Recent Developments in Transannular Reactions

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Recent Developments in Transannular Reactions

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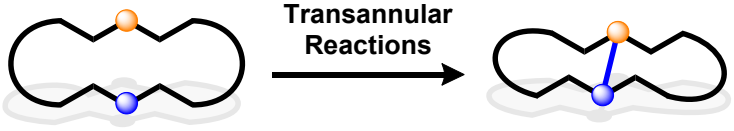
Dedicated to Prof. Dr. Joan Bosch on the occasion of his 75th birthday



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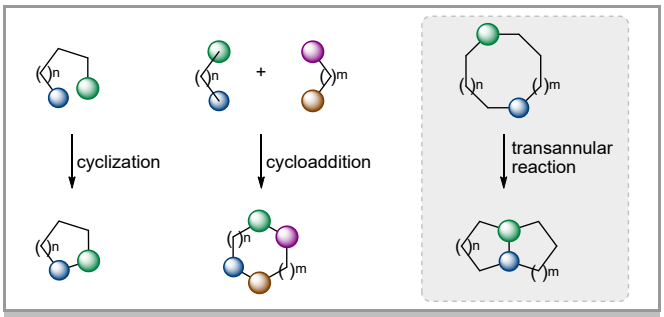
Abstract Transannular reactions have shown a remarkable performance for the construction of polycyclic scaffolds from medium- or large sized cyclic molecules in an unconventional manner. Recent examples of transannular reactions reported from 2011 have been reviewed, emphasizing the excellent performance of this approach when accessing the target compounds. This review also highlights how this methodology provides an alternative approach to other commonly used strategies for the construction of cyclic entities such as cyclization or cycloaddition reactions.

Key words Transannular reaction, Bicyclic compounds, Cyclization, Fused-ring systems, Heterocycles, Macrocycles, Natural products, Total synthesis

1 Introduction

Transannular reactions comprise a particular class of intramolecular transformations in which a new bond(s) is(are) formed between two (or more) atoms that are integrated within the structure of a cyclic starting material.[1] This reaction appears as an unconventional synthetic approach for the preparation of complex polycyclic scaffolds that are not easily accessed through other standard methodologies employed for the construction of cyclic molecules, such as cyclization or cycloaddition reactions (Scheme 1). Perhaps the main feature associated to transannular processes is the very limited degree of conformational freedom associated to the cyclic starting material which conditions the way the two reacting points can approach to each other when forming the new bond. As a consequence, the reaction outcome can be strongly influenced by steric and/or stereoelectronic effects induced by the size of the cyclic starting material or by the substituents incorporated at the ring perimeter.[2] In fact, the regioselectivity of a transannular reaction can be more influenced by the size of the new fused rings that are being formed rather than by the intrinsic reactivity of the functional groups participating in the process, which in some cases leads to unexpected reactivity patterns that can even go against several of the standard rules that govern intramolecular reactions. In addition, the conformationally rigid nature of the starting material typically facilitates stereocontrol when required.



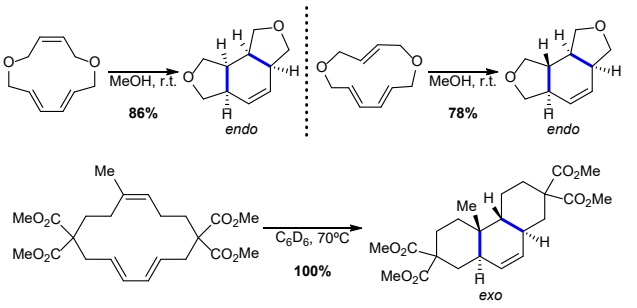
Scheme 1 Transannular reactions *vs* other conventional synthetic approaches to (poly)cyclic molecules

However, despite its enormous potential in terms of strategic bond disconnection, the transannular approach remains significantly underdeveloped as a general tool in synthesis. This can mainly be attributed to the intrinsically troublesome preparation of cyclic starting materials. As a consequence, the development of this type of reactions has gone hand in hand with methodological advances in the synthesis of medium and large rings. In this sense, the recent developments in synthetic methodology has stimulated research in this area, with a particular focus toward the application of transannular reactions as the key step in the total synthesis of complex targets. Several general reviews on transannular reactions have been published in the past, although some time ago.[1] On the other hand, a couple of reports have reviewed the use of transannular reactions in the

total synthesis of natural products.[3] This review presents the recent state of the art in the field covering the period 2011-2021, highlighting the most relevant or representative contributions in the area. The different examples have been categorized according to reaction type.

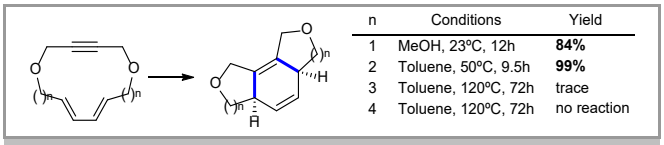
2 Transannular cycloadditions and electrocyclizations

Transannular versions of the archetypical Diels-Alder reaction have been explored and this reaction used as useful model to understand the behavior of macrocyclic substrates towards transannular processes. Early reports by Deslongchamps[4] already established the critical role played by the conformational constraints of the macrocycle at the transition state, taking into account that the substrate needs to adopt a situation in which the diene moiety stands in a *s-cis* conformation to be reactive. In this sense, although the Diels-Alder reaction is diastereospecific in nature, the *endo*/*exo* selectivity can be strongly dependent on the size and nature of the substituents placed on the starting material. A recent illustrative example on this situation can be seen in Scheme 2, in which 13-membered macrocyclic triene ethers reacted with complete diastereoselectivity to provide the corresponding *endo* tricyclic adducts in good yields and under mild conditions, while a related 14-membered triene delivered the *exo* diastereoisomer.[5]



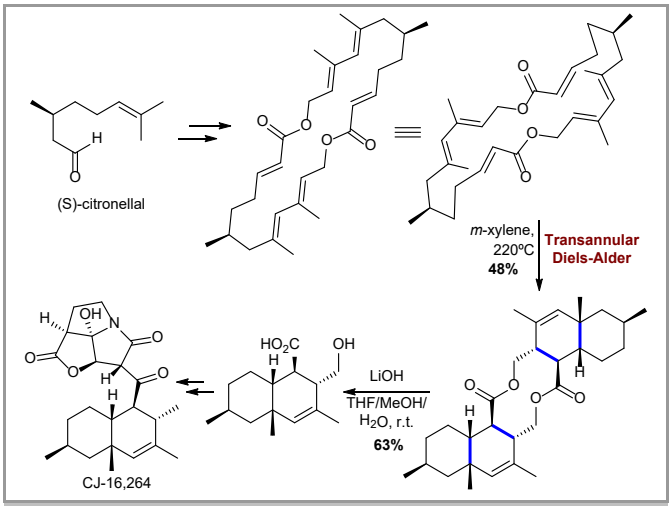
Scheme 2 Examples on the influence of the size of the macrocyclic substrate in the stereochemical outcome of transannular Diels-Alder reactions

In fact, the size of the macrocyclic starting material does not only condition the stereochemical outcome of the transannular Diels-Alder reaction but it is also a key factor influencing the reactivity of the substrate. In a series of experiments, Merlic and Houk studied the transannular Diels-Alder reaction on the macrocyclic dienyne ethers shown in Scheme 3, observing that the 12-membered substrate showed the highest tendency to undergo the Diels-Alder reaction, while the reactivity decreased as the size of the macrocycle increased.[6] This was studied with computational methods, concluding that lowering the distortion energies of the diene and dienophile in the transition state with respect to the corresponding bimolecular reaction facilitates the reaction, which can be done by either modifying the length of the tether or by inserting heteroatoms that contribute to a more flexible substrate.



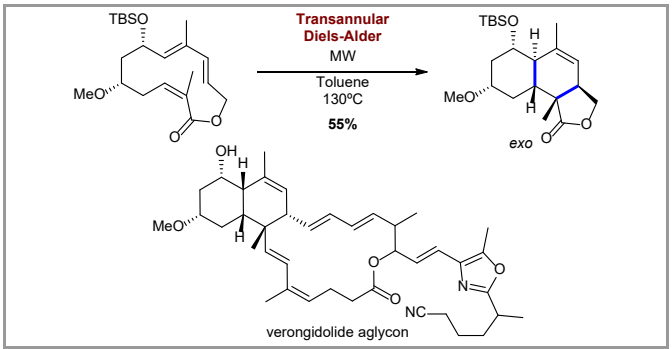
Scheme 3 Reactivity of macrocyclic dienyne ethers of different sizes towards transannular Diels-Alder reaction

The ability of cycloaddition reactions to generate simultaneously several bonds in combination with a transannular design has been the element of choice to plan the total synthesis of complex targets. Scheme 4 shows a good example of the ability of this approach applied to the total synthesis of CJ-16,264, an antibiotic of fungal origin with impressive activity against several drug-resistant bacteria.[7] The synthesis involved the preparation of a macrocyclic diester containing the required diene and dienophile moieties and that was synthesized as enantiopure material from citronellal. A double transannular Diels-Alder reaction took place after heating to 220 °C in xylene, providing the *exo* adduct in 48% yield. Hydrolysis of this diester provided two equivalents of the decaline core that constitutes the central core of the target product.



