Tandem [4+2]/[3+2] Cycloadditions of 1,3,4-Oxadiazoles with Alkenes

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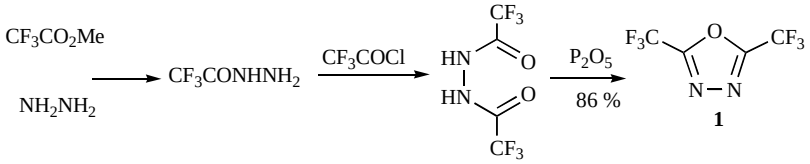
Abstract: A review on the tandem [4+2]/[3+2] cycloaddition reactions of 1,3,4-oxadiazoles with alkenes is presented. This reaction presents a powerful synthetic tool in the construction of complex polycyclic molecules in a one-pot reaction. Special attention is paid to synthesis of [n]polynorbornane and oxanorbornyl systems. In continuation, a review on the 1,3,4-oxadiazole reactions used in stereoselective total synthesis of alkaloids is given. Both intermolecular and intramolecular tandem [4+2]/[3+2] reactions are discussed. Stereospecificities and mechanistic rationale of various reactions are supported by quantum-chemical calculations (RHF/6-31G*).

Keywords: Diels-Alder reaction, dipolar cycloaddition, oxadiazoles, polycyclic molecules, reaction mechanism.

INTRODUCTION

Tandem cycloaddition reactions present a powerful synthetic protocol for preparation of complex polycyclic structures [1]. In a single reaction pot, two cycloaddition steps take place consecutively, new bonds are made in a process, in a continous sequence of reactions, without isolation of intermediates. These reactions often proceed with a high stereospecificity and efficiency. Important groups of tandem cycloaddition reactions are [4+2]/[4+2] and [4+2]/[3+2] reactions. These have been extensively used for the synthesis of the *syn*-facially fused norbornane ([n]polynorbornane) systems by employing Warrener's building BLOCK protocol [2], who recognized their synthetic advantage over a consecutive cycloaddition approaches. Tandem [4+2]/[4+2] reactions used in the synthesis of [n]polynorbornanes include small heterocycles such as 1,2,4,5-tetrazine, [3,4] 1,2,4-triazine [3], and phthalazine [5], while tandem [4+2]/[3+2] cycloadditions use 1,3,4-oxadiazoles [6, 7]. Such oxadiazoles are one type of 'molecular glue' [2] that is used to attach two building BLOCKs together. Using these protocols, a number of functionalized hetero-bridged and polarofacial [n] polynorbornanes were prepared, [8, 9] several of which showed interesting supramolecular properties [10, 11].

A variety of published examples of inter- [12] and intramolecular tandem [4+2]/[3+2] cycloaddition reactions feature reactions of nitroalkenes [13]. However, amongst heterocyclic molecular glues listed above, 2,5-bis-trifluoromethyl-1,3,4-oxadiazole **1** (**OD**) was recognized as the key reagent for construction of 7-oxabicyclo [2.2.1] moiety at the junction of two alkene components. The **OD** reagent could be conveniently prepared from hydrazine hydrate in three reaction steps in high yield (Scheme **1**) [14].



Scheme 1.

Herein we report on the versatility of the [4+2]/[3+2] cycloaddition reactions using oxadiazole in the synthesis of [n]polynorbornane molecules as well as numerous natural products. Scheme **2** shows a general type of tandem [4+2]/[3+2] cycloaddition reaction discussed in this review. Dinitrogen loss from the Diels-Alder (DA) intermediate formed in the reaction of **OD** with (cyclo)alkenes is a key element in their coupling since the generated 1,3-dipole provides a highly reactive 4π-site for reaction with the second equivalent of alkene.

1. TANDEM [4+2]/[3+2] CYCLOADDITION REACTIONS OF OXADIAZOLES WITH ACYCLIC ALKENES

Vasil'ev reported that a series of polyfluorinated 1,3,4-oxadiazoles **1**-**4** undergo a tandem [4+2]/[3+2] cycloadditions with acyclic alkenes, representative examples are given in Scheme **3**. [15] Ethylene reacts in a sealed vessel at 200-220°C with **OD** producing 1,4-bis(trifluoromethyl)-7-oxabicyclo[2.2.1]heptane **5** in 41% yield. Stereochemical or regiochemical factors come into play when the alkene bears substituents. Both regio-isomers (2,5-, 2,6-) and stereo-isomers (*exo*-, *endo*-) are then possible. The regiochemical outcome depends on the size of the substituent rather than its electronic properties. Thus, the reaction of propylene, ethyl vinyl ether, ethyl acrylate, methyl metacrylate, and isoprene give mixtures of the 2,5- and the 2,6-isomers **9**-**13** in each case, whereas reaction with styrene regiospecifically gave product **14**.

2. TANDEM [4+2]/[3+2] CYCLOADDITION REACTIONS OF OXADIAZOLES WITH CYCLIC ALKENES

A range of cycloalkenes have been found to react with **OD** to form highly symmetrical coupled products **15** (n=1,2,3,5), in which the rings were *exo*-fused to the 7-oxanorbornane subframe (Scheme **4**) [18].

Reaction with cyclopentadiene proceeds in relatively mild conditions, while cyclopentene, cyclohexene and 1,4- cyclohexadiene require more drastic conditions, heating at 140-200°C (Scheme **5**)

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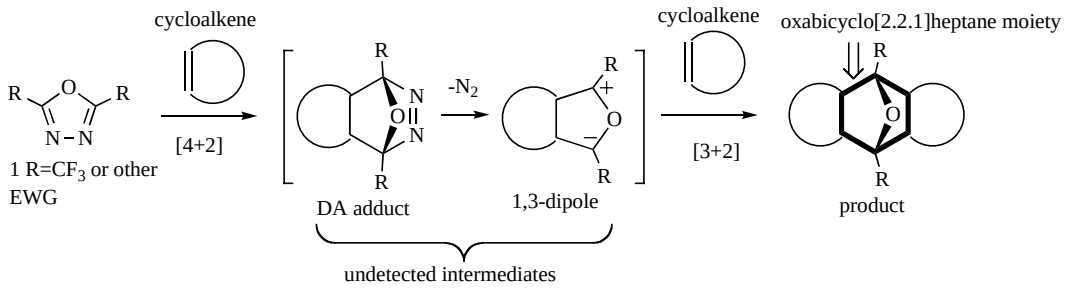
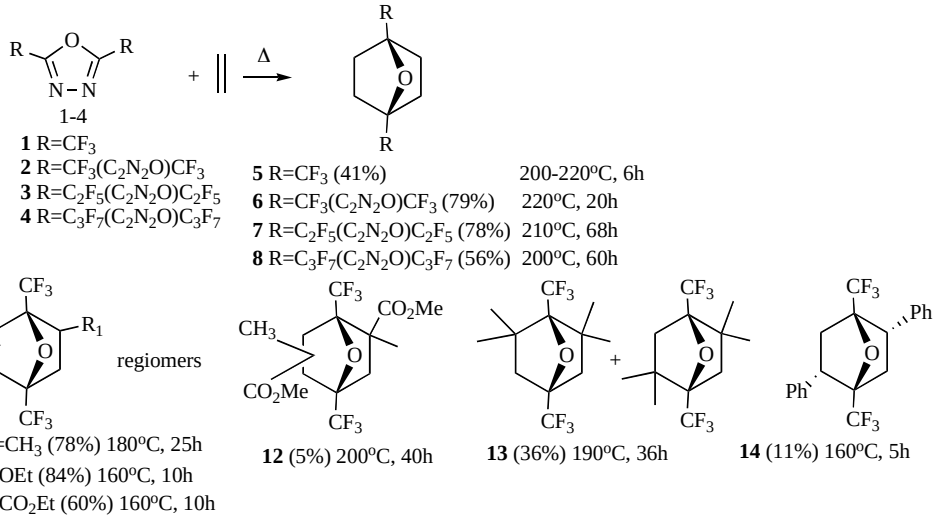
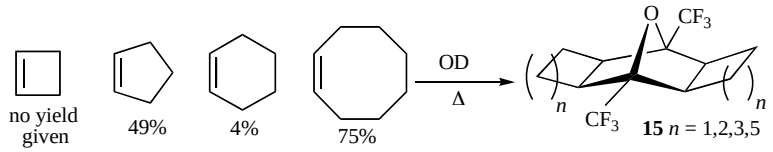


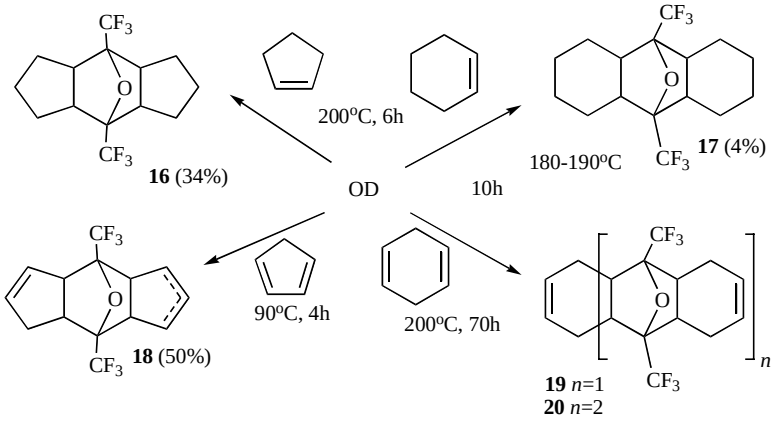
Scheme 2.



Scheme 3.



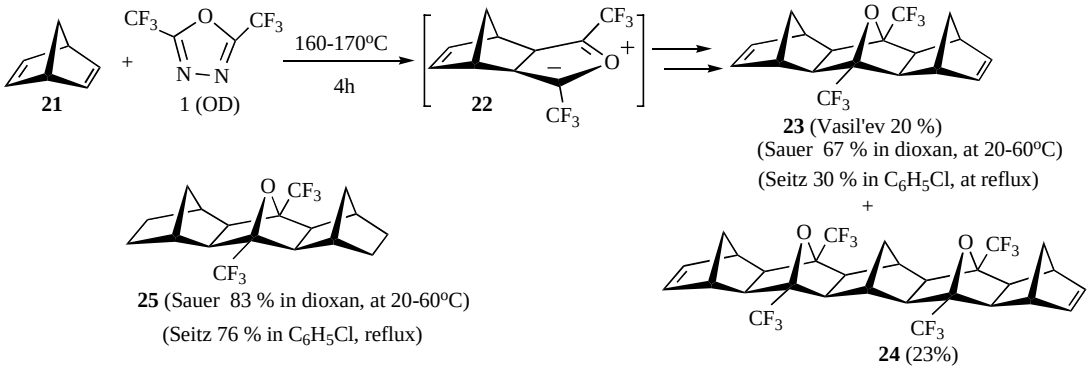
Scheme 4.



Scheme 5.

[16, 21, 38]. The ability of 1,4-cyclohexadiene to act as double 2π-component, led to the production of mixtures of 2:1 and 3:2 adducts **19** and **20**.

