Università
Ca'Foscari
Venezia

Dottorato di ricerca in Scienze Chimiche, XXIII ciclo
Scuola di dottorato in Scienze e Tecnologie
(A.A. 2010/2011)

FUNCTIONALIZED BENZOCYCLOTRIMERS: STEREOCONTROLLED SYNTHESIS AND SUPRAMOLECULAR APPLICATIONS

SETTORE SCIENTIFICO-DISCIPLINARE DI AFFERENZA: CHIM/06

Tesi di dottorato di STEFANO TARTAGGIA, matricola 955477

Direttore della Scuola di dottorato
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Department of chemistry

Abstract

Doctoral Thesis
By Stefano Tartaggia

Benzocyclotrimers are polycyclic compounds which can be obtained through self-coupling reactions of bicyclic olefins. In recent years, the research in this field demonstrated the synthetic and the supramolecular applications of this class of molecules. This work presents the optimization of a new method for the synthesis of cyclotrimers using a feasible procedure based on the Heck-type self-coupling reaction of enantiopure iodobornenes. The screening and the optimization of several functionalization reactions led to the preparation of covalent supramolecular hosts and self-assembling derivatives. In particular the condensation of benzotricamphor (a tricarbonyl cup-shaped unnatural triterpenoid) with aliphatic diamines provided imine-linked molecular cages which exhibited hosting properties for small neutral guests. On the other hand, cross-coupling reactions of benzotricamphor triflate with terminal alkynes provided new self-assembling derivatives based on the more common self-assembling forces, which are metal-ligand, H-bonding and ionic interactions. The research of other functionalization reactions for benzocyclotrimer helpfully led to a new method for the synthesis of disubstituted arylacetylenes from aryl bromides based on decarboxylative coupling reactions of acetylene carboxylic acid.

ACKNOWLEDGEMENTS

Many people have contributed, scientifically and not, to the realization of this thesis and I wish to personally thank. First of all I would like to express my appreciation to my promoter Ottorino De Lucchi for giving me the possibility of working as a member of his group. I wish to warmly thank my supervisor Fabrizio Fabris for his encouragement, support and guidance into the deep forest of organic synthesis. I am very grateful to Alessandro Scarso for having introduced me the magic word of the supramolecular chemistry and for the help with the work presented in chapter 5 and 6. I would also like to express my thank to my research group for their support, help and friendship: Andrea, Beppe, Cinzia, Enrico, Gianni, Jack, Riccardo, Romana, Stefania.

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Finally a special thank to my family and all my friends for all their support, help and encouragement that have been a great source of inspiration during all my life.

Thank you all!

Stefano

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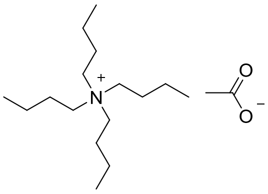
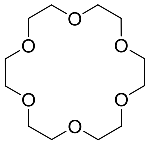
Acronyms and Abbreviations

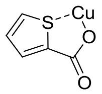
Bu_4NOAc: tetrabutylammonium acetate



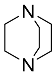
18-crown-6: 1,4,7,10,13,16-hexaoxacyclooctadecane



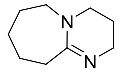
CuTC: copper(I) 2-tiophenecarboxylate



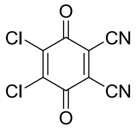
DABCO: 1,4-diazabicyclo[2.2.2]octane



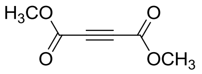
DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene



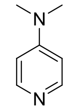
DDQ: 2,3-dichloro-5,6-dicyanobenzoquinone



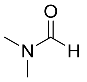
DMAD: dimethyl acetylenedicarboxylate



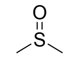
DMAP: 4-dimethylaminopyridine



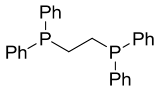
DMF: dimethylformamide



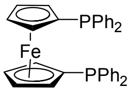
DMSO: dimethyl sulfoxide



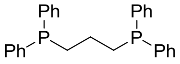
dppe: 1,2-bis(diphenylphosphino)ethane



dppf: 1,1'-bis(diphenylphosphino)ferrocene

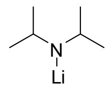


dppp: 1,3-bis(diphenylphosphino)propane

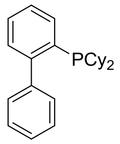


DOSY: diffusion ordered spectroscopy
HMQC: heteronuclear multiple quantum coherence

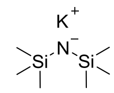
LDA: lithium diisopropylamide



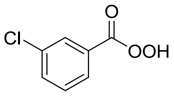
John-phos: (2-Biphenyl)di-tert-butylphosphine



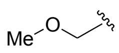
KHMDS: potassium hexamethyldisilazane



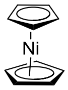
m-CPBA: *meta*-chloroperbenzoic acid



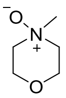
MOM: methylenemethoxy



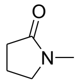
Ni(Cp)$_2$: bis(cyclopentadienyl)nickel



NMO: *N*-Methylmorpholine-*N*-Oxide

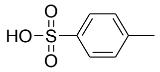


NMP: *N*-methylpirrolidone

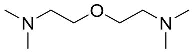


NOESY: nuclear Overhauser effect spectroscopy

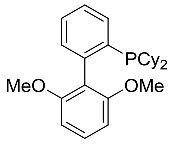
p-TSA: *p*-toluenesulfonic acid



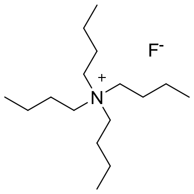
O-TMEDA: bis(2-dimethylaminoethyl)ether



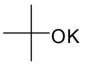
Sphos: 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl



TBAF: tetrabutylammonium fluoride

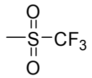


t-BuOK: potassium *tert*-butoxide

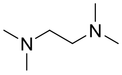


THF: tetrahydrofuran

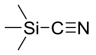
Tf: trifluoromethanesulfonate



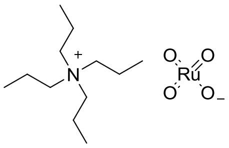
TMEDA: tetramethylethylenediamine



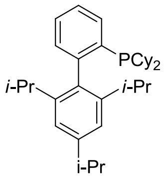
TMSCN: Trimethylsilyl cyanide



TPAP: tetrapropylammonium perruthenate



Xphos: 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl



CHAPTER 1

CYCLOTRIMERIZATION REACTIONS

Harnessing symmetry

The use of C_3-symmetric molecules has found application in several fields of chemistry taking inspiration by nature.[1] For example the C_3 symmetry found in certain enzymes[2] has inspired biomimetic C_3-symmetric catalysts.[3] As well as many symmetric molecules, many C_3-symmetric compounds have been successfully employed in asymmetric catalysis[4] and chiral recognition,[5] taking advantage of an improved selectivity in reducing competing alternatives in the number of different receptor-substrate complexes and thereby reaction paths.[4,6]

In the area of catalysis, C_3-symmetrical ligands have been employed in several processes, including cyclopropanations,[7] allylic oxidations,[8] alkynylation of aldehydes[9] and allylic alkylations[10] providing typically 70–90% enantioselectivities. Excellent results in the field of molecular recognition have been achieved with C_3-symmetric tripodal oxazoline receptors:[11]

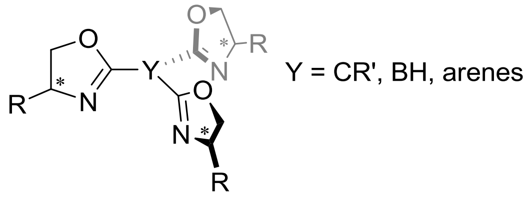


Fig. 1.1 C_3-symmetric tripodal oxazoline.

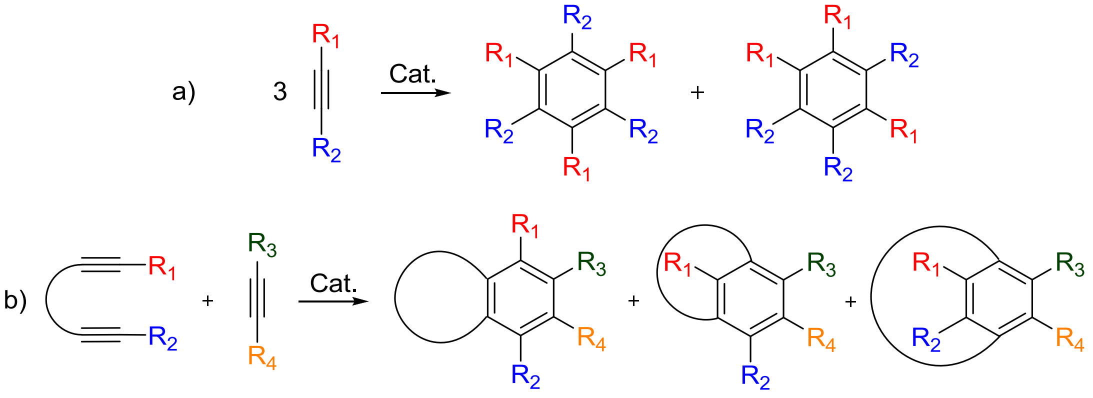
For example, the selective recognition of alkylammonium ions and amines with chiral β centres[12] has been used as models for the study of dopamine and γ-aminobutyric acid receptors,[13] therefore introducing the concept of using artificial C_3-symmetric carriers to mimic cell membranes.

The construction of molecular nanoarchitectures by using C_3-symmetrical molecules raised the attention of many chemists in recent years as they readily form helical and propellerlike conformations.[14] Nanostructures based on C_3 symmetry and chirality have been used in organogels,[15] fibers,[16] components of lipid membranes,[17] and dendrimers.[18] C_3-symmetrical functional molecules combine, as advantage, a good balance between enhanced binding properties and selectivity with the ease of synthesis and analysis, leading to future biomimetic applications of C_3 symmetry in the area of molecular recognition.[5,6]

One of the more simple, stabile, rigid scaffold leading to highly symmetric compounds is the aromatic ring. The possibility to arrange, modify and replace the six possible substituents has raised the attention of many researches in the preparation of highly symmetrical tri- or hexa-substituted aromatic rings. Cyclotrimerization reactions, in particular, can be considered the most versatile methodologies towards the preparation of fully annelated benzenes with C_3 or different degree of symmetry. Schematically, these methods can be classified in the following categories of reactions: *a)* cyclotrimerization of alkynes; *b)* cyclotrimerization of aromatic rings; *c)* condensation of aromatic or aliphatic α-methylene ketones; *d)* cyclotrimerization of suitably substituted (polycyclic) olefins.

1.1 CYCLOTRIMERIZATIONS OF ALKYNES AND ARENES

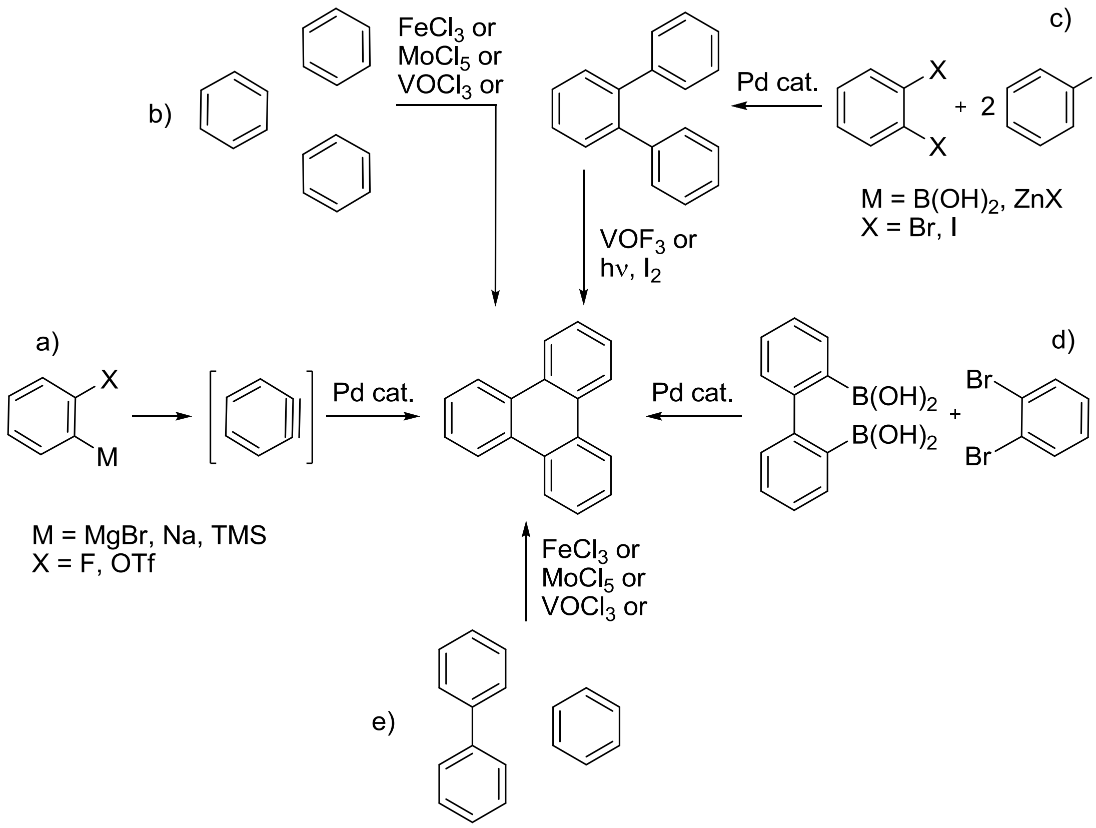
The cyclotrimerization of alkynes ([2+2+2] cycloadditions) is usually catalyzed by a transition metal (Co, Ir, Mo, Pd, Rh, Ru, Ti).[19] Unfortunately, because of the linear geometry of the starting materials it is usually not possible to obtain tris-annelated benzenes and more isomers are expected (Scheme 1.1).[19d,e] Moreover, unsymmetrical products are often obtained rather than symmetrical ones, especially when diacetylenes are used as substrates (Scheme 1.1b). The stereo- and regio-selectivity of the addition is usually controlled by one or more of the following factors: metal catalyst, ligand, electronic factors of R groups and the length of the chain connecting the two acetylenes.[19b,e,h] Although these methods are well known and deeply investigated, there are not reported examples of supramolecular applications related to compounds obtained in this manner, since they usually present flexible substituents which likely would induce low specificity and efficiency of any hypothetical receptor.



Scheme 1.1 Cyclotrimerization of alkynes.[19d,e]

Triphenylenes are an important class of cyclotrimers. The main approaches leading to triphenylenes are schematically described in Scheme 1.2.[20] Arenes *orto*-substituted with a metal along with an halide or pseudohalide group cyclize by palladium catalyzed coupling reactions, eventually through aryne intermediates (Scheme 1.2a),[21] while oxidative couplings are suitable especially for the trimerization of catechols (Scheme 1.2b).[22] Procedures which combine coupling reactions with oxidative ring closure are also reported (Scheme 1.2c).[23] Moreover, the synthesis of triphenylenes is also possible through the coupling of biphenyls with arenes by using either Pd-catalysis (Scheme 1.2d)[24] and oxidative protocols (Scheme 1.2e).[25]

All these methods efficiently afford extended aromatic systems, but they are mainly two-dimensional objects[26] which have found many applications in the field of liquid crystals.[27]

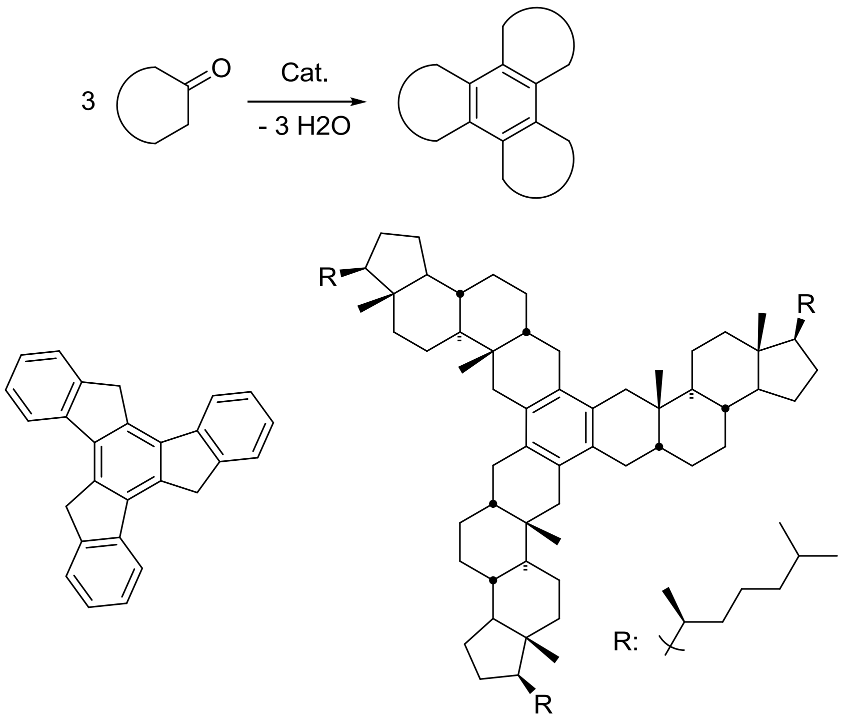


Scheme 1.2 Cyclotrimerization of arenes.

1.2 CYCLOTRIMERIZATIONS OF KETONES

The self-condensation of cyclic ketones under strongly Brønsted- or Lewis-acid conditions lead also to fully annelated benzenes (Scheme 1.3).[28] This strategy affords only symmetric cyclotrimers and is usually applied in the synthesis of truxenes, which exhibit supramolecular and photochemical applications.[29] Noticeably, two truxenes were employed for the first (and so far unique) chemical synthesis of fullerenes C_{60} and C_{78}.[30]

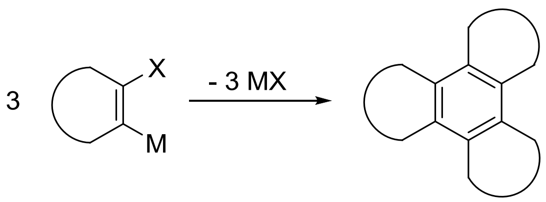
The cyclotrimers obtained by these procedures are mostly flat molecules except in the case of the highly diastereoselective condensation of a steroid ketone in which the C_3-symmetric *syn*-cyclotrimer displays a deep cavity.[31]



Scheme 1.3 Cyclotrimerization of ketones, truxene and a cyclotrimer derivated from steroids cyclization.

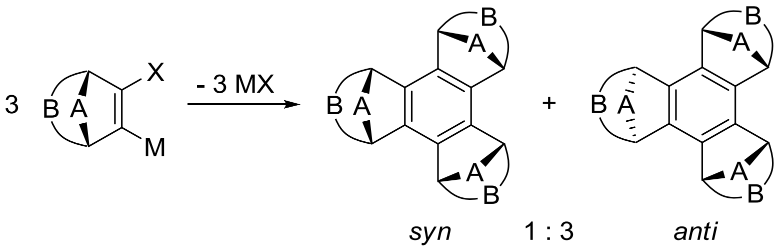
1.3 Cyclotrimerizations of Bicyclic Olefins

The fourth approach toward the synthesis of benzocyclotrimers is based on coupling reactions of olefins bearing two vicinal substituents able to act as anionic and cationic leaving groups in the presence of suitable catalysts or promoters (Scheme 1.4). Cycloalkenes were trimerized to afford essentially flat tris-annelated benzenes, since the beginning of the last century.[32]



Scheme 1.4 Cyclotrimerization of polycyclic olefins.