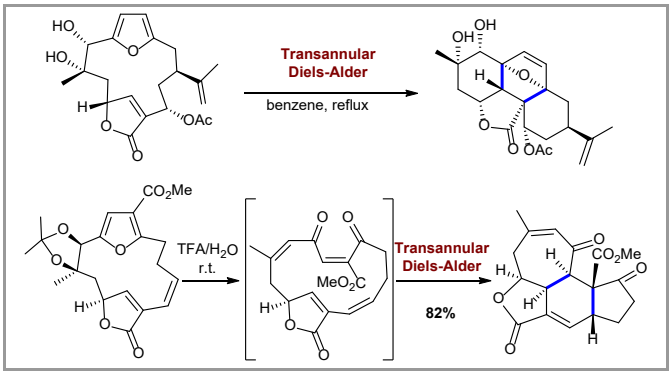
Scheme 4 Total synthesis of antibiotic CJ-16,264 using a double transannular Diels-Alder as key step

A related approach has been followed by Cossy and coworkers in an attempt to prepare the decaline core of the cytotoxic natural product verongidolide whose stereostructure has only been partially and tentatively assigned (Scheme 5).[8] In this case, although the transannular Diels-Alder reaction proceed very efficiently upon heating the macrocyclic lactone substrate under microwave irradiation, the observed *exo* selectivity was not the required one for the preparation of the target compound. Calculations also supported the kinetic preference for the substrate to undergo cycloaddition through the *exo*-TS and also disregarded the possibility for a reversible-Diels Alder process that could eventually provide the more stable *endo* product.



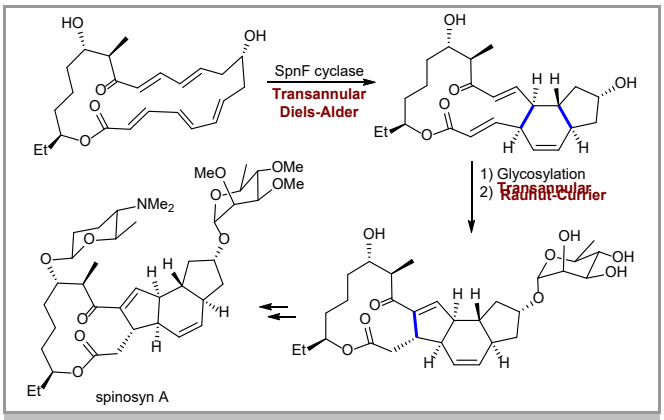
Scheme 5 Transannular Diels-Alder reaction employed to build the decaline core of verongidolide.

In other cases, transannular Diels-Alder reactivity has been observed as unexpected reaction pathway during the total synthesis of a given compound. This is the case of the attempt to access the norcembrenolide diterpenic scaffold in which a furane-containing macrocycle underwent this transannular process was converted slowly upon standing into a complex polycyclic highly oxygenated adduct or in 80 min. after reflux in benzene (Scheme 6).[9] A similar reactivity was observed by Pattenden during the attempted total synthesis of plumareillide, in this case postulating the transannular Diels Alder reaction as part of the biosynthetic pathway to this secondary metabolite.[10]



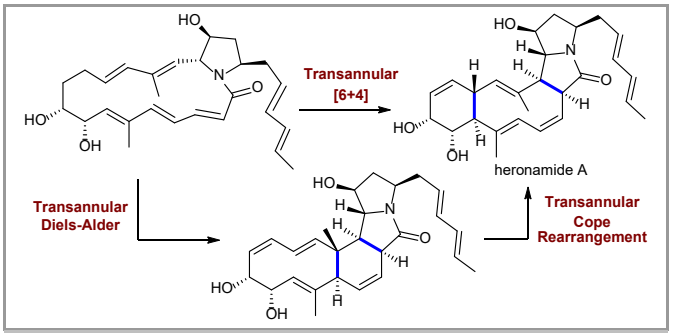
Scheme 6 Transannular Diels-Alder reaction employed to build the decaline core of verongidolide.

In fact, it has been demonstrated that a "Diels-Alderase" enzyme is involved in the acceleration of a transannular [4+2] cycloaddition during the biosynthesis of natural product *Spynosyn A* (Scheme 7). In particular, overexpression of several genes of the natural source led to the isolation of a cyclase that catalyzed the conversion of the macrocyclic tetraene substrate into a tricyclic intermediate through a reaction that was demonstrated to take place 500 times faster than the corresponding uncatalyzed process.[11] After glycosylation, a second cyclase is also involved in a transannular Rauhult-Currier-type reaction that generates the complete polycyclic scaffold of the natural product. This proposal is also supported by the fact that a previous nonenzymatic total synthesis of Spinosyn A had been reported using the same combination of transannular processes.[12] However, it should also be noted that there are computational studies that point toward an alternative mechanism that would involve an ambimodal pathway comprising both the direct [4+2] cycloaddition and a bifurcated pathway consisting of an initial [6+4] cycloaddition between the diene and triene moieties followed by Cope rearrangement leading to the thermodynamic [4+2] cycloadduct.[13]



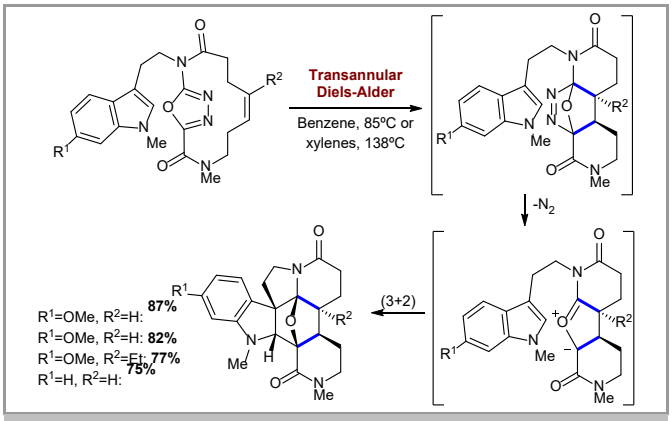
Scheme 7 Biosynthesis of Spinosyn A through combined transannular Diels-Alder and Rauhult-Currier reactions

This ambimodal [6+4]/[4+2]+Cope rearrangement reactivity profile has also been computationally studied in the context of the biosynthesis of Heronamide A (Scheme 8).[14] In this particular case, the higher thermodynamic stability of the [6+4] product explains the fact that the Diels-Alder adduct is not observed as in the case of spinosyn A. The role of water as solvent has also claimed to play a fundamental role in favouring the [6+4] cycloaddition pathway.



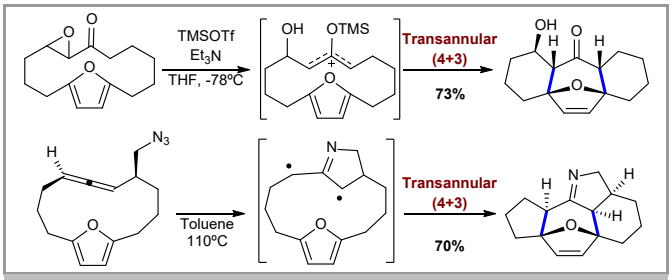
Scheme 8 Ambimodal [6+4] *vs* [4+2]/Cope rearrangement in the biosynthesis of heronamide A

Heterodienes have also been used as constituents of the macrocyclic substrate in transannular (4+2) cycloadditions. In particular, macrocyclic 1,3,4-oxadiazoles have been used as useful substrates to generate complex alkaloid frameworks related to the family of the vinca alkaloid through this approach (Scheme 9).[15] The transannular Diels-Alder reaction is followed by N_2 extrusion that generates a carbonyl ylide intermediate which underwent a subsequent intramolecular (3+2) cycloaddition with the pending indole moiety. Yields were consistently high in all substrates tested.



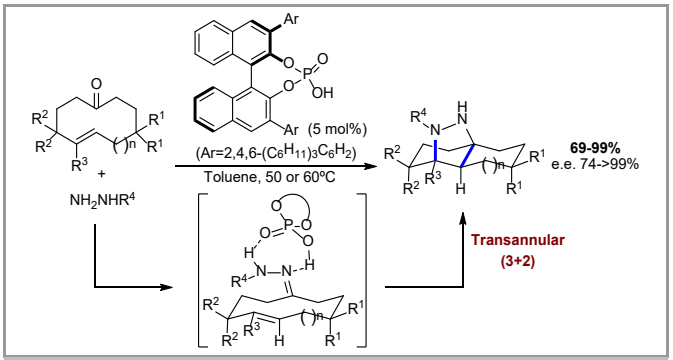
Scheme 9 Cascade transannular Diels-Alder/intramolecular (3+2) cycloaddition in the synthesis of vinblastine analogues

Diels-Alder-type reactions are not the only type of cycloadditions explored in transannular reactivity. For instance, there are a couple of recent examples showing the performance of transannular (4+3) cycloaddition chemistry for the construction of densely functionalized 8-oxabicyclo[3.2.1]octanes, which is a structural motif present in many bioactive compounds (Scheme 10). In all cases, the macrocycle incorporated a furan scaffold together with a suitable functionality for the generation of the reactive C3 component. In particular, α,β-epoxyketones were employed for the generation of the oxyallyl cation under Lewis acidic conditions.[16] The thermal intramolecular (3+2) cycloaddition between an allene and pendant azide substituent that is followed by nitrogen extrusion was used to generate the azatrimethylenemethane diyl intermediate.[17]



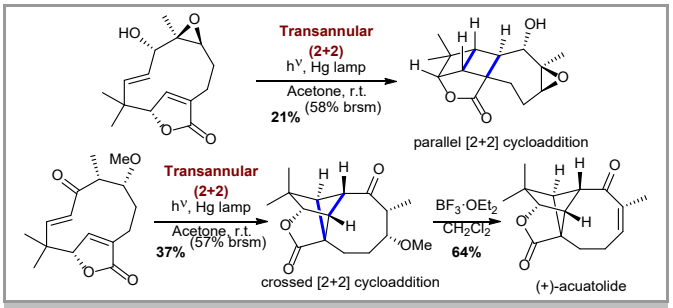
Scheme 10 Transannular (4+3) cycloadditions

