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BRIDGEHEAD OPENING OF OXA- AND AZANORBORNENES

Oxa- and azabicyclic alkenes have proven extremely useful in the synthesis of biologically active molecules of pharmaceutical interest. In particular, many highly efficient transformations have emerged in the literature as attractive methods to allow rapid access to polyfunctionalised cyclohexene derivatives in a stereo-, regio- and chemoselective fashion, mainly exploiting transition-metal catalysed ring opening reactions. This critical review will present recent progress made in this area, with main focus on those methodologies employed to prepare natural products or biologically relevant molecules.

The cyclohexane moiety is one of the most common motifs in natural products and biologically relevant molecules. Since the pioneering work by O. Diels and K. Alder the polyfunctionalised cyclohexane core of natural products-like molecules has been efficiently assembled exploiting the [4+2] cycloaddition named after the two Nobel laureates [1]. This strategy, starting from simple diene and dienofile substrates, allows for the construction of complex scaffolds with remarkable stereoselectivity; indeed, nature itself has adopted in some instances the *biological* Diels-Alder cycloaddition for the biosynthesis of a number of natural products (although to date there has been no report on the experimental data of the presence of catalyzing enzymes) [2]. More recently other two general strategies have been successfully employed towards the same goal, the first being the ring-closing metathesis of unsaturated acyclic starting materials, the second being the bridgehead ring opening of heteronorbornenyl systems. This latter strategy is especially valuable since several stereocentres can be simultaneously created with high stereocontrol in one step, mainly exploiting transition-metal catalysed reactions. This critical review will present recent progress made in this area, with main focus on those methodologies employed to prepare natural products or biologically relevant molecules.

The most commonly employed methods for cleavage of the heterobicyclic bridgehead systems are typically acid or base induced. However, although these methods reveal the latent stereochemistry existing in the bicyclic skeleton, no new stereocentres are generated. An alternative approach is represented by the nucleophile-induced ring opening that can also introduce an additional substituent with a well defined stereochemistry and is therefore extremely valuable to construct complex molecules.

A recent example applying the first methodology is described in the synthesis of the putative structure of (-)-Oryzoxymycin reported by Steel in 2003 [3]. The key step is the base-promoted ring fragmentation of oxanorbornenylamino ester (+)-**1**; the reaction proceeds as an elimination reaction involving the acidic hydrogen in the α-position to the carboxylic group, leading to cyclohexadienol derivative **2**. Further elaborations of the molecule led to final compound **3**, that helped the author to conclude that the original structure or Oryzoxymycin was misassigned, the real structure being **4** (Scheme 1).

As far as it concerns the second methodology, initially the nucleophile induced ring-opening reaction of [2.2.1]oxabicyclic alkenes was achieved using organolithium and organocuprate reagents, affording the corresponding *syn* addition products in moderate to good yields. This reaction occurs as an S_N2' displacement, where the nucleophile reacts at the alkene carbon atom distal to the leaving group (the bridgehead heteroatom), causing a con-

comitant shifting of the double bond to displace the leaving group; generally this reaction shows high selectivity for attack *syn* to the leaving group, due to stereoelectronic effects [4].

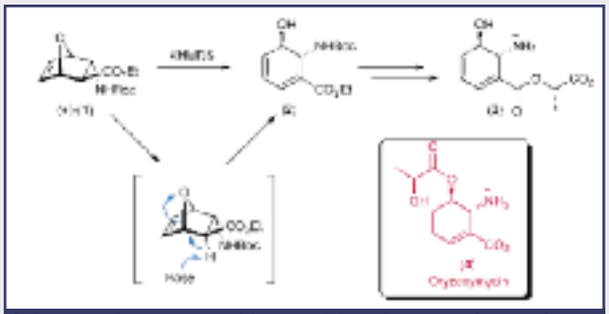
Later on, the introduction of transition metal catalysis allowed the use of softer organometallic reagents or other milder species as nucleophiles, broadening the scope of the reaction; an additional advantage of this methodology is represented by the possibility to perform enantioselective syntheses through desymmetrisation of achiral meso heteronorbornene substrates, if transition metal catalysts are used in combination with chiral ligands. This work has been pioneered mainly by the group of Lautens [5].