The coupling of two norbornadiene molecules by reaction with **OD** to form 2:1 cycloadducts of type **23** was reported by Vasil'ev in 1987 (Scheme **6**) [16]. Shortly after, Seitz [17], and independently at the same time Sauer [18, 19], reported same reactions. In one case, the on-coupled *COCOC*-[5]polynorbornane **24** alongside *COC*-[3]polynorbornane **23** was also produced [20], presumably by reaction of **23** with 1,3-dipole **22** which must have a finite lifetime for this to occur [21]. In the course of reaction, 7-oxabicyclo[2.2.1]heptane moiety is obtained at the ring junction.



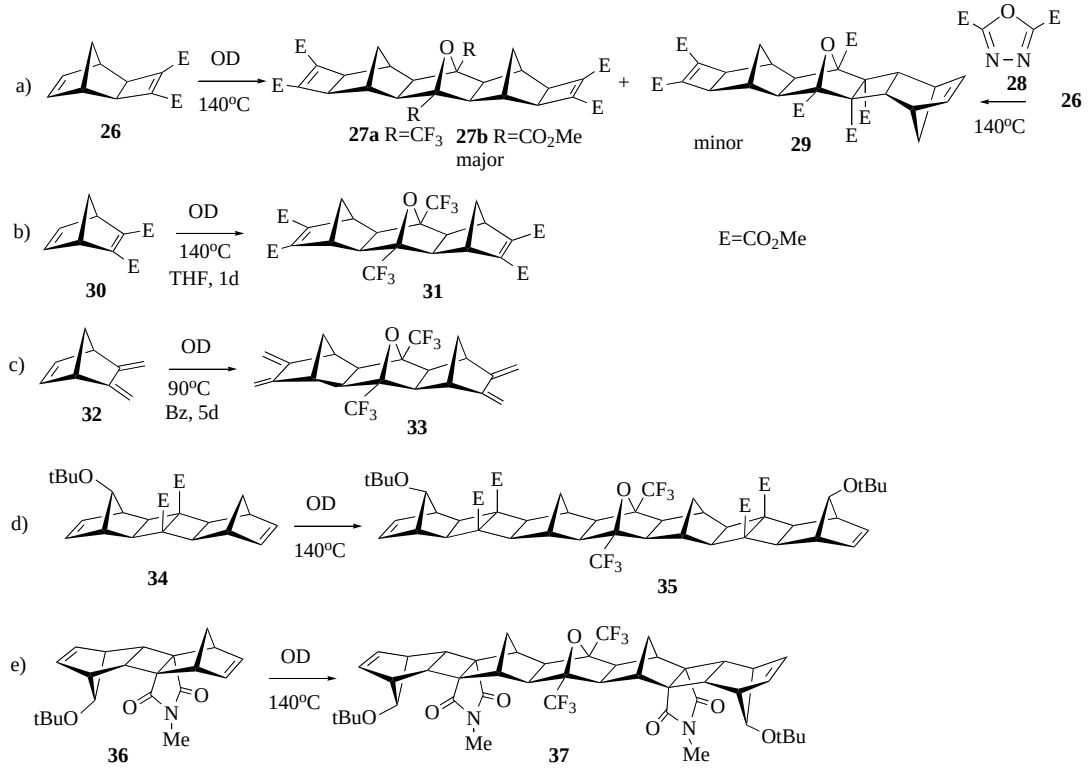
Scheme 6.

Replacement of norbornadiene with norbornene efficiently stops formation of higher polynorbornanes and only the saturated *COC*-[3]polynorbornane **25** was synthetised. This process was shown to be stereospecific and produced heterobinanes with linear (*exo,exo*-) geometry. With these findings, the **OD** reaction was established as a powerful synthetic tool for construction of [n]polynorbornanes. Interestingly, 2,5-bis-trifluoromethyl-1,3,4-thiadiazoles react in a similar manner, producing 7-thiabicyclo[2.2.1]heptane moiety at the ring junction [3, 17].

2.1. Site-Selectivity

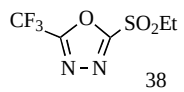
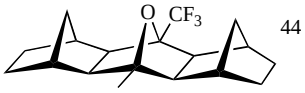
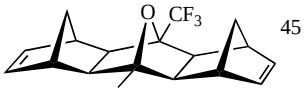
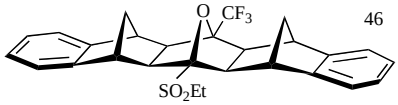
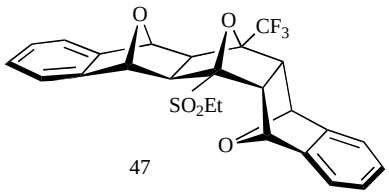
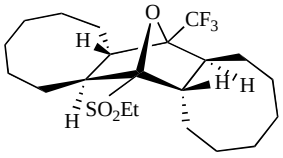
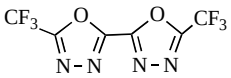
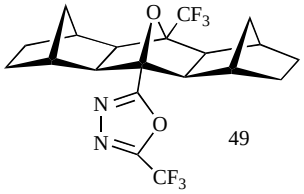
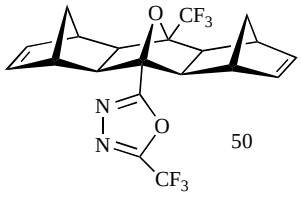
High site-selectivity has been observed in the reaction of **OD** with diester **26**, which gave exclusively the *syn*-facial product **27a** [6] derived by reaction at the norbornene site rather than the electron-deficient cyclobutene-1,2-diester π-bond (Scheme **7a**) [22]. This result compares with reaction of 2,5-di(methoxy-carbonyl)-1,3,4-oxadiazole **28** with alkene **26** under thermal conditions which produced a mixture of coupled products: the major product **27b** is formed by stereospecific coupling at the norbornene π-bond together with the products tentatively assigned as **29** and involved cyclobutene π-bond participation [6]. Analogously, 2,3-dicarbomethoxy norbornadiene **30** produced *COC*-[3]polynorbornane **31** in 33% yield (Scheme **7b**) when reacted with **OD** [37]. Site selectivity was also observed in the coupling of 2,3-dimethylenenorbornene **32**, which occurred exclusively at the *exo-face* of the norbornene π-bond to give **33** (67% yield, (Scheme **7c**) [23]. This observation is presumably due to strain on the norbornene π-bond side. In the case of π-bond screening with bulky substituents in the 7- position of norbornyl **OD** tandem [4+2]/[3+2] cycloaddition reaction takes place exclusively on the unsubstituted π-bond [24]. Site-selectivity in the oxadiazole coupling of polynorbornenes **34** and **36** has been used to produce the rigid spacers **35** and **37** (Scheme **7d,e**).

The synthetic limitation of the **OD** reactions presented so far is the fact that only symmetrical products could be synthetized (as in symmetrical through the centre of the molecule). One of the possibilities to 'desymmetrize' the reaction product was explored by Seitz. He reported that **OD** coupling of strained alkenes with unsymmetrical oxadiazoles **38** and **39** produces unsymmetrically substituted cycloadducts (Table **1**) [25]. In the case of **39**, only one



Scheme 7.

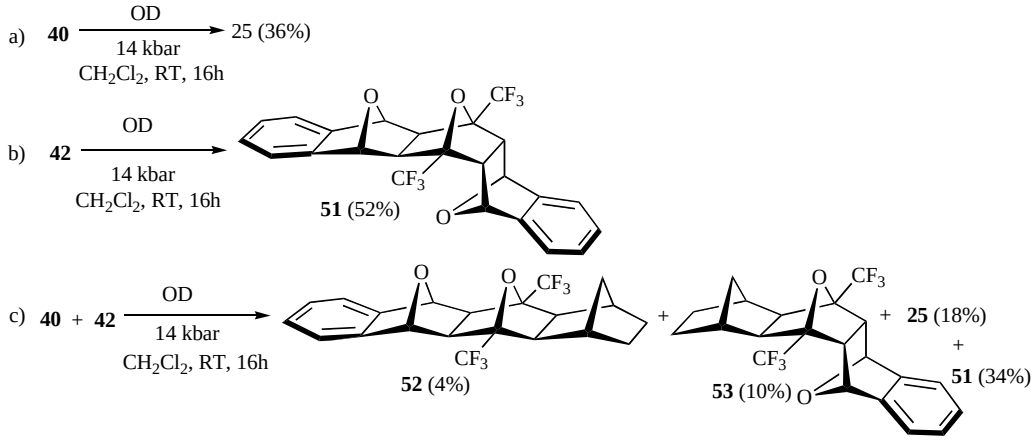
Table 1. Reactions of Strained Alkenes with Unsymmetrical Oxadiazoles 38 and 39

OD	Substrate	Products	Conditions	Yield (%)
 38	 40	 44	Chlorobenzene, 48h, reflux	18
38	21	 45	Chlorobenzene, 48h, reflux	17
38	 41	 46	Chlorobenzene, 48h, reflux	37
38	 42	 47	Chlorobenzene, 48h, reflux	25
38	 43	 48	*n*-pentane, RT, 2.5 d	68
 39	40	 49	120°C, 48h toluene	29
39	21	 50	120°C, 48h toluene	31

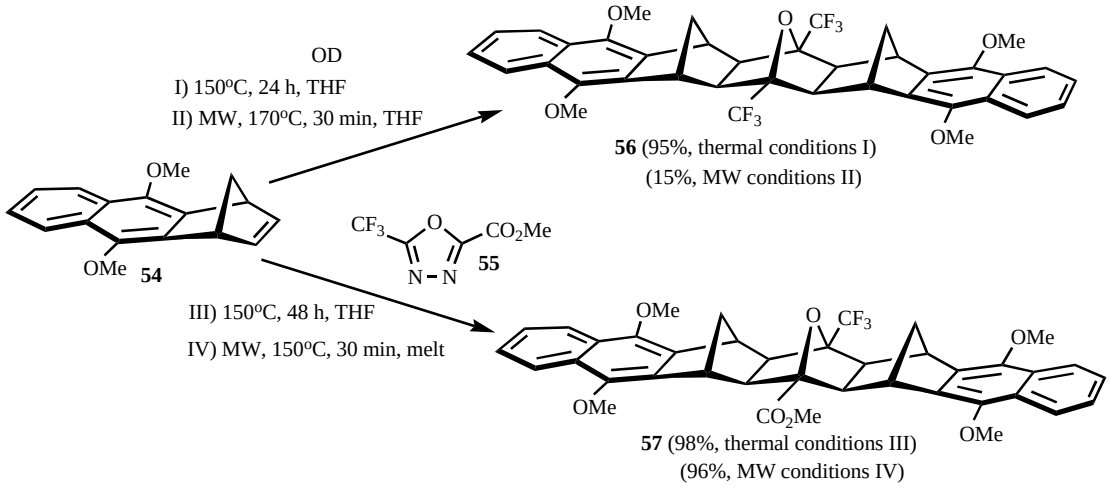
OD moiety has reacted, since the reactivity of second **OD** ring is greatly diminished by the removal of an electron-withdrawing ability of the first aromatic **OD** ring. Different reaction conditions were used, indicating that more harsh conditions are required for less reactive substrates or oxadiazoles.