Our group has also contributed to the field with one example of a Bronsted acid-catalyzed transannular (3+2) cycloaddition using hydrazones as the 1,3-dipole source (Scheme 11). In his case, a conveniently substituted cycloalkenone was employed as substrate undergoing condensation with a hydrazine, which was followed by the transannular cycloaddition process.[18] A chiral BINOL-based phosphoric acid to render the reaction enantioselective, in one of the very few examples of a catalytic and enantioselective transannular reaction that converts an achiral starting material into an enantioenriched product.[19]



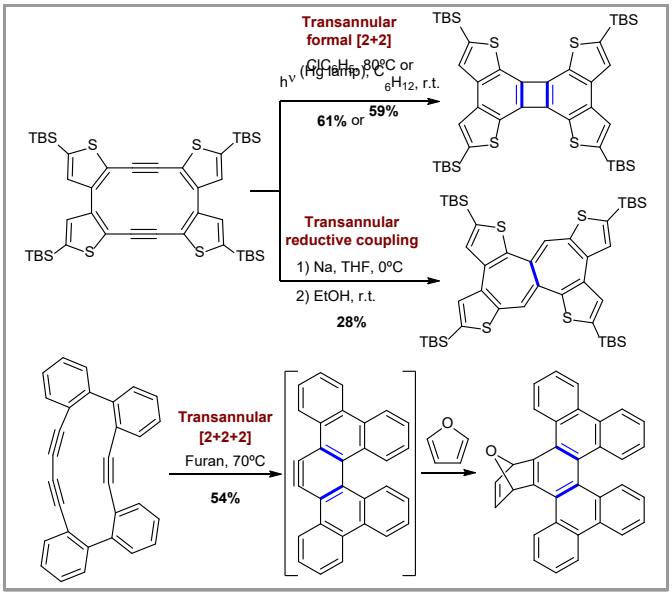
Scheme 11 Transannular (3+2) cycloaddition

There is also another reported case of a transannular [2+2] cycloaddition carried out through photochemical activation (Scheme 12).[20] In this case, the regioselectivity depended on the substitution pattern of the substrate, generating either the [2]-ladderane (parallel cycloaddition) or the bicyclo[2.1.1]heptane (crossed cycloaddition) scaffold selectively by changing the conformational preferences of the macrocycle. The latter product was converted in a single final step into natural product (+)-aquatolide.



Scheme 12 Transannular (2+2) cycloaddition

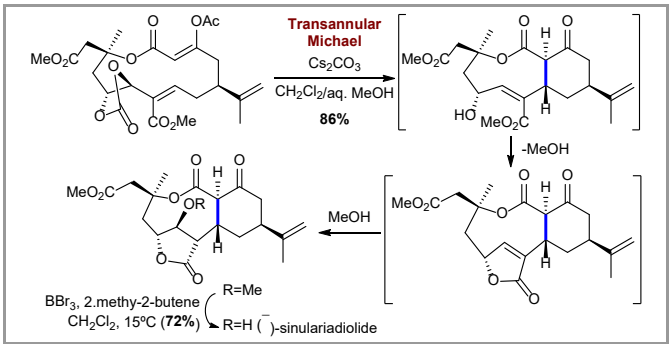
Transannular formal [2+2] cycloadditons involving alkynes have demonstrated to be very convenient of the formation of polycyclic aromatic compounds starting from macrocyclic polyenine substrates. A representative example of this type of reactivity is shown in Scheme 13, in which a thiophene-fused bisdehydro[12]annulene substrate was converted into a biphenylene-containing product through either light irradiation or by heating in chlorobenzene.[21] Mechanistically, the photochemical reaction consists on a symmetry-allowed asynchronous concerted [2+2] cycloaddition, while the thermal pathway was proposed to happen through two sequential 8π and 4π electrocyclizations. Interestingly, when the same substrate was reacted in the presence of a single electron reductant, a transannular reductive coupling between the two alkynes took place leading to the formation of a thiophene-fused heptalene.[22] On the other hand, the biphenylophane shown in Scheme 13, in which the two byphenyl moieties are tethered through three alkyne moieties undergoes thermal [2+2+2] cyclotrimerization to provide the corresponding benzyne intermediate that was subsequently trapped by using furan as dienophile.[23]



Scheme 13 Transannular reactions on a thiophene-fused bisdehydro[12]annulene and a biphenylophane

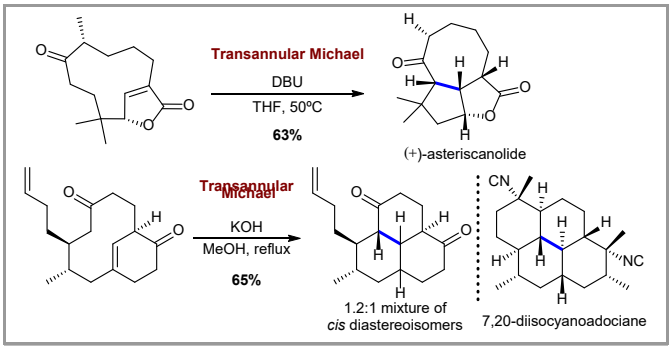
3 Transannular conjugate additions

Conjugate addition on medium or large size cyclic substrates containing both a pronuclephile and a Michael acceptor have been successfully implemented for the formation of polycyclic scaffolds. A good illustrative example on the performance of this approach is shown in Scheme 14, in which a Michael reaction in employed as key step on the total synthesis of (−)-sinulariadiolide.[24] The transannular process took place through the formation of the required β-ketoester enolate under mild conditions that reacted with the internal enoate moiety. The Michael addition intermediate subsequently underwent intramolecular lactonization through transesterification and a final conjugate addition of methanol, providing an excellent yield. (−)-Sinulariadiolide was obtained from this product by simple cleavage of the methyl ether.



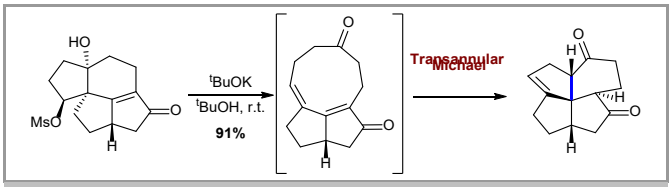
Scheme 14 Transannular Michael reaction in the total synthesis of (−)-sinulariadiolide

Other conceptually similar examples are shown in Scheme 15. Li and coworkers successfully used a transannular Michael reaction in the total synthesis of (+)-asteriscanolide,[25] in which this transannular approach enables the generation of a fused system containing a cyclooctanone core. In a different work, Vanderwall employed this approach in the total synthesis of 7,20-diisocyanoadociane.[26] Although the transannular Michael reaction took place efficiently, the stereochemistry of the obtained adduct did not match the required configuration for reaching the target natural product.



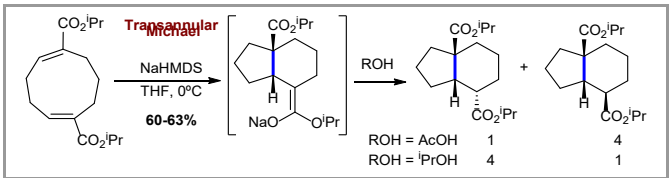
Scheme 15 Other examples of transannular Michael reactions in the total synthesis of natural products

A related transannular Michael reaction involving doubly conjugated Michael acceptors has also been escribed as part of the interconversion between the two tetracyclic systems also shown in Scheme 16.[27] When the initial substrate was treated with a strong base, a Grob-type fragmentation generated a nine-membered intermediate that contained both a ketone and an α,β,γ,δ-diunsaturated enone. Deprotonation of the former was followed by transannular Michael reaction that took place regioselectively at the β-position of the enone, in order to provide the most stable 5/6 annulated bicyclic scaffold. The overall process was found to be fully diastereoselective, being the stereochemistry controlled by the single stereogenic centre present in the intermediate formed after the Grob fragmentation.



Scheme 16 Transannular skeletal reorganization through Grob fragmentation/transannular Michael reaction.

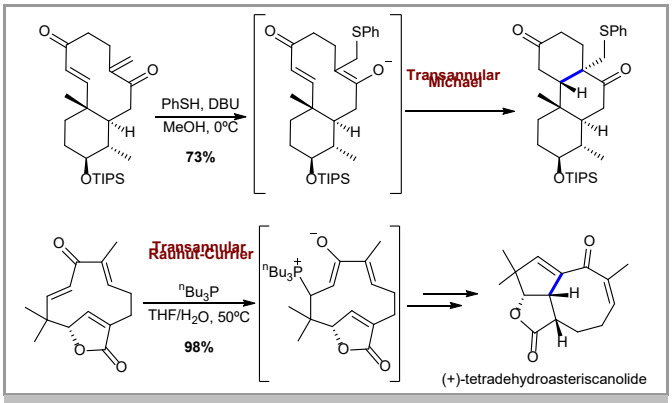
The cyclononadienes with two conjugated ester moieties shown in Scheme 17 have also showed to be good candidates for transannular Michael reaction, leading to the formation of the hydrindane bicyclo[4.3.0]nonane scaffold (Scheme 17).[28] In this case, deprotonation of one of the two equivalent enoate moieties formed the corresponding dienolate nucleophile that underwent transannular Michael reaction. This generated a second ester enolate that could be protonated under different conditions to provide either the kinetic product, in which two ester moieties arranged *trans* to each other, or the thermodynamic product.