The research aimed at the cyclotrimerization of polycyclic olefins is more recent. In this case, depending on the symmetry of the bicycle, it is possible to obtain two different compounds: the *syn*-diastereomer, exhibiting C_3-symmetry and the *anti*-diastereomer possessing C_s symmetry (Scheme 1.5). In the absence of specific expedients the *syn* to *anti* diastereomeric ratio is usually 1:3 (statistical).

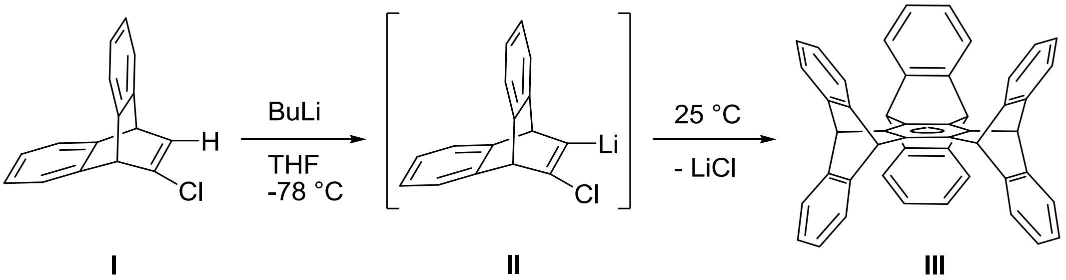


Scheme 1.5 Diastereoselectivity in the cyclotrimerization of C_s bicyclic olefins.

The genesis and the evolution of these methodologies are herein described, while the applications of the cyclotrimers so far obtained will be presented in the next Chapter.

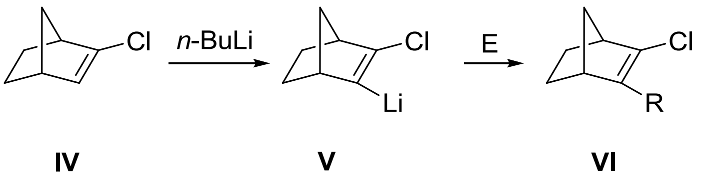
1.3.1 HIGHLY STRAINED ALKYNE CYCLOTRIMERIZATIONS

The first example of a benzocyclotrimer derived from a bicyclic olefin was reported in 1970 from the reaction of 11-chloro-9,10-dihydro-9,10-ethenoanthracene **I** with butyl lithium at room temperature, which afforded heptycene **III** in low unspecified yield. [33]



Scheme 1.6 Synthesis of heptycene.

Several years later, a series of new trimeric structures were discovered from different research programs concerning the chemistry of highly strained alkynes. In 1980 Gassman reported the synthesis of new benzocyclotrimers studying the possibility to prepare strained acetylenes from 2-chlorobicyclo[2.2.1] hept-2-ene **IV** by a treatment with *n*-BuLi followed by elimination of LiCl. The lithiated olefin intermediate **V** was found stable at room temperature and reacted with different electrophiles affording the corresponding substituted products **VI$_{a\text{-}f}$** in moderate yields.

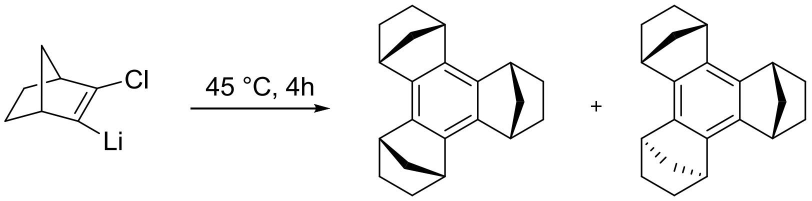


IV **V** **VI**

E	R
a: D_2O	a: D
b: CO_2	b: CO_2H
c: $ClSiMe_3$	c: $SiMe_3$
d: CCl_4	d: Cl
e: MeI	e: Me
f:$Br(CH_2)_2Br$	f: Br

Scheme 1.7 Reactions of vinyl-lithium intermediate with different electrophiles.

Considering the relative stability of the lithium intermediate **V**, the temperature at which LiCl was eliminated has been determined, establishing that **V** disappeared after 4 h at 45 °C, providing a 10% yield of a 1:2 mixture of *syn* and *anti* isomers of benzotribornane **VII.**

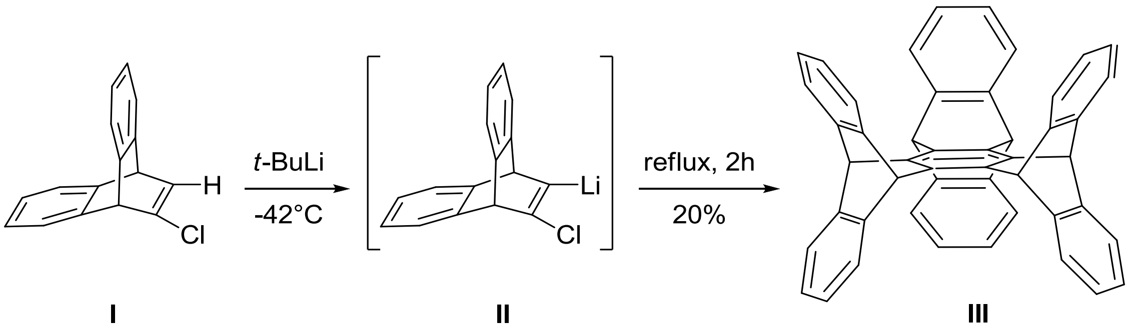


V *syn*-**VII** *anti*-**VII**

Scheme 1.8 Synthesis of benzotribornane.

Considering that two diastereoisomers were obtained, Gassman proposed that Lithiated olefin **V** eliminated LiCl to generate a highly reactive strained alkyne intermediate which trimerized unselectively to give *syn* and *anti* **VII.** [34]

Analogously, in a parallel program concerning the chemistry of iptycenes, Hart improved the conditions for the synthesis of heptycene from the reaction of **I** with *t*-butyllithium followed by the heating of the reaction mixture.[35]

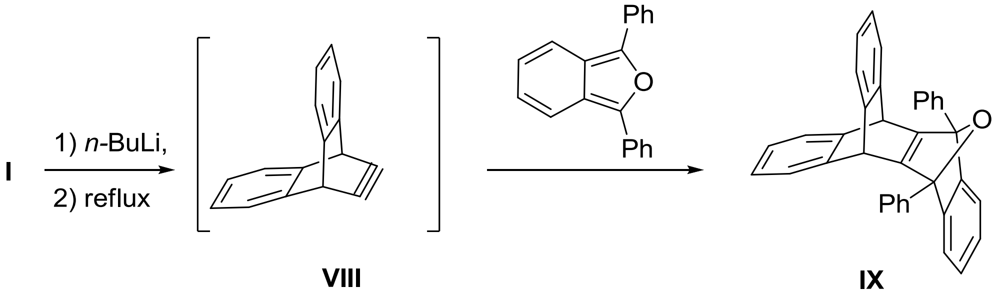


I **II** **III**

Scheme 1.9 Improved synthesis of heptycene.

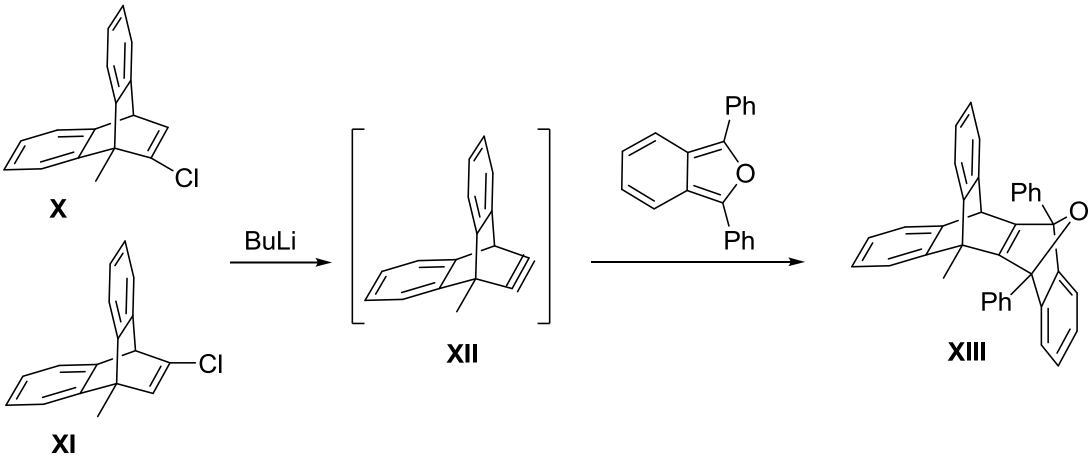
In addition to the synthesis of a number of different iptycenes,[36] Hart presented also a mechanicistic investigation of trimerization of bicyclo[2.2.2]alkenes

providing a series of evidences that confirm the existence of bicyclo[2.2.2]alkynes as reactive intermediates in the course of trimerization path.
The existence of strained alkynes was firstly proved by trapping bicyclo[2.2.2]alkyne **VIII**, generated from **I**, with 1,3-diphenylisobenzofuran.



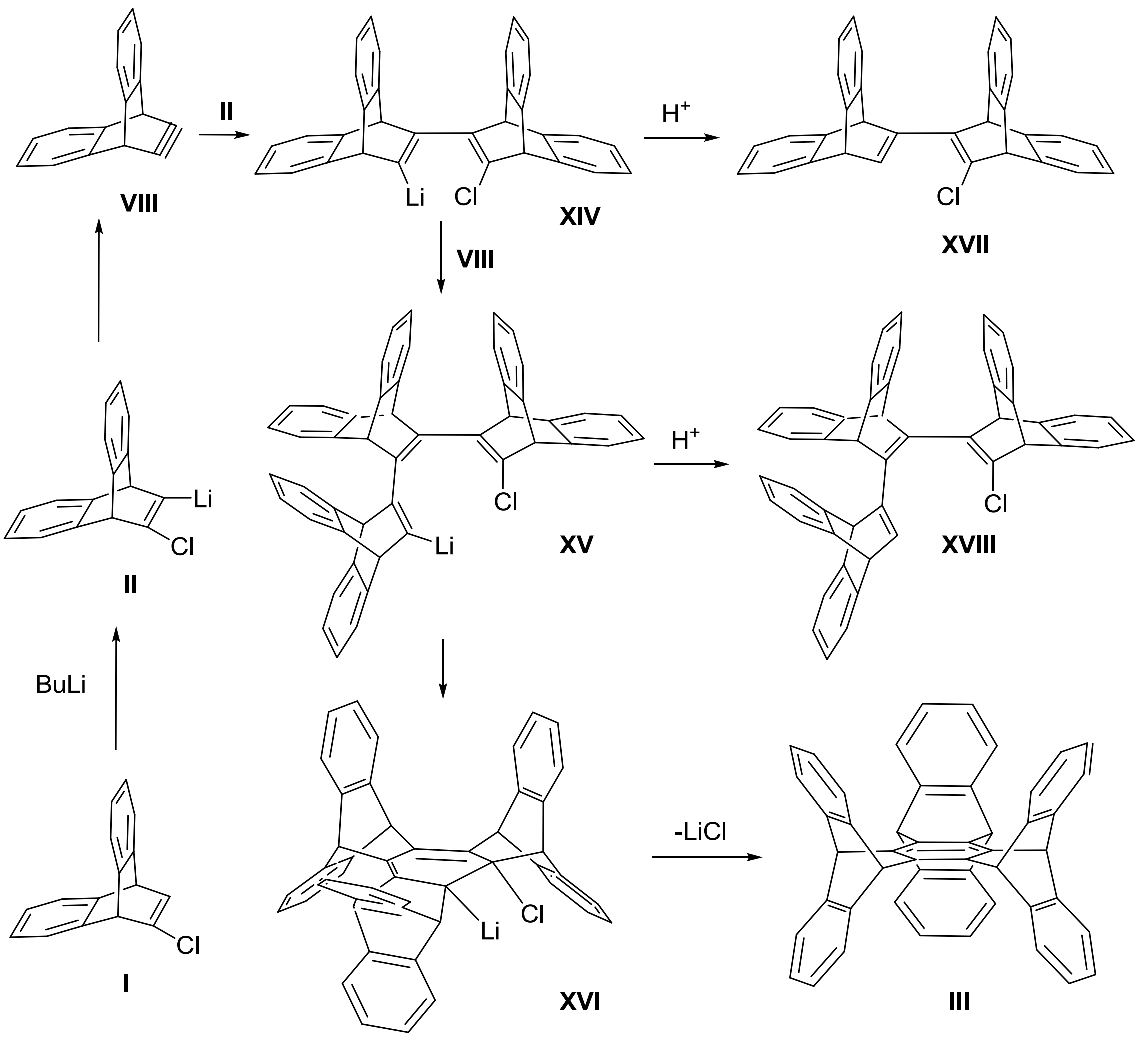
Scheme 1.10 Trapping of highly strained alkyne **VIII** derived from **I**.

The presence of alkyne intermediates was further demonstrated by the isolation of a common adduct from a mixture of chlorides **X** and **XI** and 1,3-diphenylisobenzofuran treated with BuLi and followed by heating at reflux. Since the reaction afforded the sole adduct **XIII**, a common intermediate, bicycloalkyne **XII**, is evidently formed from each precursor.



Scheme 1.11 A common adduct is obtained from chlorides **X** and **XI**.

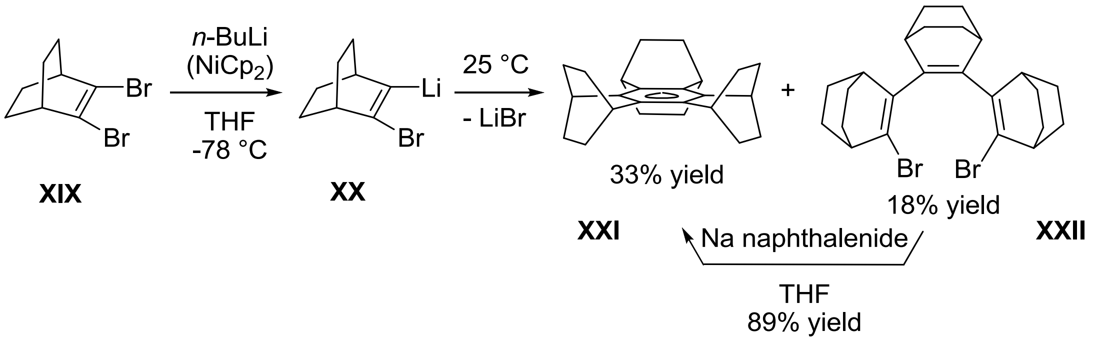
From the mechanistic viewpoint, Hart presented a possible pathway for the trimerization reaction of bicyclo-chloro-alkenes. After lithiation of **I**, LiCl is eliminated from **II** providing the alkyne intermediate **VIII.** Then, the addition of a second molecule of **II** to the reactive specie **VIII** generates **XIV**, which react with another molecule of **VIII** to produce **XV.** The open trimer **XV** can finally close the ring and lose LiCl furnishing the aromatic ring of the final product, which is heptycene.



Scheme 1.12 Tentative mechanism for the trimerization of **I**

The above mechanism was supported by the presence of the de-lithiated by-products **XVII** and **XVIII**. Furthermore, the ring closing step was completely inhibited when the reaction was carried out on **X** or **XI**, presumably for steric reasons.[37]

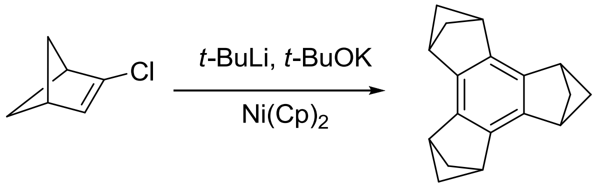
Dibromobicyclo alkenes were used also for the preparation of trimeric structures. Komatsu reported the trimerization of bicyclo[2.2.2]dibromooctene **XIX** by treatment with *n*-BuLi, in the presence (or not) of nickel complexes (Scheme 1.13). This strategy afforded also the trimeric dibromide **XXII** as byproduct, which was conveniently converted into the cyclotrimer **XXI**.[38]



Scheme 1.13 Cyclotrimerization of vinyl dibromides.

Komatsu found that the cyclotrimerizations of bicyclic-vinyl-bromides, carried out under similar conditions to that reported for analogue chlorides, furnished polymeric materials instead of trimers. This was related to the prophecy of *vic*-Li-Br olefins to undergo fast halogen-metal exchange reactions that could not provide the corresponding aromatic trimers in good yields. Komatsu suggested also that the addition of a Ni catalyst was completely useless in regard of cyclotrimerization and supported the hypothesis that cyclotrimerization reactions occur via insertion reactions of highly reactive alkyne intermediates into C-Li bonds rather than metal catalyzed coupling reactions.[39]

In 1995 Siegel presented the synthesis of the new highly strained benzocyclotrimer **XXIV** by treating 2-chlorobicyclo[2.1.1]hex-2-ene **XXIII** with a mixture of *tert*-butyllithium and potassium *tert*-butoxide followed by the addition of 10 mol % nickelocene.



XXIII **XXIV**

Scheme 1.14 Cyclotrimerization of 2-chlorobicyclo[2.1.1]hex-2-ene **XXIII**.

The isolation and characterization of structures of the type of trimer **XXIV** has inspired different research programs aimed to investigate the effect of strain imposed by small rings on the aromatic character of fully annelated benzenes. The structure of **XXIV** provided an important test to demonstrate bond alternation induced by strain in benzenoid aromatics as demonstrated by X-Ray analysis and computational calculations, which predicted ca. 0,7 Å difference between the *endo* and *exo* bond lengths of central aromatic ring.[40]

Concerning the cyclotrimerization mechanism, the authors suggested that bicyclohexine is generated as an intermediate during the formation of the benzocyclotimer. The effect and the role of the Ni catalyst remained ambiguous and unclear.

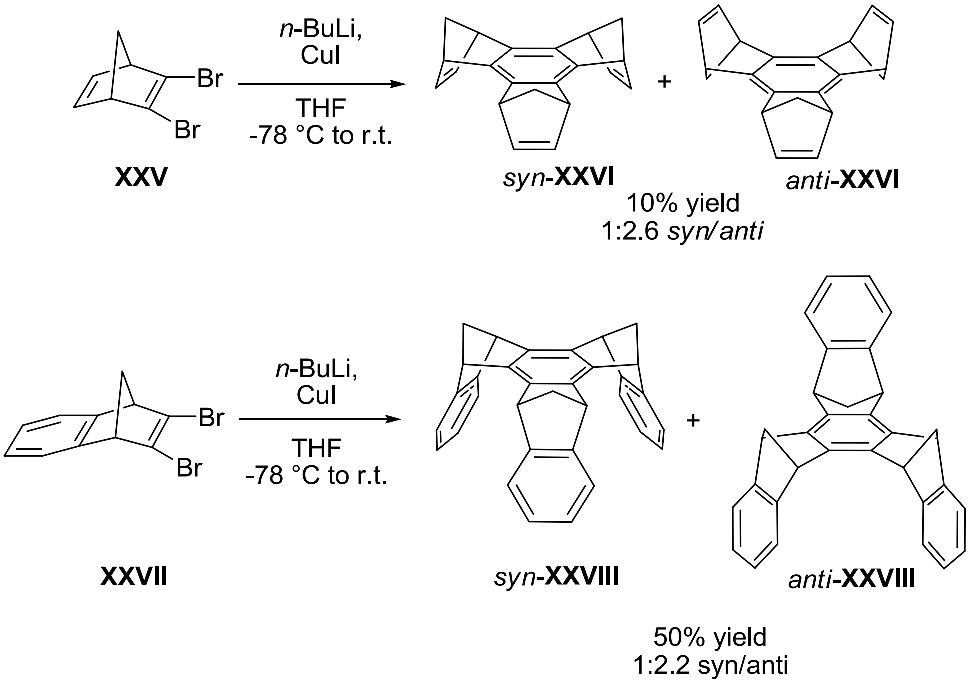
To Summarize, the first examples of cyclotrimerization reactions for the synthesis of trisannelated benzenes from bicyclic olefins, were accomplished by two routes: from chloroalkenes with organo-lithium reagents or from dibromoalkenes by metal–halogen exchange reactions. In both cases the yields were very low, usually 10 % or less and substantial amounts of polymers were formed. The use of metal catalysts such as nickel also led to unpredictable and erratic results. The presence of strained alkyne intermediates was confirmed by several evidences and could justify the poor yields obtained, by taking into account an uncontrolled reactivity that limited the selectivity.