An alternative, although inefficient route to usymmetrical products from the **OD** reaction is the cross-coupling of two alkene components with **OD**. As part of the study reporting the use of high-pressure for promoting oxadiazole coupling at room temperature, a *C*-bridged alkene **40** and an *O*-bridged alkene **42** was reacted both separately and as a mixture with **OD** [6, 26]. Yields obtained in HP reactions of **40** and **42** are moderate, or lower than these obtained in thermal conditions. The structures of the four products obtained in the mixed reaction showed that high stereoselectivity occurred in self coupling (**25** and **51**) and cross coupling (**52** and **53**, the former confirmed by X-ray analysis) between the two 1,3-dipole intermediates and the two alkenes (Scheme **8**). The *C*-bridged alkene reacted with *exo,exo*-stereospecificity, whereas the *O*-bridged alkene formed only *exo,endo*-fused products. In contrast with the thermal **OD** reaction, essentially no 2-naphthol byproduct was produced from **42** under these high pressure conditions.

The traditional conditions for **OD** coupling require strong heating for prolonged periods of time and are not conductive to the preparation of thermally sensitive materials, or the use of thermally sensitive substrates. High pressure facilitated coupling (at 1.4 GPa and room temperature) is advantageous in these cases, but reactions are limited to use of special high pressure equipment. An improvement in the **OD** coupling protocol in terms of using significantly shorter reaction times was achieved by microwave (MW) heating. Limited success was observed in the case of *C*-bridged alkenes, for instance, the best yield in reaction of **OD** with **54** was 15% when two reactants were heated at 150°C, for 2 hours, or at 170°C, for 30 minutes (Scheme **9**) [27]. On the other hand,



Scheme 8.



Scheme 9.

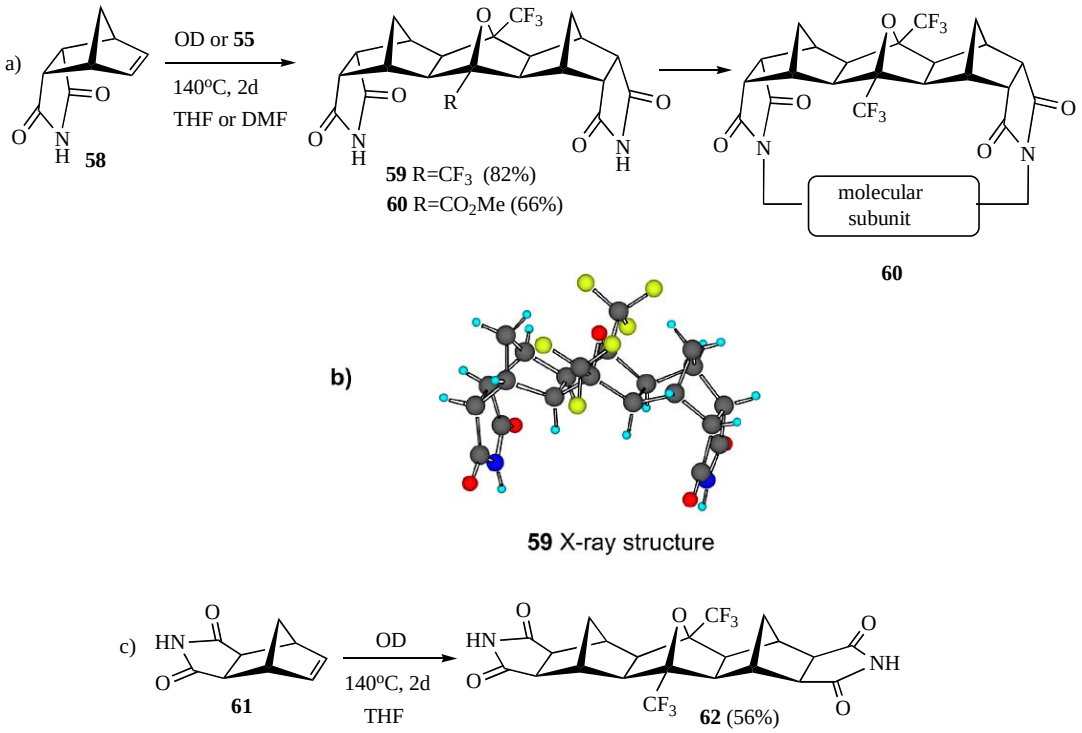
microwave heating of **54** with 1,3,4-oxadiazole **55**, without the presence of solvent gave almost complete conversion to cycloadduct **57**. Enhanced product yield is ascribed to the fact that the reaction now is much more concentrated (no solvent). Also, **55** is solid, while **OD** is liquid and is partially in the gas phase in reaction conditions, which further decreases concentration.

So far we have predominately examined the utilization of fused, or *exo*-substituted norbornyl systems in **OD** reactions. Our attention is now directed toward the utilization of *endo*-substituted norbornyl systems. The stereoselective coupling of the *endo*-isomer of norbornene-2,3-maleimide **58** has been used to produce the *syn*-oriented *bis*-succinimide *COC*-[3]polynorbornane **59** (Scheme **10a**) [28]. The structure of **59** has been confirmed by X-ray crystallography (Scheme **10b**), indicating N-N distance of 6.7 Å and convergent succinimide moieties as expected for the use of endo-substituted norbornyl compounds. This product has been converted to macrocyclic alicyclophanes by intramolecular *bis*-alkylation, where molecular subunits have exhibited increased stability (such as otherwise unstable isobenzofuran) [29], and interesting dynamic properties [30]. The use of unsymmetrically substituted oxadiazole **55** in the reaction yielded C_2-symmetrical rack **60** [31]. The use of the *exo*-imide isomer **61** and OD yielded the *bis*-succinimide **62**, which has been bis-alkylated further to produce larger macrocycles (not shown) (Scheme **10c**).

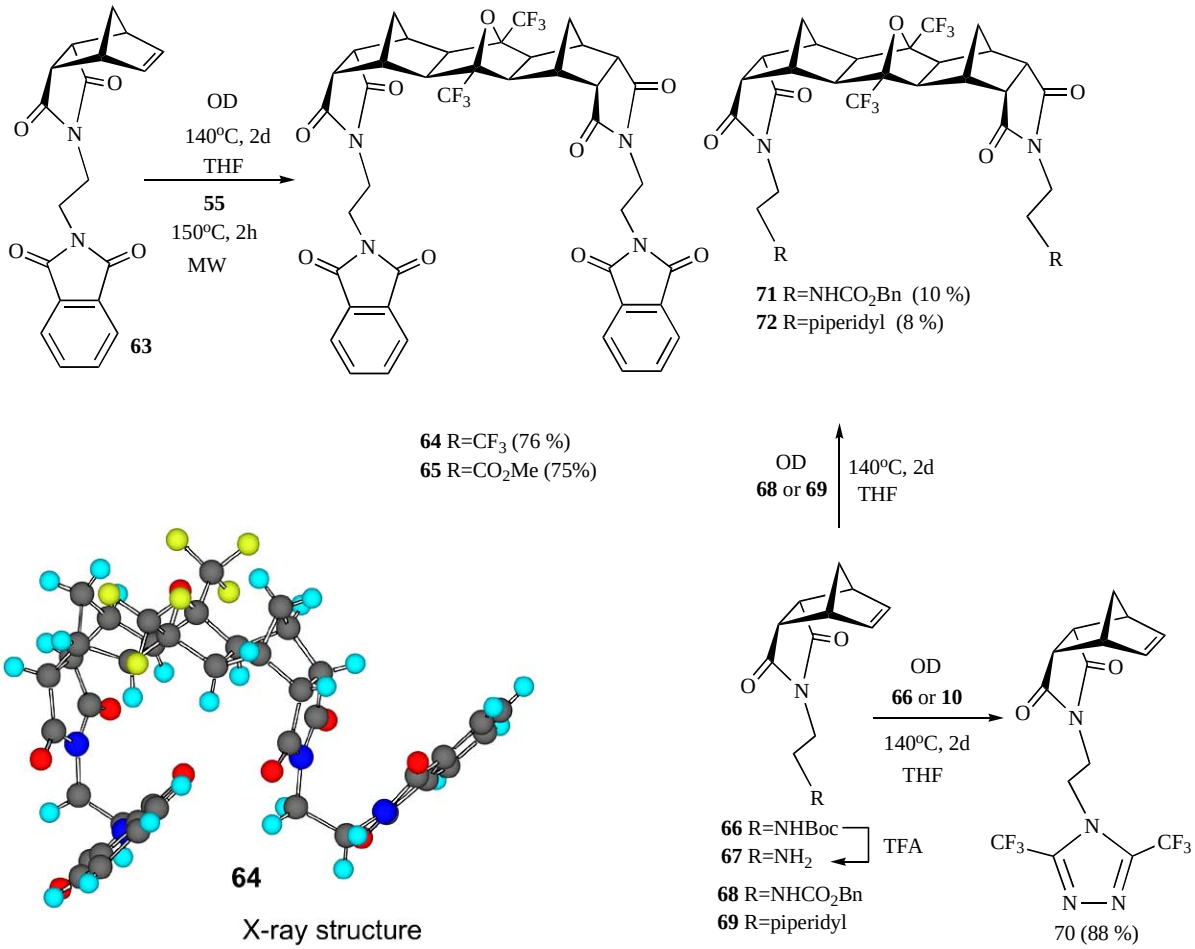
OD based reactions are carried out at high temperatures or pressures and generate a very reactive 1,3-dipole intermediate. In order to minimise the formation of side products, reactions with OD must be carried out with functional groups that are able to withstand the high temperatures and that do not react with the intermediate dipole. The influence that the choice of substituents has on the **OD** reaction, is illustrated by series of *C*-bridged substrates **63**, **66**, **67**, **68** and **69** (Scheme **11**). The reaction is limited due to possible side-reactions of substituents with **OD**. The treatment of substrates with nitrogen protection using phthalimido, benzyl or piperidyl resulted in the usual adduct being observed. The structure of product **64** was confirmed by the single crystal X-ray analysis. In addition, effective coupling of phthalimide **63** with oxadiazole **55** to product **65** was achieved under microwave irradiation (at 150°C, MW, 2h, 75%). However, It was found that **OD** coupling reactions with substrates **66** and **67** produced as a sole product 1,3,5-triazole derivative **70**, which in the case of **66** presumably takes place by *in situ* deprotection of amine.

From the above discussion we can see that only certain functional groups are able to withstand the harsh conditions that are used in **OD** reactions. Subsequent research has identified a number of functional groups capable to withstanding OD coupling reaction conditions and these are: ester, SO_2Et, ether, amide and imide functionalities, as well as benzene and quinoxaline rings, and halogens (see Scheme **12**). This list was extended to include the carboxylic acid functionality, as illustrated by synthesis of *COC*-[3]polynorbornane **74** (Scheme **12**) [32].