Scheme 17 Transannular Michael reaction on cyclononadiene diesters

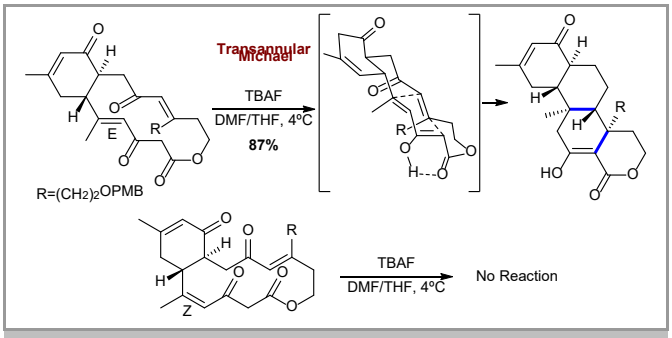
On the other hand, the enolate nucleophile required for the transannular Michael process can also be generated from another

Michael acceptor through a conjugate addition reaction that initiates a cascade Michael/transannular Michael. Two examples are shown in Scheme 18. The first one shows the use of a benzenethiolate salt to initiate a sulfa-Michael reaction on the exocyclic Michael acceptor, thus triggering a second transannular Michael reaction that closes the final tricyclic scaffold.[29] In the second example, a phosphine-catalyzed transannular Rauhult Currier is employed in the total synthesis of (+)-tetradehydroasteriscanolide.[17] This transformation consists on comprises the initial conjugate addition of the phosphine to the more activate enone Michael acceptor followed by transannular Michael reaction to the enoate and final elimination of the phosphonium salt.



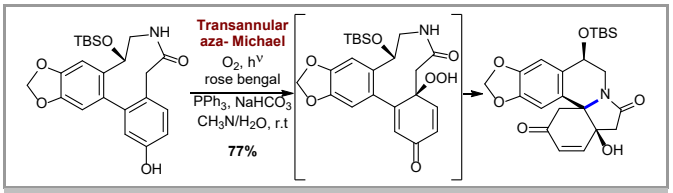
Scheme 18 Conjugate addition-initiated transannular Michael reactions

This ability of the Michael reaction as suitable platform for multiple transannular cascade processes has also been explored for the synthesis of other complex motifs. For example, a transannular Michael/transannular Michael cascade process has been evaluated as an excellent approach to the synthesis of the tetracyclic scaffold shown in Scheme 19.[30] Interestingly, the configuration of the second Michael acceptor was found to be crucial for the success of the process, observing that, while *E,E*-configured substrate reacted efficiently under the optimized conditions, those analogous substrates with a *Z,E* configuration were found to be completely unreactive. A computational study pointed towards both steric and strain effects that lead to a highly energetic transition state for the latter reaction.[31]



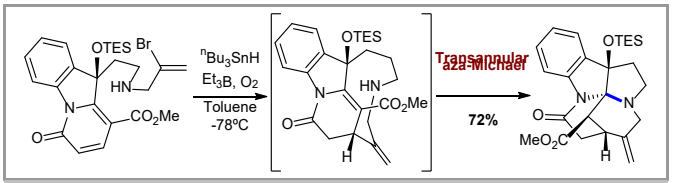
Scheme 19 Transannular Michael/Michael cascade reaction

Secondary amines inserted within the cyclic starting material are also suitable pronucleophiles to undergo transannular conjugate addition if a Michael acceptor is located at a convenient position. This is the case of the transannular aza-Michael reaction employed by Fukuyama and coworkers in the total synthesis of a variety of erithrina alkaloids, in which the benzopyrroloisoquinoline central core was settled through this approach in a single step (Scheme 20).[32] The reaction design included a cyclohexanedione as exocyclic Michael acceptor moiety at the 9-membered lactam starting material, which was generated *in situ* through oxidation of a phenolic moiety.



Scheme 20 Transannular aza-Michael reaction

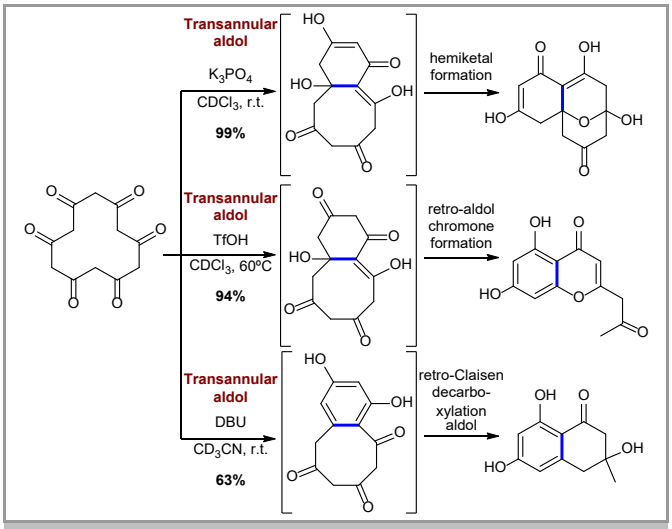
A more elaborated version of this reaction was employed by Ding and coworkers in the total synthesis of alsmaphorazine D (Scheme 21).[33] In this case, the macrocyclic starting material was generated *in situ* through intramolecular radical conjugate addition of a vinyl bromide chain to the pyridinone moiety, that generated also an enoate Michael acceptor within the macrocycle. Next, the transannular aza-Michael reaction took place as projected to generate the complete carbon scaffold of the target product as a single diastereoisomer.



Scheme 21 Transannular aza-Michael reaction

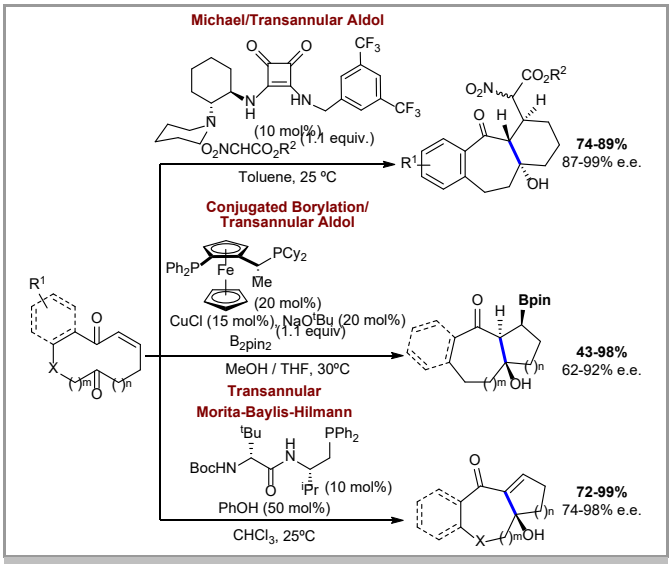
4 Transannular 1,2-addition to ketones, imines, esters and amides

There is a recent example on the application of transannular aldol reaction to a macrocyclic polyketide substrate (Scheme 22).[34] This compound was found to be very prone towards the transannular addition process under either acidic or basic conditions, generating a bicyclic intermediate that evolved to different products depending on the reaction conditions. Thus, intramolecular hemiketal formation took place when working in K_3PO_4, while a retro-aldol/intramolecular hemiketal formation led to the formation of a chromone product in the presence of triflic acid. Under basic conditions, the transannular aldol reaction was followed by dehydration, generating a benzo-fused intermediate that subsequently underwent retro-Claisen/aldol/decarboxylation cascade process to form a tetralone derivative.



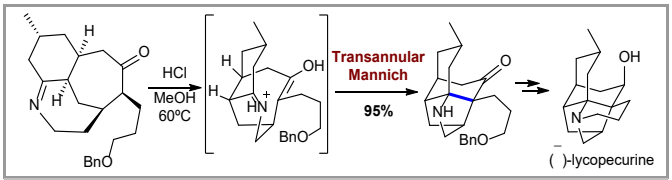
Scheme 22 Transannular aldol reaction on a macrocyclic polyketide substrate.

The enolate nucleophile participating in the transannular aldol reaction can also be generated through conjugate addition in a typical Michael-type reaction-initiated cascade process (Scheme 23). In particular, our group has developed a catalytic and enantioselective domino Michael/aldol reaction between nitroacetates and medium-sized ketoenones employing a tertiary amine/squaramide as catalyst.[35] The initial Michael reaction takes place under catalyst control, generating the first stereogenic centre with high stereoselection and the intermediate enolate undergoes the subsequent diastereoselective transannular aldol reaction that provides the final adduct as a highly enantioenriched material. The same reaction manifold can be applied to a conjugated borylation-initiated transannular aldol reaction, in this case using a chiral Cu(I) complex to catalyze the initial 1,4-addition of the nucleophilic boron species to the enone moiety.[36] In a related situation, the same type of ketoenone substrates undergo highly enantioselective transannular Morita-Baylis-Hilmann reaction under catalysis by a chiral phosphine.[37]



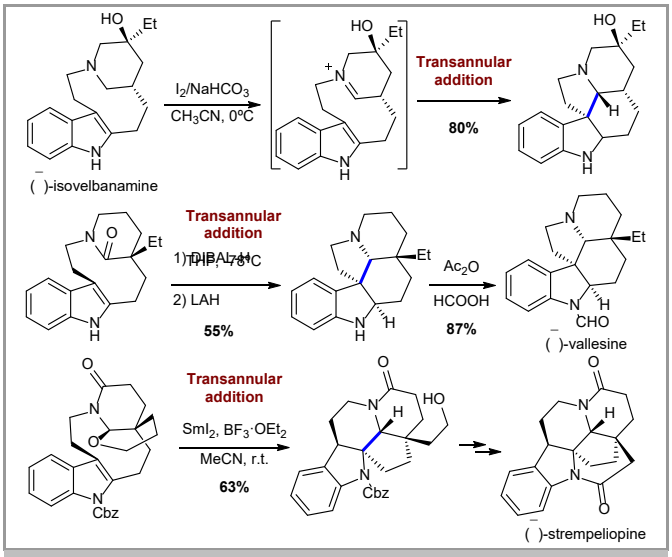
Scheme 23 Conjugate addition-initiated transannular aldol reactions

