Ultra-Strained Non-aromatic Rings

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Abstract: Ultra-strained non-aromatic rings are high-energy compounds which are attracting increasing interest – not just for their peculiar structural and reactivity features – but also as modern chemical tools for bio-orthogonal and in vivo chemistry, especially via inverse-electron demand Diels-Alder (iEDDA) and strain-promoted azide-alkyne cycloaddition (SPAAC) reactions. This mini-review covers two main classes of ultra-strained compounds: 3 to 10 membered-ring cycloalkynes and trans-cycloalkenes, including some examples of cyclic eniynes and dienes. Their molecular properties, synthesis and reactivity are presented and discussed, with an emphasis on their functionalization and subsequent applications in chemical biology.

Matteo Zanda was born near Bergamo (Italy). After the Laurea Degree in Chemistry at the University of Milan, he moved to Politecnico di Milano where he obtained a PhD in Industrial Chemistry in 1998. He then spent one year as a postdoctoral fellow at ULP Strasbourg (France). After 3 years as a junior researcher at Politecnico, in 2001 was appointed Senior Researcher of the National Research Council. He was awarded the Ciamician Medal in 2002. In 2009 he moved to the University of Aberdeen (UK), as a Professor of Medical Technologies. In 2019 he moved to Loughborough University (UK) as Director of the Centre for Sensing and Imaging Science and Professor of Biomolecular Imaging. Zanda group's research integrates bioorganic/medicinal/organofluorine chemistry with translational biomedical research and molecular imaging technologies, particularly Positron Emission Tomography (PET) with applications in brain, cardiovascular and oncology imaging. He is author of 200 articles, including 8 patent applications, and editor-in-chief of Thieme Chemistry's SYNFORM.

Raffaella Bucci (first from right) was born near Taranto (Italy). She graduated in Chemistry at the University of Milan in 2014. She obtained her Ph.D. in Pharmaceutical Science in 2018, under the supervision of Prof. Maria Luisa Gelmi. During her Ph.D., she completed an internship at ETH Zurich, joining the group of Prof. Helma Wennemers. For the successive two years she worked as Post-Doc on a project financed by Regione Lombardia in Prof. Gelmi's laboratories, developing new methodologies for the chemical functionalization of cellulose polymers with bioactive molecules. Currently she is a Visiting Post-doc in Prof. Zanda's research group working on the synthesis of cyclic peptidomimetics through cycloaddition reactions.

Nikki L. Sloan (second from right) was born in Perth, Scotland. She graduated with a 1st class MSci degree in Chemistry from the University of Strathclyde (UK) in 2011, including an industrial placement at AstraZeneca. She obtained her PhD in 2018 from the University of Glasgow (UK), under the supervision of Dr. Andrew Sutherland, on the development and radioiodination of SPECT imaging agents. Her current research interests focus on the development of new molecular probes for biomedical imaging.

Lydia Topping (second from left) received her BSc degree in Medicinal Chemistry from The University of Salford (UK) in 2019. During which she completed an Internship in the therapeutic discovery labs at Cancer Research UK developing small molecule analogues. She is currently a PhD student in Prof. Zanda's research group with her research focus on developing novel strategies of peptide cyclisation.

1. Introduction

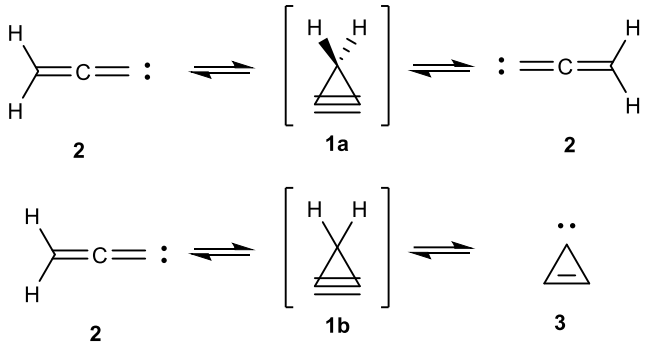
Strained hydrocarbons have traditionally represented a playground for basic researchers interested in testing the limits of creativity, imagination and synthetic skills. Fascinating and highly distorted compounds have stimulated the curiosity of generations of chemists, representing the archetype of chemical oddities, magically ephemeral, lasting less than a heartbeat. However, the coming of age of biorthogonal chemistry and the need for reactions and reagents compatible with living systems, devoid of cross-reactivity with the complex in vivo biochemical machinery, has sparked an unprecedented mass interest in this once elitist area of research. Strained molecules able to react via "click-chemistry"-type processes - such as inverse-electron demand Diels-Alder (iEDDA) and strain-promoted azide-alkyne cycloaddition (SPAAC) reactions - have become extremely popular and vitally important tools in biological chemistry and molecular imaging. This mini-review covers two main classes of ultra-strained compounds, namely cycloalkynes and trans-cycloalkenes having 3 to 10 membered-rings. Some examples of cyclic diynes, eniynes and dienes are also included. Molecular properties, synthesis and reactivity of these ultra-strained rings are presented and discussed, with an emphasis on their functionalization and subsequent applications in chemical biology. Our aim was not to provide an exhaustive coverage of this exponentially growing area of chemistry, but rather to present a selection of conceptually important examples that could stimulate further research in the field. Because of space limits, strained cumulene rings, such as cyclic allenes and bridgehead alkenes, have not been included.

2. Ultra-strained cycloalkynes

C≡C triple bonds possess a linear structure. Many alkynes fulfil this property, in line with their sp hybridisation, but the crystal packing of substituted alkynes often shows some deviations from the linear geometrics.[1] The most common way to distort a triple bond is to incorporate the alkyne functionality in a cyclic framework, with the stability of these molecules under standard laboratory conditions depending on the size of the ring. In 1983[2], A. Krebs used the term 'angle-strained cycloalkynes' to refer to distorted cycloalkynes. More precisely, all cycloalkynes having a C≡C-R angle deformation > 10° should be considered 'angle-strained cycloalkynes'.[2] According to this definition and based on computational evidence, all cycloalkynes, from non isolable cyclopropyne and cyclobutyne to the highly stable cyclononyne, fall into the 'angle-strained' category.
Strained cycloalkynes, which were considered chemical oddities at best until recently, are nowadays getting a great deal of attention because they are emerging as valuable intermediates in organic synthesis for the preparation of interesting ligands, agrochemicals, medicinal agents, natural product and materials, besides being key reagents for biorthogonal chemistry.[3]

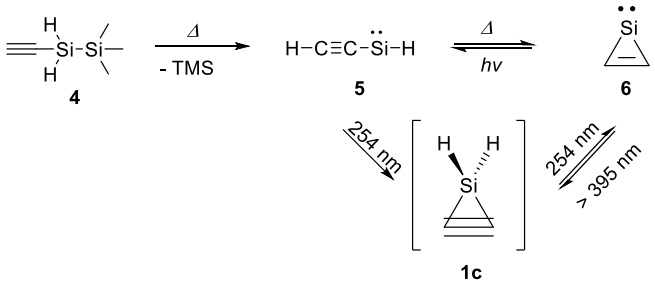
2.1. Cyclopropyne and cyclobutyne

Only theoretical investigations are present in literature regarding cyclopropyne and cyclobutyne.[4] The smallest cyclopropyne with tetragonal geometry, 1a (Scheme 1) is proposed to be a transition state in the automerization of propadienylidene 2, while the planar 1b is an intermediate in the rearrangement of 2 to cyclopropenylidene 3. The structure of cyclopropyne does not correspond to a minimum of potential energy surface, therefore it does not represent an isolable intermediate.[5] Both 1b and 3 have also been identified in the interstellar space,[6,7] where cyclopropenylidene was reported to be the most abundant of all hydrocarbons.



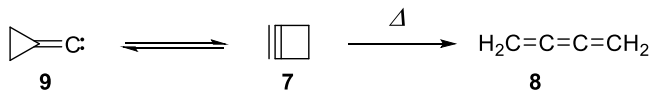
Scheme 1. Cyclopropyne and related structures.

On the other hand, a triple bond in a three-membered ring was also identified in 1994[8] using a technique based on the pulsed flash pyrolysis of 4 (Scheme 2). Consequent photolysis of 5 or 6 led to 1c, which was characterized by IR and theoretically studied by ab initio calculations[6,7].



Scheme 2. Silacyclopropyne 1c and related transformations.

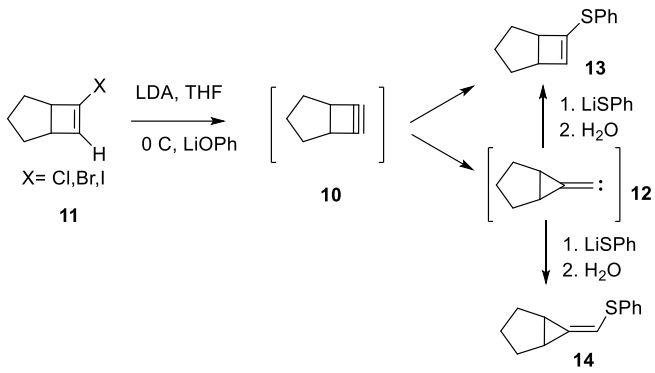
A number of complex theoretical methods have been used so far to study cyclobutyne, a molecule that has been at the centre of much speculation.[9] Ab initio calculations by Schaefer et al.[10] suggested that singlet and triplet cyclobutyne correspond to energy minima. The highly reactive 7 could thus give two isomerization processes: thermal isomerization to butatriene 8 or ring contraction to compound 9 (Scheme 3).