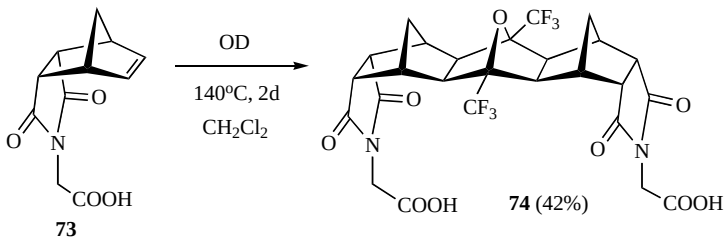
One use that **OD** reactions have been used extensively for is the synthesis of U-shaped [n]polynorbornane cavities. Such an approach is considerably more convergent than step-wise cycloaddition strategies that have been employed in polynorbornane construction (Scheme **13**). Alkene **75** reacted smoothly in high



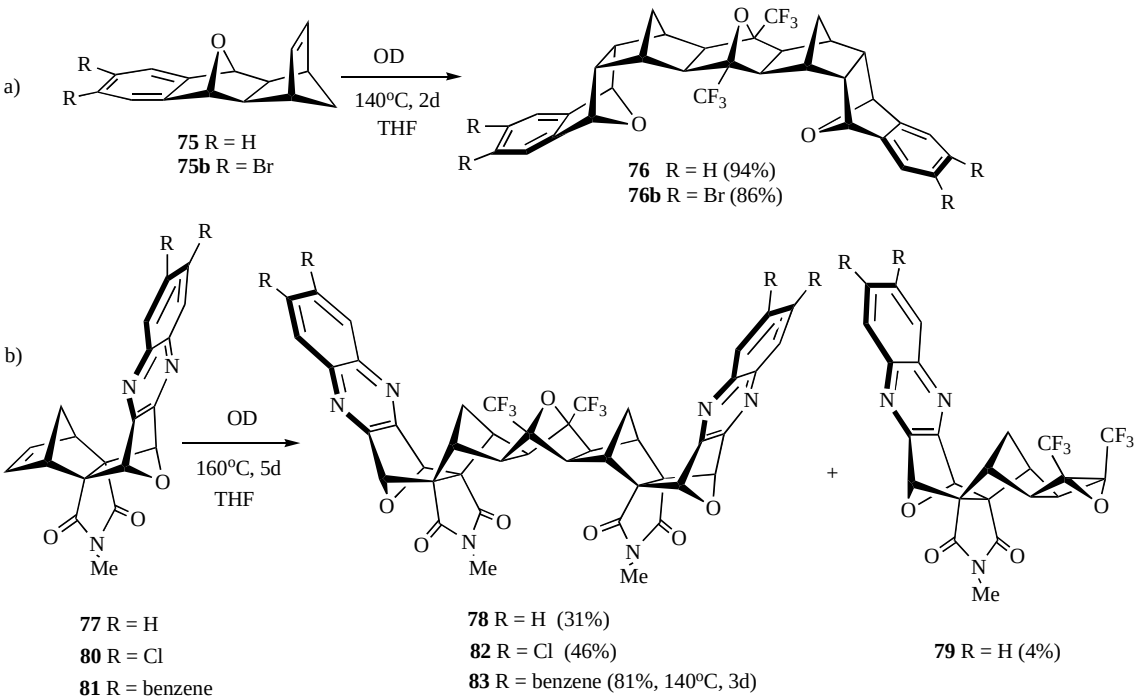
Scheme 10.

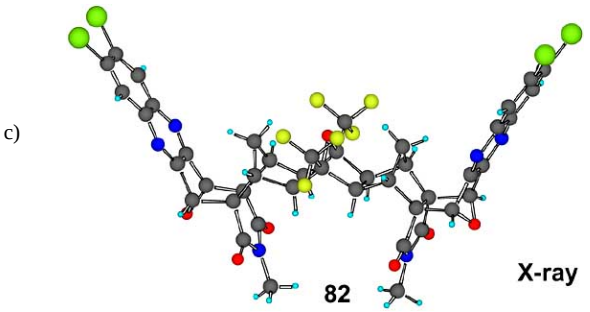


Scheme 11.



Scheme 12.



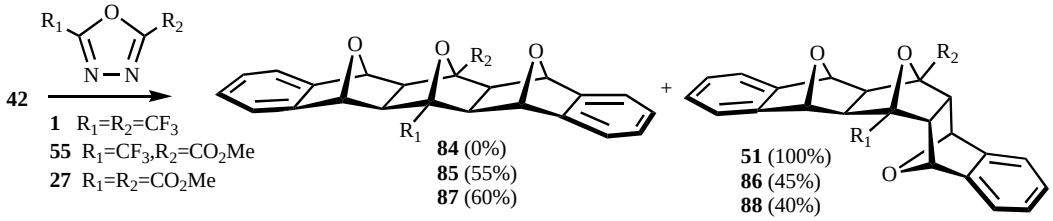


Scheme 13.

yield (94%) giving a single product **76** of desired U-shaped geometry (Scheme **13a**) [27]. Furthermore, heating of quinoxaline containing norbornene **77** with **OD** produced the U-shaped cavity **78** and the intermediate 1:1 adduct **79**, which were separated by radial chromatography (Scheme **13b**) [33]. The isolation of **79** is the first experimental evidence for the proposed intermediate in the **OD** reaction sequence. In analogous reactions with substrates **80** and **81**, cycloadducts **82** and **83** respectively were synthetised. The geometric features of X-ray structure of *bis*-quinoxaline **82** feature divergent aromatic walls and a Cl-Cl separation by 18.5 Å (Scheme **13c**). These latter substrates were employed as model compounds for the construction of 'northern hemisphere' cavity compounds [34]. These cavities can now be extended by the use of various effector groups such as crown ethers or porphyrins attached to the quinoxaline moiety.

2.2. Reactions with 7-oxanorbornenes

OD reactions of compounds containing a methylene bridge adjacent to the reacting π-bond are stereospecific [18, 40] giving 2:1 products possessing exclusively a linear (*exo,exo*-) geometry of *COC*-[3]polynorbornanes. In contrast to this, tthe results reported for 7-oxanorbornene derivatives showed a lack of stereospecificity and is some instances, inconsistency. For instance, 7-oxabenzonorbornadiene **42** when reacted with **OD** produced exclusively *endo,exo*- (angular, *anti*-facial poly-7-oxanorbornadiene, bent) O^3-[3]polynorbornane product **51** (Scheme **14**) [35]. On the other hand, *syn*-facial (*exo,exo*-) adducts **85** and **87** were prepared alongside *anti*-facial adducts **86** and **88** from 1,3,4-oxadiazoles **55** and **27**, in which ester groups are substituted for one or both of the trifluoromethyl groups within **OD** [2].

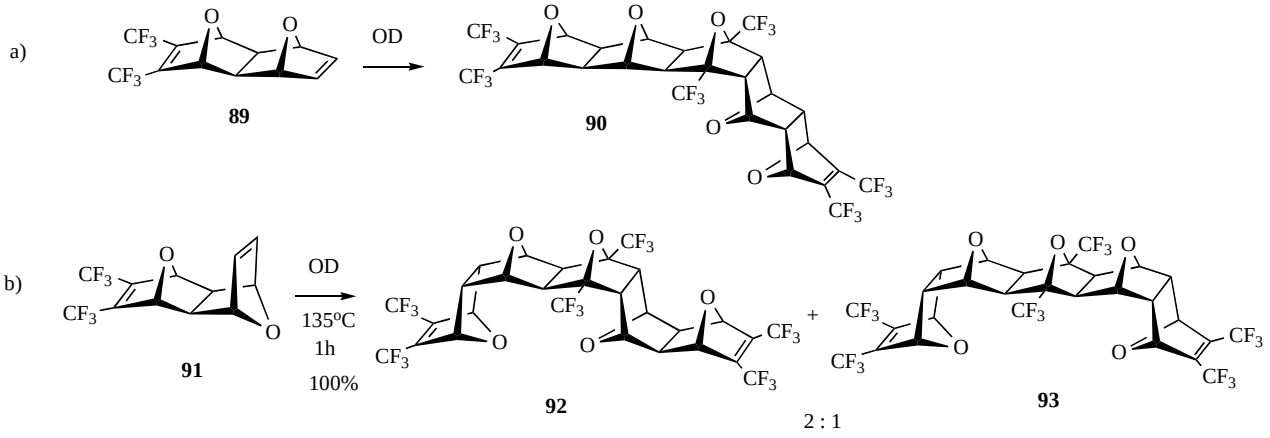


Scheme 14.

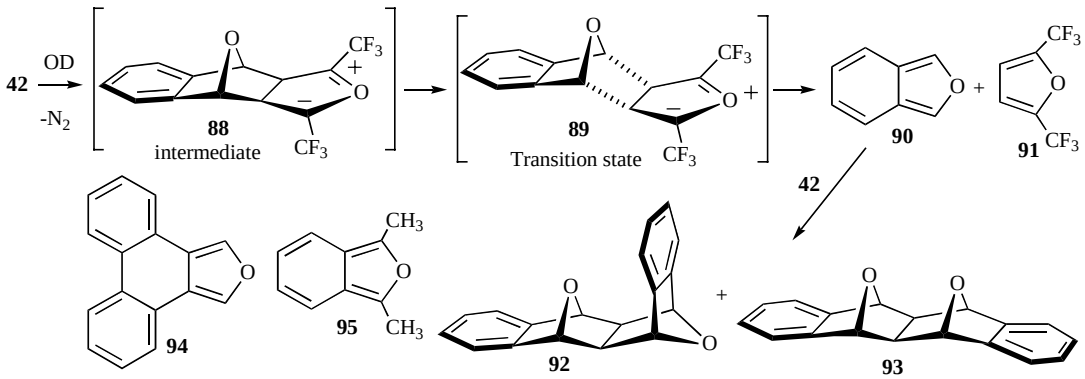
Furthermore, polycyclic bis-oxygen bridged polarofacial substrate **89** when allowed to react with **OD** produced exclusively angular geometry of O^5-[5]polynorbornane **90** (Scheme **15a**) [35]. This finding is in sharp contrast with the report on the **OD** addition to the parent *exo,endo*- isomer **91** [36]. In this particular case, reaction is not stereospecific and yields the mixture of *syn*- and *anti*-facial O^5-[5]polynorbornane *exo,endo*- and *exo,exo*- adducts **92** and **93** in approximately 2:1 ratio (Scheme **15b**).

Detailed synthetic studies of reaction of **42** with **OD** showed that in contrast to literature reports [2, 35], mixtures of isomers **84** and **51** were obtained (in ~1:2 ratio), regardless of reaction conditions employed. Classical thermal conditions (140°C, CH_2Cl_2, sealed glass vessel, 24 h), as well as non-classical conditions: high pressure (0.8 GPa, RT, CH_2Cl_2, 18 h) and microwave accelerated (CH_2Cl_2, 170°C, 45 min) were employed [37]. Alongside these main products, small quantities (5%) of side-products **92** and **93** were detected (Scheme **16**), which arise from the formation of isobenzofuran **90** by Alder-Rickert fragmentation of intermediate **88** and its subsequent Diels-Alder reaction with **42**.

