl substituted

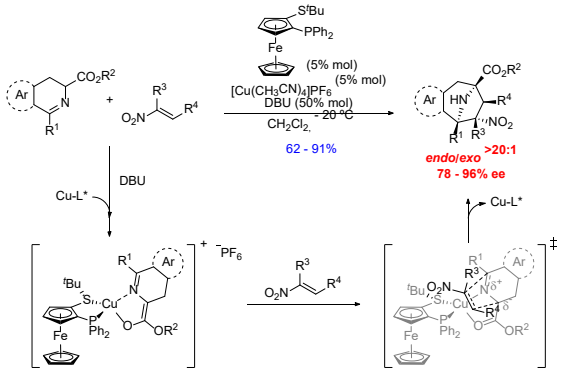
benzaldehydes through a gold(III)-catalyzed cycloisomerization/cycloaddition cascade process in which an α-methylbenzylamine unit was incorporated as chiral auxiliary (Scheme 17).[27] In the first step of the cascade, the Au(III) species catalyzed the intramolecular oxidative cycloisomerization between the nitrone and the alkyne, generating *in situ* an oxidopyridinium ylide intermediate that subsequently underwent intramolecular (5+2) cycloaddition[28] with the remaining olefin that was incorporated as pendant substituent under stereochemical control by the chiral auxiliary. Removal of the auxiliary could be easily accomplished by debenzylation under standard hydrogenolysis conditions. The reaction could be extended to more complex substrates incorporating different substituents at the alkene moiety or even using an alkyne as the dipolarophile. Some examples also showed that intermolecular reactions were also possible under this reaction design.



Scheme 17 Enantioselective synthesis of complex 8-oxabicyclo[3.2.1]octanes through gold(III)-catalyzed cycloisomerization/intramolecular (5+2) cycloaddition.

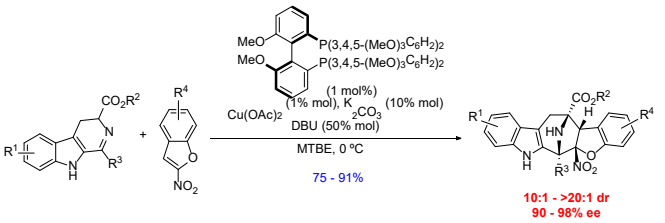
4. Catalytic enantioselective synthesis of tropane scaffolds

In the last two decades, the enantioselective catalytic reactions that allow the construction of the 8-azabicyclo[3.2.1]octane scaffold have emerged as an efficient alternative to the previously described strategies. Most of the advances in this area involve the construction of the bicyclic scaffold through cycloaddition chemistry, being the first advances in this area focussed on 1,3-dipolar cycloadditions involving the participation of azomethine ylides under Lewis acid catalysis.[16] A good example is shown in Scheme 18, in which the reaction between cyclic azomethine ylides and nitroalkenes was carried out in the presence of a copper complex that incorporated (*R*)-Fesulphos as the chiral ligand.[29] This methodology allowed the preparation of a wide variety of tropane-like alkaloids with good yields, high *exo*-selectivity and excellent enantiomeric excesses.



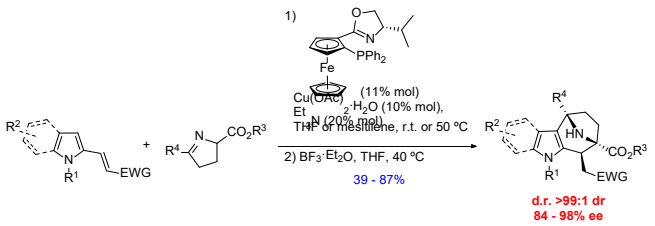
Scheme 18 Cu/Fesulphos-catalyzed (3+2) cycloaddition between cyclic azomethine ylides and nitroalkenes for the synthesis of the tropane scaffold.

In a related approach, copper/MeO-BIPHEP complexes have also been used as chiral catalysts in a similar (3+2) cycloaddition that involved 3,4-dihydro-β-carbolines as the dipole precursors and 2-nitrobenzofurans as the dipolarophile. (Scheme 19).[30] A remarkable feature of this particular reaction is the fact that it takes place together with the dearomatization of the indole scaffold. In addition, the reaction was found to be remarkably wide in scope, enabling the preparation of a wide variety of tropane-containing polycylcic derivatives with different substituents and in almost all cases providing excellent results in terms of yield, diastereo- and enantioselectivity.