When the nucleophile employed is a hydride the reaction can be also considered as a reductive ring opening; the first example that will be discussed in this review is the synthesis of a precursor of the antidepressant Sertraline **7** employing a transition metal catalysed hydroalumination of oxabenzonorbornene **5** as key step [6]. The reaction is performed in an enantioselective manner by employing DIBAL-H and Ni(COD)2 [7] in combination with (S)-BINAP as chiral metal ligand, and product **6** is obtained in 91% ee (98% after re-crystallisation). Compound **6** is then converted in 7 steps into final Sertraline with an overall 33% yield (Scheme 2). The mechanism of the reaction presumably involves few distinct steps: first the formation of an aluminonickel hydride and its aluminonickelation of **5** to form **8**, subsequently the reductive elimination of Ni(0) to form organoalane **9** (isolated) and its final β-elimination to yield **6** [8].

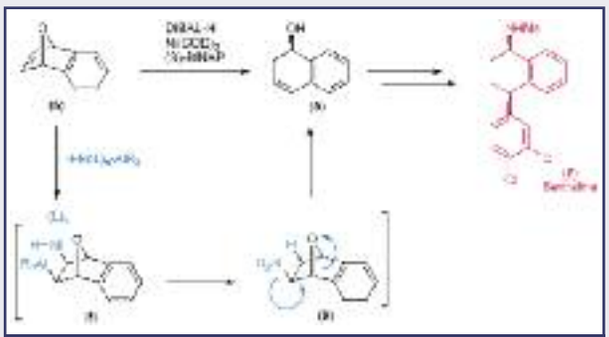
During the last fifteen years many combinations of transition metal catalysts (Ni, Pd, Rh…) and nucleophiles, both carbon-based (organozinc, organocuprate, boronic acid…) or heteroatomic (amines, alcohols, carboxylic acids...), have been employed, leading to a wide variety of final products. In general two possible pathways are possible, dependent on the nature of the catalyst and nucleophile used, accounting for the stereochemical outcome: *syn* ring opened products are generally obtained when hard nucleophiles are employed, the reaction proceeding, as in the example above, *via* a carbometallation onto the less hindered *exo* face, followed by *syn* β-elimination; soft nucleophiles (amines, alcohols, thiols...) react instead via insertion of the metal catalyst into the C-O bond, followed by nucleophile attack from the now least hindered *endo* face, resulting in final *anti* products (Fig. 1). Exceptions to this general rule are for example the *anti*-stereocontrolled copper-mediated additions of dialkylzinc [9] or Grignard reagents [10], able to further increase the stereochemical diversity.

The group of Lautens has extensively explored both these approaches, as it is reported in a comprehensive review [5], and the interest in such reactions is demonstrated not only by the great number of publications on this subject but also, for example, by industrial applications such as the recently approved patent [11] on the synthesis, in an enantiomerically pure form, of precursors of medicinally important tetrahydronaphthalene derivatives (like those illustrated in Fig. 2), *via* an improved microwave-assisted ring opening of *meso* oxabenzonorbornadiene derivatives, filed in by a group of Spanish and German researchers.

Although most of the work in this area has been done on oxanorbornene derivatives, the group of Lautens, in collaboration with the pharmaceutical



Scheme 1 - Base-promoted fragmentation of an oxanorbornenylamino ester for the construction of a cyclohexadiene scaffold



Scheme 2 - Nickel catalysed hydroalumination of oxabenzonorbornadiene for the synthesis of antidepressant Sertraline