The generality of these initial findings was verified using a range of 7-oxanorbornene substrates, **42** and **96-101**, and microwave reaction conditions, the results of which are collected in Table **2**. The results shows that MW conditions were more efficient in the case of *O*-bridged alkenes than corresponding *C*-bridged alkenes, being a powerful entry to a variety of O^3-[3]-, O^5-[5]-, and O^7-[7]polynorbornanes. The inspection of these results indicated that regardless of substrate used, two isomers were formed, favoring the (*exo,endo*-) over (*exo,exo*-) adducts in approximately 2:1 ratio. These results are in accordance with stereospecificity attained in reaction of **42** with **OD** under classical and high pressure conditions, as well as with those of substrate **91** (Scheme **14**). The exceptions of this general trend, however, are encountered in reactions of substrates **100** and **101**. Under MW conditions, substrate **100** affords adducts **84** and **85** (2.6:1 ratio), which indicates that reaction involves facile formation of an intermediate phenanthro[9,10-*c*]furan **94**. A similar side-reaction was previously observed in reaction with substrate **42**. However, in the case of **101**, this retro-Diels-Alder fragmentation to the parent isobenzofuran is much more pronounced, presumably due to larger stability of **94**. Calculated activation energies for the Alder-Rickert reaction of 1,3-dipoles and formation of isobenzofurans **90**, **94** and **95** by the RHF/6-31G* method suggests that the formation of **95** proceeds



Scheme 15.

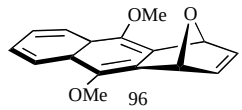
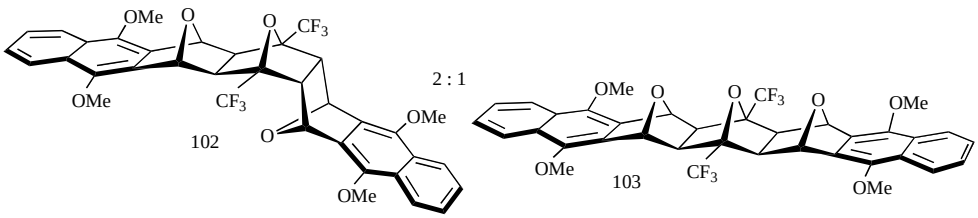
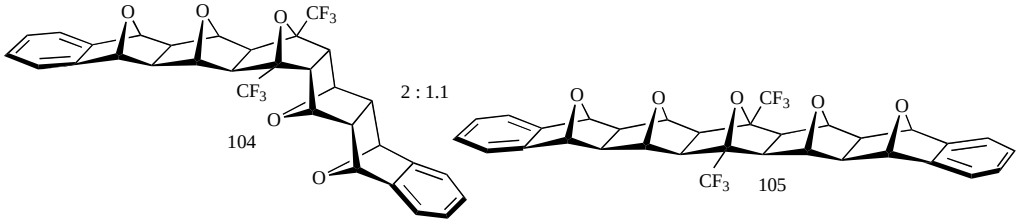
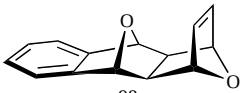
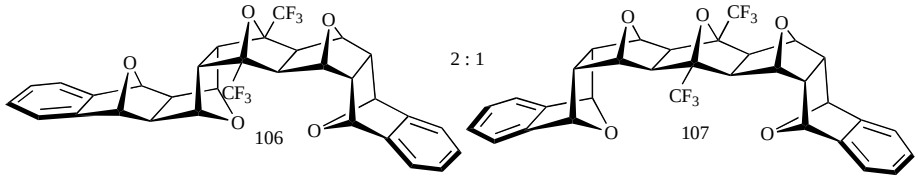
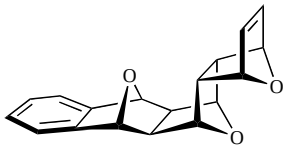
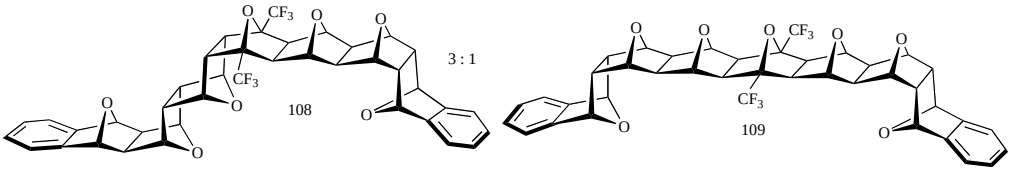
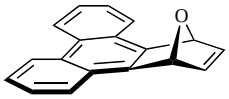
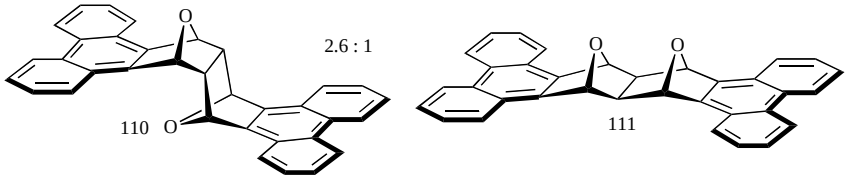
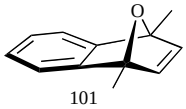
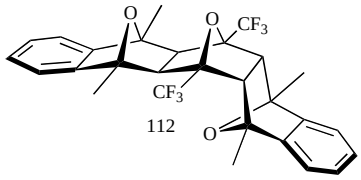
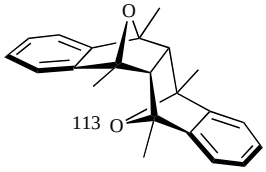


Scheme 16.

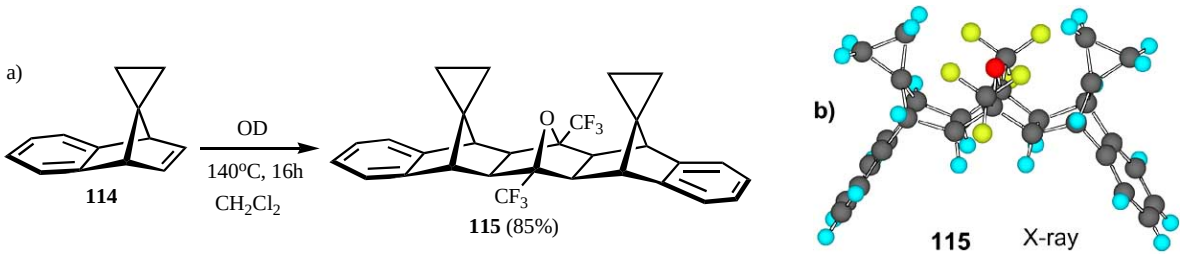
through the lowest energy barrier, leading to thermodynamically most stable product. Substrate **101** presents a special case, due to the increased sterical bulk at the bridgehead positions imposed by methyl substituents. In this particular case, the *exo,endo*- adduct of 2,9-dimethylisobenzofuran **113** was formed as a sole product. These results indicate that increased steric hindrance is a driving force for the retro Diels-Alder fragmentation of the initially formed 1:1 adduct and formation of 2,9-dimethylisobenzofuran **95**. When the **OD** coupling was conduced under milder conditions (0.8 GPa, RT, 3 days, CH_2Cl_2), a single stereoisomeric product **112** was formed with *exo,endo*- geometry.

A high stereospecificity of the **OD** reaction was also obtained when spiro-cyclopropyl substrate **114** was subjected to reaction. Although for sterically crowded *C*-bridged alkene *exo,endo*- isomer would be intuitively predicted as a favored product, *exo,exo*-cycloadduct **115** was obtained as a single product (Scheme **17a**).

Table 2. MW Reactions of 7-Oxanorbornene Substrates with 1,3,4-Oxadiazole 1

Substrate	Products (ratios)[a]
42	51 2.2:1 84
 96	 102 2 : 1 103
 97	 104 2 : 1.1 105
 98	 106 2 : 1 107
 99	 108 3 : 1 109
 100	 110 2.6 : 1 111
 101	 112
101	 113

[a] 170°C, 45 min, CH_2Cl_2



Scheme 17.

The linear structure was confirmed by X-ray single crystal determination (Scheme **17b**) and unequivocally verifies NMR spectroscopic structural assignments.

3. INTRAMOLECULAR [4+2]/[3+2] CYCLOADDITION REACTIONS

OD reaction could be used to make molecules with interesting functions, for this purpose intramolecular variant is proven to be highly efficient. When dienes were used as a bis-2π-component in DA reactions with OD **38**, intramolecular tandem [4+2]/[3+2] cycloaddition could take place, giving rise to cage products. Seitz published the first literature example featuring 1,4-cyclooctadiene, which produced cage **117** (Scheme **18**) [25]. Vasil'ev recently repeated this reaction with variously substituted oxadiazoles and obtained same the tetracyclic cage **118**-**120** (albeit with different substituents) [38, 39]. When cycloheptatriene was used as a bis-2π-component, reaction slowly occurred at elevated temperature, forming related cage product **121** (62%). This result indicates that conjugated dienes could be used for the intramolecular reaction.

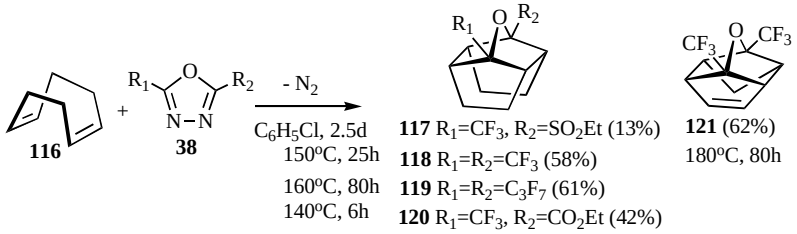
In the case of norbornadiene based 2π molecules, product from intermolecular **OD** reaction, *i.e.* intramolecular trapping of the 1,3-dipolar species has been observed by Warrener in the reaction between **OD** and 7-*tert*-butoxynorbornadiene **122** (Scheme **19**) [40]. Attack by **OD** must have occurred at the *endo*-face of the norbornadiene to allow formation of the cage product **124** and the presence of the *tert*-butyloxy group completely reversed the facial selectively observed with norbornadiene. Two isomeric dipolar intermediates **123a,b** are possible, but each forms **124** upon cyclisation.