Transannular Mannich reactions have shown to be a key tool for the construction of the central core of lycopodium alkaloids. Scheme 24 shows the strategy followed to generate the central polycyclic shared by the natural products of this family though acid-catalyzed Mannich reaction and its subsequent application to the total synthesis of (-)-lycopecurine that illustrates the performance of this approach to construct such complex scaffolds.[38] In fact, it has also been proposed that the transannular Mannich reaction is also operating in the corresponding biosynthetic pathway that takes place in the living systems. Other total syntheses of different polycyclic complex alkaloids have also been reported making use of the same concept as the strategic decision.[39]



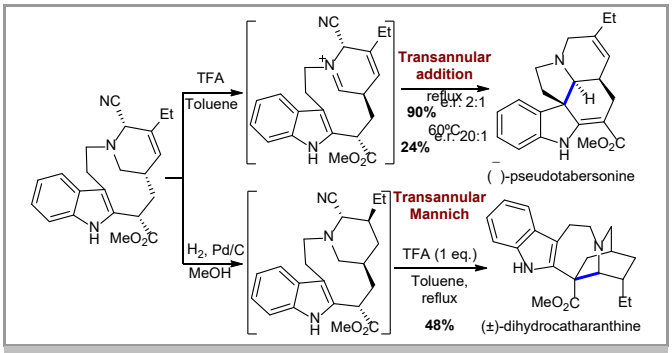
Scheme 24 Transannular aldol reaction on a macrocyclic polyketide substrate.

Another possibility consists on the incorporation of a nucleophilic indole unit as constituent of the macrocyclic core in combination with an imine or related functionality. This has been the strategy followed by Gaich for the formation of the central core of the aspidospermidine family of alkaloids (Scheme 25).[40] In this case, the reactive iminium cation electrophile was generated by oxidation of the indole-containing macrocyclic starting material isovelbanamine using iodine. An alternative approach has also been reported by Movassaghi that consisted on the generation of the same intermediate by reduction of the starting amide, which was followed by the transannular addition step.[41] This sequence was applied to the total synthesis of natural product (-)-valesine. Transannular radical addition has also been explored in related N-acyliminium intermediates, generated *in situ* from an N,O acetal-containing substrate in the presence of a Lewis acid and using SmI_2 as the reducing agent. In this case, the transannular bond formation takes place at the C2 position of the indole core, forming a different skeletal arrangement that is the common motif of the family of schizozygane alkaloids. Scheme 25 also shows the application of this methodology to the total synthesis of (-)-strempeliopine.[42]



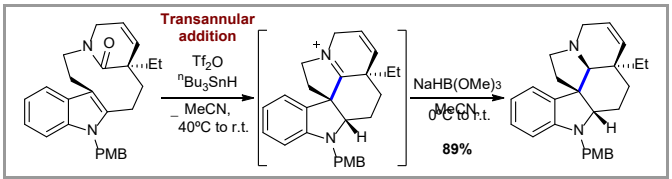
Scheme 25 Transannular addition of indoles to iminium ions.

The macrocyclic substrate shown in Scheme 26 shows a particularly interesting behavior. When reacted with TFA in toluene at reflux, it undergoes transannular indole addition to the iminium ion (formed in situ after HCN elimination) to deliver natural product (-)-pseudotabersonine in excellent yield, although as a mixture of diastereoisomers. A single diastereoisomer is obtained at lower temperatures albeit with a poorer yield. Interestingly, after reducing the dihydropyridine moiety, the resulting substrate undergoes transannular Mannich reaction in which the ester moiety participates as the nucleophile, leading to the formation of (+)-coronadinine in a moderate yield.



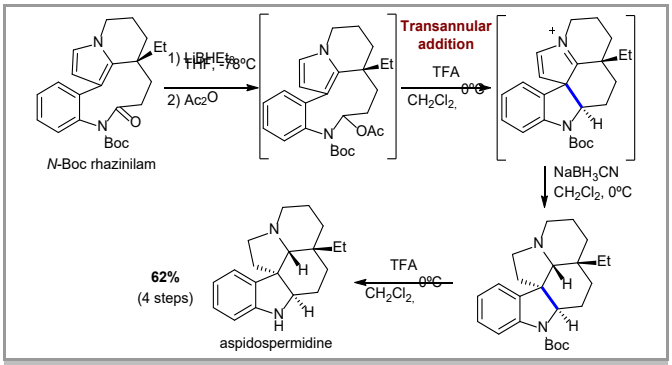
Scheme 26 Transannular addition of indoles to iminium ions for the construction of the central core of aspidosperma alkaloids.

Movassaghi and coworkers have also studied the possibility of using an amide as the internal electrophile using the $Tf_2O/{}^nBu_3SnH$ combination of reagents to promote the transannular process (Scheme 27).[43] Under these conditions, amide activation takes place in the presence of triflic anhydride, forming the corresponding iminium triflate, which is followed by the transannular reaction, which generates a bis-iminium salt. This compound is rapidly monoreduced by ${}^nBu_3SnH$ on the indole site. Subsequent *in situ* reduction of the remaining iminium moiety by the addition of $NaBH(OMe)_3$ leads to the desired tetracyclic scaffold. This reaction manifold as the key step in the total synthesis of a variety of members of the aspidosperma family of alkaloids



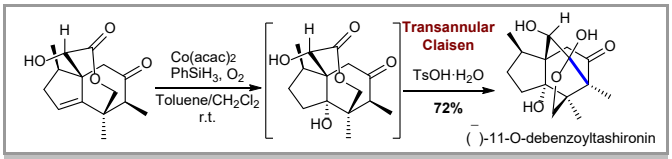
Scheme 27 Transannular addition of indoles to activated amides for the construction of the central core of aspidosperma alkaloids.

Indoles can also be used as the internal C-nucleophiles, as it can be seen in the example shown in Scheme 28.[44] This case shows the transformation of *N*-Boc protected rhazinilam into aspidospermidine through semireduction of the lactam to the *N*,*O*-hemiaminal acetate followed by acid-mediated transannular addition of the pyrrole to the iminium salt and in situ reduction that generates the complex pentacyclic scaffold in a single step. The final product was obtained by deprotection of the indole moiety.



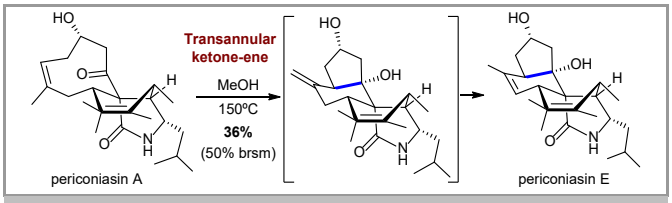
Scheme 28 Transformation of N-Boc rhazinilam into aspidospermidine through transannular reaction.

In a different context, there is also one example of a transannular modified Claisen condensation employed for the total synthesis of 11-*O*-debenzoyltashironin (Scheme 29).[45] This transformation took place after addition of *p*-TsOH to the crude reaction mixture obtained after the Co-catalyzed reduction of the alkene moiety present in the initial substrate. The intermediate formed after the reduction underwent the transannular addition of the ketone to the lactone moiety involving the formation of an enol intermediate as the nucleophile. After the 1,2-addition to the ester site the adduct resulted to be stable and did not undergo the subsequent elimination of alkoxide associated to the standard Claisen reaction, therefore isolating the final product as the corresponding hemiacetal.



Scheme 29 Transannular Claisen reaction.

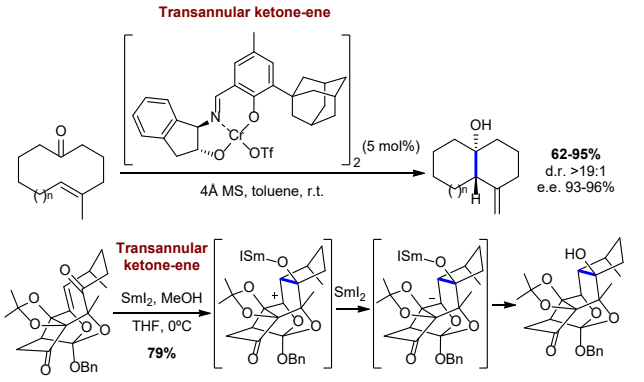
The carbonyl-ene reaction has been another manifold that has found interesting utility for the construction of carbocyclic scaffolds, with also some evidences that this type of reactivity is involved in the synthesis of isoprenoids elusive in terms of biogenetic rationalization.[46] A good example is shown with the conversion of periconasin B into periconasin D through transannular ene reaction, upon treatment in MeOH at high temperatures as shown in Scheme 30.[47]



Scheme 30 Conversion of periconiasin A into periconiasin E through tansannular ketone-ene reactions.