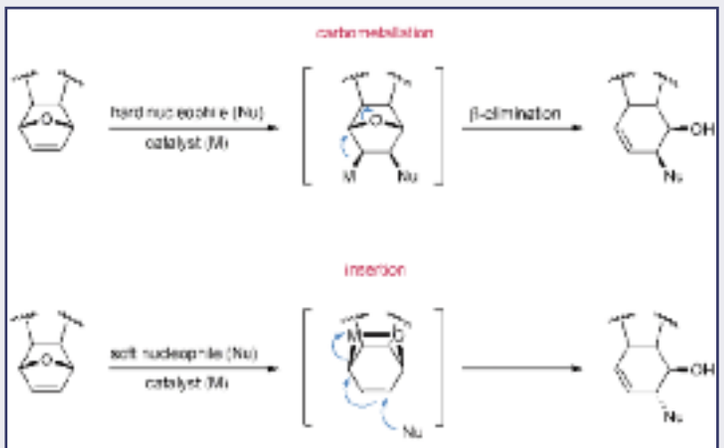


Fig. 1 - The different mechanisms accounting for the syn/anti stereoselectivity

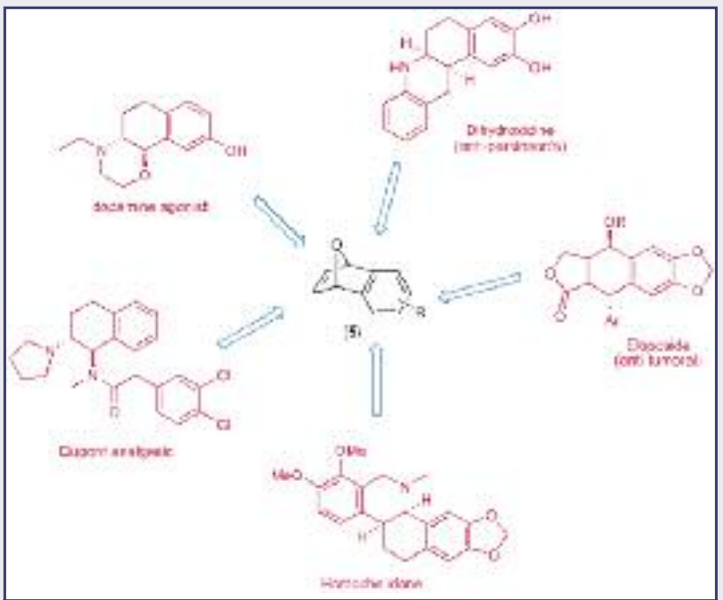
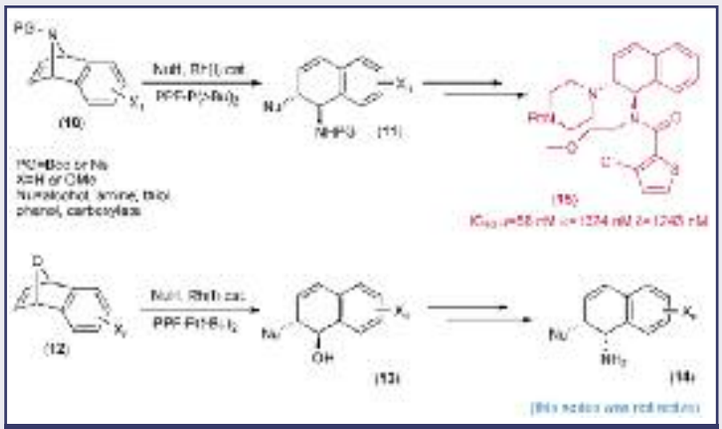


Fig. 2 - Medicinally important tetrahydronaphthalene derivatives obtainable via microwave assisted enantioselective ring opening reactions



Scheme 3 - Ring opening of azabenzonorbornadienes leading to products with relative stereochemistry complementary to that obtained from elaboration of oxabenzonorbornadiene adducts

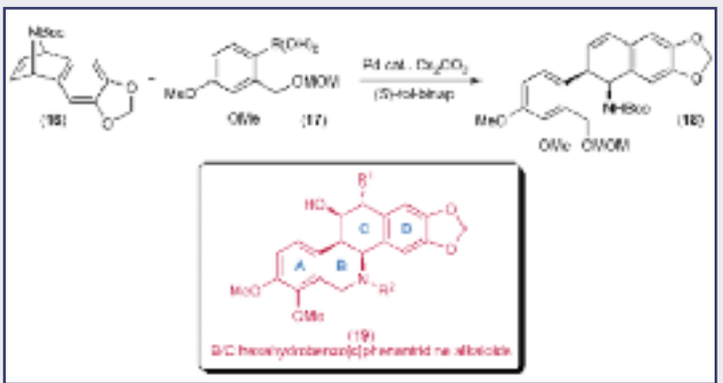
industry AstraZeneca, has also very recently studied the enantioselective ring-opening reactions of poorly reactive azabenzonorbornadienes **10** reporting an approach to the synthesis of 1-aminotetralines as μ-opioid selective ligands [12]. According to this study ring opening reactions of substrates **10** are possible both with heteroatom and carbon-based nucleophiles under appropriate conditions. When a Rh catalyst and the Josiphos-type ligand PPF-P(*t*-Bu)$_2$ are employed compounds of general formula **11** can be obtained in enantiomerically pure form. The reaction proceeds with the selective formation of the *anti* adduct, originating from the insertion of the Rh catalyst into the C-N bond of the azabicyclic substrate. It is worth noting that an alternative approach employing oxabenzonorbornadienes **12** instead, requiring transformation of the alcohol moiety of **13** into amine via S_N2 azide substitution and reduction, would lead to final products **14** with complementary relative stereochemistry. The discovery of potent and selective μ-opioid ligand **15** was reported (Scheme 3).