Reactions with acyclic dienes leads to inter- and intramolecular reactions, where as a general rule, larger separation between π bonds favours cage formation. The reaction of **OD** with divinyl sulfide occurred only at high temperature, leading to almost identical amounts of cyclic products **125** and **126**, arising from inter and intramolecular reactions respectively. This result is similar to formation of butadiene inter- and intramolecular adducts **127** and **128** (Scheme **20**). Analogously, 1,3-cyclohexadiene reacted with **OD** at 125°C forming mainly intermolecular cycloaddition product **129**, along with smaller amount of product **130**. On the other hand, reaction with divinyl ether did not proceed intramolecularly, and regiomeric **131** was obtained as the single product. It is evident that larger separation between two π-bonds in the diene favors the formation of cage adduct, such in the case of diallyl ether, where reaction rapidly proceeds at 130°C to give **132** [38]. 2,3-Dimethylbutadiene reacted with **OD** in a more complicated manner, and failed to produce double intermolecular cycloaddition product. Instead, a mixture of intramolecular product **133**, trifluoroacetamide **134** and 2-trifluoromethyl-4,5-dimethylpyridine **135** was obtained. Formation of two later products can be explained by competitive [4+2] cycloaddition of 2,3-dimethylbutadiene to the C=N bond of **OD** and subsequent fragmentation of unstable cycloadduct intermediate [38].

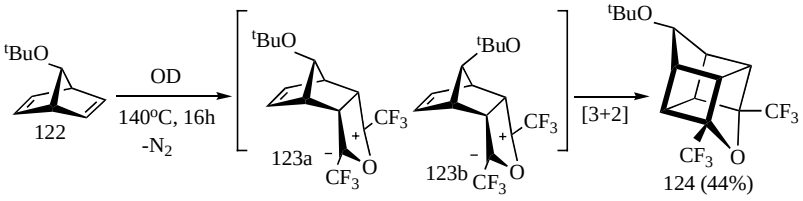
3.1. Natural Product Synthesis *via* Intramolecular OD Reaction

OD reactions were not used extensively for natural product synthesis, but when they are employed it is very effective way to achieve structures with considerable complexity. For example, intramolecular oxadiazole coupling reactions have been used by Boger and Ishikawa in natural product synthesis of vindoline and structurally related alkaloids (Chart **1**) [41].

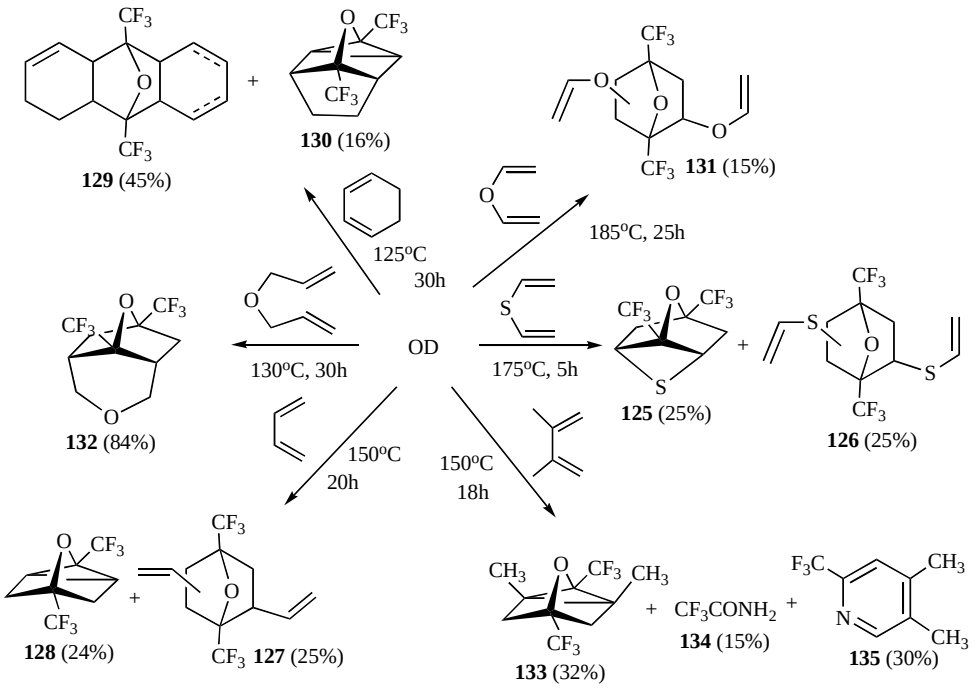
For this purpose, oxadiazole and two alkene components were in-built in the substrate. Remarkable achievement in the course of these tandem [4+2]/[3+2] cycloadditions is that three new rings were constructed with formation of four new C-C bonds and set all six stereocenters about the central six-member ring in a single step obtaining a single diastereoisomer. Classical reaction mechanism is postulated, involving [4+2] addition of oxadiazole in the first step, and formation of intermediate Diels-Alder adduct **137** (Scheme **21**) [42]. At this stage, two stereocenters are defined. Facile loss of dinitrogen from **137** allows the formation for reactive 1,3-dipole intermediate **138** and subsequent 1,3-dipolar addition to the indole moiety to give the final product.



Scheme 18.



Scheme 19.



Scheme 20.

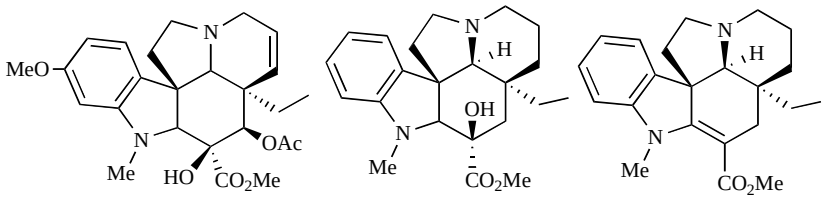
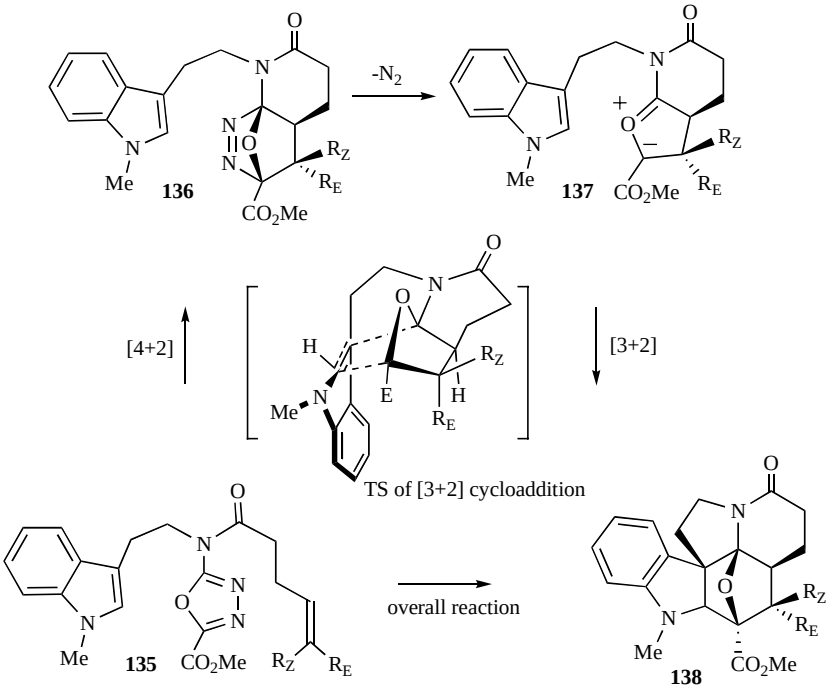


Chart 1.

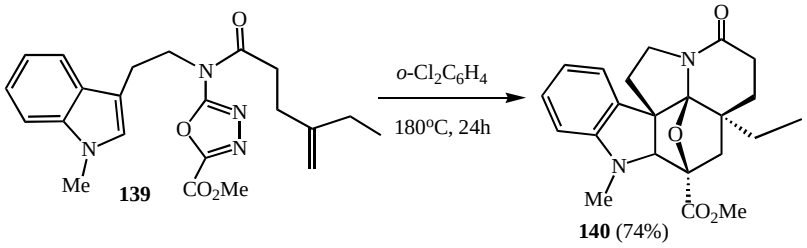


Scheme 21.

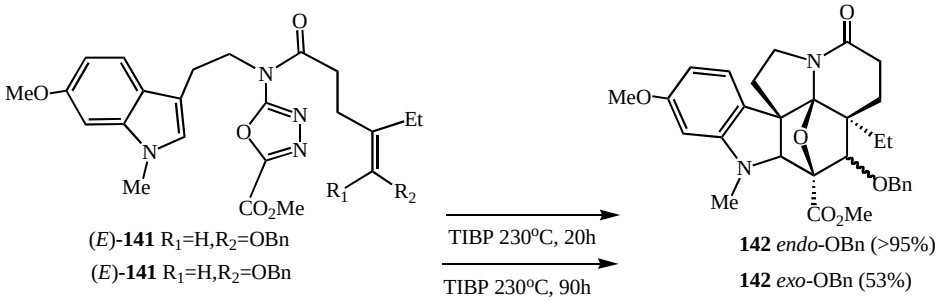
For these reactions, *o*-$Cl_2C_6H_4$ or 1,3,5-triisopropyl benzene (TIBP) were used as solvent. Reaction temperature are quite high, ranging from 180°C (3h) to 230°C (60h) for the most unreactive substrate. Isolated yields vary from 41% for (*Z*)-**135** (R_Z=OBn) to 88% for (*E*)-**135** (R_E=OBn). This reaction is one of the first uses of microwave conditions for oxadiazole tandem [4+2]/[3+2] cycloadditions, in the case of substrate **135** with R=H. In the thermal reaction (*o*-$Cl_2C_6H_4$, 180°C, 3h) obtained yield was 87%, while MW conditions (250°C, 30 min) gave 70%.

Total synthesis of natural (-)-desacetoxy-6,7-dihydrovindorosine and natural and *ent*-minovine were achieved by tandem [4+2]/[3+2] cycloaddition sequence of oxadiazole **139** (Scheme **22**) [43]. Formation of basic skeleton **140** is followed by chemical trans-formation of functionalities to obtain (-)- and (+)-vindorosine [44].