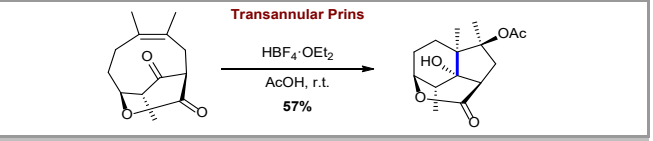
On the other hand, fundamental studies by Jacobsen have ended up in the development of a very efficient protocol to carry out transannular ketone-ene reactions in a catalytic and enantioselective way using a chiral Cr(III) Lewis acid as catalyst (Scheme 31). This methodology enables the conversion of an achiral starting material into an enantioenriched bicyclic compound with excellent enantioselectivities.[48] A reductive version of a transannular ketone-ene reaction has also been

reported using SmI_2 as the Lewis acid activator and also as reducing agent in the construction of complex polihydroxylated pentacyclic scaffolds that constitute the core of the isoryadonane family of natural products (Scheme 30).[49] The reactions consists on the transannular ketone-ene reaction between the electron rich enol ether and the internal ketone moiety that delivered the corresponding oxonium cation, the latter undergoing subsequent reduction by SmI2 to generate a carbanonic intermediate that is finally protonated by methanol to provide the final product.



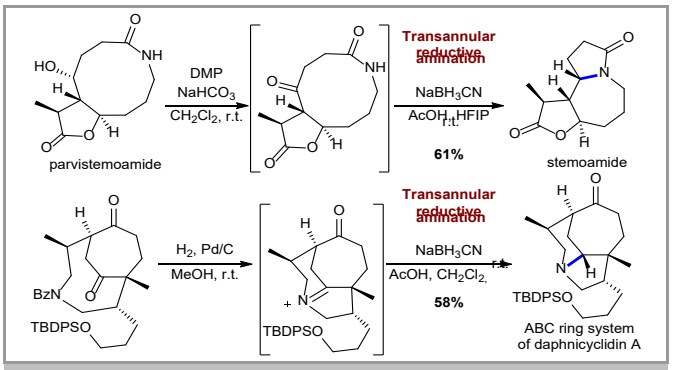
Scheme 31 Catalytic enantioselective transannular ketone-ene reaction.

There is also one example of a transannular Prins reaction reported in the last few years (Scheme 32). This reaction enabled the preparation of the bicyclo[4.3.0]nonane, which is the central motif of the family of austrodorane terpenoids.[50] The reaction converted the functionalized macrocylic cycloalkenone into the bicyclic product through treatment with a strong Brønsted acid and using acetic acid as solvent, which also participated as the nucleophilic engaged in the final quenching of the intermediate carbocation formed after the addition to the carbonyl group.



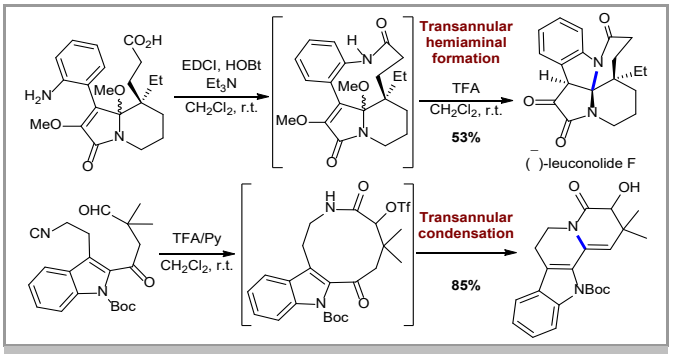
Scheme 32 Brønsted acid-mediated transannular Prins reaction.

Reductive amination reactions involving an initial transannular 1,2-addition of a secondary amine to a ketone moiety both incorporated within the cyclic framework has been used as key disconnection in total synthesis. Scheme 32 shows the application of this approach to the total synthesis of stemoamide from parvistemoamide, which also demonstrated the occurrence of this reaction as part of the biosynthetic pathway to this alkaloid.[51] In a different report, the ABC ring system of daphnicyclidin A was also constructed from the corresponding highly functionalized N-Cbz-protected cyclic ketoamide (Scheme 33).[52] This transformation required initial removal of the carbamate protecting group followed by reductive amination using a hydride reagent, as the hydrogenolytic conditions employed for the removal of the Cbz substituent were not able to promote the direct deprotection/reductive amination sequence.



Scheme 33 Transannular reductive amination reeactions.

In the same line, transannular aminal formation through 1,2-addition of an amide to an imine or iminium ion is also feasible on macrocyclic iminolactams, as it can be seen in the total synthesis of (-)-leuconolide F shown in Scheme 34.[53] In this case, the macrocyclic lactam was formed *in situ* through standard amide coupling chemistry and the subsequent treatment in an acidic media triggered the transannular aminal formation with the masked imine present at the starting material. In a similar context, transannular condensation leading to the formation of an enamine product can also take place on a conveniently substituted ketolactam (Scheme 34).[54] As it happened in the previous example, once the macrocyclic lactam had been formed, it underwent spontaneous transannular 1,2-addition of the nucleophilic amide nitrogen to the ketone moiety under Brønsted acid catalysis, in this case also being followed by dehydration to generate the final enamide.

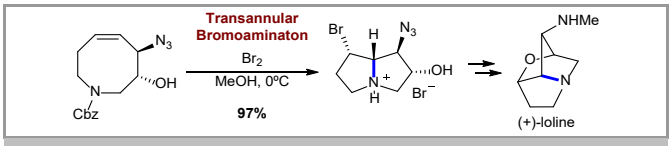


Scheme 34 Transannular aminal and enamine formation reactions.

5 Transannular reactions *via* electrophilic activation of olefins

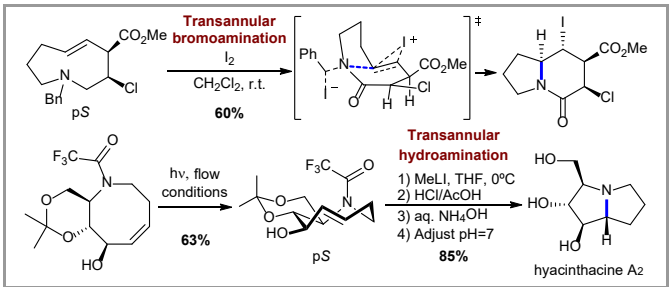
Alkenes can be placed in the structure of the cyclic starting material as reactive sites that, upon electrophilic addition, generate an intermediate reactive species that can undergo transannular reaction with another nucleophilic functionality present within the cyclic scaffold. In this sense, a variety of pronucleophiles can be introduced at the carbocyclic starting material which, together with the different reagents available for electrophilic addition with the alkene moiety makes this approach a very powerful solution in synthesis. A representative example is shown in Scheme 35, in which a transannular bromoamination is employed as key step in the total synthesis of indolizidine alkaloid (+)-loline.[55] An enantioenriched unsaturated *N*-Cbz azocane was employed as key substrate that

underwent *in situ* *N*-deprotection and subsequent diastereoselective transannular addition through the corresponding bromomiranium intermediate unpon reaction with molecular bromine. The regioselectivity of the bromiranium ring-opening process was governed by the size of the two small ring systems generated in the transannular process, being the formation of the indolizidine scaffold over the other possible 1-azabicyclo[4.2.0]octane alternative. This methodology has also been successfully used in the last years for the synthesis of quinolizidine alkaloids using 9-membered unsaturated cyclic amines as substrates.[56]



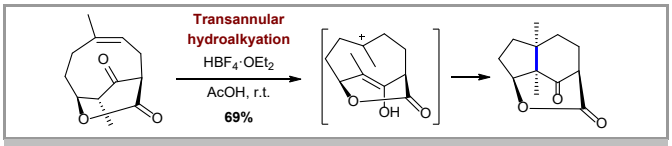
Scheme 35 Catalytic enantioselective transannular bromoamination in the total synthesis of (+)-loline.

An interesting situation appears when the 8- or 9-membered cyclic amine substrate incorporates a trans-configured endocyclic alkene moiety. This type of substrates present planar chirality due to the high energy barrier required to interconvert the two enantiomeric conformers, associated to the large strain energy present in the cyclic scaffold required to accommodate the *trans*-alkene. Scheme 36 shows the application of this strategy to the synthesis of indolizidinones from diastereomerically pure *pS*-configured planar chiral azoninones, showing complete planar to central chirality process during the transannular bromoamination reaction, that also proceeds through activation of the alkene through the formation of a iodiranium intermediate.[57] In a similar approach, the diastreomerically enriched *pS* enantiomer of the starting material was obtained through photochemical *cis*/*trans* isomerization.[58] This *trans*-configured substrate underwent spontaneous transannular hydroamination after *N*-deprotection followed by stirring in a neutral aqueous solution.



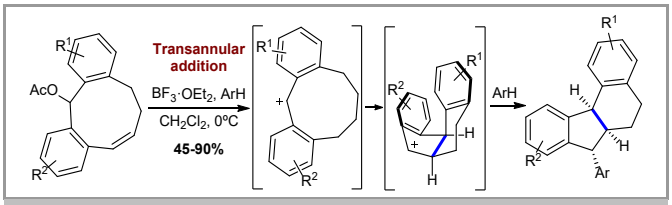
Scheme 36 Catalytic enantioselective transannular reactions using unsaturated cyclic amines with planar chirality.