However when Rh is replaced by Pd and boronic acids are employed as nucleophiles the *syn*-stereoselectivity is restored, as shown in the synthesis of the B/C hexahydrobenzo[c]phenantridine alkaloids of general formula **19**, a group of isoquinoline alkaloids [13]. A retrosynthetic analysis reveals that the tetralin core displays the desired *syn*-stereochemistry of the aryl and amino substituents at C-13 and C-14 and can therefore be assembled by an enantioselective metal-catalysed addition/ring-opening of an opportune phenylboronic acid **17** to azabicyclic alkene **16**. A suitable substituent on the phenylboronic acid would allow then for the cyclisation of the B ring, while stereoselective epoxidation of the ring-opening derived double bond would allow for the introduction of the correct functionalities on the C ring (Scheme 4). Optimisation of the conditions of the key ring-opening reaction resulted to be challenging but finally led to intermediate **18** in 90% yield and 91% ee by employing the chiral catalyst (*S*)-tol-binap (binap=2,2'bis(diphenylphosphanyl)-1,1'-binaphtyl).

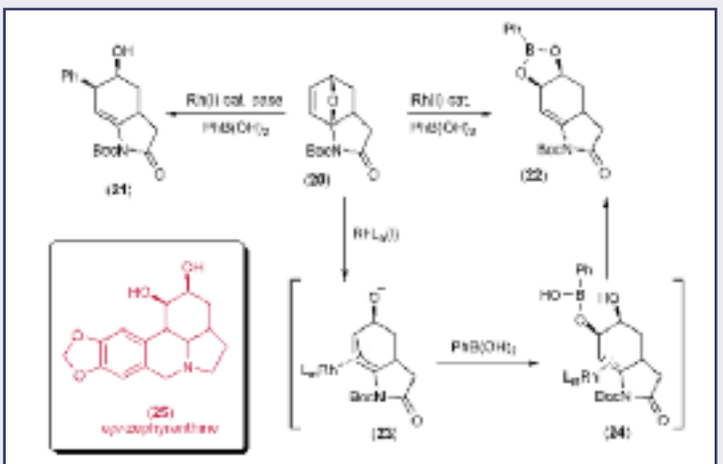
A different outcome of the reaction of oxabicyclo alkenes with boronic acids has been recently reported by Padwa for the synthesis of the tetracyclic framework of the Erythrina alkaloids [14]: in this case the key step is a Rh(I) complex catalysed addition of phenylboronic acid to oxabicyclic compound **20**, derived from the intramolecular Diels-Alder cycloaddition of an imidofuran. When the reaction is performed without added base the addition of the C-nucleophile derived from the phenylboronic acid, leading to **21**, is suppressed and a different process takes place [15]: the oxabicyclic adduct undergoes a Rh(I)-catalyzed oxygen elimination reaction as the first step, perhaps as a consequence of the Lewis acidity of PhB(OH)$_2$, and gives the ring-opened intermediate **23**. This intermediate then undergoes reaction with the boronic acid from the side opposite to the rhodium metal to produce **24**, which eventually affords **22** by cyclization and liberation of rhodium(I) hydroxide (Scheme 5). Compound **22** can then be elaborated to obtain tetracyclic frameworks such as the one of *epi*-zephyranthine **25**. This particular ring-opening process occurs with a stereochemical outcome paralleling the results of alkylative ring-opening but opposite to those of the Rh-catalysed alcoholisys and aminolysis of oxabicyclic alkenes.

The same reaction outcome is observed when oxabicyclo adduct **20** is treated with catalytic $SnCl_2$ in the presence of acetone: in this case a dioxolane intermediate is formed instead of the boronate **22**. This approach has been applied by pharmaceutical company Infinity to prepare a combinatorial library of octahydroindolinones with a solid-phase approach [16].