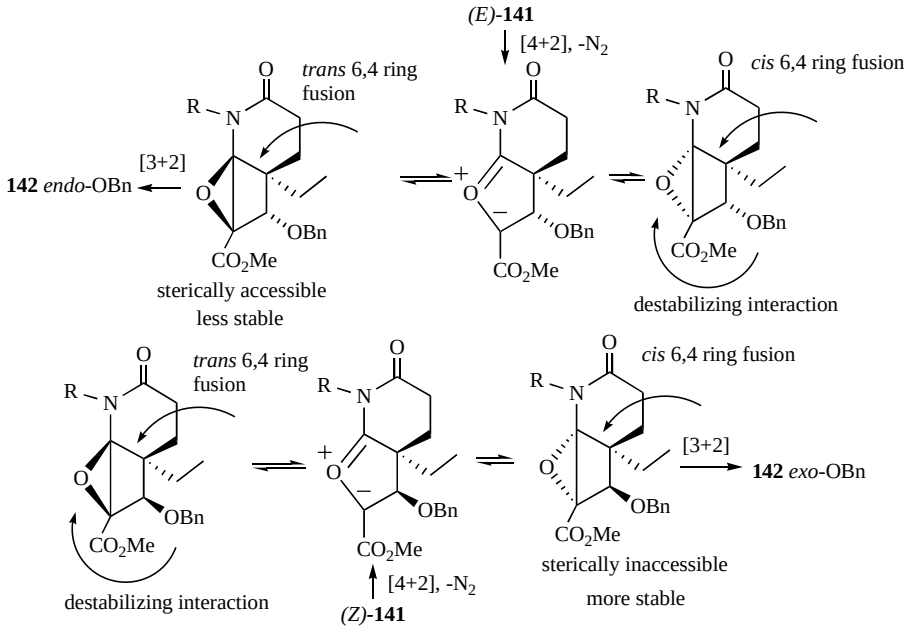
Intramolecular OD reaction offers a straightforward synthetic route to vindoline alkaloids. The tandem [4+2]/[3+2] cycloadditions of (*Z*)-**141** and (*E*)-**141** provide complete stereochemistry found in the pentacyclic skeleton of the Aspidosperma alkaloids, introducing all the functionality found in (-)-and (+)-vindoline [45]. Reaction of (*Z*)-**141** directly introduces the naturally occurring C4 OAc β-stereochemistry **142***endo*-OBn, whereas (*E*)-**141** provides C4 epimer **142***exo*-OBn (Scheme **23**). Interestingly, dilution of the reaction dramatically increases yield, suggesting that a intermolecular 1,3-dipolar cycloaddition reaction of **141** may compete with the intramolecular cycloaddition cascade at the higher reaction concentrations. In these reactions, the [4+2] cycloaddition is the fast step for (*Z*)-**141**, which is a reversal of what is observed with (*E*)-**141** and other substrates. The reason for this difference may be in transition state for the 1,3-dipolar cycloaddition. TS of (*E*)-**141** suffers a destabilizing interaction of its central oxygen with the (*Z*)-OBn substituent that decelerates the reaction (Scheme **24**). Another reason could be the stabilization of the (*E*)-OBn substituent of (*E*)-**141** in its TS (anomeric effect). It is also possible that the



Scheme 22.



Scheme 23.



Scheme 24.

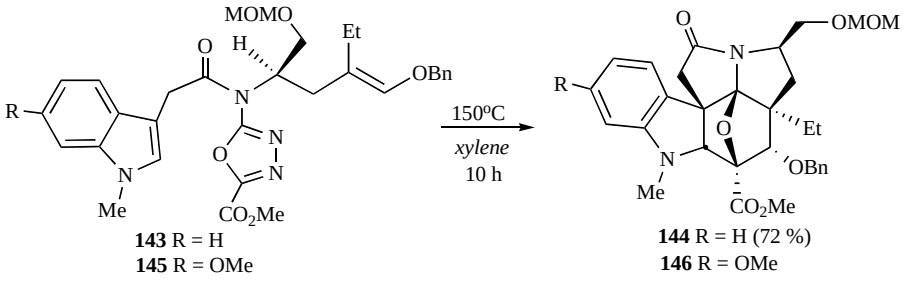
preferred stereochemistry of the corresponding cyclobutene epoxide intermediate or their relative stability may dictate the relative ease of the 1,3-dipolar cycloaddition.

Recently Boger published results on the development of an asymmetric total synthesis of (-)-vindoline based on an implementation of the tandem [4+2]/[3+2] cycloaddition reaction [46]. In this variant of the reaction, the tether linking the dienophile in **143** bears a chiral substituent that sets the absolute stereochemistry of the remaining six stereocenters (Scheme **25**). At the same time, dienophile linking tether was reduced in length by one carbon atom, while the activating acyl chain carbonyl is positioned in the dipolarophile tether. The [4+2] cycloaddition then afforded a fused five-membered ring in product **144**. A subsequent, ring expansion reaction provided a six-membered ring. The substrate **145** bearing the indole methoxy group, participated in the cycloaddition cascade in an analogous fashion, and the cycloadduct **146** was subjected to next synthetic step without purification.

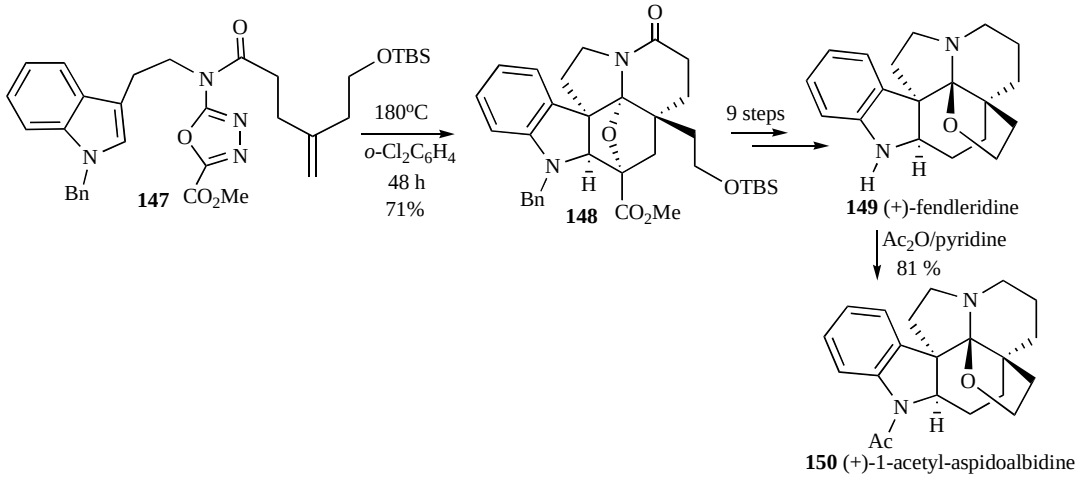
The tandem oxadiazole cycloaddition reaction was also used by Boger [47] to synthetise basic skeleton of (+)-fendleridine and (+)-1-acetylaspidoalbidine (Scheme **26**). Key reaction occurred cleanly at 180°C in *o*-dichlorobenzene to afford **147** in yields as high as 71% as a single diastereomer. The cycloaddition of the corresponding free alcohol was also investigated but was unsuccessful, resulting in intramolecular transesterification. From the intermediate **148** the total synthesis of (+)-fendleridine **149** and (+)-1-acetylaspidoalbidine **150** was achieved in nine synthetic steps.

The use of 2-amino-*N*-substitited-1,3,4-oxadiazoles enriches the library of functionalized oxadiazole reagents. It is found that *N*-acylation (an electron-withdrawing substitution) of the oxadiazole C2 amino group is required for sufficient [4+2] cycloaddition reactivity. There is a little distinction whether it is incorporated into the dienophile or dipolarophile tether, in both cases *N*-acylation accelerates reaction (Scheme **27**) [42].

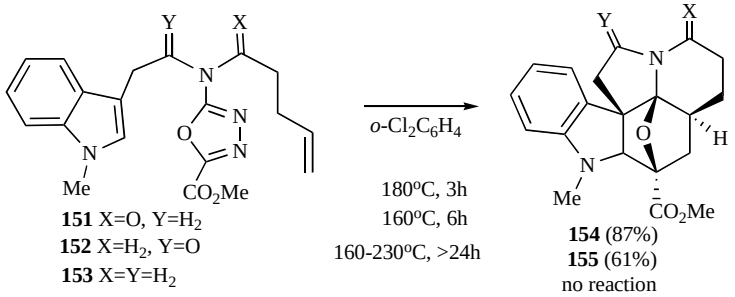
A mechanistically important detail is the finding that the initial [4+2] cycloaddition is faster than the subsequent [3+2] cycloaddition. Some experimental evidence on the reaction quenched prior completion indicates that cyclobutene epoxides **156** may be reversible transient intermediates in the slower thermal reactions (Scheme **28**) [42].



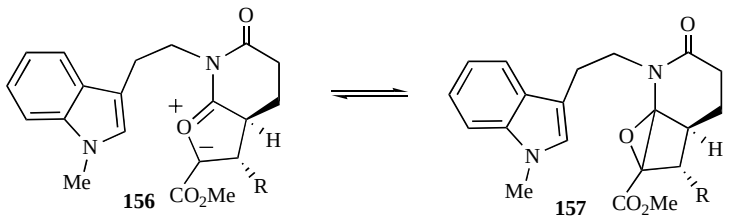
Scheme 25.



Scheme 26.



Scheme 27.



Scheme 28.

In some instances, 7-oxabicyclo[2.2.1]heptane moiety of product is unstable in reaction conditions and undergoes an oxa ring opening, such as in the case of substrate **158**, which produced **159** (Scheme **29**) [42].

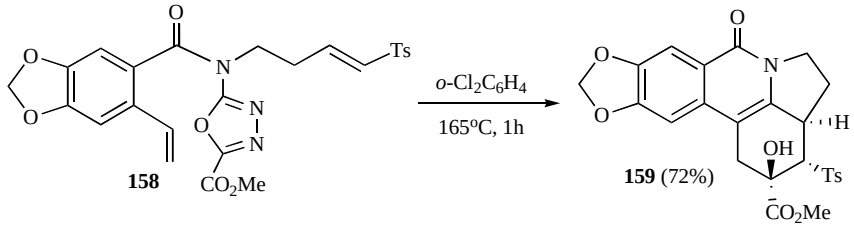
4. OD REACTIONS WITH ALKYNES

Alkynes are known to act as sources of π electrons in cycloaddition reactions [48]. In particular, alkynes react with **OD** via tandem [4+2]/[4+2] cycloadditions, involving reactive intermediates possessing a furan diene moiety. They were obtained when the initial DA-adducts rapidly ejected dinitrogen in a process of stabilization of the reactive species by aromatization. For instance, the reaction between **OD** and benzyne, produced the 9,10-dihydro-9,10-epoxyanthracene **161** [17], presumably by way of 1,3-bis(trifluoromethyl) isobenzofuran **95** (Scheme **30a**). Similarly, cyclooctyne afforded the adduct **163**, via furan intermediate (Scheme **30b**) [18].