Carbon-based nucleophiles can also be engaged in this type of reactivity, as it happens in the example shown in Scheme 37.[59] In this case, the activation of the alkene moiety was carried out by the addition of a strong and non-nucleophilic Brønsted acid such as HBF_4, generating an intermediate carbocation species in which regioselectivity is governed by the Markovnikov rule. Transannular addition reaction of the nucleophilic enol species led to the formation of the final tricyclic adduct that has the general skeletal arrangement that can be found in the family of the pinguisane sesquiterpenoids. It is interesting to note that the same substrate incorporating a tetrasubstituted alkene moiety (with an additional methyl substituent) provided a completely different reactivity, this undergoing transannular Prins reaction, as shown in Scheme 32



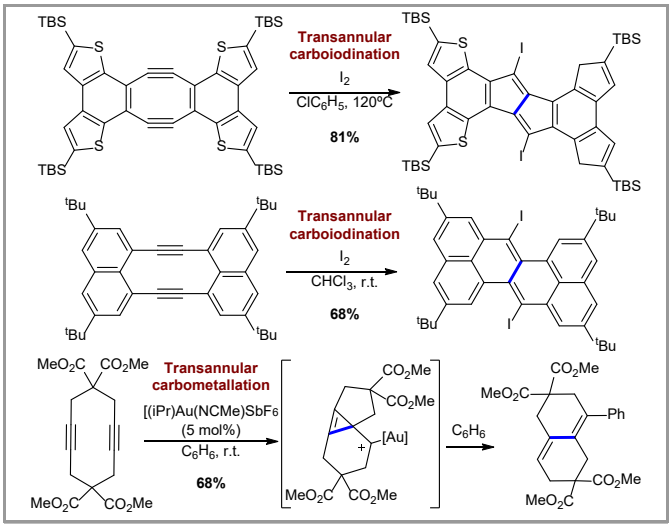
Scheme 37 Brønsted acid-mediated transannular hydroalkylation via carbocation/enol intermediates.

As an alternative, alkenes can also participate as the nucleophilic site reaction with a carbocationic intermediate located within the macrocyclic scaffold and which is generated from a different functional group. This is the case of the transannular reaction shown in Scheme 38 that involves the generation of a benzydryl cation from the corresponding acetoxy-substituted substrate under Bronsted acid activation.[60] The reaction design also included an external electron-rich arene reagent that is engaged in the final quenching of the second carbocation intermediate formed after the transannular reaction. All compounds were formed as single diastereoisomers



Scheme 38 Brønsted acid-mediated transannular alkylation of benzydryl carbocations

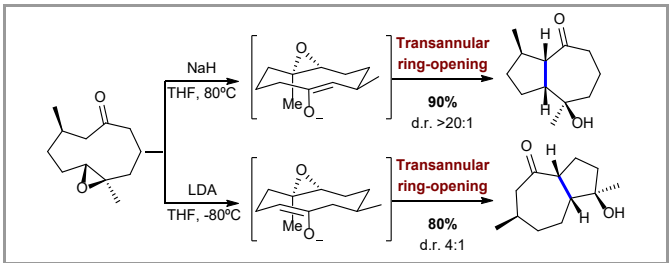
Transannular halofunctionalization has also demonstrated to be a useful tool in the synthesis of extended aromatic materials, using macrocyclic substrates containing conjugated alkynes within their structure. Some examples of this reactivity are shown in Scheme 39. The first reaction shows the formation of a polycyclic diiodinated pentalene in good yield from a bisdehydro[8]annulene[61] and the second example comprises the transannular carboiodination of tetradehydro[10]annulene, leading to the formation of a zethrene product, also in very high yield.[62] Both cases illustrate the high chemical efficiency attained through the application of transannular approaches for the synthesis of molecular architectures that typically provide poor yields when constructing through standard cycloaddition or cyclization chemistry. The latter reaction can also be carried out through the activation of the annulene substrate under Au(I) catalysis, undergoing transannular carbometallation and generating a gold-stabilized cyclopropenylmethyl cation, which is subsequently quenched by the presence of an arene as the nucleophilic trap.[63]



Scheme 39 Transannular reactions on annulene substrates.

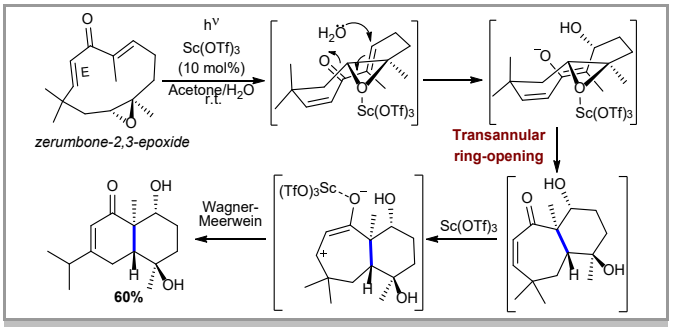
6 Transannular ring-opening of epoxides

There are several recent examples that show the possibility of using epoxides as the electrophilic counterpart in transannular reactions. Two of these reports make use of an enolate as the internal nucleophile. In the first example (Scheme 40), a macrocyclic ketoepoxide was deprotonated to generate the reactive enolate species that underwent the projected transannular reaction.[64] Interestingly, the regioselectivity of the reaction towards the desired adduct could be controlled by using either kinetic or thermodynamic conditions for the deprotonation step, in which both enolate led to different regioisomeric 5/7 annulated adducts by opening the epoxide through its less substituted carbon atom.



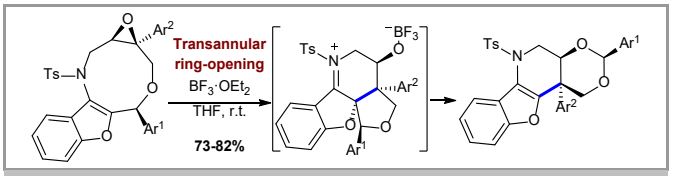
Scheme 40 Transannular ring-opening of epoxides with ketone enolates

Scheme 41 shows a similar transformation but employing a conjugate addition reaction to generate the nucleophilic enolate species.[65] In this particular case, the geometry of one of the alkenes present in the macrocyclic starting ketoepoxide had to be adjusted from *trans* to *cis* in order to be able to form the final transannular reaction product, which was accomplished by *in situ* photochemical isomerization. After this isomerization had taken place, the substrate underwent conjugate addition of water to the less hindered enone moiety, which was followed by the transannular ring-opening of the epoxide, the latter assisted by the presence of a Lewis acid-catalyst. The formed 6/7 annulated adduct was also reactive under the reaction conditions and underwent a subsequent Wagner-Meerwein rearrangement in the presence of the Lewis acid to delivered the final decalone-type product in a 60% overall yield from the starting epoxide.



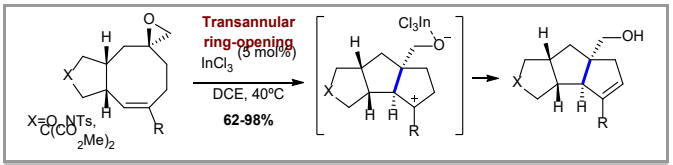
Scheme 41 Cascade photoisomerization/conjugate addition/transannular ring-opening of epoxide/Wagner-Meerwein rearrangement.

There is also a report showing that 2-aminobenzofuran moieties can also participate as the internal nucleophile that undergoes transannular reaction with an epoxide moiety (Scheme 42).[66] In this example, the starting benzofuran-fused epoxy-1,5-oxazonines were prepared as enantioenriched material through a palladium-catalyzed (5+4) cycloaddition process followed by diastereoselective epoxidation and the subsequent Lewis acid-promoted transannular reaction took place with complete preservation of the enantiomeric excess of the starting material. In addition, the *N*-tosyliminium ion intermediate formed after the transannular process underwent rearrangement that involved cleavage of one of the furan moieties followed by acetal formation with the remaining alkoxide substituent. This final process is driven by the stability gain associated to the recovery of the aromaticity at the benzofuran core.



Scheme 42 Cascade transannular ring opening of epoxide/rearrangement on benzofuran-fused epoxy-1,5-oxazonines.

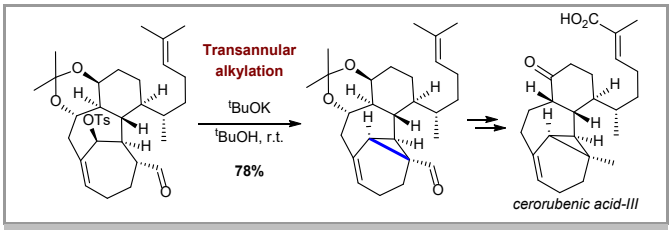
Exocyclic epoxides have also been employed in transannular ring-opening using an alkene as the internal nucleophile (Scheme 43).[67] The reaction was carried out through the activation of the epoxide with a substoichiometric amount of a Lewis acid such as $InCl_3$, providing the corresponding tricyclic products in excellent yield. The reaction also demonstrated the possibility to incorporate a variety of substituents at the alkene core, especially performing well when aryl moieties were introduced at this position due to their ability to stabilize the carbocationic intermediate that is formed on the epoxide ring-opening event that has finally to undergo elimination to generate the final insaturation present on one of the cyclopentane subunits.



Scheme 43 Transannular ring opening of exocyclic epoxides

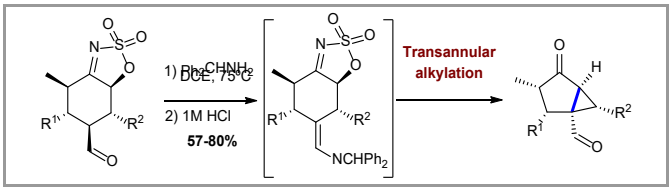
7 Transannular alkylations of enolates and related species

Installing a good leaving group in the structure of the macrocyclic substrate together with a pronucleophilic site able to generate an enolate reagent upon deprotonation has been used as a strategy for carrying out ring-contraction reactions via transannular alkylation. This is the approach taken for the construction of the complex polycyclic system of natural product cerorubenic acid III (Scheme 44).[68] In this transformation, the 6/3 fused bicyclic scaffold was formed through deprotonation of the α-hydrogen of the aldehyde moiety followed by transannular S_N1-type alkylation, with the internal tosylate acting as the leaving group that generated a stable allylic carbocation as the electrophilic site. The reaction proceeded with complete diastereoselectivity and was performed at a multigram scale, demonstrating the robustness of the experimental procedure.