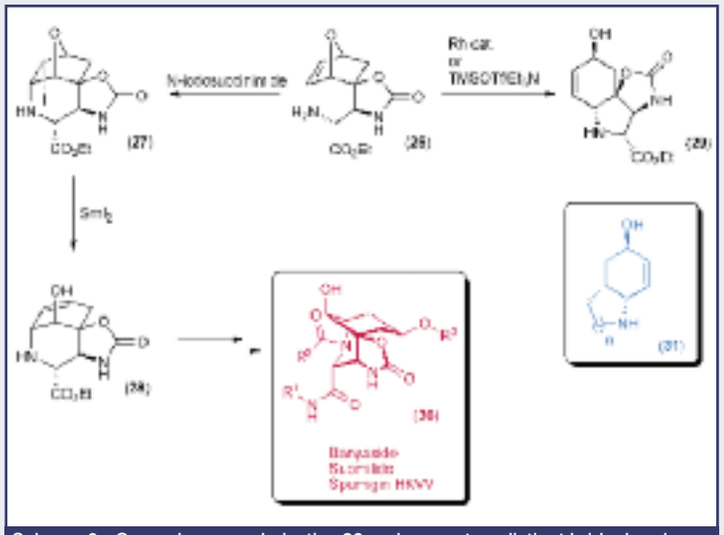
Carreira in 2008 reported the synthesis of the common core of natural products Banyaside, Suomilide and Spumigin HKVV **30** exploiting an unusual *syn* iodoamination of bicyclic adduct **26** followed by SmI_2 mediated reductive



Scheme 4 - Pd-mediated ring opening of an azabenzonorbornadiene derivative in the stereoselective synthesis of the tetrahydronaphthalene core of a group of isoquinoline alkaloids



Scheme 5 - A different fragmentation reaction mediated by Rh catalysts and boronic acids in the absence of an added base



Scheme 6 - Oxanorbornene derivative 26 undergoes two distinct bridgehead opening reactions according to the conditions employed

elimination of iodo compound **27** to give **28**, formally an allylic displacement reaction [17]. During a study aimed at the search of a method for the direct conversion of **26** to **28**, the author reported an unexpected transformation involving the opening of the oxabicyclo heptene intermediate. Indeed, the reaction of **26** in the presence of a Rh catalyst did not lead to the expected adduct **28** *via* allylic displacement, but compound **29** instead in 67% yield [18]. The hypothesis that in this case the Rh complex could function as an electrophilic activator of an allylic leaving group, prompted the authors to investigate the same reaction in the presence of a Lewis acid, finding that the exposure of compound **26** to TMSOTf/Et_3N affords **29** in 95% yield. The reaction, in this case, proceeds as an S_N1 or S_N2 process, instead of the usual S_N2', and therefore 1,4-disubstituted cyclohexenes are obtained. The scope of this novel reaction was then investigated and hexahydroindoles (n=1) and octahydroquinolines (n=2) of general formula **31** were synthesised. Such compounds represent the core structures of various Amaryllidaceae alkaloids and therefore a new methodology for their preparation was devised, although not yet reported to date (Scheme 6).

We have recently investigated the ring opening of oxanorbornenyl peptidomimetics derived from an intramolecular Ugi reaction. This study is part of a project were oxanorbornenyl derivatives have been employed as pluripotent substrates in Diversity Oriented Synthesis (DOS) [19]. DOS represents a new methodological approach that in recent years is gaining more and more importance in the field of organic synthesis. While traditional target oriented synthesis is directed towards the obtainment of specific compounds, the goal of DOS is the efficient and automatizable preparation of collection of substances characterized by high diversity content, in terms of skeletons, appendages and stereochemistries. One way to achieve this is to employ pluripotent substrates [20], which are molecules that can be synthetically elaborated, according to their functional groups, in many different ways, independent one to the other, each way leading to a different molecular skeleton. In our approach [21] the pluripotent substrate is not a single entity but a collection of molecules with a common skeleton, generated in a combinatorial fashion with the aid of multicomponent reactions, already displaying all or most of the final decorative elements: this library of compounds is then further elaborated to generate 'n' different combinatorial libraries, each with a different core structure. The ground-braking nature of this "star-burst" approach is that not only the various building blocks of the multicomponent step but also the subsequent elaborations are introduced in a combinatorial fashion; thus the final compounds, although deriving from a common substrate, are structurally different and can cover a higher portion of the chemical space, compared to classic combinatorial libraries where all the members of one library are characterised by the same core. Fig. 3 shows all the transformations that enantiomerically pure oxabicyclic peptidomimetic **32** undergoes when subjected to the opportune reaction conditions [22-24]. In particular, compounds **33** and **34** [25] can be obtained *via* a bridgehead ring opening process mediated by metal catalysts (Scheme 7); combinations of Ni catalyst, Zn and iodoarenes or Rh catalyst and amines or Pd catalyst and boronic acids have been investigated, the latter being the most efficient methodology. As expected for the mechanism of this reaction and as demonstrated by NMR experiments, the ring-opening occurred with *syn* stereoselectivity, as a result of *exo* attack of the nucleophile to the oxabicyclic unit.