Scheme 3. Cyclobutyne and related structures.

Since calculations suggested no interconversion energy barrier between 7 and 9, the ring contraction would be immediate, making it impossible to characterize compound 7, not even with IR spectroscopy. These calculations also suggested that bicyclo[3.2.0]-hept-6-yne 10 could form as a fleeting intermediate in the reaction of 6-halobicyclo[3.2.0]-hept-6-ene with a strong base.[11] To experimentally test these calculations, halides 11 (Scheme 4) were treated with LDA in the presence of lithium thiophenolate affording thioethers 13 and 14 as products, which may indeed

be formed from the intermediate 10. Carbene 12 is proposed to partly form as an additional intermediate during the process.

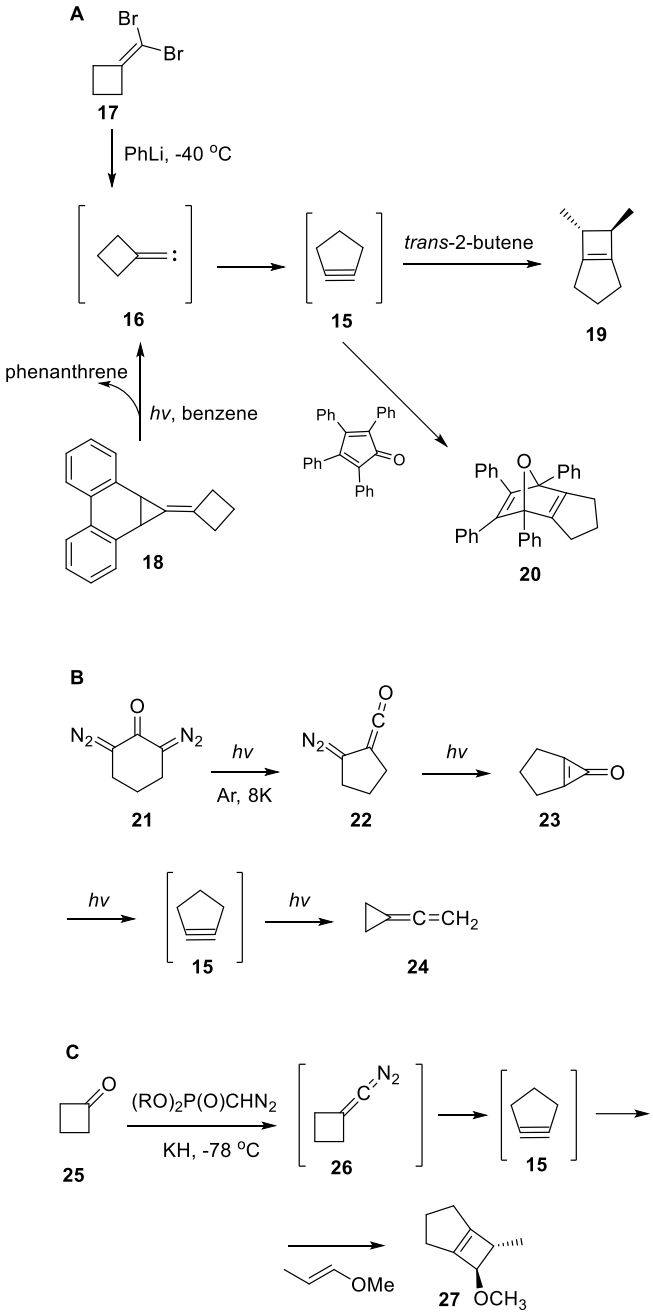


Scheme 4. Bicyclo[3.2.0]-hept-6-yne and related structures.

Recently, Sun and co-workers published further calculations on the energy and properties of cyclobutyne as a transition state.[12]

2.2. Cyclopentyne

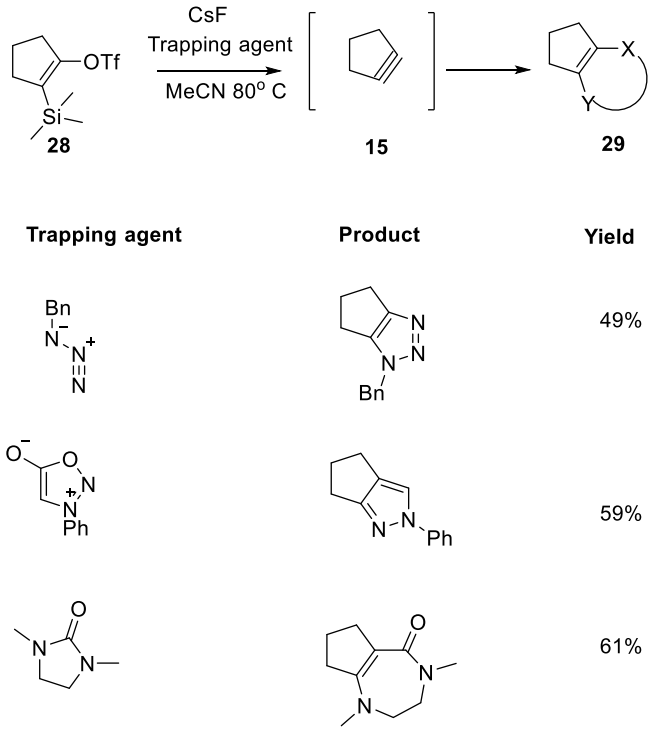
There are several methods in the literarure for the synthesis of cyclopentyne 15[4]. Typically, they rely on the use of rather harsh conditions, such as strong base, fluoride salts, or oxidizing reagents, high temperature or irradiation of the starting material. Due to its instability at r.t., after its generation the cyclopentyne intermediate is made to react with trapping agents usually through cycloaddition reactions. One approach is the ring expansion of the corresponding cyclobutylidenecarbene 16[13–15] (Scheme 5A), which can be obtained either by debromination of compound 17 or by photolysis of compound 18 with loss of phenanthrene.[16] Cyclopentyne 15 can be trapped with trans-2-butene affording 19 or with tetraphenylcyclopentadienone giving the Dies-Alder adduct 20. Chapman at al. in 1981[17] published another route to 15 via photodecomposition of 2,6-diazocyclohexanone 21 (Scheme 5B). Irradiation (>274 nm) in argon at 8 K first gave the diazoketene 22 and then cyclopropenone 23. Continued irradiation (>254 nm) caused decarbonylation and gave ultimately the allene 24, through the intermediate 15.[16] In another example (Scheme 5C),[18,19] cyclobutanone 25 was converted into 15 via 26 using the anion of FAMP generated with KH at -78 oC, which was then converted into the cycloadduct 27.



Scheme 5. Preparations of cyclopentyne 14 via: A) ring expansion; B) photodecomposition; C) Horner-Wadsworth-Emmons reaction.

In 2014, Medina and co-workers[20], reported a study on the use of cyclopentyne and cyclohexyne as intermediates in the synthesis of heterocyclic compounds. The syntheses were supported with computational studies to understand the observed regioselectivities. Cyclopentyne 15 was prepared from silyl triflate 28 by treatment with CsF, leading to the formation of heterocycles 29 - having one or more newly formed C-X bonds - in satisfactory yields (Scheme 6). These results proved also that intermediate 15 can react not only via [2+2] cycloadditions or Diels-Alder reactions but through a range of cycloaddition reactions too.

PCM(THF)/M06-2X/6-311+G(2d,p) calculations supported the observed results. In fact, the significant angle-strain of cyclopentyne was revealed by the large deviation of the internal ring angles (116°) from the ideal linear arrangement of alkynes. The strain was calculated to be ~74 kcal mol−1, meaning that 15 has ∼10% calculated diradical character.[21]



Scheme 6. Heterocycles synthesis from cyclopentyne 15.

2.3. Cyclohexyne

Cyclohexyne 30 (Fig. 1) is an extensively studied angle-strained cycloalkyne, mainly because of the structural analogy with benzyne and benzene. Being very reactive, it had to be characterized trapped in a matrix at -100 oC.[9] The first report on cyclohexyne dates back to the work of Robert in 1957.[22] Since then, cyclohexyne has represented the subject of extensive computational studies to predict its reactivity and it became the synthon for the total synthesis of natural compounds carried out by different groups, from Carreira[23] to Nicolaou[24], from Danishefsky[25,26] to Myers[27,28].