1.3.2 COPPER(I,II) PROMOTED CYCLOTRIMERIZATIONS

Because of the poor yields obtained by the above procedures, there was a need of new efficient cyclotrimerization methodologies. New protocols compatible with a greater class of substrates were required especially for the preparation of functionalized cyclotrimers, in order to develop and investigate a wide range of possible applications for this class of molecules.

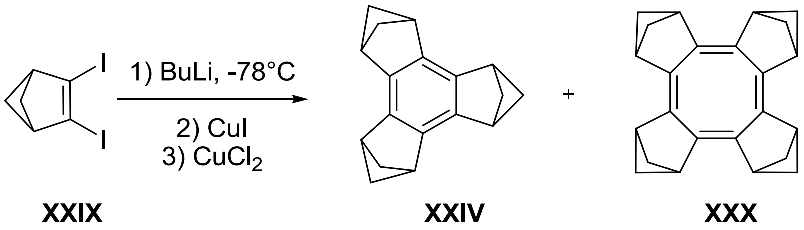
The introduction of copper promoters was reported in 1996 for the synthesis of benzotrinorbornenes **XXVI** from dibromonorbornadiene **XXV** (Scheme 1.15). The authors found that chloronorbornadiene under the conditions which successfully led to cyclotrimerization of simple bicyclic alkenes, was unable to provide the expected cyclotrimer. Copper salts were necessary to promote efficiently the reaction, while Ni catalysts were completely useless.[41]

Similarly, the reaction carried on dibromobenzonorbornadiene **XXVII** afforded a 1:3 mixture of *syn/anti* isomers of benzotri(benzonorbornadiene) **XXVIII** in 50% overall yield:[42]



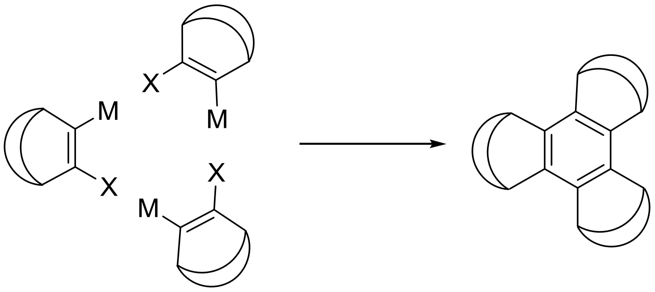
Scheme 1.15 Copper(I) promoted cyclotrimerization of vinyl dibromides.

Concerning the cyclotrimerization of dihaloalkenes, the previously reported trimer **XXIV** was prepared from diiodoolefin **XXIX** by an original procedure reported in 2001. The cyclotrimerization was accomplished by the sequential addition of Cu(I) and Cu(II) chlorides to the lithium derivative of **XXIX**. The final product was obtained in 43% yield, while in absence of $CuCl_2$ was isolated the cyclooctatetraene **XXX** in 21% yield.[43]



Scheme 1.16 Improved methodology for the cyclotrimerization mediated by copper.

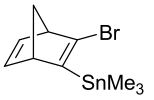
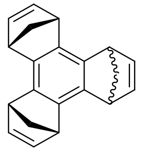
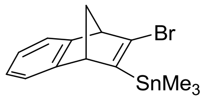
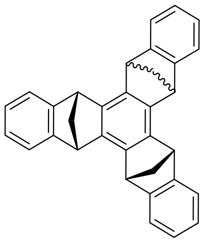
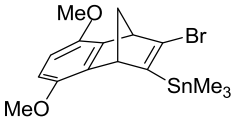
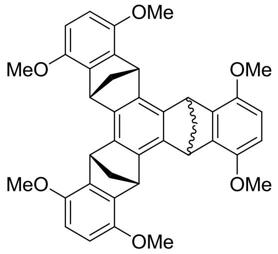
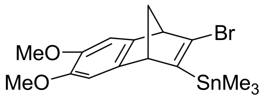
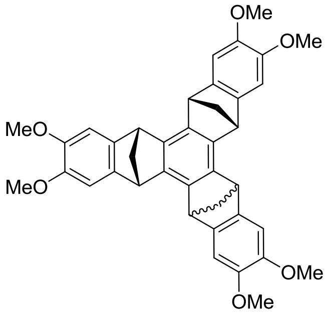
The use of copper salts in cyclotrimerization reactions increased the possibilities to prepare functionalized cyclotrimers. The modification of the substrates by placing an halogen atom, acting as a leaving group X, at one carbon and a suitable organometallic fragment M at the other, further improved these reactions by promoting coupling reactions to trisannelated aromatic product rather than uncontrolled polymerization. The most successful results were obtained using bicyclo-alkenes containing the trimethylstannyl group as "metal" along with bromine as a leaving group.



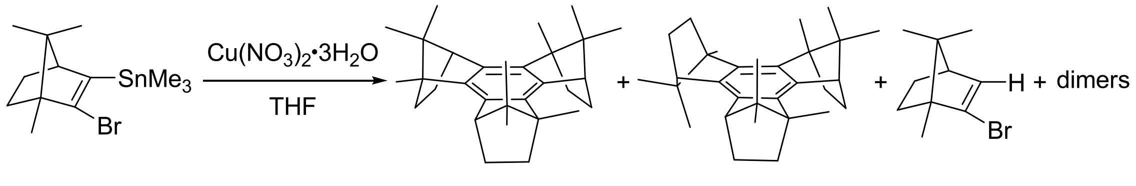
Scheme 1.17 "Head to tail" chain type cyclotrimerization.

The first reported cyclotrimerization of bromo(trimethylstannyl)alkenes was carried out with $Cu(NO_3)_2 \cdot 3H_2O$ affording trimers as a 1:3 *syn/anti* mixture up to 80% yield.[44]

Table 1.1 Cyclotrimerization of bromo(trimethylstannyl)alkenes with $Cu(NO_3)_2 \cdot 3H_2O$.

	substrate		product	Overall yield (%) (*syn/anti* ratio)
XXXI		**XXVI**		80 (1:3)
XXXII		**XXVIII**		70 (1:3)
XXXIII		**XXXV**		15 (1:9)
XXXIV		**XXXVI**		47 (1:3)

The unfavorable *syn*/*anti* ratio was initially ascribed to the fact that the employed substrates were in racemic form and consequently they could not perform selective reactions. Thus, the cyclotrimerization on enantiopure substrates, which should lead stereoselectively only to *syn*-isomers, was attempted. Unfortunately, treatment of the enantiopure *vic*-bromo-tin olefin, obtained from (+)-camphor, with $Cu(NO_3)_2{\cdot}3H_2O$ provided only 5% of the *syn*-cyclotrimer together with 45% of the *anti* isomer and a considerable amount of dimers and proto-de-stannylated product.

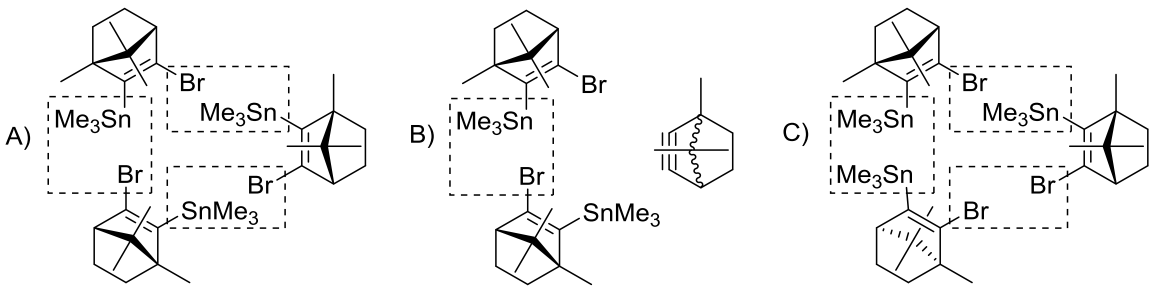


5% 45% 20%

XXXVII *syn*-**XXXVIII** *anti*-**XXXVIII** **XXXIX**

Scheme 1.18 Cyclotrimerization of (+) camphor.

The formation of the *anti*-isomer, as major product was explained by two possible mechanisms (Scheme 1.19). In the first, the reaction was supposed to proceed through the formation of a dimeric unit by MX-coupling followed by the reaction with a bornyne intermediate (mechanism B). The *anti* product was consequently favored due to steric reasons. Alternatively, a Sn-Sn homo-coupling produced a C_2-symmetric dimer which could react with a third molecule of the substrate to produce the *anti*-cyclotrimer (mechanism C). Since a certain amount of the C_2-symmetric dibromo-dimer was detected in the reaction mixture, mechanism C was assumed the most probable.[45]



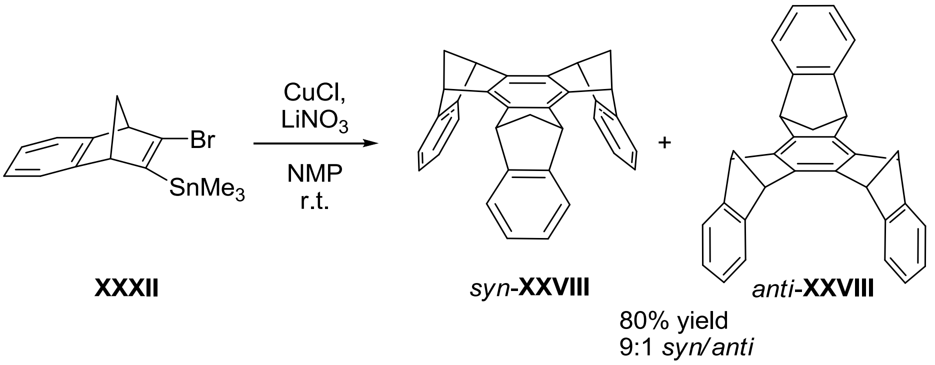
hetero-coupling: *syn*-cyclotrimerization

bornine intermediate: *syn*/*anti* cyclotrimerization

Sn-Sn homocoupling: *anti*-cyclotrimerization

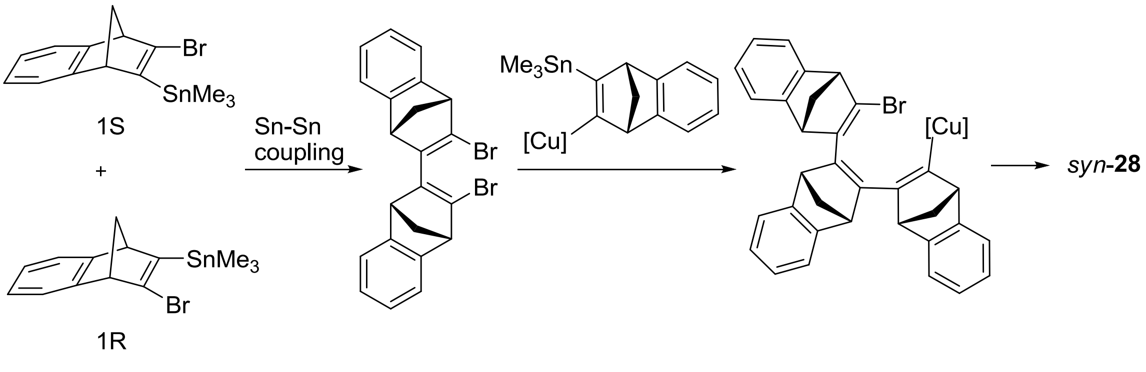
Scheme 1.19 Possible origin of stereoselectivity in cyclotrimerizations of enantiopure substrates.

The improvement of the *syn/anti* ratio in cyclotrimerization reactions was achieved by combining different copper precursors in presence of lithium salts and chelating co-solvents (DME), resembling a known protocol for the coupling of vinylstannanes by using CuCl as the sole promoter.[46] Under such conditions, the cyclotrimerization of benzonorbornadiene **XXXII** in NMP or DMF in presence of LiCl or $LiNO_3$ led to 80% yield of trimers with a 9:1 *syn/anti* ratio.[47]



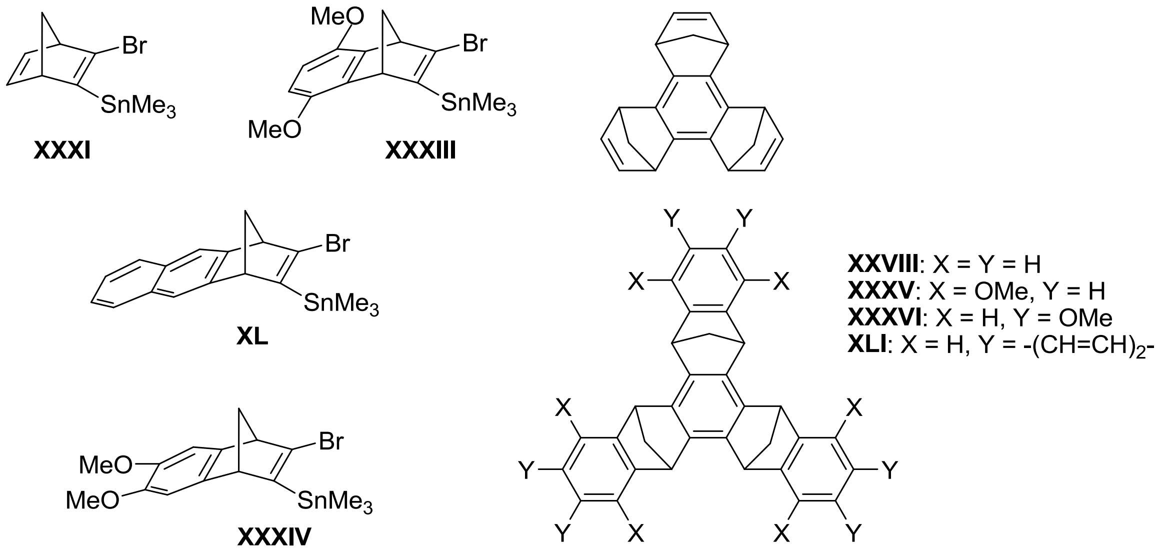
Scheme 1.20 Enhanced stereoselectivity in cyclotrimerization of bromo(trimethylstannyl)alkenes.

Since the use of a racemic mixture of **XXXII** should lead to a statistic 1:3 mixture of *syn/anti* isomers, this excellent selectivity to the *syn*-benzocyclotrimer was rationalized considering a Cu-mediated Sn-Sn coupling between opposite enantiomers to produce a diastereomeric C_s-symmetric dibromide. This intermediate coordinated a copper specie and reacted with a third molecule of monomer to produce the *syn*-benzociclotrimer.[48] The favored coupling between opposite enantiomers was supported by the observation that the reaction of enantiopure substrates afforded in general poorer yields and selectivity than corresponding reagents in racemic form.



Scheme 1.21 Proposed pathway for the cyclotrimerization of a racemic mixture.

A series of benzocyclotrimer were efficiently prepared using this procedure:

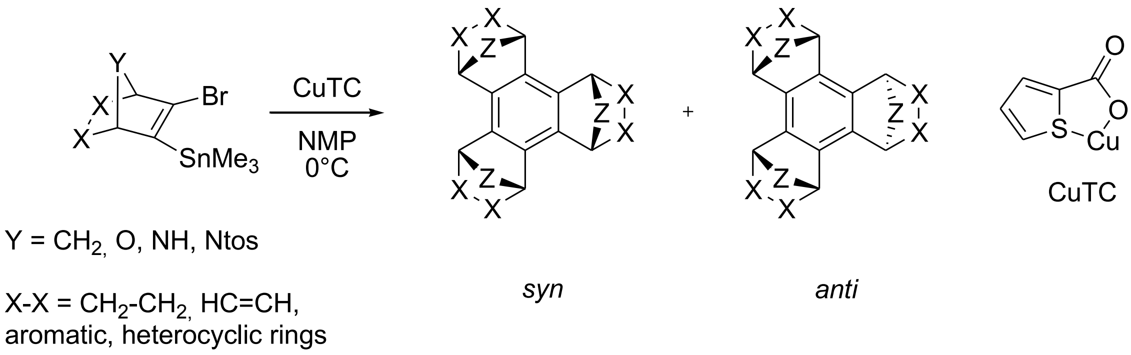


XXVIII: X = Y = H
XXXV: X = OMe, Y = H
XXXVI: X = H, Y = OMe
XLI: X = H, Y = -(CH=CH)$_2$-

Scheme 1.22 Substrates tested for cyclotrimerization with CuI in NMP or DMF in presence of $LiNO_3$ or LiCl at room temperature and related products.

Despite the good yields and selectivity, some negative aspects decreased the opportunity of the previous methods and represented a limit in the preparation of functionalized benzocyclotrimers. A narrow range of functional groups were tested and a great amount of Li and Cu salts was required to promote efficiently the reaction (5-6 eq. in respect of substrate). Thus, the research was prompted to the investigation of more active Cu promoters which might be used in reduced amount and which could maintain acceptable, or higher *syn/anti* ratios.

In this contest, the synthesis of benzocyclotrimers from *vic*-bromo(trimethylstannyl)bicycloolefins had a sudden acceleration with the introduction of copper(I) 2-thiophenecarboxylate (CuTC), which presented some advantages in respect of other Cu salts: it was inexpensive, air-stable and non-hygroscopic. More interestingly, the use of CuTC made possible the preparation of a broad range of functionalized benzocyclotrimers under very mild conditions, affording good results which could not be obtained with previous methodologies (Scheme 1.23, Table 1.2).[49]



Scheme 1.23 Cyclotrimerization of bromo(trimethylstannyl)alkenes using CuTC.

Table 1.2 Substrates and products of CuTC-promoted cyclotrimerizations.