Three features make our approach interesting and original: (1) the presence of various additional functional groups that could interfere with the reaction, (2) the not-symmetrical bicyclic system that could lead to two distinct regioisomers, (3) the chiral information that is intrinsic in the substrate and therefore renders the search for enantioselective catalysts unnecessary.

Concerning the first point, despite the presence of functional groups such as amines, alcohols, esters and amides in the substrate, that could for example sequester the metal catalyst or react with the nucleophile, the reactions proceeded smoothly at 50 °C in the presence of a *bis*-phosphine ligand and Cs_2CO_3, paralleling the results obtained with simpler substrates.

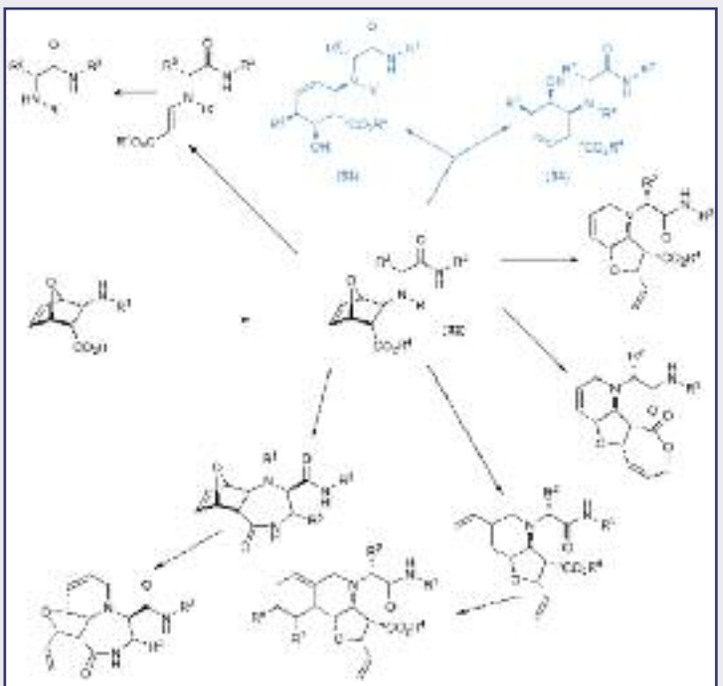


Fig. 3 - The possible elaborations of pluripotent substrates 32. Usually all these transformations require only one synthetic operation

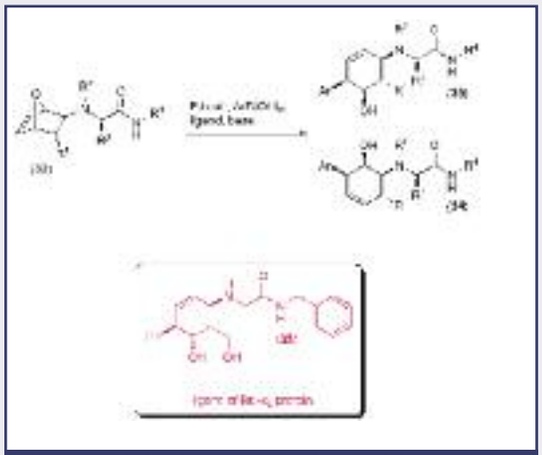
With regard to the second point outlined, there are already examples of unsymmetrical bicyclic substrates employed in ring opening processes, like for example the previously described 2-substituted 7-oxanorbornene **26** reported by Carreira or the bridgehead substituted oxabenzonorbornenes used by Lautens [26], however in these cases the substituents bringing the asymmetry are either in proximity to the site of breakage or directly involved in the ring-opening process, therefore the selective formation of one regioisomer is generally observed.