Extensive and detailed quantum mechanical calculations showed that cyclohexyne can act as an electrophile, contrary to its simplest relative acetylene (Fig. 1). This is due to the overlap reduction of the in-plane p orbitals, leading to lower energy of the triple bond (76 kcalmol-1 for acetylene vs 35 kcal mol-1 for cyclohexyne). Moreover, the ring-strain entails a reduction of LUMO energy while the HOMO orbital remains unchanged.[22] Furthermore, ab initio calculations proved that cyclohexyne has also diradical or dicarbene character.[18,19]

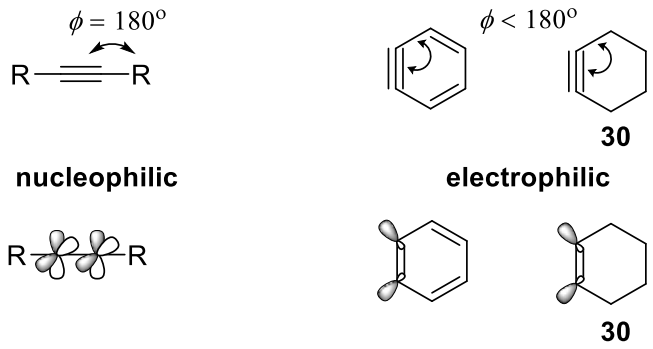
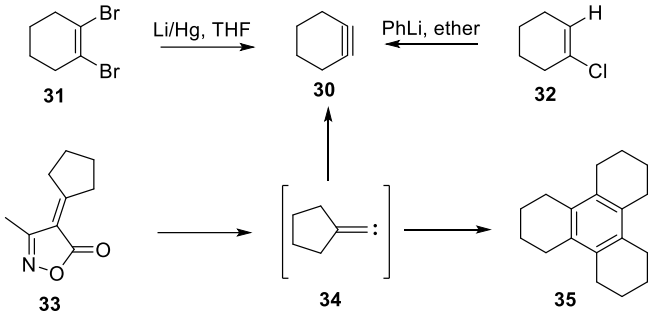


Figure 1. Cyclohexyne vs acetylene orbitals.

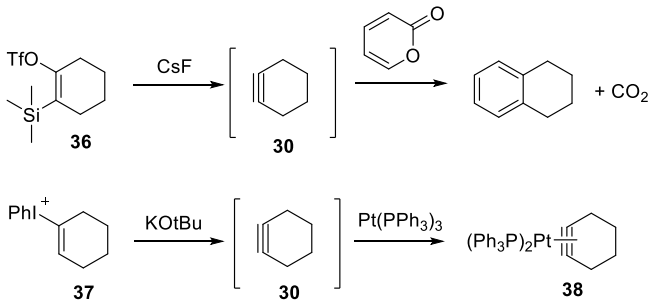
Since cyclohexyne 30 is extremely reactive, it was quickly trapped in a matrix for characterization experiments as soon as synthesized. In the early 1960s, Wittig[29] showed that it is possible to

obtain 30 from the debromination of 1,2-dibromocyclohexene 31 (Scheme 7) or via dehydrochlorination of 1-chlorocyclohexene 32. Another synthetic route (Scheme 7)[30] consists in the pyrolysis of compound 33 at 700 °C and 10-4 torr, going through the fragmentation of carbene 34. After characterization, the sample was warmed up to r.t. triggering the formation of trimer 35.



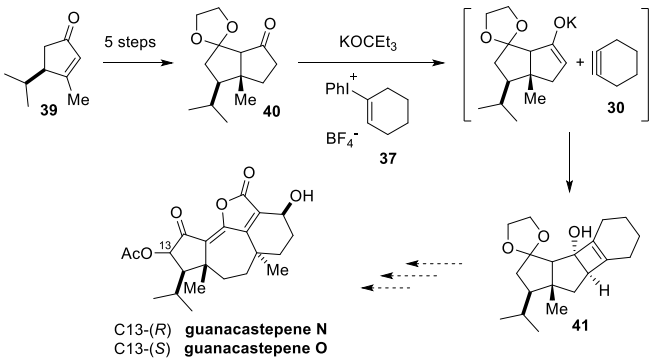
Scheme 7. Wittig's cyclohexyne preparation and trimerization.

Unfortunately, Wittig and later the Caubere' group observed that in the elimination process leading to 30, 1,2-cyclohexadiene, namely cycloallene, could be formed as a by-product.[31,32] This problem could be avoided by using a different synthetic route, starting from triflate 36 (Scheme 8), in the presence of CsF at r.t.[33] The Fujita group reported on the generation of 30 from the iodonium salt 37 (Scheme 8) in the presence of a strong base[34]. Intermediate 30 was then trapped and isolated as Pt complex 38.



Scheme 8. Alternative preparations of cyclohexyne 30.

In 2012, the Carreira group developed the synthesis of two natural products, Guanacastepene N and O[35] (Scheme 9). The synthesis starts with the conversion of enone 39 to the corresponding pentalenone 40 in 5 steps and 36% yield, which was then treated with the cyclohexyne precursor 37 and KOCEt3, giving the cyclobutanol 41 as a single diastereomer, through a [2+2] cycloaddition reaction in 74 % yield. Theoretical studies on these cycloaddition reactions with cyclohexyne as intermediate were reported by the Houk group in 2012.[36]



Scheme 9. Carreira's synthesis of guanacastepene N and O.

The reactivity and conformation of cyclohexyne was computationally studied by Medina et al.[20] using the PCM(THF)/M06-2X/6-311+G(2d,p) method. It was found that, in comparison with cyclopentyne 15, cyclohexyne 30 possesses a more relaxed internal angle and a strain of 44 kcal mol-1, in accordance with the known C2-symmetric structure. It must be noted that – as expected - 3-methoxycyclohexyne 42 (Fig. 2) is also distorted, with the calculated internal angle at C1 and C2 of 138° and 124°, respectively. This different distortion is attributed to the electron-withdrawing nature of the C3 methoxy group. For this reason, the authors predicted a nucleophilic attack could only occur at C1, the more linear alkyne terminus (Figure 2)[20].

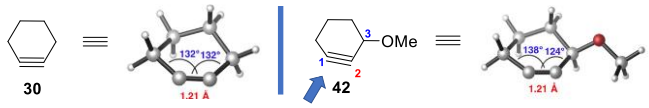
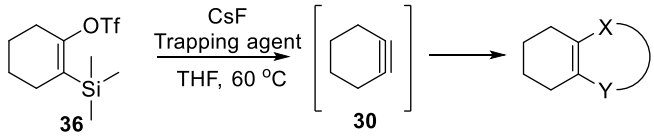
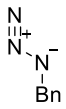
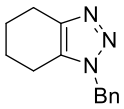
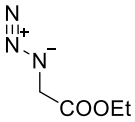
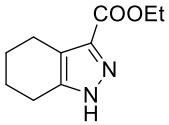
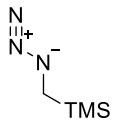
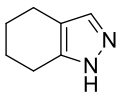
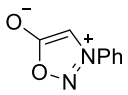
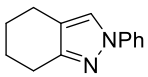
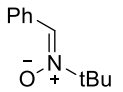
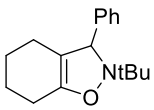
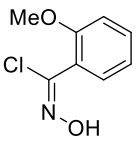
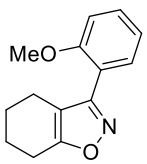


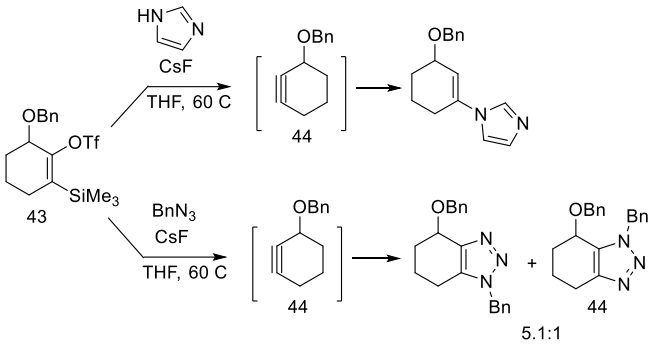
Figure 2. Computational studies on the structure of cyclohexyne vs 3-methoxycyclohexyne.

All these computational studies on 30 and 42 were essentially confirmed by synthetic studies shown in Schemes 10 and 11, respectively. 3-BnO-cyclohexyne 44 (Scheme 11) was obtained from 43 and used instead of 3-methoxycyclohexyne 42, for synthetic convenience.



Trapping agent	Product	Yield
		94%
		98%
		82%
		82%
		61%
		90%

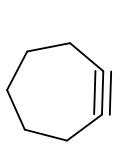
Scheme 10. Synthesis of heterocycles from cyclohexyne.



Scheme 11. Preparation and reactions of 3-BnO-cyclohexyne 44.

2.4. Cycloheptyne

The chemistry of cycloheptynes has been studied mostly through computational work.[37,38] In comparison with the smaller cycloalkynes discussed above, cycloheptyne 45 (Fig. 3) is more stable. In fact, in dilute CH2Cl2 solution this cycloalkyne shows a half-life < 1 minute at -25 oC and about 1 hour at -78 oC. Nevertheless, it is known that the insertion of one or more methyl groups in the immediate vicinity of the triple bond drastically increases its stability, as for 46 (Figure 3)[39].



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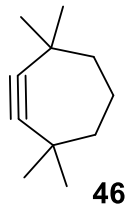


46

$t_{1/2}$ < 1 min (-25 ^{o}C)
$t_{1/2}$ 1h (-76 ^{o}C)

$t_{1/2}$ <1h (25 ^{o}C, neat)
$t_{1/2}$ 1d (25 ^{o}C, 0.2 M)

Figure 3. Stability of cycloheptyne 45 vs tetramethyl-cycloheptyne 46.