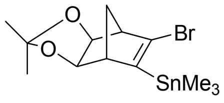
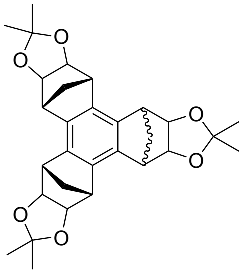
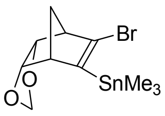
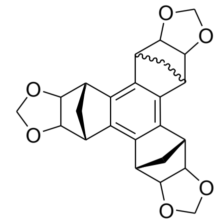
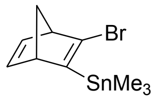
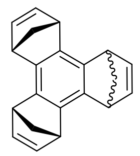
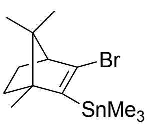
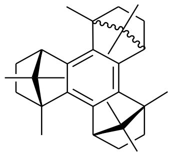
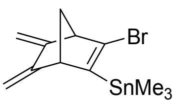
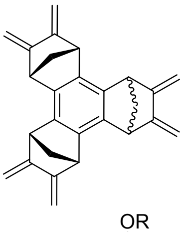
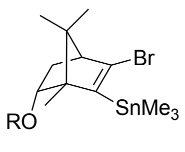
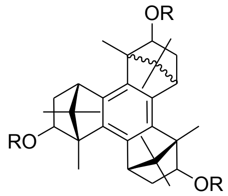
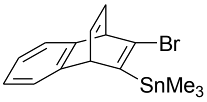
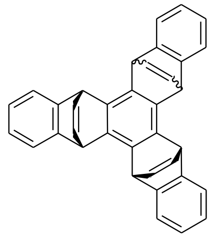
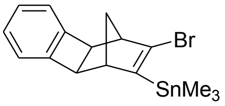
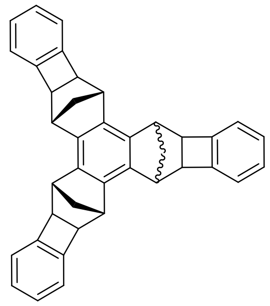
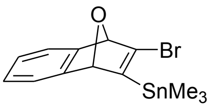
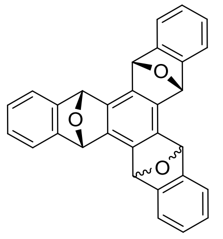
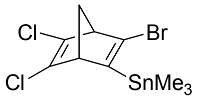
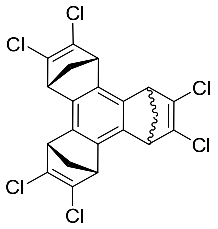
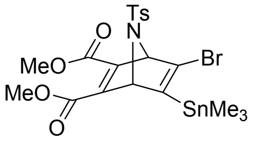
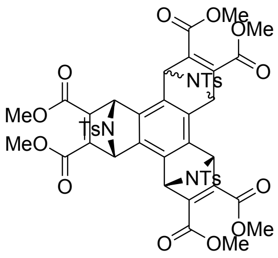
	substrate		product	Overall yield, % (*syn/anti* ratio)
XLII		**LI**		98 (1:4)
XLIII		**LII**		70 (1:8)
XXXI		**XXVI**		94 (1:3)
XXXVII		**XXXVIII**		98 (1:6)
XLIV		**LIII**		98 (1:4)
XLV		**LIV**		R: Me 82% (10:0) R: MOM 86% (5.5:1) R: MEM 93% (5:1)

Table 1.2 Substrates and products of CuTC-promoted cyclotrimerizations.

substrate		product		Overall yield, % (*syn/anti* ratio)
XLVI		**LV**		33 (1:2.3)
XLVII		**LVI**		70 (1:9)
XLVIII		**LVII**		85 (1:0.8)
XLIX		**LVIII**		90 (1:2)
L		**LIX**		82 (1:1.2)

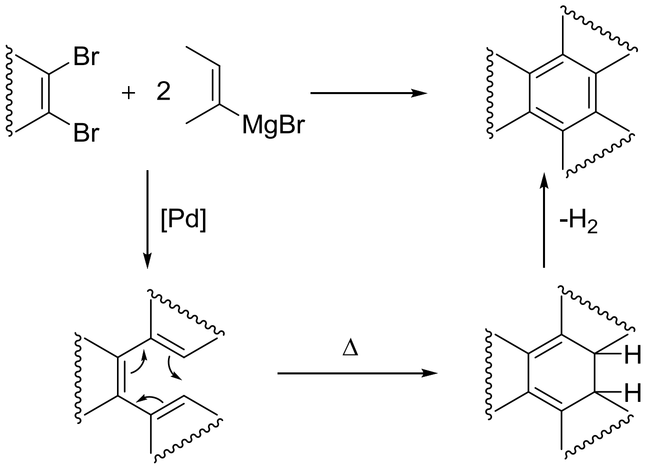
The use of CuTC in cyclotrimerization reactions efficiently led to the synthesis of several functionalized benzocyclotrimers by reducing the problems of the proto-de-stannilation of substrates or the large formation of dimers, which plagued the previous methods. As shown in Table 1.2, *syn/anti* ratios were variable: in some case unfavorable values were found, while for other instances excellent ratios were obtained. In case of borneol derivatives **XLV**, the high stereoselectivity obtained was supposed to result from a sort of template effect induced by *endo O*-substituents, which helpfully promoted the *syn*-cyclotrimerization of the substrate.[50] However, heterogeneous data concerning *syn/anti* ratios suggested a combination of more pathways acting in copper-promoted cyclotrimerizations (Scheme 1.19). Moreover, the complications derived from the use of racemic substrates could play also a negative role.

1.3.3 PALLADIUM CATALYZED CYCLOTRIMERIZATIONS

In parallel to the development of copper-promoted cyclotrimerizations, the possibility of synthesizing benzocyclotrimers by palladium catalyzed coupling reactions was also investigated.

Grignard reagents

The first reported palladium catalyzed cyclotrimerization afforded symmetrical and unsymmetrical benzocyclotrimers by reacting dibromoalkenes with 2 equivalents of vinyl Grignard reagents in the presence of $PdCl_2(PPh_3)_2$ (Scheme 1.24).

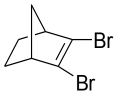
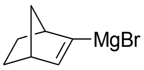
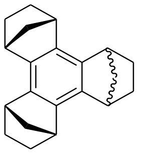
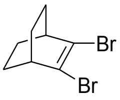
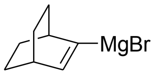
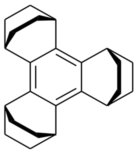
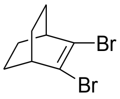
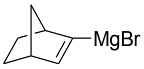
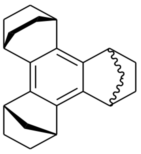
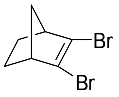
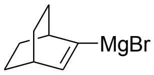
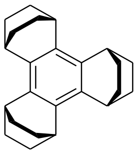
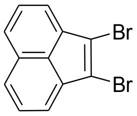
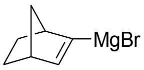
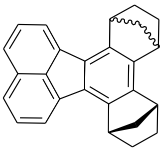
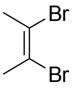
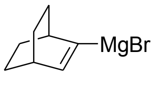
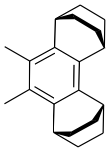
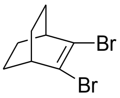
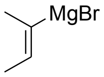
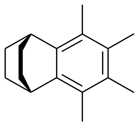


Scheme 1.24 Cyclotrimerization of Grignard reagents with vinyl dibromides.

The reaction was supposed to proceed through the palladium catalyzed coupling of the Grignard reagent on the dibromoalkene to a linear hexatriene intermediate. Then the cyclization step to dihydrobenzene occurred by a sigmatropic rearrangement and the final aromatization was achieved by loss of H_2.

Despite the limited scope due to the nature of the substrates, the reaction afforded trimers in good yields (Table 1.3).[51]

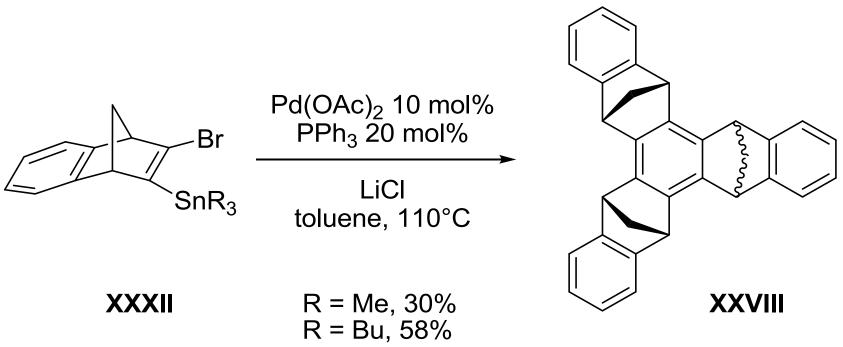
Table 1.3 Vinyl dibromides and Grignard reagents tested in Pd-catalyzed cyclotrimerization.

	dibromoalkene	Vinyl Grignard		product	Overall yield (%) (Syn/anti ratio)
LX			**VII**		94 (1:3)
XIX			**XXI**		97
XIX			**LXIII**		93 (1:1)
LX			**LXIV**		92
LXI			**LXV**		84 (1:1)
LXII			**LXVI**		76
XIX			**LXVII**		84

Stille coupling

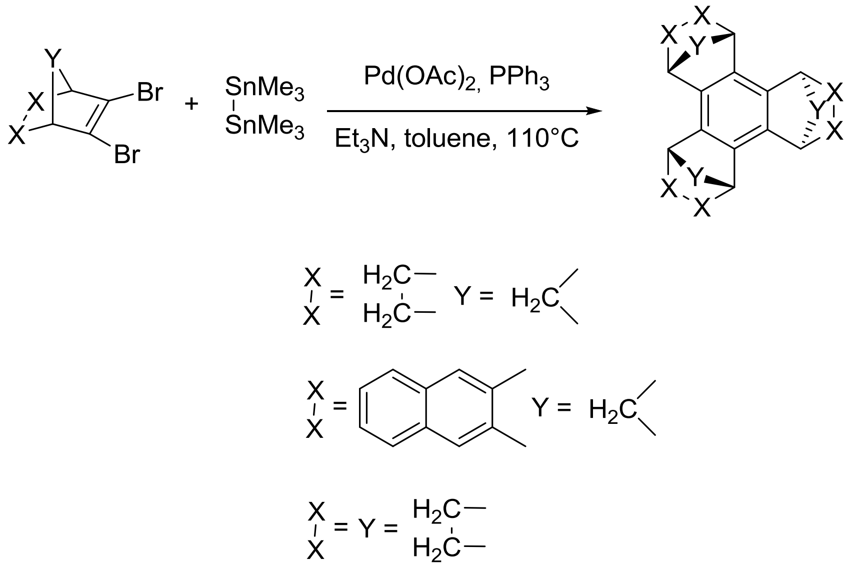
The *vic*-bromo-stannyl olefins used in copper promoted cyclotrimerizations were also tested as substrates in palladium catalyzed cyclotrimerizations (Stille coupling) because it was expected a high selectivity to *syn*-isomers by chain type mechanisms (see Scheme 1.19, mechanism A).

Early attempts to trimerize bicyclic-olefins by Stille coupling afforded relatively low yields of trimes with low selectivity. Cyclotrimerization of **XXXII** produced a 3:1 *syn/anti* mixture of expected trimer **XXVIII** in 30% yield, while the tributyl-stannyl analogue furnished only the *anti* isomer in 58% yield.



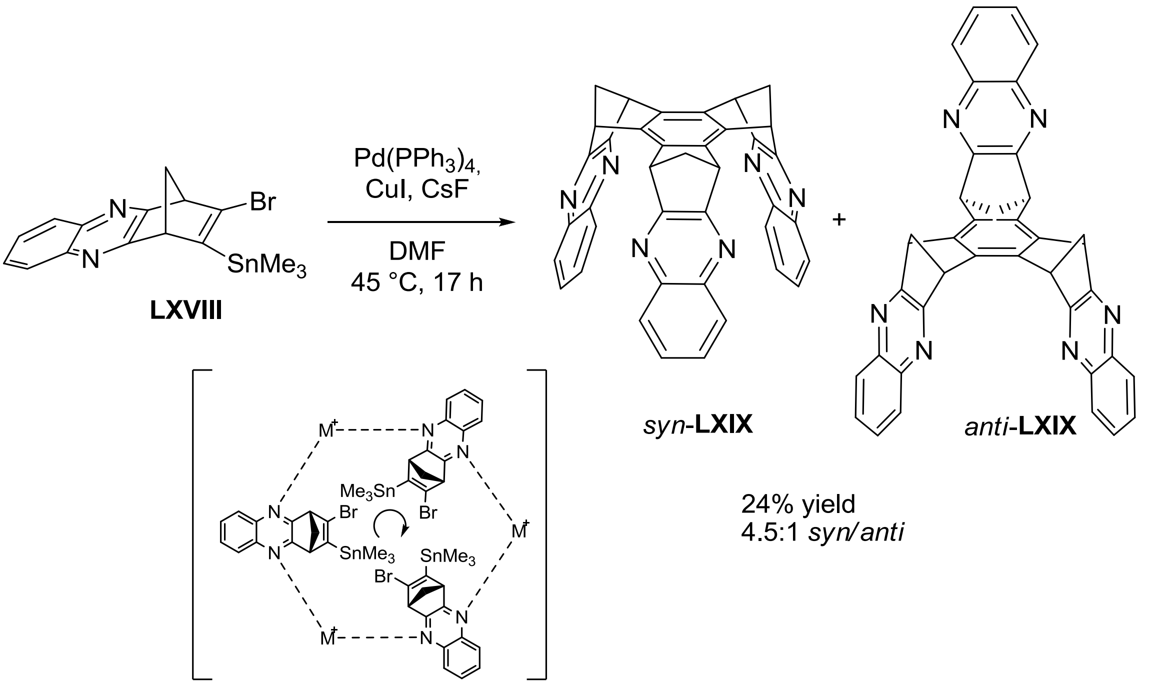
Scheme 1.25 Stille-type coupling of bromo(trimethylstannyl)alkenes.

In the case of dibromo-olefins the Grigg methodology was applied,[52] in which the tin derivative was produced *in situ* by the addition of hexamethylditin, but the reaction afforded only *anti*-trimers in almost quantitative yield.[53]



Scheme 1.26 Cyclotrimerization of dibromoolefins under Griggs conditions.

The unfavorable *anti*-diastereoselectivity found in Stille-type cyclotrimerization reactions, was reversed by an original procedure described by Badjić for the trimerization of **LXVIII.** The author reported that the reaction did not occur by using Pd or Cu catalysts alone, but the combination of the two metals was essential to promote the cyclotrimerization. Moreover, the diastereoselectivity in favor of the *syn*-isomer increased in presence of an excess of CsF, whereas Li salts or different fluoride counterbalancing cations had negative effects. This was justified by taking into account a possible template effect of Cs cations, which coordinated the substrate during the cyclization process and directed the cyclotrimerization to the *syn*-isomer.[54]

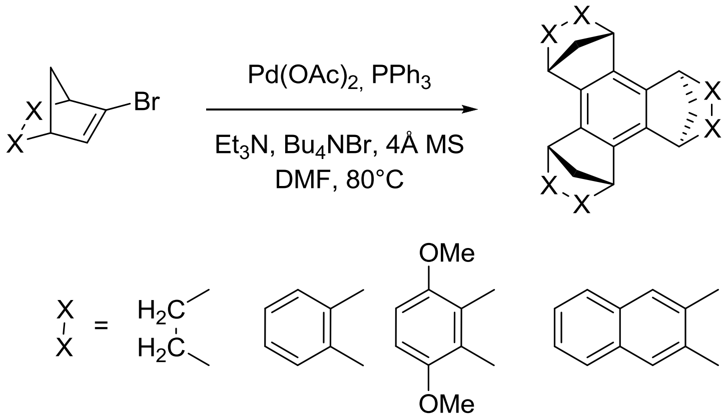


Scheme 1.27 Stille-like cesium-assisted cyclotrimerization of a pyrazine-substituted bicycloolefin.

Heck type cyclotrimerizations

The research on palladium catalyzed cyclotrimerization reactions could not exclude Heck type self-couplings of bicyclic olefins which contain an halide and a proton both in vinyl position.

First palladium catalyzed cyclotrimerizations of bicyclic bromoalkenes, performed on norbornene derivatives, led to cyclotrimers in high yield but with a fully *anti*-selectivity.[55]



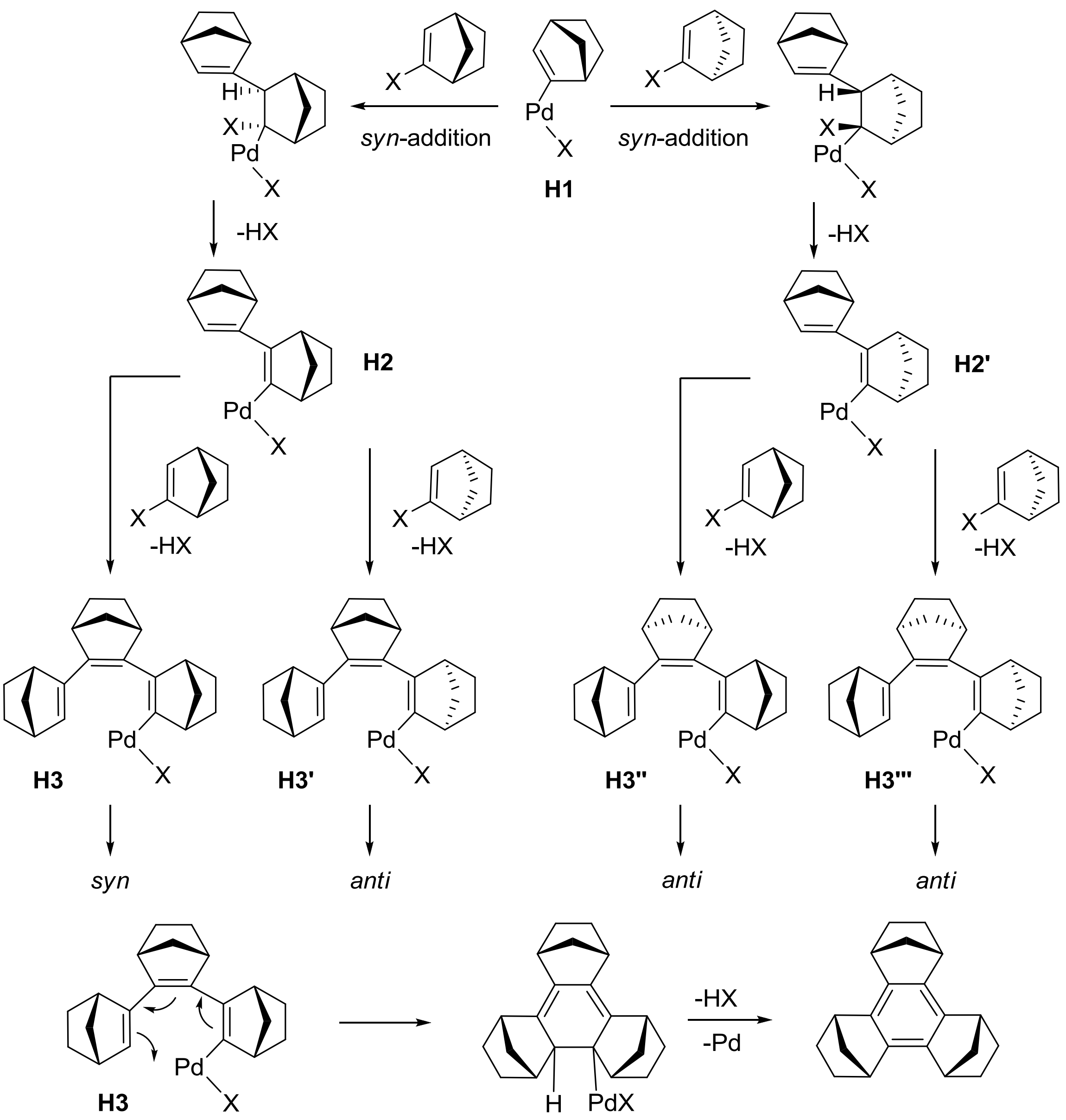
Scheme 1.27 Heck type cyclotrimerization of bicyclic bromoalkenes.

As shown in Scheme 1.28, the formation of the benzocyclotrimer is essentially an oligomerization process proceeding through a series of Heck type self-couplings to a linear trimer, which then rearranges by a 6-π-electrocyclization reaction to afford the final aromatic product.