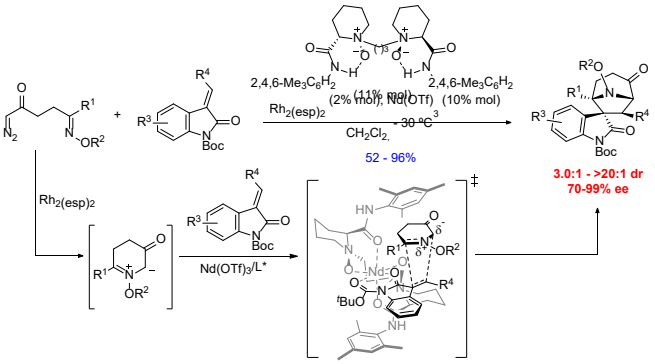
Scheme 19 The enantioselective synthesis of densely substituted tropane derivatives by (3+2) cycloaddition between azomethine ylides and 2-nitrobenzofurans

Another approach to tropanes with a fused pyrrole or indole ring has been reported (Scheme 20).[31] In this case, the formal (3+2) cycloaddition between 2-vinylpyrroles or 2-vinylindoles and cyclic ketimines in the presence of a chiral ferrocene-based copper complex provided the desired tropane derivatives in good yields, as well as with complete diastereoselectivity and excellent enantiomeric excesses. Mechanistically, the reaction took place in two steps, initiated by the Michael addition of the α-aminoester moiety to the electron-poor vinylindole reagent under catalyst control followed by intramolecular aza-Friedel-Crafts reaction, that had to be promoted by the subsequent addition of an external Lewis acid such as $BF_3{\cdot}OEt_2$, the latter taking place with complete diastereoselection under substrate control.



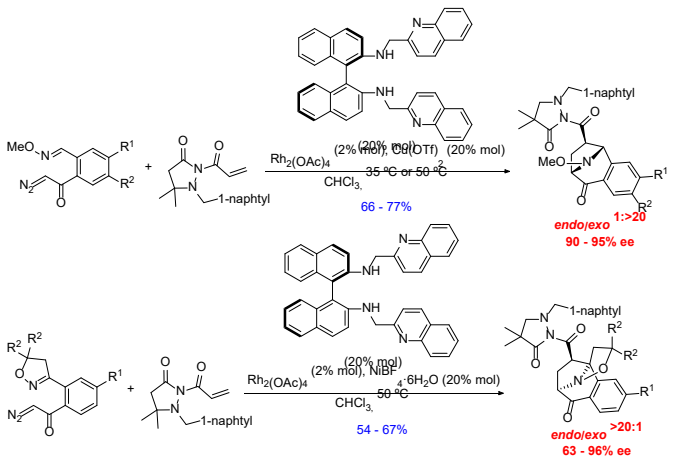
Scheme 20 Enantioselective synthesis of indole- and pyrrole-fused tropane derivatives through one-pot enantioselective Michael addition followed by intramolecular Friedel Crafts reaction.

An alternative procedure for the formation of cyclic azomethine ylides, involves the intramolecular *N*-alkylation of azomethine compounds with diazoalkanes under Rhodium catalysis.[32] This is the strategy followed by Antonchick, Waldmann and coworkers in the reaction shown in Scheme 21.[33] The (3+2) cycloaddition with the dipolarophile, in this case an alkylideneoxindole reagent, had to be promoted by the incorporation of a Nd(III) complex as chiral Lewis acid, in an overall process that involves the orthogonal, dual participation of two different catalysts. The best performance in terms of enantiocontrol was found when the bis(pypecolamidinium *N*-oxide)-type ligand shown in Scheme 21 was employed.



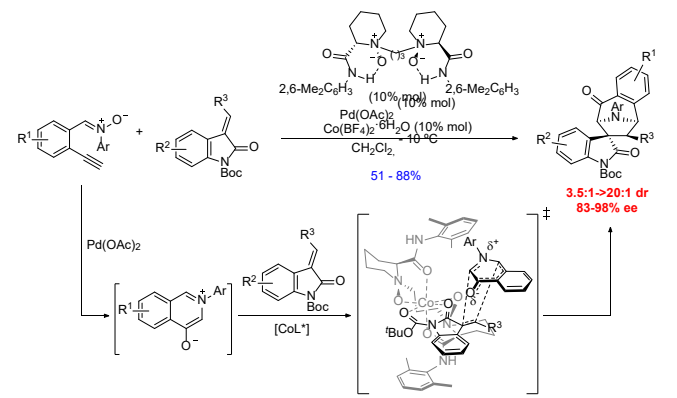
Scheme 21. The enantioselective synthesis of tropane derivatives through (3+2) cycloaddition under dual Rh/Nd catalysis