The large deviation of the internal ring angle from the linear disposition of the Csp3–CΞC atoms, 145.47 °C, make the cycloheptyne prone to isomerization and dimerization. Yavari et al. explained the possible conformations of cycloheptyne 45, using ab initio calculations[40]. Cycloheptyne has two geometries: the envelope (Cs) and the twist-one (C2) (Fig. 4). The interconversion between the two Cs envelope conformations occurs via C2 symmetric transition state. The energy of twist transition state resulted to be 34.0 kJ mol-1.

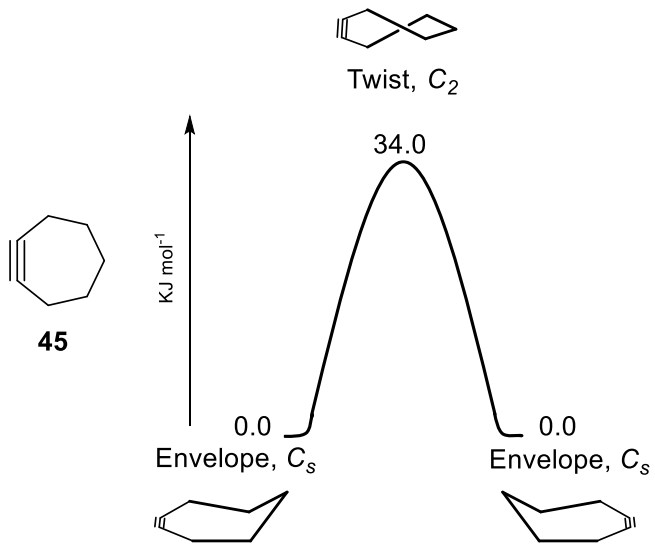
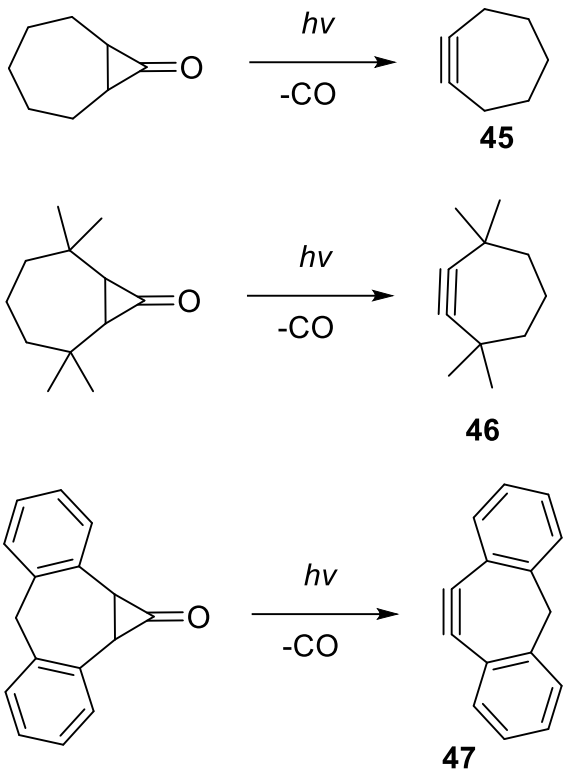
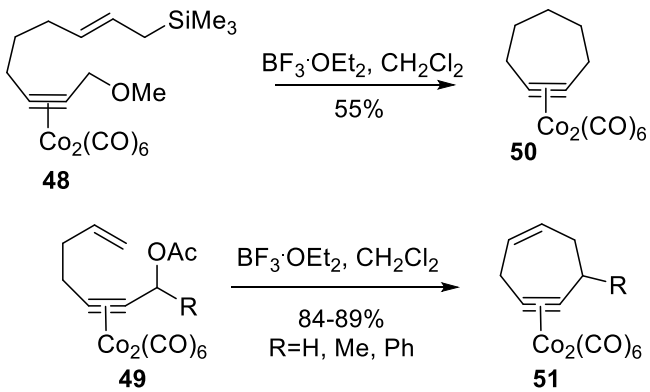


Figure 4. Energy profile of cycloheptyne conformations.
Krebs and co-workers synthesized compound 45 and other more stable analogues 46 and 47 by irradiation of the corresponding cyclopropenones (Scheme 12).[41]



Scheme 12. Krebs photosynthesis of cycloheptynes 45-47.
As already mentioned for cyclohexyne, cycloheptyne can also be trapped as a platinum complex. This is generated from 45, by treatment with Pt(Ph3P)3. The increased stability is due to the deviation of the triple bond from the linearity by ca. 40°, 5° from 45.[42]
The synthesis and reactivity of Cobalt complexes of cycloheptyne, such as 50 and 51 (Scheme 13) was also reported.[39] These compounds can be stored and handled under standard laboratory conditions. Different methods for the synthesis of cycloheptyne-Co complexes were described. One of the most common ones is the Nicholas reaction (Scheme 13). It is based on the generation of a cation in propargylic position to an alkyne-Co2(CO)6 group, as in 48 and 49 (Scheme 13), usually by coordination of an oxygen-based moiety by a Brønsted or Lewis acid, leading to a carbocation which is trapped intramolecularly.



Scheme 13. Preparation of cobalt-cycloheptyne complexes.

2.5. Cyclooctyne

The CΞC bond in cyclooctyne 52 (Fig. 5) is much less strained in comparison with the already described small-ring cycloalkynes above, therefore this molecule is more stable and easily available, representing a versatile compound in organic synthesis. After publication of the detailed review by Krebs and Wilke in 1982 on strained cycloalkynes[2], structural chemists became more interested in the conformation of this very reactive, albeit quite stable molecule.[43] Since cyclooctyne is the smallest cycloalkyne that can be isolated in standard lab conditions, detailed conformational studies by IR, NMR, electron diffraction and computational analyses have been carried out.[4,44] It was found that the C-CΞC-C unit in cyclooctyne is still deformed, with a CΞC-C angle of 154.5°, with different accessible conformations. Work by Yavari and co-authors[40] showed that the chair conformation with C2 symmetry is more stable that the twisted conformation. The authors used DFT calculations to investigate the interconversion energy between the two forms. The interconversion between the chair conformation with a C2 axis and the twist-boat (TB) takes place via a twist transition state and the chair conformation was found to be more stable than the twist-boat by 11.t kJmol-1. The interconversion of 52-TB with its mirror images takes place via the formation of a 52-Boat as transition state. The calculated energies for the transitions state 52-Twist and 52-Boat is 37.8 kJmol-1 and 26.4 kJmol-1 respectively (Fig. 5).

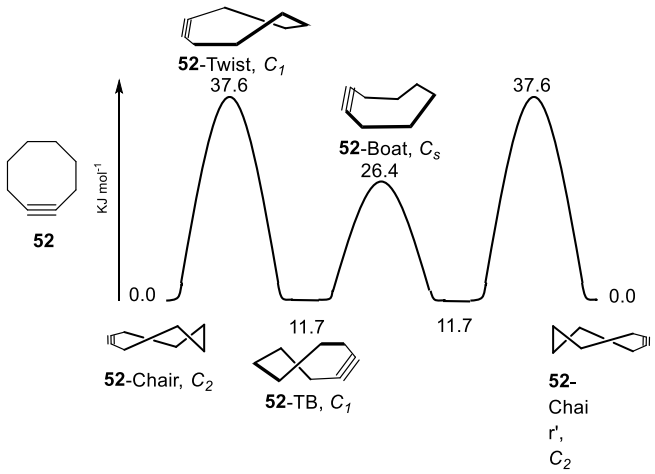
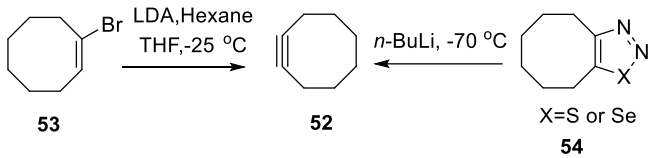


Figure 5. Energy profile of cyclooctyne conformations.

The most convenient method to prepare cyclooctyne 52 was published by Brandsma and Verkruijsse in 1978,[45] starting from the readily available 1-bromocyclooctene 53, which is dehydrobrominated with LDA in very good yield (Scheme 14). An alternative method was published by Meier at al., using the 1,2,3-thiadiazole or 1,2,3-selenodiazole precursor 54 with butyl lithium at low temperature (Scheme 14).

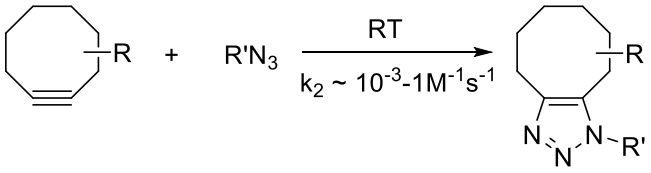


Scheme 14. Syntheses of cyclooctyne 52.

Nowadays, cyclooctyne 52 and its derivatives are commonly used in organic synthesis for a wide range of different applications. Thanks to their peculiar reactivity, resulting from the deformed C-CΞC-C unit, these compounds are ideal reagents for different reactions in synthetic organic and biological chemistry[46–48] or even as trapping agents for the characterization of very reactive molecules[49]. Some selected examples are discussed below.