In the case of compound **32**, instead, being the asymmetry-bringing substituents not directly bound to the reactive site, substrate control is not observed and the two possible regioisomers are obtained almost in equal amount, with a moderate preference for compound **34**. Although this outcome is considered a disadvantage in target oriented synthesis, from the point of view of DOS a synthetic approach that at the same time is convergent (*i.e.* able to assemble complex entities in few synthetic steps) and divergent (*i.e.* able to produce in one step two distinct compounds) has an added value because a higher grade of diversity is straightforwardly achieved.

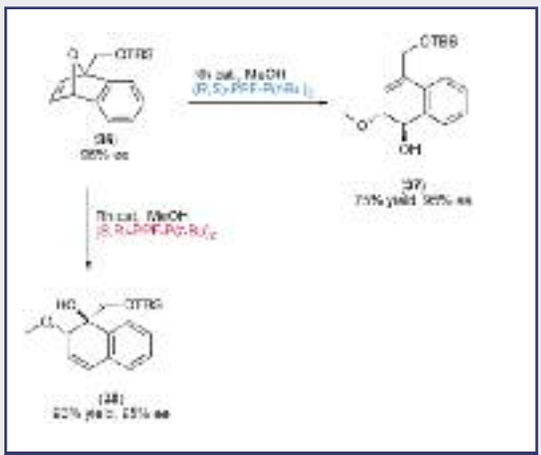
Regarding the third issue, the use of a chiral catalyst is unnecessary due to the intrinsic chiral information of substrates **32**. However use of chiral ligands could, in principle, direct the reaction towards the selective formation of either regioisomer, thus making this substrate uncontrolled reaction a reagent controlled one. This idea has been very recently demonstrated by Lautens in the case of compound **36**: selective formation of **37** or **38** by Rh catalysed methanolysis is solely ruled by the specific enantiomeric Josiphos ligand employed (Scheme 8) [27].

The compounds obtained with the DOS approach outlined in Fig. 3 have served to discover, applying a multidisciplinary approach in collaboration with Prof. G. Bifulco of the University of Salerno and Prof. M. Pellecchia of the Burnham Institute for Medical Research, compounds like **35**, new ligands of the Bcl-x_L anti-apoptotic protein (Scheme 7) [28], originated by elaborations of bridgehead opened adducts **33**.

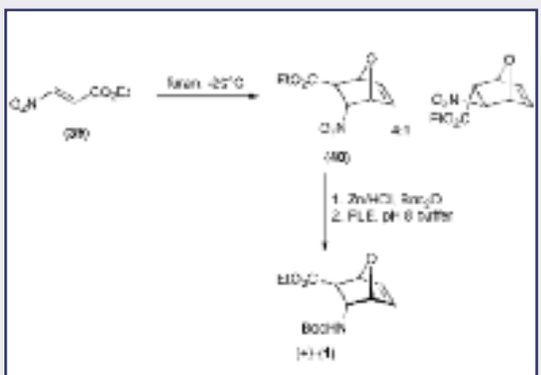
In conclusion, new stereoselective chemical reactions and new strategies for the synthesis of stereochemically complex bioactive compounds remain a focus of intense activity in organic chemistry. Oxa- and azanorbornene compounds are valuable intermediates which can address these needs: the development of improved methodologies exploiting novel substrates/reagents, employing more efficient catalysts/ligands and yielding final compounds with complementary regio and stereochemistries has been an extensive subject of research during the last decade. A lot of effort has been put not only in the application of these methodologies to the preparation of bioactive compounds but also in understanding the sometimes complex mechanisms laying behind the reaction outcomes. The knowledge gained during the last few years will surely lead to additional improvements in the near future.



Scheme 7 - Regiodivergent synthesis of cyclohexenol derivatives using a multicomponent approach



Scheme 8 - Reagent controlled ring opening of asymmetrical chiral oxabenzonorbornadiene



Scheme 9 - Diels-Alder reaction of furan with nitroacrylate 39 and subsequent elaborations

Appendix: synthesis of the oxa- and azabicyclic substrates

The ongrowing applications of norbornene derivatives in synthetic organic chemistry, not only in the bridgehead ring opening reactions illustrated in this review, make actual the demand for novel and more efficient routes to such compounds with opportune functionalisation. So far, strategies based on the Diels-Alder reaction employing furan or pyrrole derivatives as dienes remain the most widely investigated ones.