A similar dual catalytic system has also been used to generate benzo-fused 8-azabicyclo[3.2.1]octanes in an enantioselective manner, in this case using a Cu(II) complex with a BINAM-type chiral ligand as the Lewis acid species involved in the enantioselective 1,3-dipolar cycloaddition, once the azomethine ylide had been formed from the starting diazooxime reagent under Rh-catalysis. (Scheme 22).[34] The use of *N*-substituted acryloylpyrazoles as dipolarophiles was found to be crucial to obtain high regioselectivity, also providing the required handle for chelation with the Lewis acid catalyst that results into a conformationally rigid transition state during the cycloaddition process. Remarkably, *exo/endo* selectivity could also be modulated through modification of the oxime moiety of the starting diazoalkane reagent and moving to Ni(I) as the Lewis acidic metal centre, being able to obtain in a diastereodivergent manner each of these two possible diastereoisomer with high enantiomeric excess.



Scheme 22 Diastereodivergent enantioselective synthesis of benzo-fused tropane derivatives through (3+2) cycloaddition under dual Rh/Lewis acid catalysis

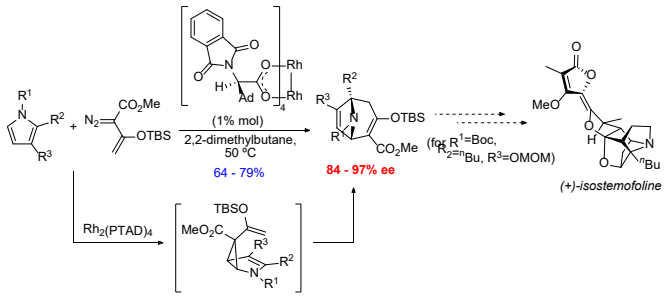
Recently, an enantioselective modified version of the reaction shown in Scheme 17 has been reported using a dual Pd/Co catalyst system (Scheme 23).[35] In this case, cycloisomerization of the *ortho*-alkynyl substituted benzaldehyde nitrone took place in the presence of the Pd catalyst, that generated the required oxidopyridinium ylide and this subsequently underwent intermolecular (5+2) cycloaddition with alkylideneoxindoles in the presence of the chiral Co(II) Lewis acid catalyst. Ligand screening showed that a chiral bis-pipecolinic acid-derived *N,N*-dioxide was the best performing one in terms of enantiocontrol, enabling the preparation of a wide variety of adducts with high yield and excellent diastereo- and enantiomeric excesses.



Scheme 23 The enantioselective synthesis of tropane derivatives through cascade Pd-catalyzed cycloisomerization followed by Co(II)-catalyzed intermolecular (5+2) cycloaddition

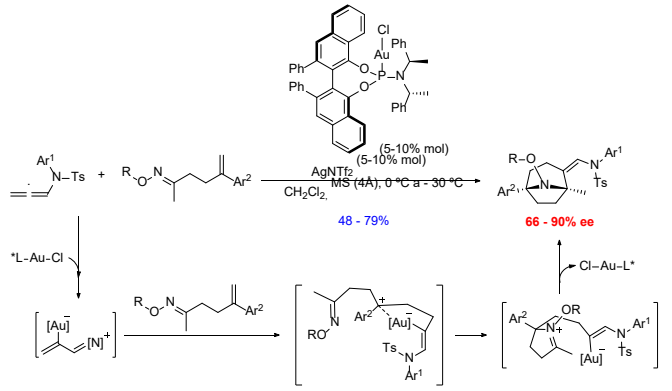
In an alternative approach, chiral rhodium catalyst, $Rh_2(PTAD)_4$, has been used the (4+3) cycloaddition between pyrroles and 2-(siloxy)vinyldiazoacetate by Davies and coworkers (Scheme 24).[36] This process is an enantioselective version of the cascade cyclopropanation/Cope rearrangement reaction shown previously in Scheme 14. In this particular case, the reaction provided excellent diastereoselectivities and enantioselectivities for a wide variety of substituted tropanes prepared through this methodology. Remarkably, the reaction

is rather wide in scope with respect to the possibility of using pyrroles with different substituents, also proceeding with excellent regioselectivity, determined by the formation of the less sterically encumbered cyclopropane intermediate. This methodology was also employed for the formal total synthesis of (+)-isostemofoline, in which the enantioselective formal (4+3) cycloaddition provided directly one of the key intermediates of a previously reported synthesis of this natural product in a racemic form.[37]