Bioorthogonal Bond Forming Reactions

The concept of 1,3-dipolar cycloadditions was introduced by Huisgen and co-workers, who developed this reaction into a powerful method for the synthesis of five-membered heterocycles[50]. Since 2004, when Bertozzi and co-workers[51] published their groundbreaking paper on the use of cyclooctyne in biorthogonal reactions, the development of azide and tetrazine cycloaddition with 52 and its derivatives (Scheme 15) has generated widespread interest for the labelling of cellular components via bioorthogonal reactions. Thanks to the strain activation of cyclooctynes, which is in the right range for this type of applications, the reaction proceeds at a rate that is sufficient for in vivo labelling, while avoiding the use of the toxic copper(I) catalysts commonly used in "click chemistry" with terminal alkynes.[52] As a result, the reaction between cyclooctynes and azides is often referred to as "copper-free click chemistry." Bertozzi et al. first applied this reaction, already described by Krebs in 1961[43], for bioorthogonal chemistry.



Scheme 15. SPAAC reaction of cyclooctyne.

The reaction was made biocompatible, avoiding the use of copper, but the reduction of the reaction rate lead to the obtainment of a mixture of isomers. Starting from cyclooctyne 52, over the years, many research groups have developed different derivatives, shown in Fig. 6, measuring their Second-Order Rate Constants in the SPAAC reaction with benzyl azide.[53]

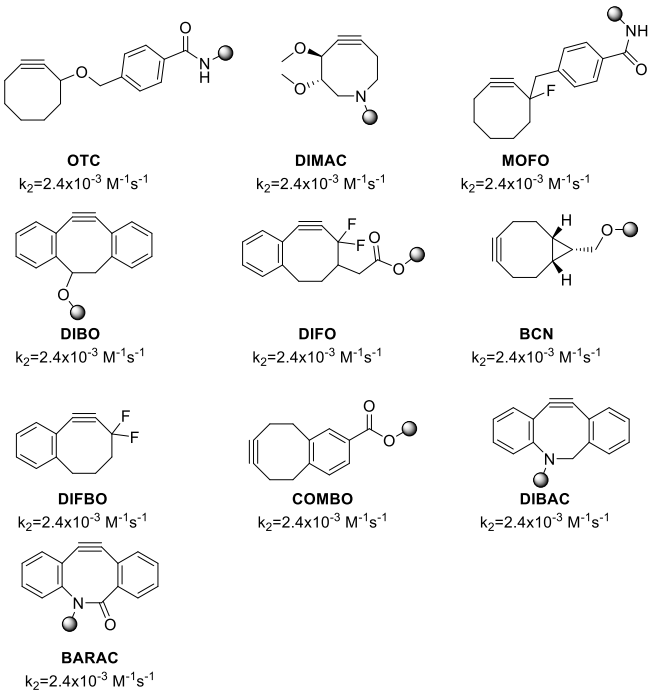
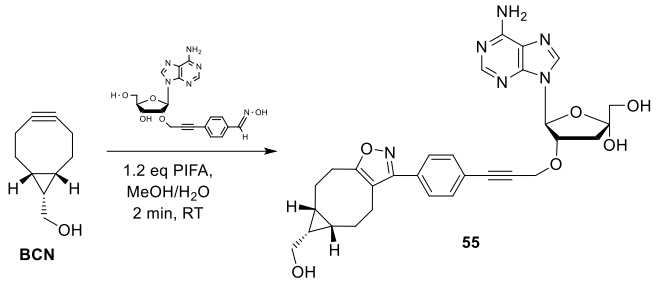


Figure 6. Cyclooctyne derivatives and their rate constants in the SPAAC reaction with benzyl azide.

It is not difficult to imagine the variety of applications that this SPAAC reaction has found over the years: from modification of purified proteins to cell surface labelling. It was applied in vitro to fibroblast cells and later in vivo on zebrafish and mice[52]. Very recent papers have shown its use for functionalizing different nanomaterials[54], i.e. nanoparticles[55] for tumour imaging and 18F PET[56] and SPECT[57] imaging. Due to the success of the SPAAC reaction, other dipole reagents have been studied for promoting faster cycloadditions, such as nitrones and nitriloxides in

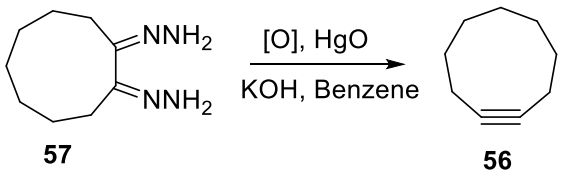
SPANOC (strain-promoted alkyne-nitrile oxide cycloaddition) reactions.[52] Indeed, nitriloxides show an increased reaction rate, about 12-fold faster when compared to azides. For example, van Delft et al.[58] reported the reaction between the already mentioned BCN (Scheme 16) and benzonitrile-N-oxide, resulting in a much faster reaction than with the relative benzylazide, leading to the nucleoside construct 55. The major drawback of nitriloxides is their tendency to dimerize during the reaction, but several biorthogonal SPANOC reactions have been developed, where the problem is avoided or minimized with the generation of the nitriloxide in situ. An interesting application was reported by Sanders et al. with the synthesis of bifunctional molecules by SPAAC and, after nitriloxide generation, SPANOC[59].



Scheme 16. A bifunctional cyclooctyne leading to nucleoside constructs.

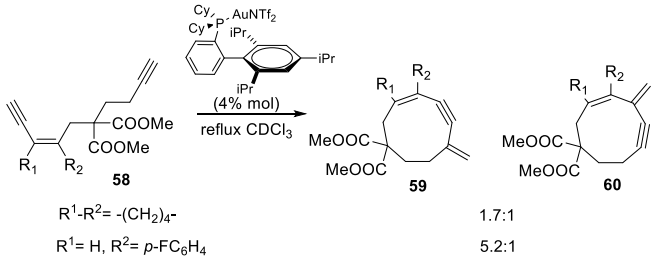
2.6. Cyclononyne

Only few reports are present in the literature regarding cyclononyne and most of them are based on theoretical studies. Cyclononyne 56 (Scheme 17) is the last cycloalkyne discussed in this section. While cyclodecyne has almost linear CΞC triple bond (CΞC-C angle of 171.6°) and minimal distortion, cyclononyne still belongs to the 'angle-strained cycloalkyne family, having a CΞC-C angle of 160.2°.[4] Cyclononyne has been obtained by various elimination reactions from several precursors but was often found as a mixture with their allenic and dienic isomers. In 1952, Blomquist et al. reported the synthesis of cyclononyne 56 by a modification of the Curtius route, oxidising 1,2-bis-hydrazones such as 57 and avoiding the formation of the undesired by-products.[60]



Scheme 17. Synthesis of cyclononyne.

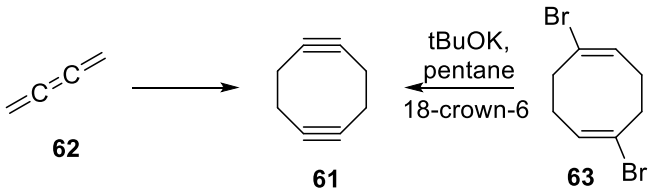
More recent work, published by Obadachian et al.[61], described the cycloisomerization of 1,9-diynes 58 (Scheme 18) into the corresponding cycloalkynes 59 and 60 by gold-catalysed alkyne-alkyne coupling. The reaction was monitored by NMR using 4% of gold catalyst in refluxing CDCl3.



Scheme 18. Synthesis of functionalised cyclononynes.

2.7. 1,5-Cyclooctadiyne

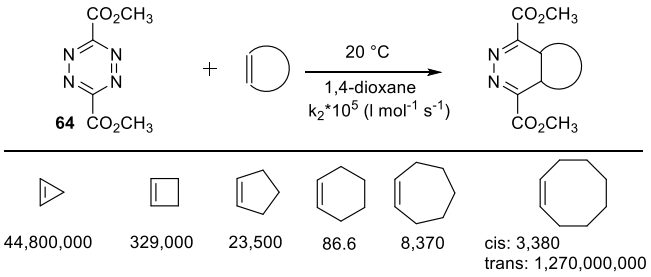
1,5-cyclooctadiyne 61 (Scheme 19) is a planar molecule and the CΞC-C angle deviates from the linearity by 20.7°, slightly less than in cyclooctyne.[4] It was prepared for the first time in 1975 by Wirtz and co-workers[62] via dimerization of butatriene 62, in rather low yields. An improvement was reported by Meier in 1994, by treating the dibromide 63 with tBuOK in pentane[63] (Scheme 19).



Scheme 19. Synthesis of 1,5-cyclooctadiyne.