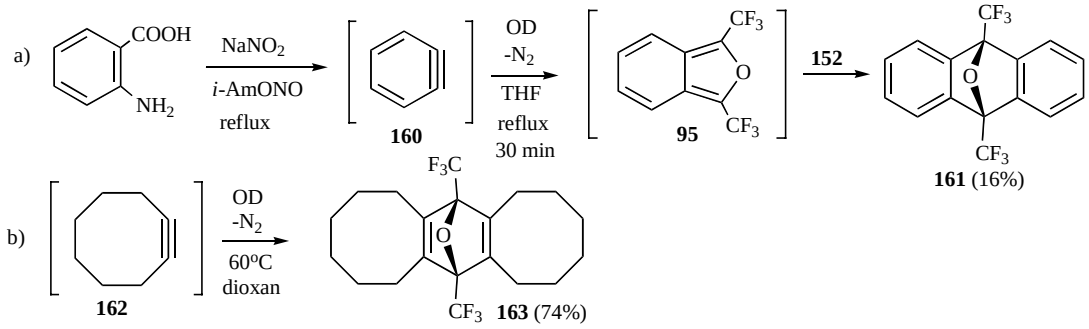
Reactions with alkyne equivalents, which are the precursors for the synthesis of anhydrolycorinone, follows the same reaction mechanism as described in Scheme **26**. The enhanced reactivity of the enol ether in **164** supersedes the entropic preference for closure to provide a fused five-versus six- membered ring [42]. Sequential [4+2] cycloaddition reactions were observed upon warming **164** first at 165°C for 30 min and then at 230°C for 18 h. The product **165** is formed by an initial Diels-Alder cycloaddition reaction followed by loss of N_2 to generate a carbonyl ylide that eliminates methanol to furnish the furan ring. The second [4+2] cycloaddition follows, with a subsequent ring-opening of the resulting oxabicyclo[2.2.1]heptene cycloadduct and elimination of H_2O, to produce anhydrolycorinone skeleton **166**, which could be also produced in the single reaction step from **164** (Scheme **31**) [49].

5. MECHANISTIC CONSIDERATIONS

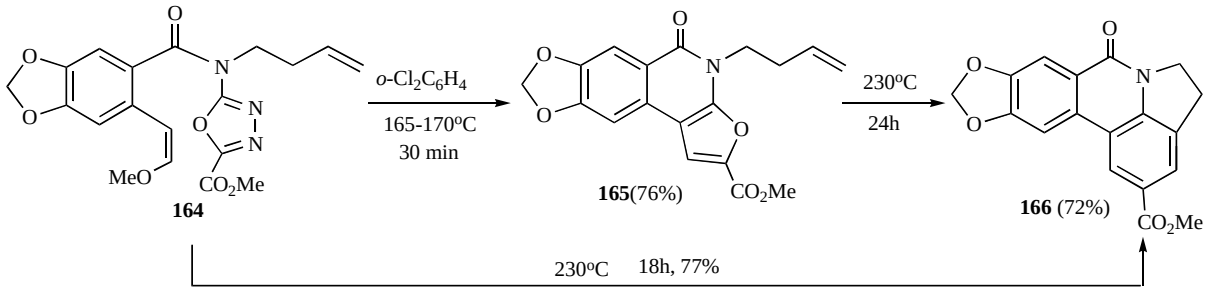
The reaction mechanism of tandem [4+2]/[3+2] cycloadditions of oxadiazoles with alkenes and alkynes was briefly been discussed



Scheme 29.



Scheme 30.



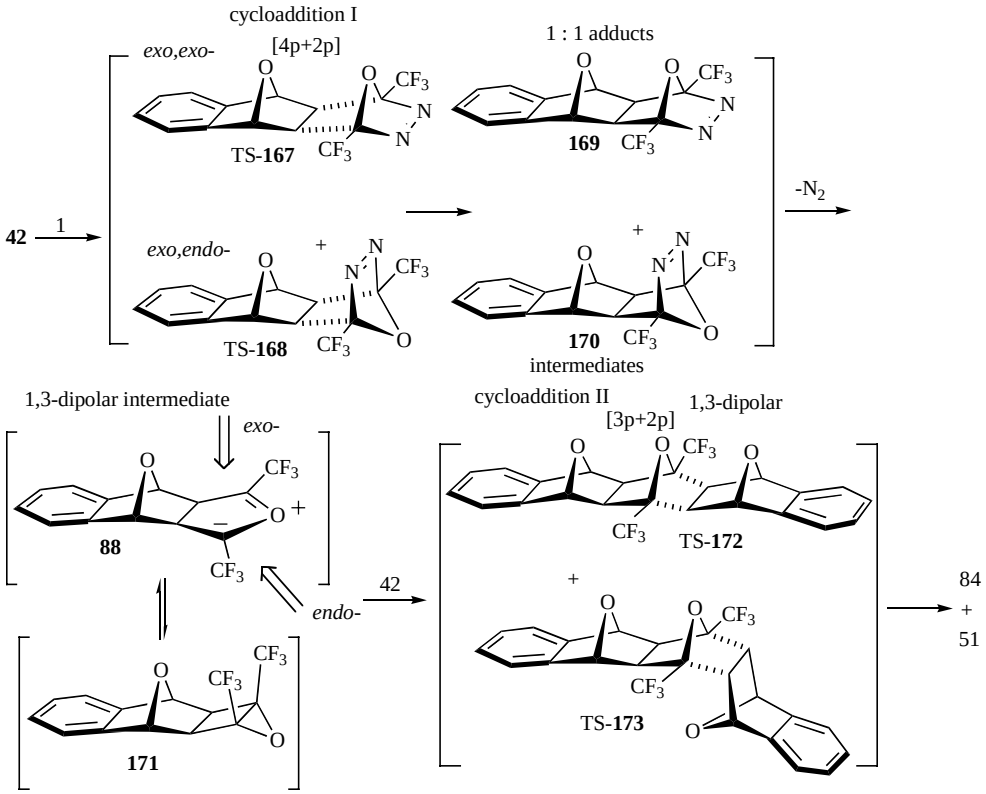
Scheme 31.

in the previous sections. Here, a more detailed reaction mechanism for the **OD** reaction with model substrate **42** is discussed and results from quantum-chemical calculation studies reported.

Two separate cycloaddition reactions are considered to be involved in the coupling process (Scheme **32**). The first cycloaddition is a Diels-Alder reaction between the alkene and 1,3,4-oxadiazole, an [4π+2π] addition, and which is a reverse electron-demand process [50]. The second cycloaddition is the 1,3-dipolar addition, [3π+2π] of a second alkene (same or different) with the 1,3-dipolar intermediate **88** (or epoxide **171**) and this is a regular electron-demand process. This intermediate is obtained by dinitrogen expulsion from the 1:1 adducts **169** and **170** formed in step I. Looking in detail to this cycloaddition cascade, it is evident that the first cycloaddition proceeds *via* a transition state which could be either of the *exo,exo-* or *exo,endo-* orientation (**167** and **168**). Depending on the atom present at the 7-norbornyl position, one of these orientations may be favored. RHF/6-31G* calculations predict that in the case of a 7-oxa bridge the *exo,exo-* orientation is preferred by less that 1.0 kcalmol^{-1}, indicating that the presence of both intermediate products **169** and **170** should be expected from the reaction. This prediction on the stereochemical outcome of the DA reaction is in good agreement with the stereospecificities calculated for reactions of other cyclic dienes with norbornenes. [51-54] In addition, **169** is thermodynamically more stable, indicating that the stereospecificity of the [4+2] addition of **OD** is kinetically controlled process. The existence of these two intermediates has not been experimentally proven. Elimination of dinitrogen from **169** and **170** gave the proposed 1,3-dipolar intermediate **88**, which is the reversible transient form of cyclobutane epoxide **170**. Due to the high reactivity of the proposed intermediate **88** and the harsh reaction conditions, scarce evidence for the existence of intermediate **170** has appeared in the literature (Schemes **12** and **27**). By dinitrogen elimination, any stereochemistry established by the initial [4+2] addition has been lost, since the 1,3-dipole is planar.

Since both intermediates **169** and **170** afford the same 1,3-dipole **88** by dinitrogen elimination, it follows that the stereochemical outcome of the **OD** coupling reaction is determined in the second (3+2) cycloaddition step. Eight different approaches of the two reactants are feasible. Four modes of dipolarophile **42** approach are from the bottom (*endo-*) π- face of intermediate dipole **88**, and four approaches from the top (*exo-*) π- face of **88**. These alternatives give rise to seven stereoisomeric O^3-[3]polynorbornane products, but only two of these products have been experimentally identified in the case of *O*-bridged alkenes (*exo,exo-* and *exo,endo-* **84** and **51**). In the case of *C*-bridged alkenes, specifically the *exo,exo-* product was obtained [7].

The factors determining the experimentally observed stereospecificity of the **OD** coupling reaction with 7-oxanorbornenes were studied by quantum-chemical calculations (RHF/6-31G* method, followed by single point energy calculations using B3LYP, BMK and MP2 methods). It is evident from calculations that the cycloaddition reaction on the *exo-* π-face of the approaching **42** is greatly favored over the *endo-* π-face attack. This prediction is in good accordance with published results on norbornene π-facial selectivity [5, 51-54]. A plausible explanation for this preferred *endo-* approach to **88** is offered by Fukui's non-equivalent π-orbital extension concept [55]. Calculations indicate that in FMOs of **88**, an orbital non-equivalency between the *exo-* and *endo-* π-faces exists. There is a slightly larger electron density located on the *endo-* face of 1,3-dipole moiety, which is in combination with the steric hindrance caused by the methylene bridge on the *exo-* face and causes preference for the *endo-* face of 2-oxa-cyclopenta-1,3-diene system. These ground-state preferences are mirrored in transition state calculations, revealing that transition states **TS172** and **TS173** for reaction of **88** with **42** have the smallest activation energies (E_a) and hence are the preferred reaction pathway. The results show that the relative activation energies $(E_a)_{rel}$ for these two modes are similar regardless of the computational level employed and predict the same stereochemical



Scheme 32.

preference, with almost identical energy differences $\Delta(E_a)_{rel}$. The $\Delta(E_a)_{rel}$ between **TS172** and **TS173** are smaller than 2 kcalmol^{-1}, which not large enough to achieve stereospecific cycloadditions to be observed in the laboratory. Therefore, one should expect formation of the mixture of two isomers experimentally. This conclusion is in full accord with experimental results. The inclusion of solvent effects into calculations by means of IPCM/B3LYP/6-311+G**//RHF/6-31G* methods revealed no influence on $\Delta(E_a)_{rel}$. This finding is consistent with gas-phase calculations and also with experimentally observed non-sensitivity of OD reactions to solvent polarity.

The replacement of the oxygen bridge in dipolarophile **42** with a methylene group (CH_2, in **41**) has a significant influence on the activation energies for **TS172** and **TS173**. The RHF/6-31G* method estimated **TS172**/**TS173** $\Delta(E_a)_{rel}$ is 3.9 kcalmol^{-1}, what is almost twice as much as the value calculated for the oxygen bridge systems, indicating a larger preference for formation of linear *exo,exo*- cycloadducts. This difference has been assumed to arise from the repulsive interactions of *O,O*-lone pairs [5], which are supported by calculated electrostatic potential surfaces for **TS172** and **TS173**. Oxygen lone pairs in the linear TS strongly interact, while in the case of CH_2 bridges, the interaction is solely steric in nature (leading to formation of *exo,exo-OOC*-[3]polynorbornane). Calculations of the parent 1,3,4-oxadiazoles, where one or both trifluoromethyl groups are replaced with carbomethoxy groups also show preference for formation of *exo,endo*-products, by 1.6 and 1.9 kcalmol^{-1}, respectively (RHF/6-31G* level). These results suggest that steric interference introduced by oxadiazoles is less important in determining of stereospecificities than oxygen lone pair repulsions.

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