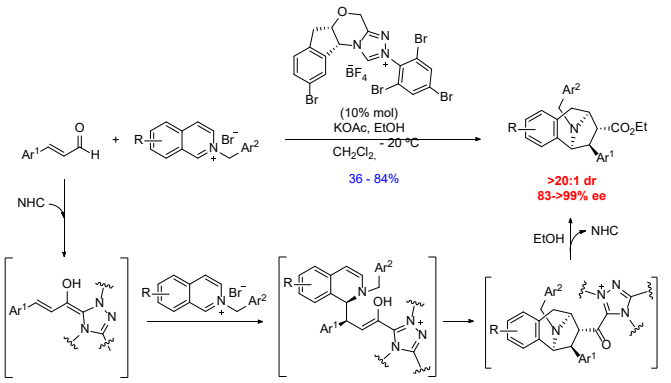
Scheme 24 Rhodium-catalyzed enantioselective (4+3) cycloaddition for the synthesis of tropanes and application in the formal synthesis of (+)-isostemofoline

Gold catalysis has been employed by Mascareñas, López and coworkers in the (2+2+2) cycloaddition between *N*-tosylallenamides and γ-alkenyl oximes, employing a chiral phosphoramidite as ligand (Scheme 25).[38] This reaction involved the initial activation of the electron-rich allene by the gold complex, followed by the addition of the olefin to the activated allenamide, this stage being the stereodefining step. This key initial intermediate is described as a configurationally stable carbocation, in which the rotation around the C1–C2 bond is restricted due to an electrostatic interaction between C1 and the gold(I) atom. The subsequent intramolecular reaction between the oxime nitrogen and the gold-stabilized benzylic carbocation occurred in a stereospecific manner, generating a cyclic iminium ion that, finally, underwent aza-Prins cyclization, generating the final tropane derivatives and regenerating the gold catalyst.



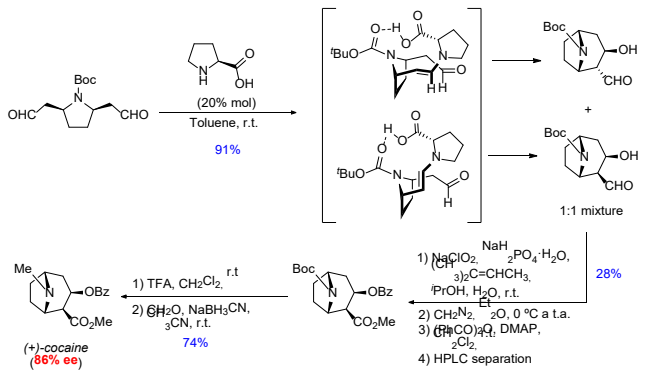
Scheme 25 The enantioselective synthesis of tropane derivatives by gold-catalyzed (2+2+2)-cycloaddition between *N*-tosylallenamides and γ-alkenyl oximes

On the other hand, organocatalysis has also been used as an alternative methodological approach for the enantioselective construction of the 8-azabicyclo[3.2.1]octane scaffold. An straightforward method relies on the organocatalytic activation of an electron-poor alkene that participates as the dipolarophile involved in formal (3+2) cycloaddition chemistry with azomethine ylides. For instance, the enantioselective cycloaddition between isoquinolinium ylides and enals has been described under the activation of the enal with a chiral *N*-heterocyclic carbene (NHC) as catalyst (Scheme 26).[39] The overall process consists on a double Mannich reaction, initially started by the Breslow intermediate participating as an homoenolate equivalent and in also involving the dearomatization of the isoquinoline core. Incorporating ethanol to the reaction scheme as the nucleophilic additive that releases the carbene was required for catalyst turnover. The reaction was found to proceed with moderate yields and excellent diastereo- and enantiocontrol for a variety of differently substituted isoquinolinium salts and cinnamaldehyde derivatives, while β-alkyl substituted enals provided poor yields and enantioselectivities.