3. Ultra-strained cycloalkenes

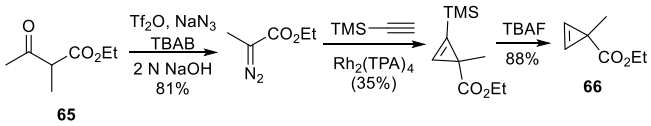
Cycloaddition of unsaturated strained systems with 1,3-dipoles are important reactions in click chemistry, with strained cyclic alkenes considerably more reactive towards 1,3-dipole systems than standard olefins, overcoming the activation energy barrier that is observed with unstrained alkenes.[64] Particularly important, in this respect, are medium-sized trans-cycloalkenes which constitute a family of molecules with ring sizes between seven and nine atoms, possessing a highly distorted trans-double bond.[65,66] This class of molecules can be used in a plethora of chemical reactions, including natural product synthesis and bioorthogonal reactions; bioorthogonal chemistry being one of the broadest uses.[67–69] trans-Isomers of cyclic alkenes are the more reactive isomers due to geometric and electronic distortions, and ring strain arising from non-ideal geometries, such as distorted sp3 angles, pyramidal sp2 carbons and twisted p bonds.[70] Increasing ring strain has been shown to greatly enhance the reaction rate for both SPAAC and iEDDA reactions. This has been investigated by Sauer et al., who calculated the rate constants for a range of cycloalkenes in an iEDDA reaction with tetrazine 64.[71] They found that the reaction rate increased from cyclohexene < cis-cyclooctene < cycloheptene < cyclopentene < cyclobutene < cyclopropane < trans-cyclooctene, with the trans-cyclooctene displaying a much higher reaction rate than the other investigated cycloalkenes (Scheme 20). cis-Cyclopropene and cis-cyclobutene are strained enough that they can take part in iEDDA reactions with fast reaction rates. However, the ring strain for cis-cyclooctene, cis-cyclohexene and cis-cyclopentene is low, and as such these will not be discussed in this section. For the trans-cycloalkenes, trans-cycloheptene and trans-cyclooctene have considerable strain, whereas smaller ring size than cycloheptene is excessively strained and, thus far, the trans-isomers for cyclohexene or smaller have not been isolated.[72] Discussed here is the synthesis, stability and uses of small strained cis-cycloalkenes and medium-sized trans-cycloalkenes.



Scheme 20. Rates for IEDDA reaction of different cycloalkenes with 3,6-dimethoxycarbonyl-tetrazine 64.

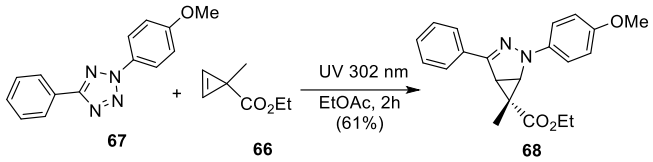
3.1. cis-Cyclopropene and cis-cyclobutene

Cyclopropene has been used extensively in click chemistry,[73,74] mainly for targeting biomolecules in vitro as well as in live cells.[75] Yu and co-workers reported the synthesis of the cyclopropene scaffold 66 using a 3 step synthesis from 65 in 22% overall yield (Scheme 21).[76]



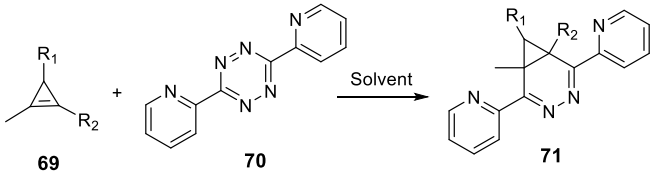
Scheme 21. Synthesis of cyclopropene 66.

Cyclopropene 66 was used in a bioorthogonal reaction with tetrazole 67 to give product 68 (Scheme 22), by irradiation using 302 nm UV light for 2 hours. The group also showed that unnatural amino acids containing the cyclopropene group could be used in a cycloaddition reaction with tetrazole 67. The cyclopropene group could be incorporated into proteins and used to label these in vitro and in vivo.[76]



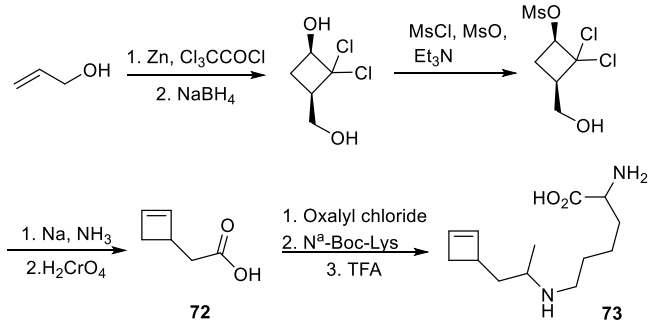
Scheme 22. Use of cyclopropene 66 in a bioorthogonal reaction.

Another example of cyclopropenes being used in bioorthogonal chemistry was reported by Patterson and co-workers,[75] who engaged 69 in iEDDA reactions with a number of tetrazines, such as 70 (Scheme 23). The reactions produced covalent adducts 71 in high reaction rates and yields. Despite the high reactivity, these have also been shown to be stable enough under biological conditions for use in biological labelling.[75]



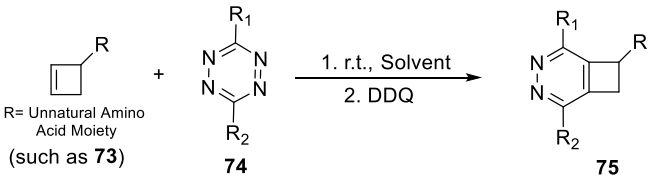
Scheme 23. iEDDA reaction between cyclopropenes and tetrazine 70.

Cyclobutene has also been reported to be a versatile scaffold for use in bioorthogonal reactions due to its small size and excellent stability. Liu and co-workers[77] reported the synthesis and incorporation of cyclobutene acetic acid 72 into amino acids 73 and potentially proteins (Scheme 24).



Scheme 24. incorporation of cyclobutene ring into amino acids.

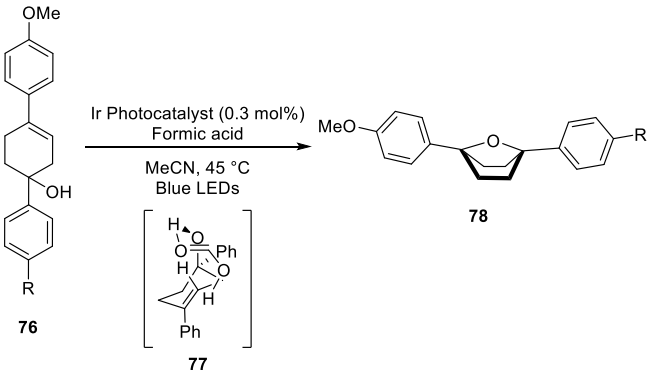
These unnatural amino acids (such as 73) were used to rapidly label, with a fluorescent tag, both purified and intact proteins in live cells via an iEDDA reaction with tetrazines 74, followed by oxidation using DDQ, leading to constructs like 75 (Scheme 25).



Scheme 25. IEDDA reaction between cyclobutene-amino acids and tetrazine.

3.2. trans-Cyclohexene

trans-Cyclohexenes have been reported as having an exceptionally high level of strain and an extremely short lifetime. In 1987, ab initio calculations reported cis-cyclohexene to be 56 kcal mol-1 more stable than the trans-isomer, with the activation energy barrier for the trans to cis isomerisation calculated to be as low as 15 kcal mol-1.[78] Further calculations reported the chair conformer of trans-cyclohexene to be the lowest energy conformation.[79] These results indicated that trans-cyclohexene was a local minimum and as such, it should be possible to generate this under inert conditions. These have indeed been observed as transient species in photochemical reactions using UV light, with lifetimes as short as 9 µs at room temperature.[80,81]
More recently, Weaver and co-workers generated trans-arylcyclohexenes such as 77 using visible light and an iridium catalyst from 76 (Scheme 26).[82] Due to the exceptionally high level of strain in the trans-cyclohexene ring, and consequent very short lifespan, the reaction required a hydroxyl group beta to the alkene to allow coordination of formic acid by hydrogen-bonding. This forced the ring into the trans-isomer, before hydration of the alkene to give cyclic bridged ethers (78) as products. The authors argued that the formation of these trans-cyclohexenes without the use of UV light would open up new synthetic opportunities with trans-cyclohexenes as intermediates.

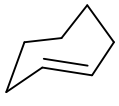


Scheme 26. Generation and reaction of transient trans-cyclohexene species.

3.3. trans-Cycloheptene

trans-Cycloheptene 79 is so strained that it is unstable at room temperature, despite computational studies - including semi-empirical calculations - suggesting the contrary.[83] Initial Investigations into the stability of trans-cycloheptene suggested this is due to ‘twisting’ of the double bond, but Squillacote et al.[83] conducted a study that indicated that the high bond strain in trans-cycloheptene is rather due to a second order process, i.e. an ‘interrupted’ dimerization. The conformation of trans-cycloheptene also plays a role in the reactivity and stability of the molecule. It possesses four different structural conformations with the preferred conformation

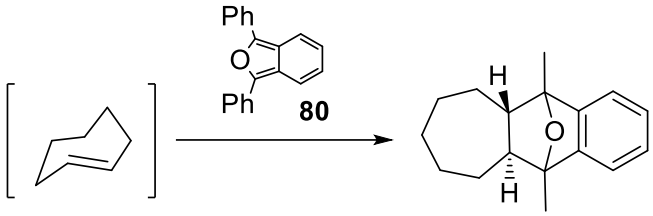
resembling the chair conformation of cycloheptane (Fig. 7). This conformation is chiral and has C1 symmetry. [84]



79

Figure 7. Preferred conformation of trans-cycloheptene.