The full *anti*-selectivity is more difficult to explain. A simplified tentative mechanism, which takes into account all the possible species generated from a racemic mixture of the substrate, is described below. The first oxidative addition of the haloalkene on Pd provides **H1**. Then, a second molecule of substrate inserts into Pd-vinyl bond to afford new Pd-vinyl complexes **H2** and **H2'**. A third haloalkene inserts again to generate vinyl trimers **H3**'s. The ring closure to the aromatic product is finally obtained by a 6-π-electrocyclization reaction followed by elimination of HX and restoration of the Pd catalyst. In Scheme **1.28** is summarized the situation created by the use of a racemic mixture of the substrate.

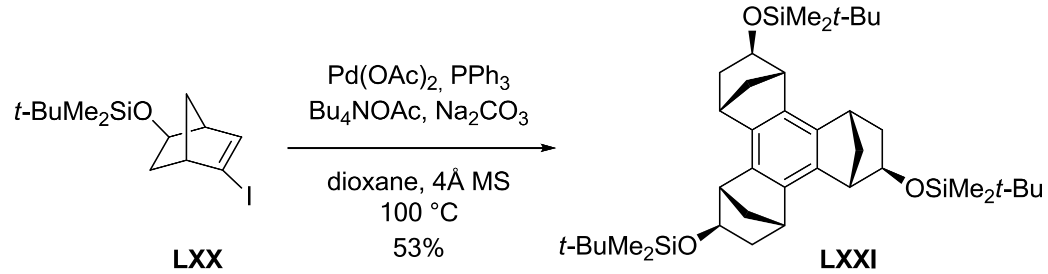
Since both enantiomers can react through insertion steps, then four possible trimers **H3**, **H3'**, **H3''**, **H3'''** are possible and one could expect a 1:3 mixture of *syn/anti* trimers.

Considering that fully *anti*-selectivity was observed, the four possible pathways clearly exhibit different kinetic profiles, making the routes to the *anti* product favored with respect to the *syn* isomer. This is likely related to the diastereomeric relationship between the different intermediates **H2'**s and **H3'**s, which exhibit different energies of formation and therefore also kinetic profiles.[55] Interestingly, the reaction carried out on enantiopure bromonorbornadienes or iodobornenes under the same conditions,[56] led only to modest yields of product, which was found as mixture of *syn* and *anti* isomers.



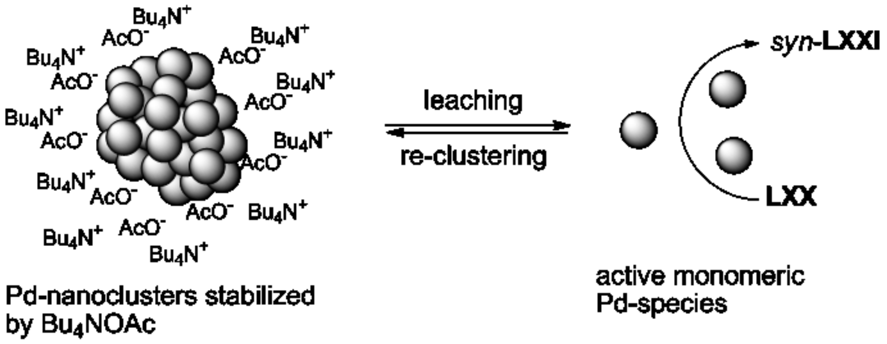
Scheme 1.28 Symplified mechanism of Heck type cyclotrimerization. The cyclization step is referred to the *syn*-isomer.[55]

The last innovation about cyclotrimerizations of bicyclic olefins was reported in 2007 by H. Sakurai, which described a new method for *syn*-selective cyclotrimerization of enantiopure iodonorbornenes. The screening of reaction conditions showed that the choice of solvent and base were crucial to improve the yield of the reaction and the use of a large amount of Bu_4NOAc (10 eq.) was necessary as well.[57]



Scheme. 1.29 Improved conditions for Heck type cyclotrimerization.

As suggested by the authors, the catalytic activity is related to the formation of palladium nanoclusters in equilibrium with monomeric metallic species in which the reaction takes place. For Mizoroki-Heck reaction, it is known that the active catalytic species are constituted by atomic palladium atoms leaching from nanoclusters.[58]



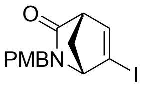
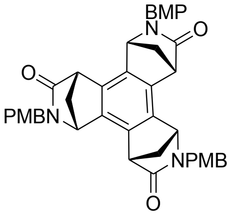
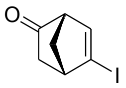
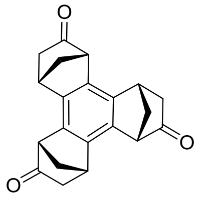
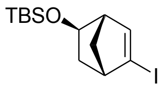
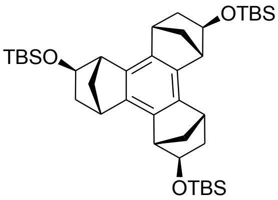
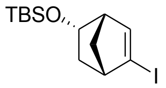
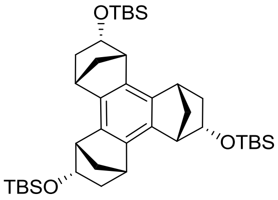
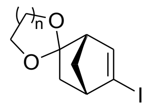
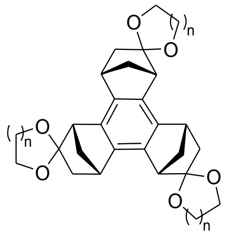
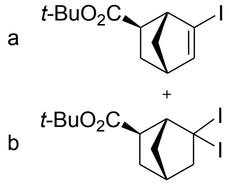
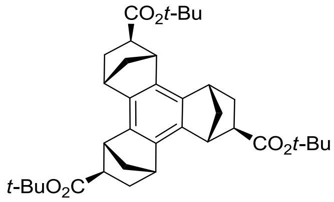
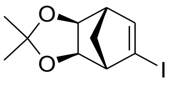
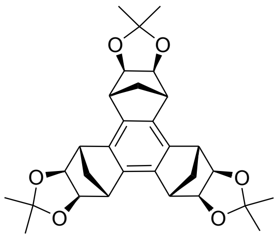
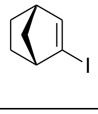
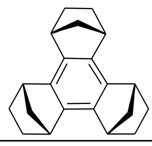
Scheme 1.30 Possible equilibrium between Pd-nanoclusters and active catalytic species.

As demonstrated by TEM imagines of the reaction mixture, the concentration of Bu_4NOAc had a strong influence on the size of palladium nanoparticles and on the yield of the reaction. For example, at high concentration of Bu_4NOAc the size of nanoparticles decreases and the yield increases, meaning that the presence of the tetrabutylammonium salt has an active role in stabilizing nanosized palladium by avoiding its coalescence.

The proposed mechanism is the same indicated in Scheme 1.28 (route through **H2** and **H3**), in which only one enantiomer is involved, and therefore only the *syn*-isomer is expected. Since there are two insertion steps at sterically hindered positions, the present reaction might be controlled by the monomeric Pd species continuously leaching from stabilized Pd nanoclusters.[59]

The general methodology was applied to several functionalized iodobornenes and the results are summarized in Table 1.4

Table 1.4 Heck type cyclotrimerization of enantiopure iodobornenes.

	substrate		product	Overall yield (%) (Syn/anti ratio)
LXXII	 (PNB = *p*-methoxybenzyl)	**LXXIX**		57 (100:0)
LXXIII		**LXXX**		49 (95:5)
LXX	 (TBS = *t*-BuMe$_2$Si)	**LXXI**		53 (90:10)
LXXIV		**LXXXI**		0
LXXV		**LXXXII**		0
LXXVI		**LXXXIII**		32 (89:11)
LXXVII		**LXXXIV**		60 (78:22)
LXXVIII		**VII**		26 (77:23)

The reaction found applicability for different substrates, including geminal diiodide **LXXVIb**, except for those compounds with substituents at the *endo* position of the norbornene skeleton (**LXXIV** and **LXXV**, Table 1.4). These substrates did not afford the expected trimers, therefore suggesting that *endo*-sobstituents might block either insertions or the cyclization step in the reaction pathway.[60]

1.4 SUMMARY

The cyclotrimerization of bicyclic olefins had a considerable evolution since the synthesis of heptycene, which was obtained the first time in “unspecified” yield in 1970. The cyclotrimerization of highly strained alkyne intermediates, obtained from vinyl halides, constituted the first approach towards the synthesis of benzocyclotrimers, but this method led to low or modest yields together with a limited possibility of functionalizations.

The development of copper promoters, since 1996, increased the possibility to prepare functionalized benzocyclotrimers using a wide range of substrates and led to a general increase of overall yields and diastereoselectiviy.

Finally, Pd-catalyzed cyclotrimerizations are a useful tool to prepare symmetric and unsymmetric cyclotrimers from Grignard reagents, and *vic*-bromo-stannyl olefins. However, Heck type cyclotrimerization of enantiopure iodonorbornenes, reported in 2007, represents so far the most convenient method for the synthesis of benzocyclotrimers in good yields and high selectivity with regard to *syn*-isomers.

1.5. REFERENCES

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CHAPTER 2

PROPERTIES AND APPLICATIONS OF BENZOCYCLOTRIMERS

This Chapter will describe the most important features and applications so far reported for benzocyclotrimers derived from cyclic olefins. As it will be discussed in details, the annelation by small cyclic units on aromatic rings has a strong effect on aromaticity of the system, while the cavities offered by these molecules have inspired their use as molecular receptors in supramolecular chemistry.

2.1 FULLY ANNELATED BENZENES: AROMATIC OR NOT AROMATIC?

This first section deals with the main chemical-physical properties of benzocyclotrimers. These molecules should be regarded as tris-annelated benzenes rather than benzocyclotrimers, to focus the point of view about the influence of annelation by small rings on the aromatic character of the central benzene unit. In order to understand these effects, several experiments and theoretical calculations are present in literature, including also electrochemical measurements, X-ray analysis and computational studies.

2.1.1 MILLS-NIXON EFFECT

One of the milestone in the history of organic chemistry is the concept of aromaticity. In general it is accepted to consider the π-electronic cloud delocalized on the benzene skeleton, averaging single and double bonds of the aromatic ring.

This can be explained by the resonance of two limit forms or through a molecular orbital diagram, which usually accounts for a better explanation of chemical bond and consequently provides also a good model for the chemical bonds in benzene.

Despite these models, the synthesis of starphenylene, reported in 1986,[1] provided a remarkable exception with regard to the normal structural equilibrium found in aromatic rings.

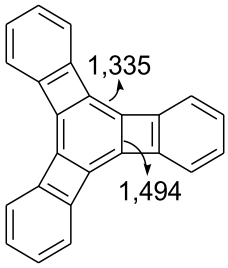


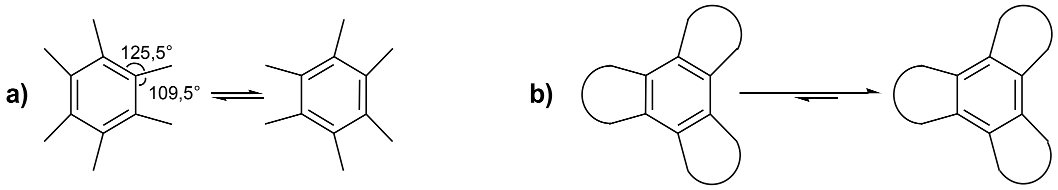
Fig. 2.1 Bond distances in Å of starphenylene.

The X-ray structure showed a pronounced difference of bond length between the exocyclic and endocyclic bonds of the central aromatic ring, with regard to the cyclobutane units, whereas the outer rings were almost completely delocalized, therefore suggesting an alternation of single and double bonds. The reason for bond localization in the central ring was ascribed to an aromaticity-antiaromaticity interplay, because the delocalization of π-electrons in the central ring would cause cyclobutadienic character in the four-membered rings, which are strongly antiaromatic. Thus, the formation of three cyclobutadienes is energetically unfavorable as compared to the loss of aromaticity in the central ring.

In the following years the issue interested several chemists which argued about the effects of the strain imposed by cyclic annelations on aromaticity and structural properties of aromatic compounds.

The effect of annelation on benzene was firstly questioned by Mills and Nixon in 1930. At that time, one of the most accepted models for the structure of benzene was the Kekulè idea of a fast interconversion between two equivalent isomers with alternating double and single bonds (oscillation theory). Moreover, as suggested by van't Hoff, the structure of benzene could present two angles for each substituent, which are constantly flipping in the course of the equilibrium between the two tautomers.

Mills and Nixon, strongly convinced about the Kekulè model, proposed that if the structure of benzene was modified by forcing a change of the bond angles of two adjacent positions, then the permanence of the single bond should be favored between those carbon atoms, therefore freezing out one Kekulè structure.[2] The forced modification of bond angles could be achieved for example by strain imposed through the annelation with a small ring.



Scheme 2.1 a) Kekulè/van't Hoff model of oscillating structure of benzene. b) Mills and Nixon idea of bond fixation by annelation with small rings.

Despite the inadequate model used by Mills and Nixon for their proposal, the structural modification of annelated aromatic rings with cyclic units has been generally defined as "Mills-Nixon effect". This was questioned for a long time founding supporters and opponents, especially in the community of theoretical chemists.

One of the first opposition about the Mills Nixon effect was proposed by L. Pauling by introducing the concept of resonance,[3] in which the structure of aromatic rings were described as resonance hybrids and benzene was depicted as a single symmetrical form. In this contest, it was proposed also that the degree of stabilization of the overall structure due to resonance would cause only a slightly geometrical perturbation by any annelating ring.

The question remained unsolved for a long time, especially due to the lack of experimental results which could corroborate any theoretical analysis, but the synthesis and characterization of starphenylene, after almost 60 years, reopened the discussion about structural aspects of the Mills-Nixon proposal. In addition the use of sophisticated computational methods in combination with high accuracy X-ray crystallography of benzocyclotrimers, synthesized over the 90's, allowed the reformulation of the Mills-Nixon effect in modern terms.

In particular, the issue has turned into the understanding if (and how) an aromatic ring can be distorted through structural changes caused by annelation, and whether a situation of bond fixation can be possibly achieved inside a benzenoid ring. Different points of view are found in recent literature.

The first is represented by J. Siegel and Vollhardt, which reported the synthesis of several benzocyclotrimers and studied the effect of annelation on the structure of the central aromatic rings, by combining computational studies and X-ray structures. They concluded that the strain produced by annelation with small rings is effective in modify the structure of aromatic rings imposing a greater π-character to *exo* bonds. However, bond length differences are only slightly pronounced to provoke loss of aromaticity of the system, even by annelation with cyclopropane or cyclobutane rings (structures **LXXXV**, **LXXXVI**, **XXIV**, Fig. 2.2).

On the other hand, when annelation concerns cyclic unsaturated rings such as cyclobutene or benzocyclobutane (structures **LXXXVII**, **LXXXVIII**, **LXXXIX**, Fig. 2.2), the effect is more clear, observing a pronounced bond localization which can be ruled out through antiaromatic effects.[4]

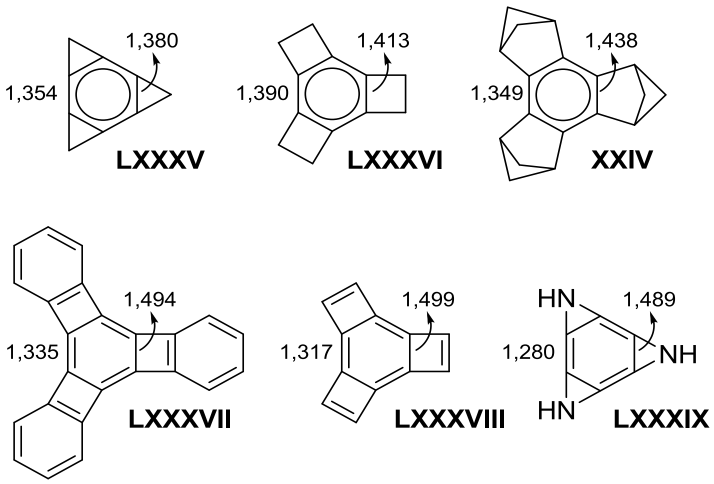


Fig. 2.2 Bond lengths in selected examples of tris-annelated benzenes. According to Siegel, benzenoic character remains for simple annelation with aliphatic rings, whereas unsaturated groups are able to localize double bonds in the exoxyclic positions. Structures **LXXXV**, **LXXXVIII**, **LXXXIX** have only been calculated.

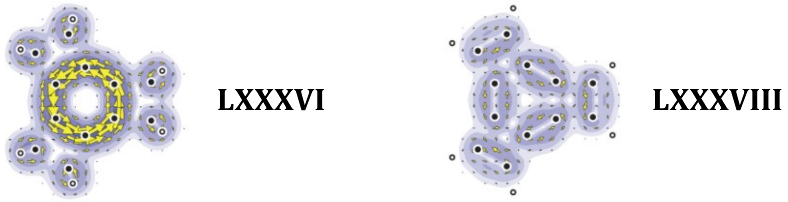
A second opinion about structural consequences of Mills-Nixon effect is found in few papers by A. Stanger, which presented other examples of calculated benzocyclotrimers and demonstrated that in all tris annelated benzenes exist a more or less pronounced bond alternation. Nevertheless, unlike Siegel proposal, the length differences between *endo* and *exo* bonds have a strong correlation uniquely with the degree of strain imposed by annelation, independently to any aromatic-antiaromatic interplay.[5]

Several years after the Siegel-Stanger arguments about a modern view of the Mills-Nixon effect, a new idea about the bonds in annelated benzenes was reported by Fowler and Jenneskens, presenting a different view of the problem by the analysis of ring current.

This last work attempted a connection between clamping strain, bond alternation and aromaticity on model compounds constituted of benzenes containing annelated cyclopropa-, cyclobuta-, and cyclobutadieno- rings, alone and in combination. The reported computational analysis was based on magnetic criteria by calculating the diatropic π-ring current map (the current generated by circuitation of aromatic π-electrons under the influence of an external magnetic field) for several test molecules.

In molecules composed of a central benzene ring annelated with fully saturated bridges like **LXXXVI**, the map shows a single, central, diatropic π-ring current which is substantially uniform and follows the circuit of bonds. Therefore, despite some small modulations in shape, symmetry, and intensity of the current, all compounds in this class exhibit a typical benzene aromatic ring current.

In contrast, for structures containing at least one unsaturated cyclobutadieno bridge, the central current is weakened and the π-map for these molecules is dominated by a strong paratropic current within the unsaturated four-membered rings. In the tris(cyclobutadieno)benzene **LXXXVIII**, the circuitation of the central benzene is completely disrupted, producing a classical example of a fully localized pattern that is indicative of a set of three isolated double bonds.[6]



LXXXVI

LXXXVIII

Fig. 2.3 Maps of π-current density in **LXXXVI** (aromatic) and **LXXXVIII** (not aromatic).

The orbitalic view of π-current gives an account to interpret the phenomena. In aromatic rings the ring current arises from translationally allowed HOMO-LUMO transitions. Clamping of the benzene with saturated groups produces a bond alternation and a reduction of molecular symmetry, but the orbitalic diagram remains essentially unchanged, as the extra (usually σ) orbitals from the clamping groups lie outside the active π-space and therefore HOMO-LUMO transitions are only slightly perturbed. Thus the diatropic ring current survives with almost the same strength as free benzene.