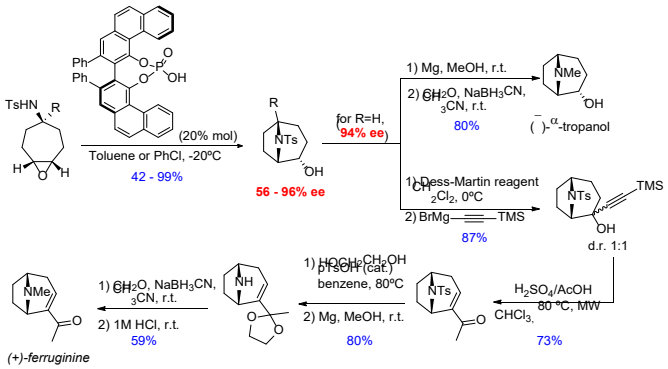
Scheme 26 Enantioselective synthesis of tropane derivatives through formal (3+2) cycloaddition between enals and isoquinolinium ylides under NHC-catalysis

In a different strategy, the intramolecular proline-catalyzed aldol reaction has been employed as the key step in the synthesis of (+)-cocaine (Scheme 27).[40] The tropane scaffold was generated directly from the *meso* diastereoisomer of a 2,5-bis(formylmethyl)pyrrolidine derivative through the aldol reaction between the two aldehyde moieties that proceeded via enamine activation. The overall process took place together with the desymmetrization of the starting material that ended in the enantioselective formation of the bicyclic aldol adduct, although as a 1:1 mixture of diastereoisomers as a result of the competitive participation of two possible chair-like transition states. This mixture of epimers was subjected to Pinnick oxidation, methyl ester formation and *O*-benzoylation, in which the undesired diastereoisomer could be removed by HPLC purification. Removal of the *N*-Boc group followed by *N*-methylation by reductive amination provided (+)-cocaine in 86% ee.



Scheme 27 Total synthesis of (+)-cocaine through proline-catalyzed dessymetrizative intramolecular aldol reaction

A different dessymetrizative approach has been taken for the enantioselective formation of tropanes. In this case, a chiral phosphate was employed as Brønsted acid catalyst to promote the enantioselective pseudotransannular ring opening of 1-aminocyclohept-4-ene-derived epoxides, that took place with excellent yield and enantioselectivity for the formation of a family of 5-substituted 8-azabicyclo[3.2.1]octan-2-ol derivatives (Scheme 28).[41] One of the compounds prepared was employed as the key starting material for the synthesis of (–)-α-tropanol and (+)-ferruginine in a 2- and 6-step sequence respectively. α-Tropanol was obtained just by changing the *N*-protecting tosyl substituent by an *N*-Me group. For the synthesis of (+)-ferruginine, the lateral side chain was introduced by oxidation of the alcohol followed by alkynylation of the formed ketone, which took place without any diastereoselection. However, this was irrelevant, as the enone moiety of the final product could be directly constructed from this mixture of epimers through Ruppe rearrangement. Completion of the synthesis only involved the removal of the tosyl group and *N*-methylation, although this also required the intermediate protection of the ketone moiety as an acetal.



Scheme 28 Total synthesis of (+)-ferruginine and (–)-α-tropanol through the enantioselective Brønsted acid-catalyzed desymmetrization of 1-aminocyclohept-4-ene-derived epoxides.

Conclusions

The different examples presented in this review show the tremendous progress made by synthetic chemists with respect to the development and discovery of new efficient methodologies for the stereoselective construction of the 8-azabicyclo[3.2.1]octane scaffold. Literature shows the growing tendency to employ asymmetric catalysis as the methodological approach, in line with the new demands by the society and the chemical industry for more sustainable approaches for the preparation of fine chemicals. In this context, there is still a lot of room for improvement in this area, also observing that most of the catalytic and enantioselective approaches to the tropane scaffold have not already been employed in total synthesis for the preparation of a target natural product or drug. On the other hand, from the different cases in which the methodologies presented herein have been employed to prepare a selected natural product, while the key reaction employed to build up the tropane core of the target molecule has been fully optimized in most cases to provide high yield and stereocontrol, there were still a long number of step required to reach to the final product. In many cases, these only involved routine functional group interconversions. However, it is somewhat surprising that, despite the rather simple nature of the final structure of these tropane alkaloids synthesized so far, the number of such "cosmetic" reactions employed after the central 8-azabicyclo[3.2.1]octane core has been constructed is surprisingly high in most cases,[42] which still calls for new developments and advances, trying to avoid such lengthy synthetic routes.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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