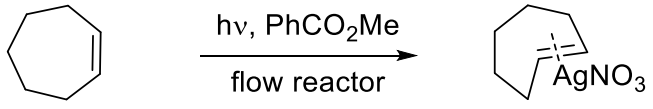
Due to the instability of trans-cycloheptene, its use within bioorthogonal chemistry is limited. Santucci III and co-workers have reported a iEDDA reaction with 1,3-diphenylisobenzofuran (80) (Scheme 27) to produce the bicyclic ether 81, although in a low yield of 6%.[85] trans-Cycloheptene 79 can be synthesized in situ from trans-1,2-cycloheptene, thiocarbonate and trimethyl phosphite.[72]



79 81

Scheme 27. Diels-Alder reaction using trans-cycloheptene.

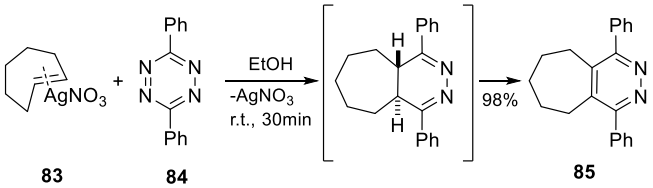
trans-Cycloheptene can however be trapped as the silver nitrate complex and subsequently used. Fang and co-workers synthesised trans-cycloheptene photochemically from cis-cycloheptene (82) using a closed loop photochemical flow reactor via metal complexation of the trans-isomer.[86] This involved the trans-isomer being selectively retained by the silver nitrate (83), while the cis-isomer 82 runs off with silica within the flow reactor. The silver nitrate metal complex 83 was formed in a 53% yield (Scheme 28), a significant improvement on the 6% yield for the free trans-cycloheptene.



82 83

Scheme 28. Synthesis of trans-cycloheptene as the AgNO3 complex.

The AgNO3 complex 83 is stable for bench use for several hours and when stored at -18 oC the complex can be stable for weeks. This trans-cycloheptene-AgNO3 complex 83 can be reacted directly with tetrazine 84, first by metal dissociation, followed by an iEDDA and finally oxidation to give the pyridazine 85 (Scheme 29).

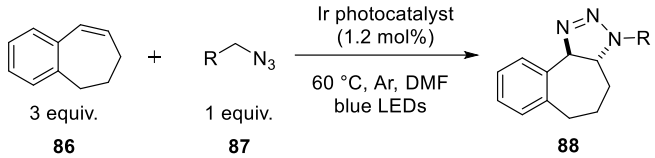


83 84 85

Scheme 29. Diels-Alder reaction using trans-cycloheptene.AgNO3.

An interesting recent example of trans-cycloheptene use in click chemistry has been reported by J. D. Weaver and co-workers.[87] Conjugated (Z)-cycloheptene 86 can be transiently switched to the (E)-alkene using visible light, before it undergoes a cycloaddition with a number of alkyl azides (87), to give the major isomer 88 (Scheme 30). The reaction was unsuccessful with cyclohexene or cyclooctene. This was also applied to modified proteins that were soluble in organic solvents, with

work ongoing to design a water soluble photocatalyst that would allow the reaction to take place under aqueous biological conditions.

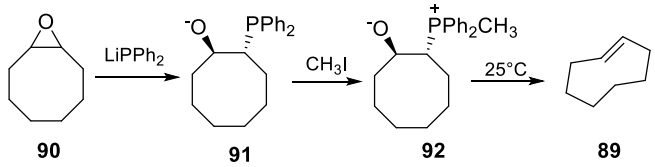


Scheme 30. Visible light induced formation of trans-cycloheptenes and SPAAC reaction.

3.4. trans-Cyclooctene

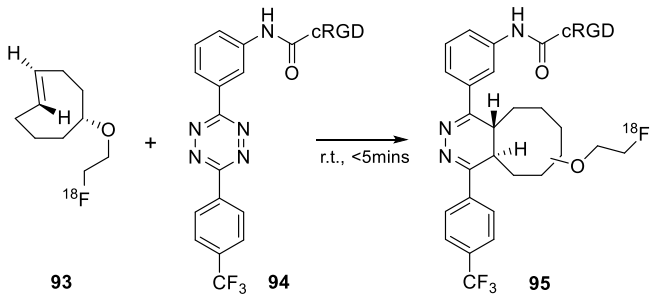
trans-Cyclooctene 89 has a central role in bioorthogonal reactions with tetrazines due to its high conformational strain.[88] There have been several reviews published on biorthogonal labelling and copper-free click chemistry with trans-cyclooctene.[88,89] As such, this mini-review will briefly discuss the synthesis and conformation of this highly strained isomer, followed by a couple of recent examples of its use.

trans-Cyclooctene was first synthesised by Corey et al. in 1965 by olefin inversion, via a thionocarbonate or trithiocarbonate intermediate, as for trans-cycloheptene.[72] It has also been prepared by olefin inversion from the epoxide 90 (Scheme 31).[90] This can be opened with lithium diphenylphosphide in an SN2 reaction, to give the trans-product 91, followed by methylation to give the phosphorus betaine 92, and finally cis-elimination to give solely the (E)-alkene 89 in 70% yield.



Scheme 31. Synthesis of (E)-cyclooctene 89 via phosphorus betaine.

Radiolabelled trans-cyclooctene 93 was used by Fox et al. in a bioorthogonal ligation reaction with tetrazine derivatives to produce new biomolecular probes for PET imaging, such as the RGD-conjugate 95.[91,92] The iEDDA reaction between the trans-cyclooctene derivative 93 and tetrazine 94 gave near quantitative yield of the 18F labelled product within minutes (Scheme 32). Compound 95 showed increased metabolic stability compared to previous fluorine-18 labelled cyclooctene probes.[93]



Scheme 32. Bioorthogonal ligation of trans-cyclooctene with tetrazine derivative.

Calculations have predicted the half-chair conformation of trans-cyclooctene to be higher in energy than the crown conformation (Fig. 8), with ab initio studies showing that there is a relative energy difference of 5.9 Kcal/mol.[65] It was therefore speculated that non-crown conformations of trans-cyclooctene would accelerate the reactivity, by lowering the transition state barrier for the reaction.

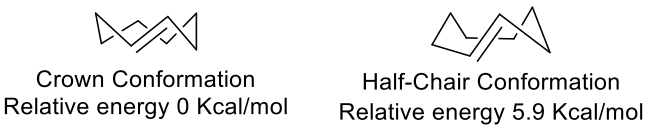
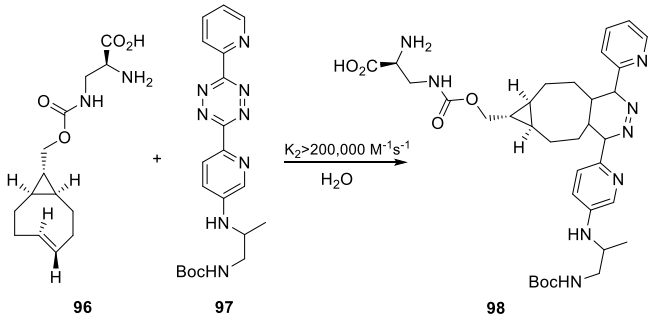


Figure 8. Conformations of trans-cyclooctene.

This was exploited in bioorthogonal reactions conducted by Selvaraj and Fox.[94] These authors found that carrying out a cis-ring fusion between cyclopropane and trans-cyclooctene to give analogues such as 96 resulted in the Diels-Alder reaction proceeding at higher rates, with k2 values exceeding 200,000 M-1 s-1 for the reaction with 97, leading to the construct 98 (Scheme 33). This is one of the most reactive dienophiles reported to date for biorthogonal reactions.



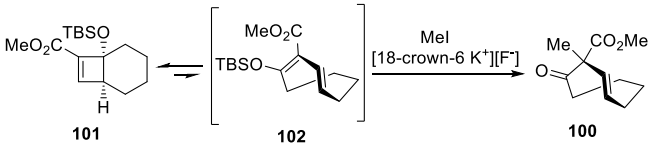
Scheme 33. iEDDA between a tetrazine and cis-ring fused trans-cyclooctene.

3.5. trans-Cyclononene

Yavari and co-workers investigated the conformational properties of trans-cyclononene 99 and found it has two enantiomers which interconvert rapidly, and 7 geometries which are important to the description of the conformational features.[95] The unsymmetrical chair-chair (Fig. 9) was found to be the most stable conformation.

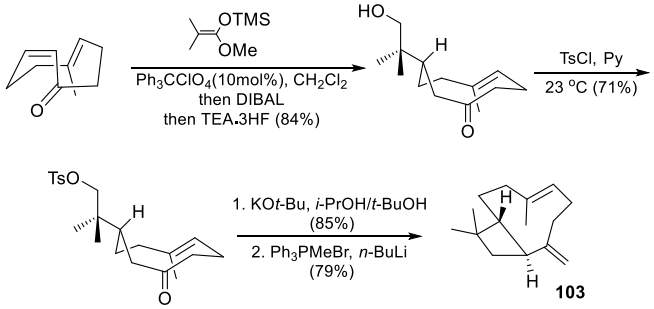
Figure 9. Chair-chair conformation of trans-cyclononene.

trans-Cyclononene derivative 100 can be prepared by a 4□ electrocyclic ring opening reaction from a cis-fused cyclobutene (101), progressing via a cis,trans-siloxycycloalkadiene intermediate (102), in addition to other cycloalkenes, with yields of up to 92% (Scheme 34).[96] The reaction conditions were investigated and it was reported that the torquoselectivity during cyclobutene ring opening was highly controlled by an electron-donating siloxy-substituent, resulting in the proceeding Heck reaction to be regioselective on the distorted trans-double bond.