On the other hand, when unsaturated groups are attached, the conjugation with the π-system of central aromatic unit generates a new set of π-orbitals into the frontier region. This new orbitalic situation generates π→π* allowed transitions which are responsible for the paratropic ring current found in the map and which can be related to localized double bonds, while the HOMO-LUMO levels which generate the diatropic ring current in benzene, are considerably pushed apart.[6,7]

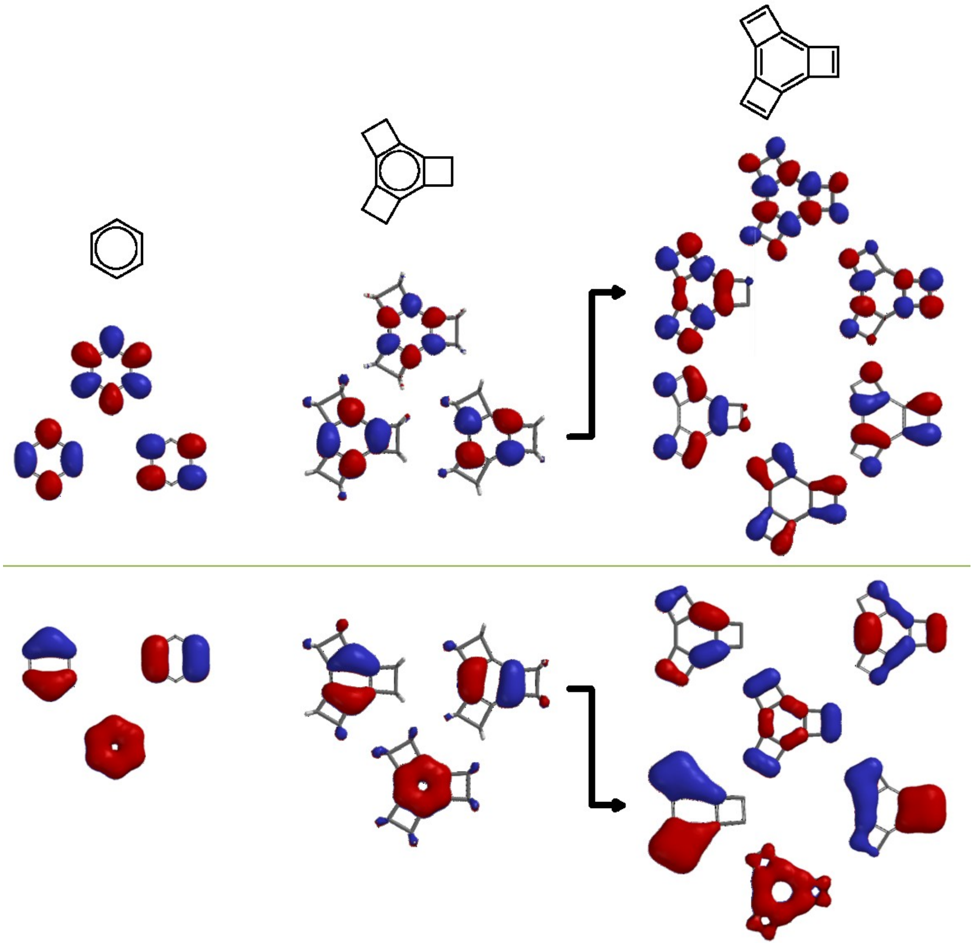


Fig. 2.4 Molecular orbital diagrams of benzene (left), **LXXXVI** (centre) and **LXXXVIII** (right).

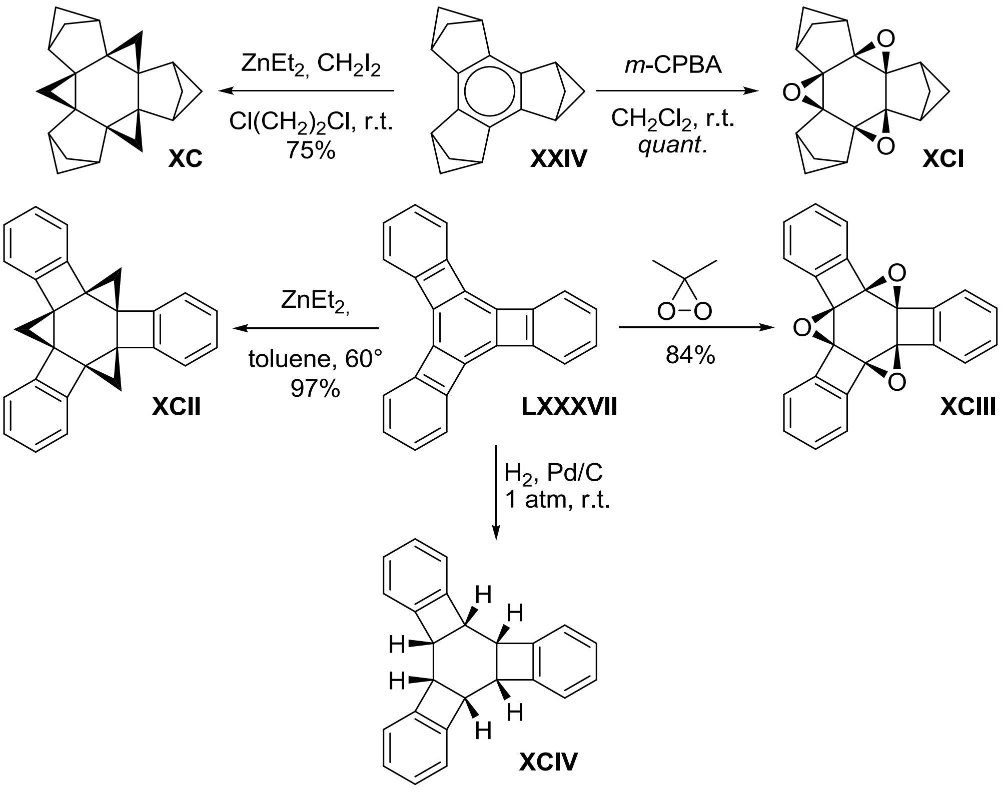
The latter model about the ring current in tris-annelated benzenes probably close the debut about the long issued Mills-Nixon effect. As the molecular orbital theory provides the best basis to any discussion about chemical bond, it is now possible to give an explanation for bond alternation found in benzocyclotrimers. The length difference between exocyclic and endocyclic bonds of the central benzenic unit is often found and it is related to the re-equilibration of the structure under the strain imposed by annelation with small rings. Nevertheless, the aromaticity of the system is substantially retained when annelation is with aliphatic rings as the orbitalic diagram levels remain close to that of free benzene.

In few cases aromaticity is lost. Unsaturated clamping rings produce a new manifold of orbitals which, at practical effects, produce three isolated double bonds, usually fixed in the exocyclic positions to annelating rings and thereby originating the elusive behavior of cyclohexatriene.

2.1.2 REACTIVITY OF FULLY ANNELATED BENZENES

The Mills-Nixon effect was issued for a long time pursuing the discussion usually in structural terms, but the distortion of benzene, imposed by strain effects through the annelation with small rings, has also a strong influence on its chemical reactivity.

Hydrogenation experiments, as well as cyclopropanations and epoxidations were performed for benzocyclotrimers **XXIV**[8] and **LXXXVII**[9] by Komatzu and Vollhardt respectively, founding a relative high reactivity of these compounds in respect of what one could expect from a “normal” benzene.



Scheme 2.2 Reactivity of the aromatic ring in **XXIV** and **LXXXVII.**

Epoxidation as well as cyclopropanation of **XXIV** and **LXXXVII** provided the corresponding products in good yields and noticeably these reactions were carried under conditions in which aromatic compounds are usually inert. As expected, hydrogenation of **LXXXVII** led easily to the reduction of the central benzene whereas the terminal aromatic rings survived to these mild conditions**.**

The enhanced reactivity found for **XXIV** and **LXXXVII** is a further proof of bond localization and is directly correlated with the structural modification created by annelation. As compound **XXIV** should be aromatic for the previous considerations (see the above Paragraph) one could conclude that the relative stability of benzene is not a direct consequence of π-electron delocalization, but it is related to a structural equilibrium which makes benzenoid molecules less reactive than olefinic compounds.

In fact, when aromaticity is conserved but the structure is distorted as in **XXIV**, then the stability of the aromatic system is considerably decreased.

2.1.3 ELECTROCHEMICAL PROPERTIES

One of the first evidences that demonstrate the influence of annelation on the properties of aromatic rings, was based on electrochemical experiments. In particular, cyclic voltammetry (CV) represents a useful tool in the study of reversibility of chemical reactions involving redox processes, including those related to aromatic compounds.

Early studies in this sense were performed by Komatsu, who reported CV experiments of a fully annelated benzene with bicyclo[2.2.2]oct-2-ene units and found a well-defined reversible oxidation peak in MeCN at $E_{1/2}$ 1.25 V (E_{pc} 1.29 V) vs Ag/Ag^+. Analogous measurements carried on hexamethylbenzene (HMB) exhibited an irreversible oxidation peak (E_{pa} 1,38 V) which was ascribed to a proton loss in benzylic positions.

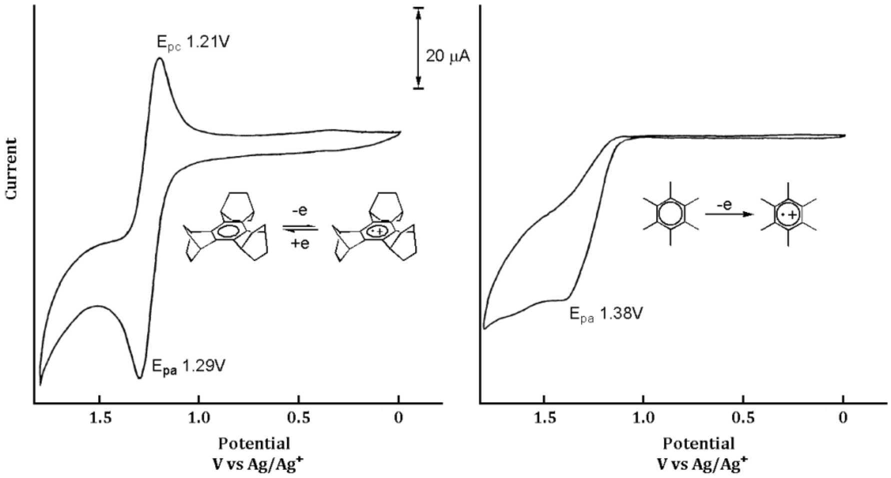
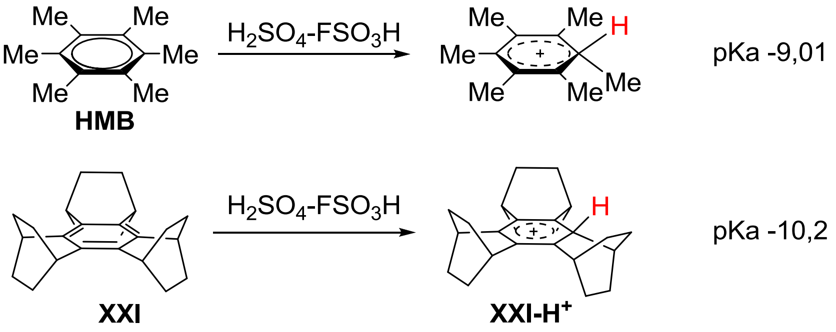


Fig. 2.5 Cyclic voltammograms of cyclotrimer **XXI** and hexamethylbenzene.

These results indicated that **XXI** is more stable than non annelated fully substituted benzenes because of the generation of cation-radicals that are not prone to lose benzylic protons as in the case of HMB. The reasons of this unusual stability are ascribed to a protection of the supposedly labile C-H bond at the benzylic carbon by the steric hindrance offered by the rigid σ-frameworks fixed in the plane of the π-system. Additionally, the positively charged π-system can be stabilized by the inductive electronic effects from the three annelating bicyclooctene units and by the possible σ-π conjugation between the π-system and the σ-bonds of the aliphatic frameworks. Thus the stabilization of central benzene ring derives from a combination of steric “protection” and hyper-conjugative effect induced by the annelating cyclic aliphatic units.[10]

On the other hand protonation experiments on **XXI** showed that the corresponding arenium ion **XXI-H$^+$** is less stable and less basic than corresponding HMB. Thus, the annelation of the benzene ring with three rigid bicyclo-[2.2.2]octene frameworks impose considerable molecular strain upon transformation to the arenium ion and this destabilization exceed the electronic stabilization gained by annelation with bicyclo[2.2.2]octene units..[11]



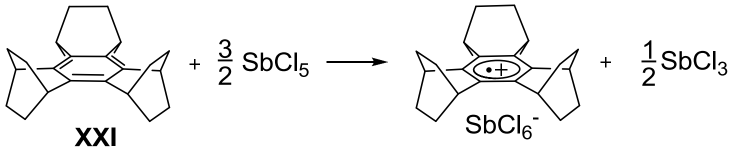
Scheme 2.3 Acidity constants for **HMB** and cyclotrimer **XXI**.

2.2 APPLICATIONS OF BENZOCYCLOTRIMERS

Tris-annelated benzenes found applcations in synthetic and supramolecular chemistry due to a combination between C_3 symmetry and concave shape. The stabilization effects created by byclic annelation led to the synthesis of new stable tropilium ions and cycloheptatrienes, while few members of this class of molecules inspired the design of new synthetic routes toward the preparation of fullerene fragments. Finally, *syn*-benzocyclotrimers represent C_3-symmetric scaffolds, in which is possible to induce recognition properties on their cavities through the introduction of opportune functionalizations.

2.2.1 PREPARATION OF STABILE ARENIUM IONS

To demonstrate the stabilization effects on arenium ions created by bicyclic-annelations, Komatsu reported the preparation of the radical cation of **XXI** (and other polycyclic aromatic compounds fully annelated with bicyclooctane units) by treatment with $SbCl_5$ at 0 °C and found that the corresponding salt was stable enough to be fully characterized.[12]

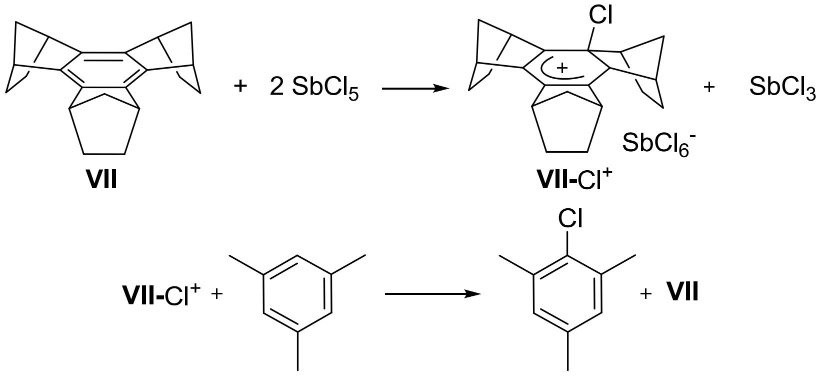


XXI

Scheme 2.4 Generation of the radical-cation of **XXI**.

In contrast, few years before Kochi studied a similar reaction between *syn*-benzotribornane **VII** and $SbCl_5$ at -78 °C, obtaining a relatively stable arenium ion which included the chlorine atom into the structure, therefore freezing out a sort of

Wheland intermediate. This stable cation was isolated, characterized by X-ray and used as chlorinating agent for other aromatic compounds.[13]

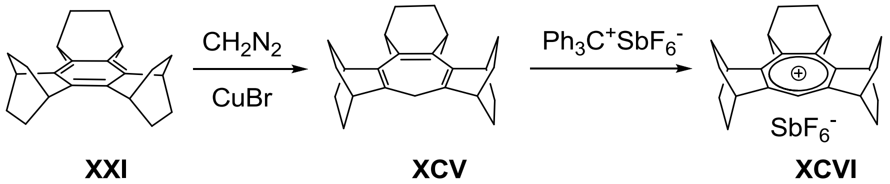


Scheme 2.5 Generation of chloro-arenium cation of **13** and chlorination of mesitylene.

The generation of **VII-**Cl^+ can be considered an electrophilic aromatic substitution "stopped" at level of the σ-complex. In addition, the same author demonstrated that **XXI** and **VII** were able to coordinate electrophiles, especially NO^+, providing isolable π-complex which were more stable than those obtained with other not-annelated fully substituted benzenes.[14]

Within this research, Komatsu investigated also the synthesis of a new tropilium ion from **XXI**, as further evidence that annelation has an effect in stabilizing carbocations.

The ring expansion of **XXI** was performed with CuBr as catalyst in presence of a large excess of diazomethane and the resulting cycloheptatriene **XCV** was treated with $Ph_3C^+SbF_6^-$ to give the salt **XCVI**$\cdot SbF_6$ in 91% yield.



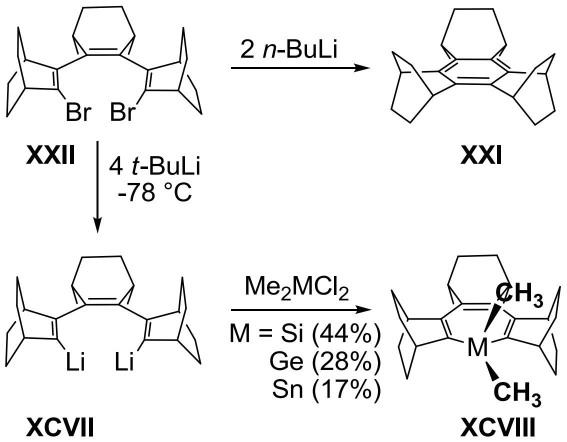
Scheme 2.6 Generation of a stabile tropilium ion.

The stability of this ion was demonstrated by the high value of pK_{R^+} = 13.0 (the highest value ever reported at the time) and the highly negative reduction potential (E_{pc} = -1.120 V, whereas for unsubstituted tropylium ion is -0.510 V).

Moreover, Komatsu found a linear correlation between pK_{R^+} and E_{pc} values for a series of substituted tropylium ions, concluding that annelation with bicyclo[2.2.2]octene units determined the maximum stabilization of the series. Thus the cyclic 6π/7C system in **XCVI** is strongly stabilized due to hyperconjugative effects in combination with a kinetic "protection" of benzylic protons (Paragraph 2.1.3).[15]

Within this research, the same author reported the synthesis of 1,1-dimethylsila-, -germa-, and –stannacycloheptatriene from dibromide **XXII** through a modified procedure for the synthesis of **XXI**.