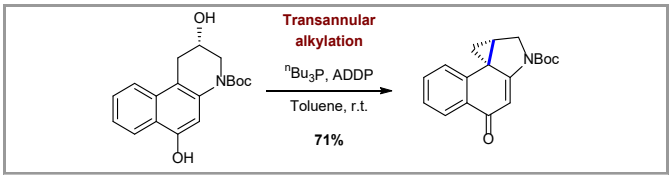
Scheme 44 Transannular alkylation in the total synthesis of cerorubenic acid III.

A similar ring contraction on densely functionalized oxathiazole-2,2-dioxide-fused cyclohexanecarbaldehydes has also been described, in this case proceeding through the generation of an enamine intermediate as the reactive nucleophilic species upon condensation with benzydrylamine (Scheme 45).[69] This reaction also makes use of the leaving group ability of the alkylsulfamate imine moiety, which underwent the transannular alkylation through an S_N2 process that took place with complete inversion of configuration. The resulting *N*-sulfonylimine formed after the alkylation was hydrolyzed *in situ* by acidic aqueous work-up leading to the final highly substituted bicyclo[3.1.0]hexane family of products. The high temperature required for the transannular process also promoted the epimerization of the methyl-containing stereogenic centre favouring the all-*cis* thermodynamic product.



Scheme 45 Transannular alkylation on oxathiazole-2,2-dioxide-fused cyclohexanecarbaldehydes under enamine activation

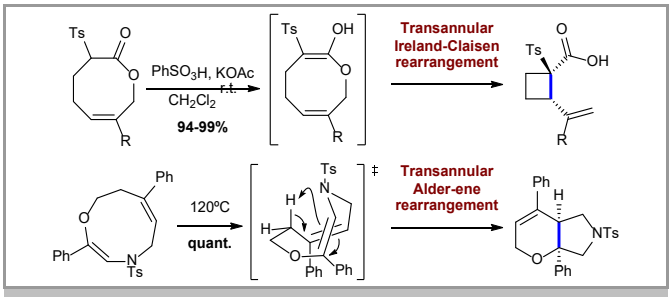
Transannular Friedel-Crafts-type alkylations have also been applied for the development of analogous ring-contraction reactions using an *N*-protected 1,2,3,4-tetrahydrobenzo[*f*]quinoline-2,6-diol as substrate (Scheme 46).[70] The reaction involved the participation of a phenol as the nucleophilic site and an alcohol as the alkylating agent, the latter requiring activation under Mitsunobu conditions by means of the combination of $^nBu_3P$ and 1,1'-(azodicarbonyl)-dipiperidine (ADDP). Under this reaction design, the dienol moiety of the phenol ring undergoes transannular reaction with the electrophilic alkoxyphosphonium salt intermediate, generating the 3-azabicyclo[3.1.0]hexane scaffold and also leaving a conjugated enone moiety in the previous position occupied by the phenol ring due to the impossibility to recover aromaticity because of the generation of the quaternary spirocyclic carbon atom.



Scheme 46 Transannular alkylation of N-Boc-1,2,3,4-tetrahydrobenzo[f]quinoline-2,6-diol under Mitsunobu conditions

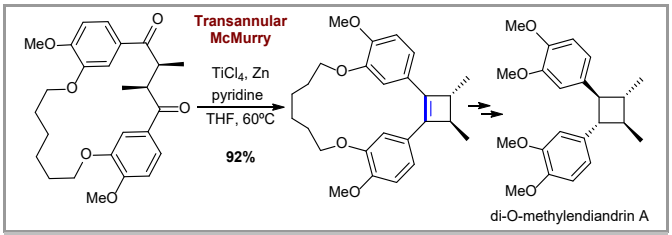
8 Miscenaleous transannular reactions

There are a couple of examples of transannular rearrangements reported in the last years (Scheme 47). On the one hand, the 8-membered unsaturated lactone shown in Scheme 45 was found to be an excellent substrate to undergo transannular Ireland-Claisen rearrangement to provide a variety of 1-tosyl-2-vinyl-substituted cyclopropane carboxylic acids in excellent yields and as single diastereoisomers.[71] This reaction required for a high acidic α-H to the ester moiety for the formation of the required enol ether under mild acidic conditions, which was accomplished by placing an activating tosyl substituent at this position. On the other hand, there is a very recent report showing that the doubly unsaturated 1,3-oxazinone also depicted in Scheme 47 undergo smoothly transannular Alder-ene rearrangement under thermal conditions to provide the corresponding hexahydropyranepyrrole in a quantitative yield.[72] This bicyclic product was also isolated as a single diastereoisomer, in agreement with the diastereospecific nature of the concerted rearrangement reaction.



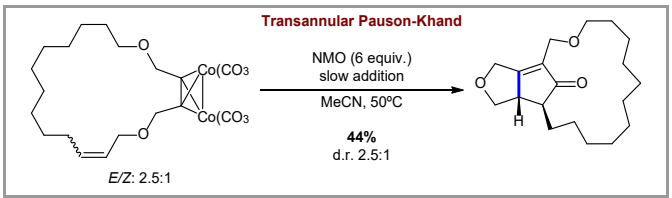
Scheme 47 Transannular Ireland-Claisen and Alder-ene rearrangements

In a different context, there is also one report regarding a transannular McMurry reaction employed for the synthesis of cyclobutane-containing lignane di-**O**-methylendiandrin A (Scheme 48).[73] Interestingly, working with a conformationally more rigid macrocyclic substrate provided a true advantage at the time of installing the two *syn*-arranged methyl substituent at the starting material with high degree of diastereoselectivity. The transannular McMurry rearrangement took place under otherwise standard reaction conditions providing an excellent yield of the desired cyclobutene product, which was converted into the target lignane in only two additional steps.



Scheme 48 Transannular McMurry reaction

Finally, there is one example of a transannular Pauson-Khand reaction described in the literature that has been carried out on a macrocyclic dicobalt enyne complex (Scheme 49).[74] The reaction employed an excess of N-methylmorpholine N-oxide (NMO) as promotor to activate the loss of a carbonyl group form the cobalt complex and also had to be conducted under highly diluted conditions in order to avoid intermolecular byproducts. The starting material was employed as a 2.5:1 mixture of cis/trans diastereomers, retaining the diastereomeric ration on the final Pauson-Khand product.



Scheme 49 Transannular Pauson-Khand reaction

9 Concluding remarks

The different examples presented in this review illustrate the high performance of the transannular reactions as key strategic decisions when facing the synthesis of topologically complex polycyclic scaffolds. In fact, many successful total syntheses of complex natural products have been achieved using a transannular process as a crucial step in the construction of the carbocyclic core of the target material. In addition, transannular reactivity also operates in the biosynthetic pathways devised by Nature for the synthesis of many secondary metabolites, which has also been demonstrated in many examples. Most of the impressive recent advances have also relied on the true advancement of synthetic methodologies available for the preparation of the medium- or large-sized cyclic starting materials, whose preparations can be a synthetic challenge by itself. In many cases, the transannular approach benefits from the narrow degree of conformational freedom of the macrocyclic starting material to guarantee a highly regio- and diastereoselective reaction. In this sense, the stereochemical outcome, and very often the regioselectivity of the process is generally governed by the nature of the starting material and the associated stereoelectronic effects that condition its three-dimensional arrangement during the reaction. As a consequence, most of the methodologies reported essentially rely on the use of a chiral starting material obtained previously in an enantioenriched form when a single enantiomer of the target compound is desired. However, very recent advances have also demonstrated the potential of catalytic and enantioselective versions of several transannular reactions that install the stereogenic elements in a controlled fashion during the transannular process.

In conclusion, the potential of transannular reactions in total synthesis is expected to contribute in the future with many exciting examples of complex total syntheses, in line with the current research activity. Moreover, important advances in the development of new methods enabling the stereocontrolled preparation of complex carbocyclic by enantioselective catalysis are also expected to be reported in the near future. Challenging aspects that also need to be solved are associated with the need for methodologies or strategies to overcome the inherent reactivity of a given macrocyclic substrate to provide a determined regioisomer or diastereoisomer when reacting under substrate control. All these future challenges make to foresee that the field is still expected to be highly dynamic and prolific with respect to new contributions in the coming years.

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Conflict of Interest

The authors declare no conflict of interest.

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Biosketches

Paste photo in this space	**Jose L. Vicario** was born in Elda (Alicante, Spain) in 1973. He graduated from the University of the Basque Country in 1996 and received his PhD in 2000 at the same University. After postdoctoral studies in 2002 at the RWTH Aachen (Germany), under the supervision of Prof. Dieter Enders, he returned to the Department of Organic and Inorganic Chemistry of the University of the Basque Country to start his independent career, where he is currently Full Professor. Current research interests focus on the design of new methodologies in asymmetric synthesis, especially asymmetric organocatalysis, and the stereocontrolled synthesis of pharmacologically active compounds. **Efraím Reyes** was born in Galdakao (Bizkaia, Spain) in 1978. He graduated from the University of the Basque Country (UPV/EHU) in 2001 and received his PhD in 2006, under the direction of Prof. Dr. D. Badia and Prof. Jose L. Vicario. After postdoctoral studies in 2007-2008 at the Center for Catalysis of the University of Aarhus (Denmark) under the supervision of Prof. Dr. K. A. Jørgensen, he returned to the Research Group of Asymmetric Synthesis (UPV/EHU), where he is currently working as Associate Professor in the field of asymmetric organocatalysis. Uxue Uria (Associate Professor,), Luisa Carrillo (Full Professor) and Liher Prieto (Assistant Professor) all of them at the University of the Basque Country.