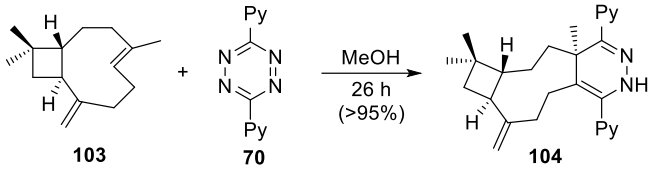
Scheme 34. Synthesis of a trans-cyclononene from cis-fused cyclobutenes.

A second synthesis of trans-cyclononene derivatives has been reported by Larionov and Corey, who used this compound in the synthesis of □-Caryophyllene 103 (Scheme 35), which is a natural product that contains a trans-cyclononene core. This synthesis of 103 was completed in four steps with a relatively high yield.[97]



Scheme 35. Synthesis of ?-Caryophyllene; a natural product containing a core trans-cyclononene.

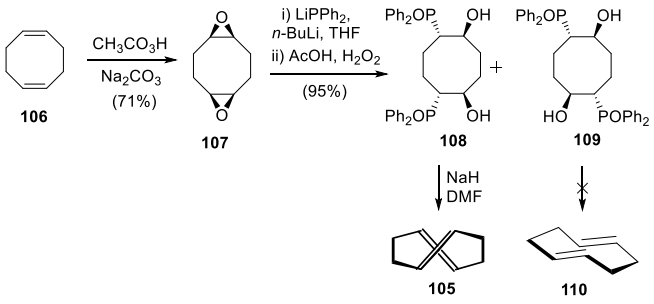
This particular natural product containing a trans-cyclononene core has been used in bioorthogonal reactions.[98] Wu and co-workers reported the use of ?-Caryophyllene (103) in an iEDDA reaction with tetrazines such as 70 (Scheme 36), leading to constructs like 104, which could be applied to in vitro protein labelling and live cell imaging.



Scheme 36. iEDDA reaction between ?-Caryophyllene and tetrazines.

3.6. trans-Cyclodienes

There are also families of medium-sized cycloalkadienes that possess high strain energies. The highly strained (E,E)-1,5-cyclooctadiene 105 (Scheme 37) has been prepared and has been shown to take part in two consecutive click reactions.[99] This compound was first synthesised in 1969 by Whitesides et al.[100] by irradiation of (Z,Z)-1,5-cyclooctadiene 106 with copper(I) chloride, albeit in very low yield. This was prepared again in 1987 by Noth et al., who controlled the stereochemistry via an SN2 opening of the diepoxide 107 (Scheme 37), similar to the synthesis of (E)-cyclooctene 89.[101] The β-hydroxydiphenylphosphine oxides 108 and 109 were isolated before cis-elimination with sodium hydride to give (E,E)-1,5-cyclooctadiene (105) in yields of ~20%. These authors also showed this compound to favour the twist conformation (105) over the chair conformation (110). Leeper et al.[99] later prepared the highly strained (E,E)-1,5-cyclooctadiene using the same method. 105 was used in two separate, consecutive click reactions, allowing fluorescent labelling of EL4 cells by reaction with azide groups on cell-surfaces.



Scheme 37. Synthesis of (E,E)-cyclooctadiene.

For cyclononadiene to have increased strain energies the configuration is required to be either (E,Z) or (E,E). (E,Z)-cyclonona-1,5-diene 111 (Fig. 10) can be prepared using several methods and possesses six geometries which are considered to be important to conformational interconversion.[102] Three of these geometries correspond to energy minima and the remaining

three to energy maxima. The lowest energy conformation of (E,Z)-cyclonona-1,5-diene is the unsymmetrical twist (Fig. 10).

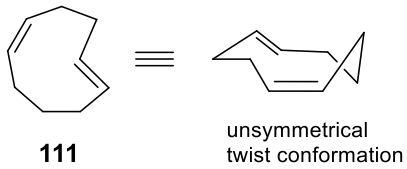


Figure 10. Unsymmetrical twist conformation of (E,Z)-cyclonona-1,5-diene.

(E,E)-Cyclonona-1,5-diene 112 only exists as a transient species but is calculated to be one of two diastereoisomeric families; parallel and crossed (Figure 5). The crossed family is thought to be more stable in comparison to the parallel family.[102]

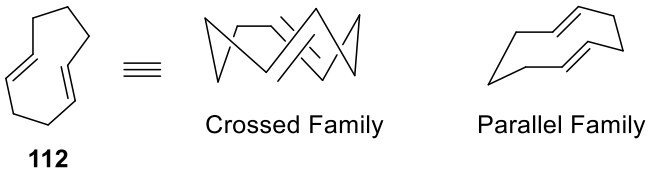
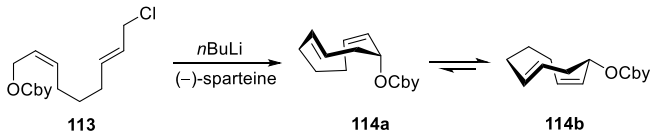


Figure 11. The two different diastereoisomeric families of (E,E)-cyclonona-1,5-diene.

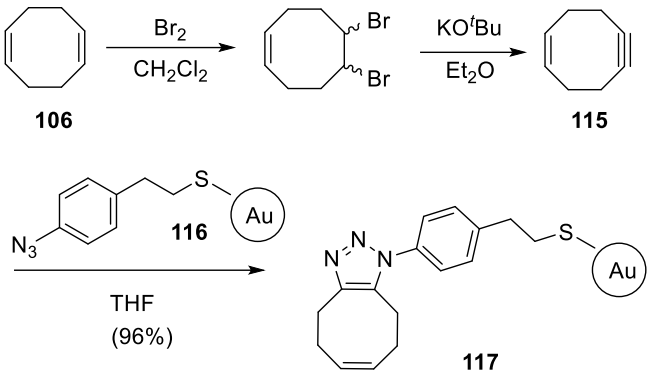
(Z,E)-cyclonona-2,7-diene 114a,b was synthesised by Hoppe et al. via an enantioselective allylic lithiation of 113 mediated by nBuLi and (–)- sparteine, resulting in an enantioselective ring closing process (Scheme 38).[103]



Scheme 38. Enantioselective synthesis of (2Z,7E)-cyclononadiene.

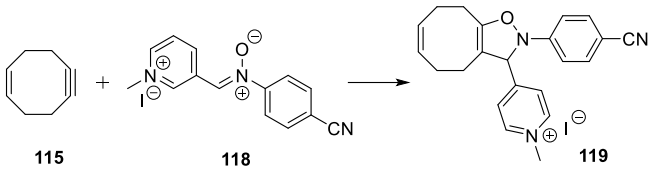
3.7. Cycloalkenynes

There are limited examples of cycloalkenynes in the literature. Cycloalkenynes as small as cyclohepten-3-yne were generated and trapped as described in several papers in the 1980s.[104] However, these were never isolated. In 1990, both cyclohexatriene and cyclohexen-3-yne were prepared in situ and reacted with diphenylisobenzofuran to give the products from the [4+2] cycloaddition.[105] In 2019, Workentin and co-workers reported the synthesis of (Z)-cyclooctene-5-yne (115) (Scheme 39) and used this in a SPAAC reaction with thiolate-protected gold nanoclusters [(CH3(CH2)7)4)N][Au25(SCH2CH2-p-C6H4-N3)18 (116).[106] With the azide group on the surface of the nanoparticles, it allows for postassembly modifications of these. Due to the highly strained nature of 115, the reaction is complete in under 5 minutes in different solvents, giving the triazole 117 in 96% yield.



Scheme 39. Synthesis of (Z)-cycloocten-5-yne and reaction with azide containing gold nanoparticles.

The same group have also reported the reaction of 115 with nitrone 118 in a strain-promoted alkyne-nitrone cycloaddition (SPANC) to give the isooxazoline product 119 (Scheme 40).[107]



Scheme 40. Reaction of (Z)-cycloocten-5-yne with nitrones.

4. Conclusions

The field of ultra-strained compounds has seen a renaissance in recent years and a meteoric rise in interest among the scientific community, mainly due to the advancement of structurally distorted cyclic molecules such as cyclopropene, cyclooctyne, and trans-cyclooctene, which feature a good compromise between chemical stability and reactivity towards iEDDA and SPAAC reactions. This has led to a dramatic increase in the use of these highly reactive molecules in chemical biology, especially for the labelling of peptides, biopolymers and cells through “click-chemistry”-type processes. We hope this mini-review will represent a useful resource for researchers interested in applying ultra-strained non-aromatic rings to bio-orthogonal reactions for labelling biologically - important molecules. We also hope it will stimulate further blue-sky research – which remains invaluable for achieving breakthrough discoveries and pursuing true scientific innovation, as clearly demonstrated by the work described here, that ultimately led to the development of the chemical tools and protocols underpinning the precision medicine revolution.

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Keywords: Cycloalkenes • Cycloalkynes • strain • bioorthogonal • cycloadditions

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