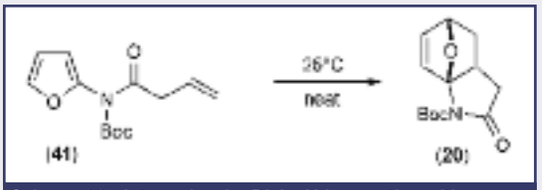
Due to the modest reactivity of furans and pyrroles as a consequence of the loss of their aromaticity, only extraordinarly good dienophiles react to form respectable yields of the corresponding 7-oxa or 7-azabicyclo[2.2.1]heptene derivatives. For this reason the Diels-Alder adducts often require post-cycloaddition elaborations to convert the electron withdrawing groups required by the cyclocondensation into the functional groups needed by the final compounds. In addition, such functionalities can be elaborated *via* kinetic resolution or desymmetrisation steps in order to prepare enantiomerically pure (hetero)norbornene derivatives; this strategy represents a valid alternative to the employment of chiral catalysts in the Diels-Alder reaction.

Indeed, oxanorbornenylamino ester **1** is obtained by reaction of furan with highly activated nitroacrilate **39**, where the nitro group, used to accelerate the Diels-Alder reaction and to direct it to the kinetically favoured *endo* adduct **40**, is subsequently reduced to the desired amine (Scheme 9). Enantiomerically pure **1** can be obtained by selective PLE mediated enzymatic hydrolysis of the undesired (-)-enantiomer starting from the racemic mixture.

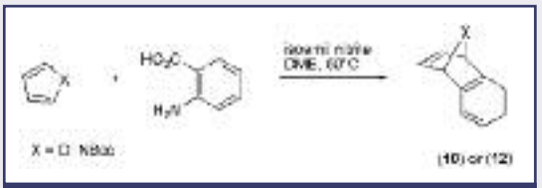
A similar approach is employed to obtain precursors of derivatives **32** and **26**: in the former case a Diels-Alder reaction between furan and maleic anhydride is followed by an alcoholysis/desymmetrisation (mediated alternatively by quinine or quinidine depending on the specific enantiomer requested) and a Curtius rearrangement to selectively convert the carboxylic acid into a protected amine. In the latter case an enantioselective cycloaddition with 2-bromoacrolein catalysed by Corey's oxaborolidine is followed by an aldol reaction and an elimination.

Diels-Alder cycloadditions can be favoured also by applying an intramolecular approach, as for example in the case of derivative **20**, obtained under mild conditions from compound **41**: despite the fact that the terminal alkene is not activated by electron withdrawing substituents, the intramolecular reaction proceeds smoothly at room temperature (Scheme 10).

Finally, benzofused compounds such as **10** or **12** can be efficiently prepared by reaction of furan or pyrrole derivatives with *in situ* generated benzyne, prepared by treatment of antranilic acid with isoamyl nitrite (Scheme 11) [29].



Scheme 10 - Intramolecular Diels-Alder reaction with iminofuran 20



Scheme 11 - Diels-Alder reaction with in situ generated benzyne

Andrea Basso graduated in Chemistry from the at the University of Genova in 1995. He then moved to the University of Southampton (UK) where he obtained his Ph.D. in 2000 and continued his scientific education as postdoctoral fellow first at the Institüt für Molekulare Pharmazie of the University of Basel (CH) and then back in Genova, where he became assistant professor in 2005. He has been recipient of various young investigator awards (i.e. Federchimica, Pfizer, CINMPIS) and his main interests are combinatorial chemistry, multicomponent reactions and solid-phase organic synthesis.

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RIASSUNTO

Reazioni di apertura del ponte eteroatomico in sistemi ossa- ed azanorbornenici

Alcheni di natura ossa- ed azabiciclica si sono dimostrati composti estremamente versatili nella sintesi di sostanze biologicamente attive. In particolare sono state recentemente messe a punto trasformazioni molto efficienti che, a partire dai sopracitati composti, portano alla formazione di sistemi cicloesenici polifunzionalizzati in maniera stereo-, regio- e chemioselettiva. La maggior parte di queste trasformazioni utilizza reazioni di apertura del ponte eteroatomico catalizzate da metalli di transizione. Questa rassegna critica riporta i risultati più recenti ottenuti in questo campo, con particolare attenzione a quelle metodologie utilizzate per la sintesi di prodotti naturali o sostanze di interesse farmacologico.