Reaction of dibromide **XXII** with 2 equiv of *n*-BuLi in THF at room temperature resulted in cyclization to **XXI**. In contrast, in presence of an excess of *t*-BuLi, the dilithiated compound **XCVII** was generated. This was then reacted with dichlorodimethyl-silane, -germane, and -stannane to give the metallaepins of general formula **XCVIII**

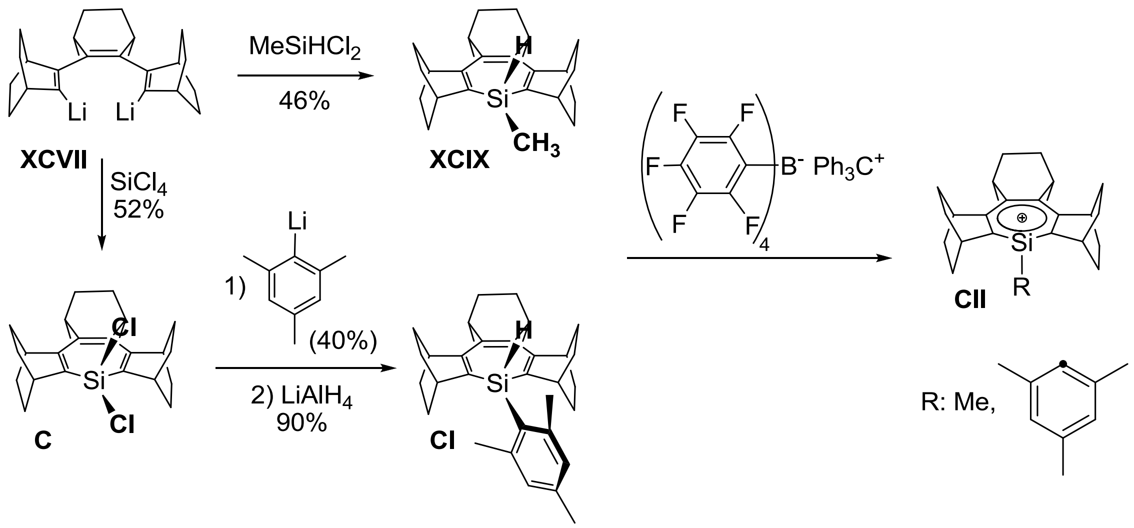


Scheme 2.7 Synthesis of cyclotrimer **XXI** and metallepins **XCVIII** from dibromide **XXII**.

From X-Ray characterization of metallaepins **XCVIII**, the most notable difference in their structures is the M-C (ring) bond length. As the atomic radii increases from Si to Sn, the M-C bond was elongated while the lengths of the rest of the triene-part of the seven-membered ring remained essentially the same.

Although the structures of **XCVIII** were found to be similar in the solid state, their behavior in solution was quite different with each other. Since the heterocyclic ring is not planar, a boat to boat interconversion takes place through a planar transition state. The activation energy for such ring inversion was demonstrated to increase from Si to Sn, thus Si-metallaepin inverts rapidly whereas Sn metallaepin is fixed, based on NMR time-scale. This was primarily attributed to the increase in strain in the planar structure at the transition state. Thus the carbon-metal bond length and the relative stability of the planar transition-state structure for the ring inversion were correlated.[16]

Similarly, Komatsu reported also the synthesis of silatropylium ions to study possible stabilization effects by bicyclic annelation as in the case of tropylium ion. The synthesis begins from dilithiated specie **XCVII** which was treated with $MeSiHCl_2$ to obtain silepine **XCIX**. Alternatively, **XCVII** was reacted with $SiCl_4$ to prepare the dichloro silaepin **C**, in which a Cl atom was replaced with mesyl-Li and the other one was removed by reduction with $LiAlH_4$. The silatropylium ions **CII** were finally obtained through hydride abstraction with $Ph_3CTPFPB$. These new silatropyliums were found stable only in dichloromethane under inert atmosphere and below -50 °C. From NMR characterization the ionic character (Si NMR) and the aromatic behaviour of the molecules has been demonstrated, as well as the Lewis acid character. The ionic character was therefore lost by coordination with MeCN and the molecules were slowly decomposed when coordinated with perchlorate anion.[17]

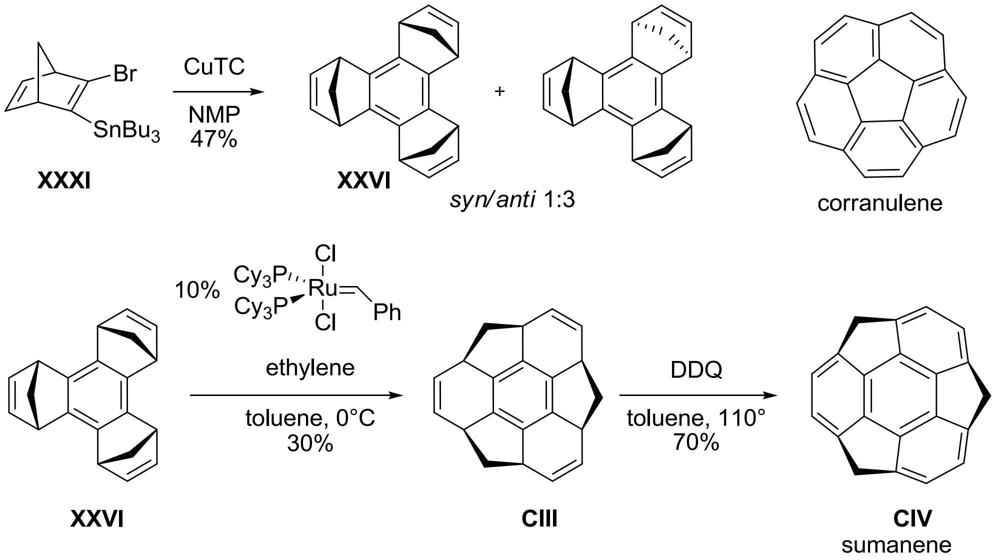


Scheme 2.8 Synthesis of silatropilium ions stabilized by bicyclo-octane frameworks.

2.2.2 SYNTHESIS OF FULLERENE FRAGMENTS

Syn-benzotrinorbornadiene represented the first functionalized benzocyclotrimer derived from bicyclic olefins.[18] This molecule was investigated as a possible precursor of sumanene, which has been synthesized and reported in 2003 by Sakurai and Hirao. Sumanene is the smallest fullerene unit which maintains the fullerene curvature.

A previously known compound related to sumanene is corranulene, whose preparation require harsh conditions (flash vacuum pirolysis) and the functionalization results troublesome, whereas sumanene presents benzylic positions in which further transformations are predictable. In addition, the synthesis of sumanene is based on a multi step procedure featuring bowl-shaped intermediates and mild reaction conditions.

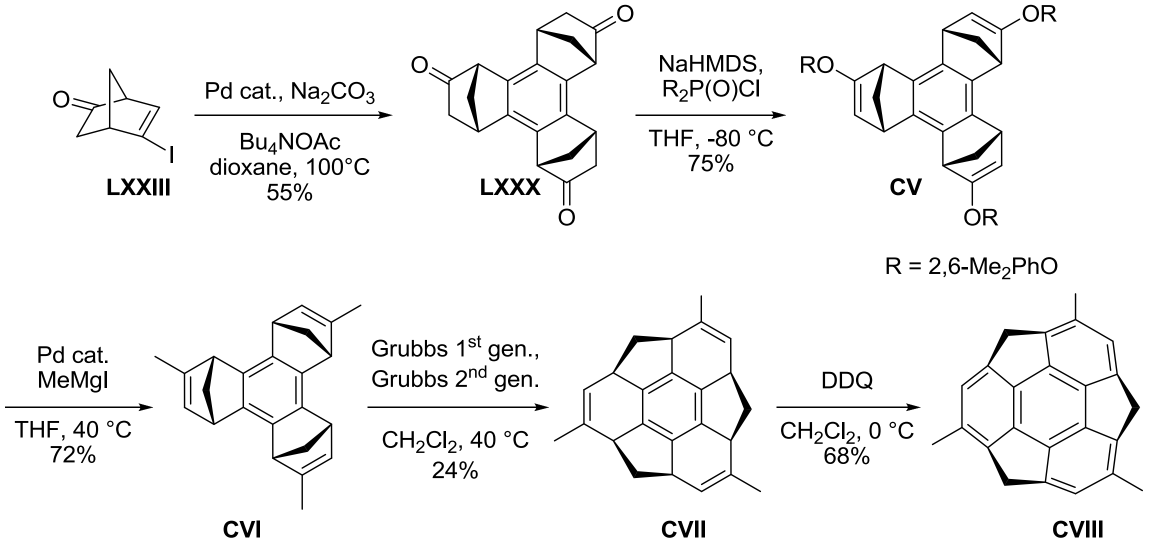


Scheme 2.9 Synthesis of sumanene.

Norbornadiene derivative **XXXI** provided *syn* and *anti*-benzotrinorbornadienes **XXVI** by copper promoted cyclotrimerization (see Chapter 1) and the alkene-bridge exchange was successfully achieved on *syn*-**XXVI** by the Ru-catalyzed tandem ring-opening (ROM) and ring-closing metathesis (RCM) reactions. In contrast, tandem ROM-RCM reaction did not proceed from *anti*-**XXVI**. Finally, sumanene **CIV** was obtained from the oxidation of **CIII** by DDQ (dichlorodicyanoquinone).[19]

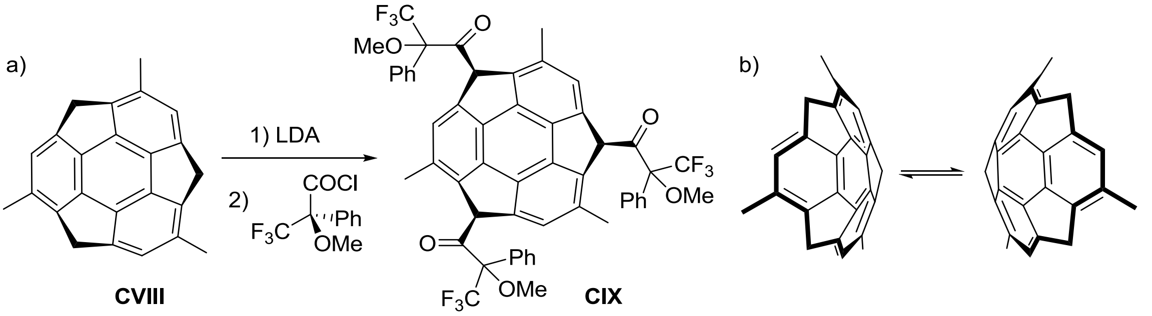
Since sumanene is not planar, a bowl chirality was expected by the introduction of substituents in the aromatic moieties. Sakurai reported the synthesis of trimethylsumanene **CVIII** in which the bowl chirality derived from the chirality at the level of sp^3 carbons of the precursor **LXXIII**.[20]

In this synthesis the trimerization step was carried out from vinyl iodide **LXXIII** through a syn-selective Heck type cyclization (see Chapter 1) and the carbonyl groups of the corresponding cyclotrimer **LXXX** were converted to methyl-substituted olefins. Finally, the metathesis step was carried from **CVI** with Grubbs' first and second generation catalysts and aromatization to **CVIII** was achieved with DDQ (Scheme 2.10).



Scheme 2.10 Synthesis of trimethyl sumanene.

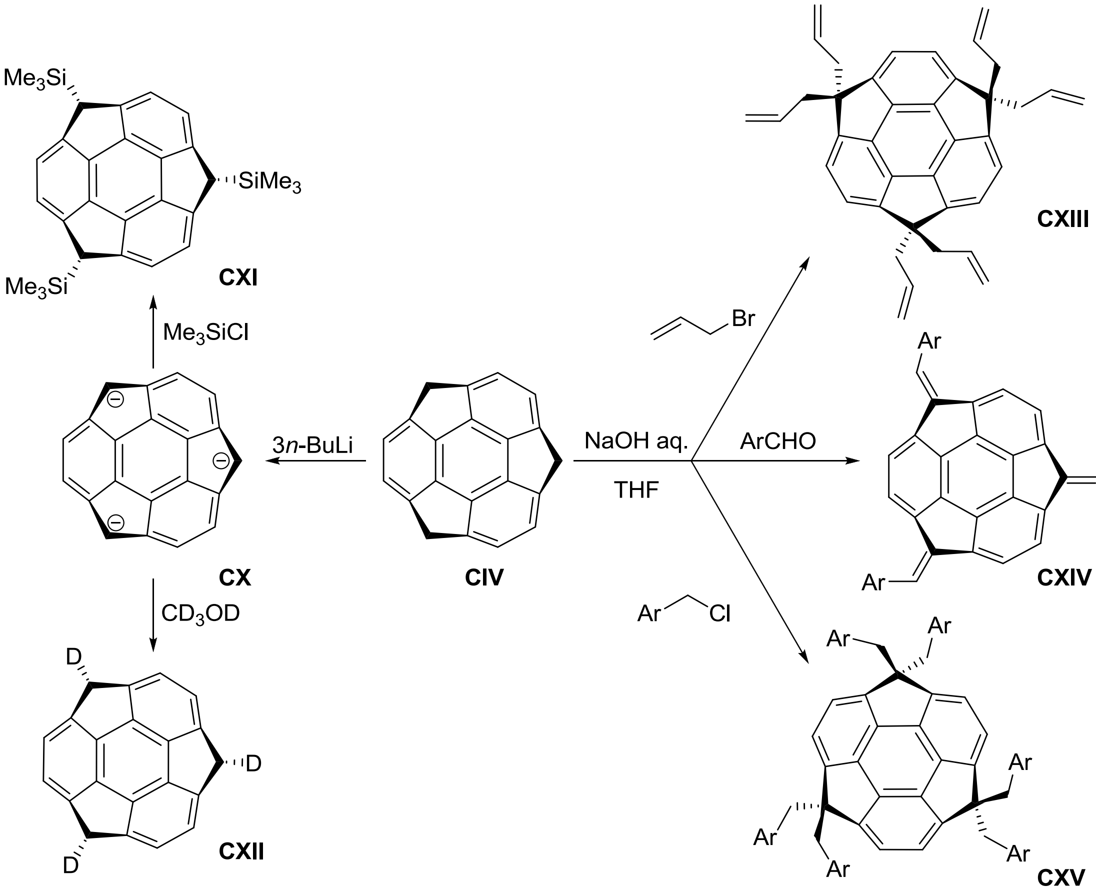
Unfortunately, the bowl inversion is possible at room temperature and this led to a slow racemization process. However the enantiomeric excess was evaluated as 90% on the basis of NMR measurements of a derivative of **CVIII** in which racemization was blocked.[20]



Scheme 2.11 a) Block of bowl racemization by functionalization on benzylic positions of sumanene. b) bowl chirality of sumanene.

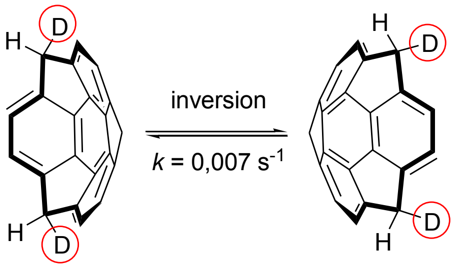
Functionalizations of sumanene

Functionalization of sumanene was possible at the benzylic positions by the deprotonation with strong bases followed by the addition of electrophiles, such as Me3SiCl, D+ (from CD3OD), allyl and benzyl halides. Aromatic aldehydes were also used in condensation reactions (Scheme 2.12).[21]



Scheme 2.12 Reactions at the benzylic positions of sumanene.

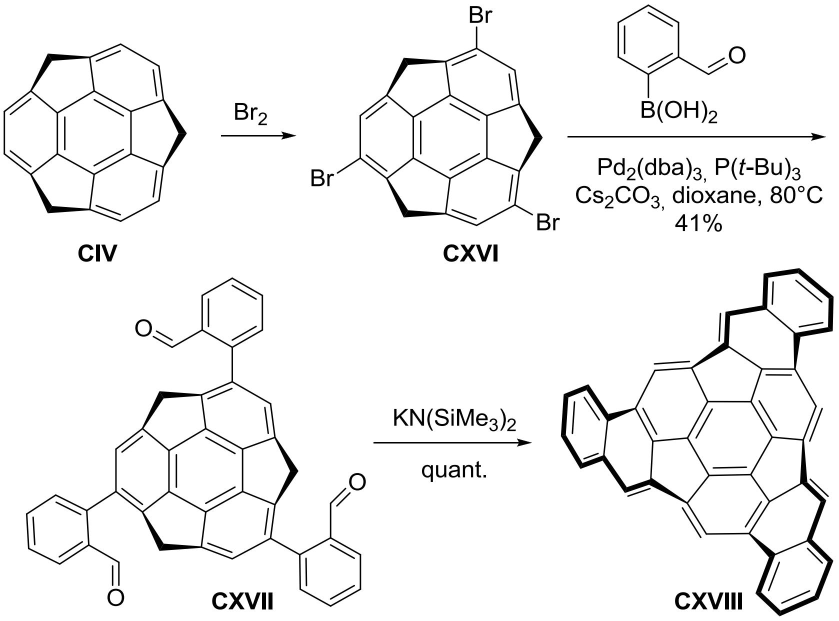
Interestingly, deuteration of the tris anion **CX** is achieved with fully *exo*-selectivity to the corresponding **CXII,** allowing the determination of bowl interconversion rate by EXSY 2D NMR measurements of the chemical exchange rate of the benzylic protons. To evaluate the exchange rate of the benzylic protons is necessary to replace selectively only one of the two benzylic protons with another group in order to distinguish between the two interconverting species.



Scheme 2.13 Bowl to bowl inversion of trideuteriosumanene.

Kinetic experiments showed that one interconversion of sumanene occurs each 143 s (rate constant: 0,007 s^{-1} in $CDCl_3$, at 298 K) and is considerably slower than corranulene which interconverts 200000 times per second.[21a]

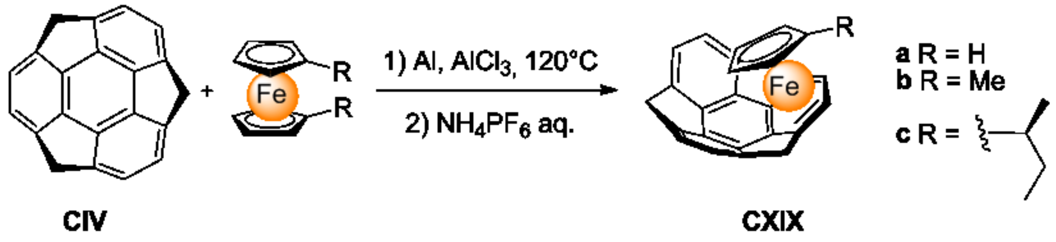
Functionalization of sumanene is possible also at level of the aromatic part of the molecule. Hirao reported, for example, a procedure for the enlargement of sumanene **CIV** through bromination of the aromatic framework, obtaining **CXVI**, followed by a coupling reaction with 2-formylphenylboronic acid to produce **CXVII**. Finally intramolecular cyclization to **CXVIII** was achieved by the condensation of aldehydes groups at the benzylic positions in presence of $KN(SiMe_3)_2$.[22]



Scheme 2.14 Synthesis of trinaphtosumanene.

Coordination properties

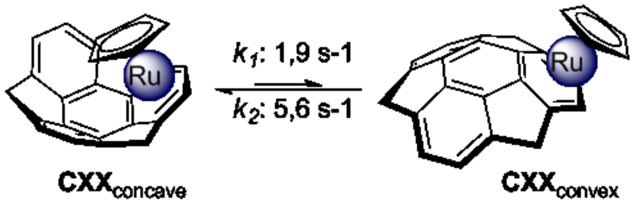
As fullerenes and nanotubes exhibit complexing properties for transition metals[23], Hirao investigated the possibility to coordinate metals with sumanene by the ligand exchange with a cyclopentadienyl group of several ferrocenes. The reaction was carried in the presence of an excess of aluminum powder and aluminum chloride without solvent at 120°C, finally replacing the counteranion of the crude complex with hexafluorophosphate, giving $[CpFe(\eta^6\text{-sumanene})]PF_6$.



Scheme 2.15 Synthesis of a π-bowl complex using sumanene as concave ligand.

Ferrocenyl moiety in the final complex **CXIX** was coordinated in the concave part of sumanene and bowl to bowl inversion was considerably slow. Moreover, rotation of Cp ligand was allowed only in **CXIXa**, whereas in **CXIXb** and **CXIXc** rotation was restricted due to steric hindrance of substituents. However, complex **CXIXa-c** represented the first class of endohedral metal complexes of fullerene fragments. They are expected to find application in the surface activation and functionalization of fullerenes and nanotubes, in order to develop new functional materials.[24]

On the other hand, the analogue Ru complex **CXX** [CpRu(η^6-sumanene)]PF$_6$ has been prepared in a similar way to the iron complex **CXIX**, but it exhibited a faster interconversion rate. NMR exchange experiments have shown that the ratio between the convex and concave species at the equilibrium was 3:1, whereas in the case of ferrocene complex the inversion was almost negligible. Moreover, the activation energy for bowl interconversion was smaller than that of the free sumanene alone, therefore leading to a faster interconversion rate. [25]



Scheme 2.16 Bowl-to-bowl inversion of [CpRu(η^6-sumanene)]$^+$ and related kinetic constants.

Perspectives

Finally, preliminary experiments suggested possible electronic applications. For example, Hirao demonstrated that sumanene crystals exhibited high electron mobility with large anisotropy by time-resolved microwave conductivity methods.[26]

Thus, sumanene may find possible applications as electrical material, for example by the preparation of derivatives in which the bowl-to-bowl interconversion is fully controlled and thereby would afford new building blocks for molecular machines, molecular devices and molecular switches.

2.2.3. Supramolecular Chemistry of Benzocyclotrimers

The cup-shaped structure of *syn*-benzocyclotrimers could not be excluded for supramolecular applications. In fact, the cavities offered by these molecules provide possible scaffolds for the synthesis of supramolecular hosts upon the suitable functionalizations. The first observation in this sense was the formation of stabile π-complexes between **XXI** or **VII** and NO^{+}[14b] which opened the possibility of viewing these molecules as potential receptors for small guest molecules.

Syn-benzo(tribenzonorbornadiene) provided one of the first application as supramolecular host. The cavity of this cyclotrimer exhibits a highly negative electrostatic surface potential, therefore giving a chance for complexing guests with extended π–surfaces. For example, complexation experiments demonstrated that *syn* benzo(tribenzonorbornadiene) was able to form a complex with fullerene in acetonitrile.[27]

Fig. 2.6 π-complexes of: a) *syn*-benzotribornane with NO^{+} and b) *syn*-benzotribenzonorbornadiene with fullerene.

In recent years, the methodologies for the preparation of functionalized benzocyclotrimers became more efficient and therefore the interest on the study of possible applications of these molecules increased, especially in supramolecular chemistry.

Syn-benzotriborneol[28] **CXXI** was the first reported enantiopure benzocyclotrimer bearing important functionalizations. The three hydroxyl groups are placed in *endo* positions at the rim of the rigid bornane skeleton and are forcedly directed to the centre of the cavity. With this particular conformation, triol **CXXI** exhibited complexing properties, by H-bonding, toward water molecules[29] and, as

CXXI is enantiopure, in presence of a racemic mixture of 1-phenylethylammonium chloride, a preference of complexing one of the two enantiomers was observed and was evaluated in 2:1 ratio.[30]

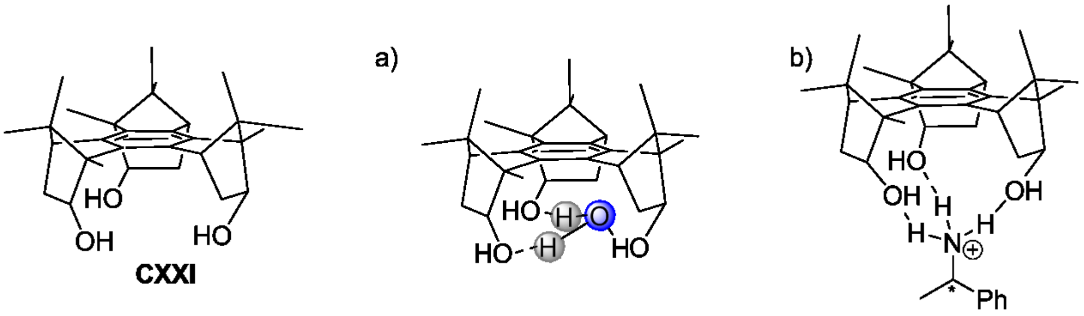
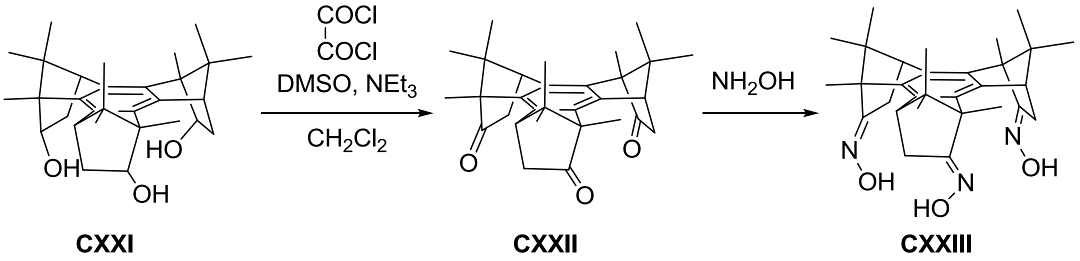


Fig. 2.7 Supramolecular complexes of *syn*-benzotriborneol **CXXI**: a) with water, b) with phenylethylammonium ion.

Syn-benzotriborneol was used also for the further transformation to benzotricamphor **CXXII** through the oxidation of the hydroxyl groups by the Swern protocol. Benzotricamphor was then conveniently reacted with hydroxylamine to afford the corresponding trioxime **CXXIII**.



Scheme 2.17 Synthesis of benzotricamphor **CXXII** and benzotricamphor-oxime **CXXIII** from benzotriborneol **CXXI**.

Benzotricamphor-oxime **CXXIII** exhibited supramolecular properties by acting as host for small neutral guest molecules. Indeed, oximes provide both H-bond donors (OH) and acceptors (N), thus in presence of small neutral guests trioxime **CXXIII** self-assembles into a dimeric capsule, by the formation of a H-bonding network between two molecules of cyclotrimer and therefore encapsulating the guest.

The capsule formation was confirmed by inclusion experiments of methane, easily observable with NMR, which displayed a 2:1 ratio between trioxime and guest signals.[31]

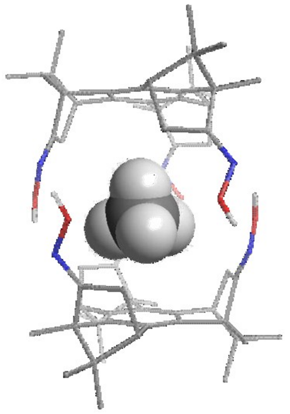
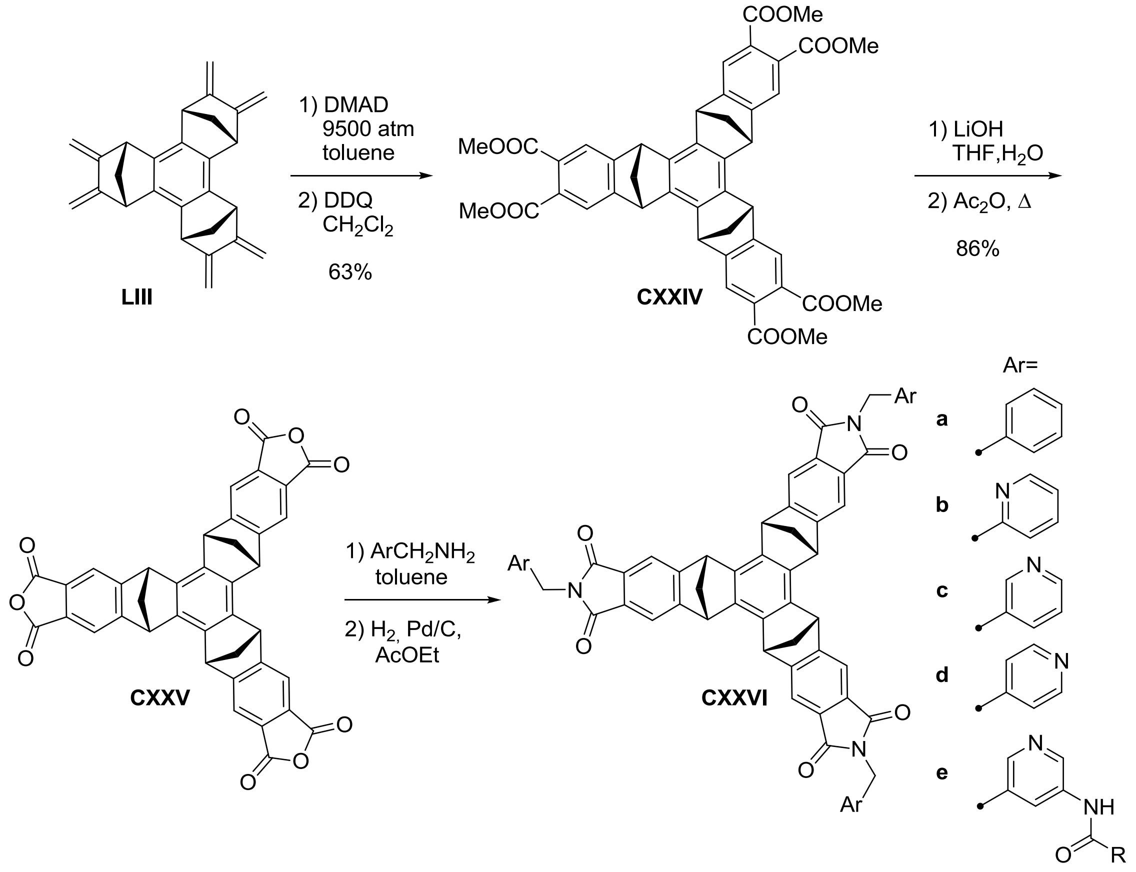


Fig. 2.8 Dimeric capsule of trioxime **CXXIII** and encapsulated methane.

Benzotriradialene **LIII** is used also as precursor of supramolecular hosts. This molecule presents three *cis*-diene moieties at the rim of a tribornene skeleton in a rigid fashion and are susceptible of cycloaddition reactions. High pressure Diels-Alder reaction with dimethyl acetylenedicarboxylate (DMAD), followed by aromatization with DDQ, provides the hexaester **CXXIV**. After the conversion to anhydride **CXXV**, the reaction with benzylamines affords new cup-shaped compounds **CXXVI** with a deep cavity. These products are defined "molecular baskets" by the author.



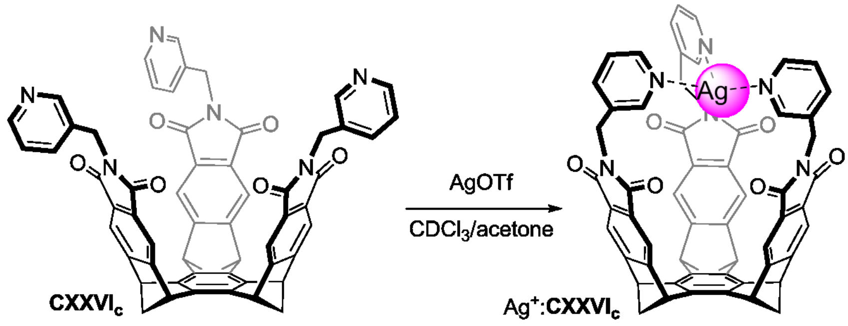
Scheme 2.18 Synthesis of molecular baskets from benzotriradialene **LIII.**

In absence of specific interactions or binding sites, molecular basket **CXXVI$_{a}$** was unable to display any supramolecular behavior in solution whereas in the solid state solvent molecules were found occupying the cavity.[32]

Molecular baskets **CXXVI$_{b\text{-}d}$** can enclose the inner space through the coordination of a transition metal, eventually allowing the coordinatively unsaturated metal to further bind another molecule by placing it inside or outside the cavity.

Complexation experiments showed that **CXXVI$_{c}$** and **CXXVI$_{d}$** were able to be folded by the coordination of Ag while **CXXVI$_{b}$** led to a range of undefined metal-basket oligomers. The calculation of thermodynamical parameters for the enclosing processes provided positive values both for ΔH° and ΔS° for **CXXVI$_{c}$** and negative data in the case of **CXXVI$_{d}$.** Thus the coordination of **CXXVI$_{d}$** is enthalpycally driven, whereas the formation of **CXXVI$_{c}$**-Ag is driven by entropy.

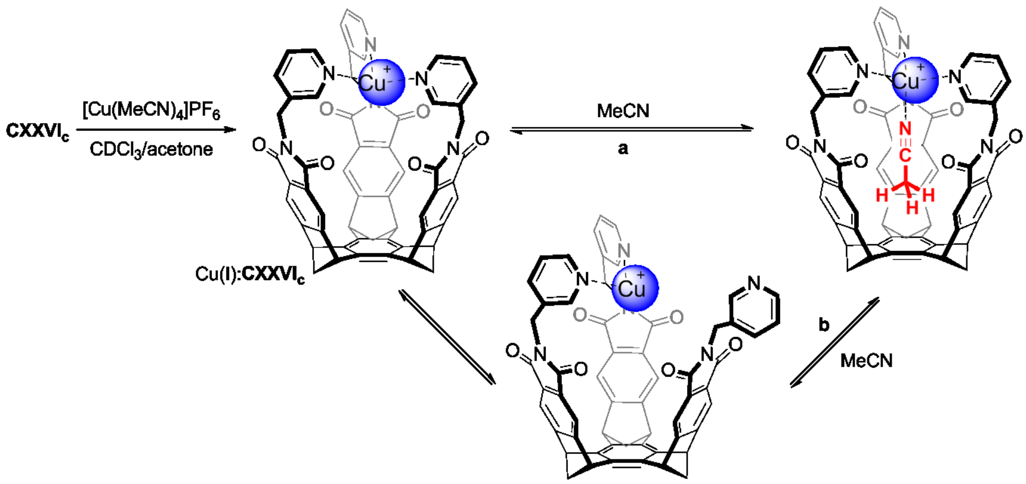
Nevertheless, despite the closure was achieved by coordination with Ag, these baskets were not able to host guests in solution, whereas in the solid state solvent molecules resided into the cavities.[33]



Scheme 2.19 Folding of molecular basket **CXXVI$_{c}$** by coordination of silver.

The closure of basket **CXXVI$_{c}$** was possible also by coordination of Copper(I) featuring a tetracoordinate Cu(I) bound to three pyridines of the basket and the remaining insaturation could coordinate a molecule of MeCN, by placing it inside the cavity. The process is driven by enthalpy as a result of the formation of an additional metal-ligand coordination bond which takes place in the encapsulation event.

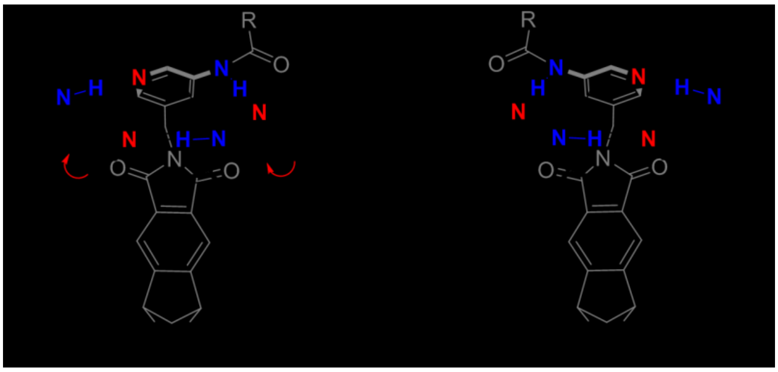
However, on the basis of kinetic investigations of the inclusion process, the exchange of MeCN was dynamical and was ascribed to a "gate" opening by the dissociation of a pyridine from the metal or an in/out exchange through a slight expansion of the host.[34]



Scheme 2.20 Folding of **CXXVI$_c$** by coordination of copper and possible inclusion mechanisms of MeCN by: a) exchange through host apertures and b) entrance in correspondence of a "gate" opening.

Despite the closure of molecular baskets by metal-ligand interactions has been well investigated, H-bond interactions provided a more dynamic and tunable system for the basket folding, such as in **CXXVI$_e$**.

In this basket the folding occurs by a clockwise or an anticlockwise H-bonding network (Scheme 2.21) and results in two opposite conformations which interconverts through the rotation of the gates. [35] This movement can be viewed as the operation of a butterfly valve in opening or closing the basket aperture for the guest exchange.[36]



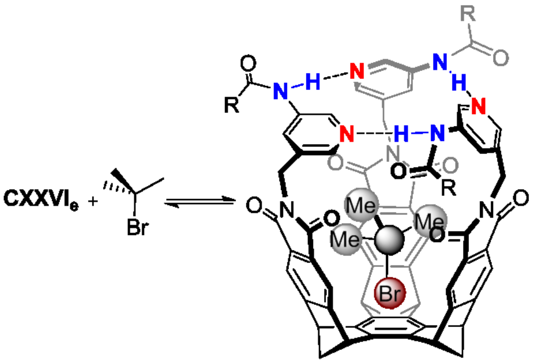
Scheme 2.21 Clockwise and anticlockwise H-bonding network of basket **CXXVI$_e$**.

From complexation experiments, resulted that basket **CXXVI$_e$** was able to host halomethanes with different efficiency as a function of their size. The largest guest CBr_4 showed the highest affinity for occupying the cavity, whereas decreasing the numbers of halogen atoms the binding affinity was reduced, as demonstrated by the relevant thermodynamical parameters. The enthalpic contribution was found similar for all guests (ca. 4 kcal/mol), while entropic values became more negative from CBr_4 to CMe_4. This was ascribed to a restricted motion of the rotatable methyl groups within the cavity.[37]

Fig. 2.9 CBr_4 incapsulated into basket **CXXVI$_e$** and relevant thermodynamical and kinetic data for the inclusion process.

As anticipated above, the kinetic of guest exchange in molecular baskets is correlated to a dynamical equilibrium between two conformers, which interconvert by the rotation of the pyridine moieties along the connection to the rigid part of the basket. The revolving of the gates opens the apertures in which the guest can enter and leave the cavity and is correlated (LFER) with the thermodynamical stabilities of the complexes. Considering the inclusion of different guests (Fig. 2.9), coherence was found between thermodynamic and kinetic stabilities, leading to stable complexes when the guest entrance (k_{in}) is fast and guest departure is slow (k_{out}).[38]

This correlation was further demonstrated by studying the encapsulation of a common guest using molecular baskets of the type of **CXXVI$_e$**, in which the gates were modified through the introduction of opportune substituents. Indeed, from reported data it was observed that the thermodynamical stability as well as kinetic constants, decreased from electron-donating to electron-withdrawing groups placed on the gates, meaning that stable basket-guest complexes were obtained when the interconversion was fast.[39]



R	k_{gates} (s^{-1})	k_{in} (M-1s-1)	k_{out} (s^{-1})	ΔG° (kcal/mol)
CH_3	108	524	4.7	-2.1
CF_3	4	0.7	0.07	-1.0

Scheme 2.22 Encapsulation of *t*-BuBr into baskets **CXXVIe** (selected examples: R = CH_3, CF_3) and relevant kinetic and thermodynamical parameters. k_{gates}: kinetic parameter for the revolving of the gates; k_{in} and k_{out}: kinetic parameters for the entrance and departure of the guest; ΔG°: standard free energy for the inclusion process.

The perturbation of electron density, caused by substituents R, has an effect on the stability of intramolecular hydrogen bonds and can be accounted through the observed trend of kinetic parameters. Precisely, H-bonds are weakened by using electron-donating groups and thereby the gates revolve faster, whereas the H-bond strength is increased by electron-withdrawing-groups, making the gates rotate slower.[39]

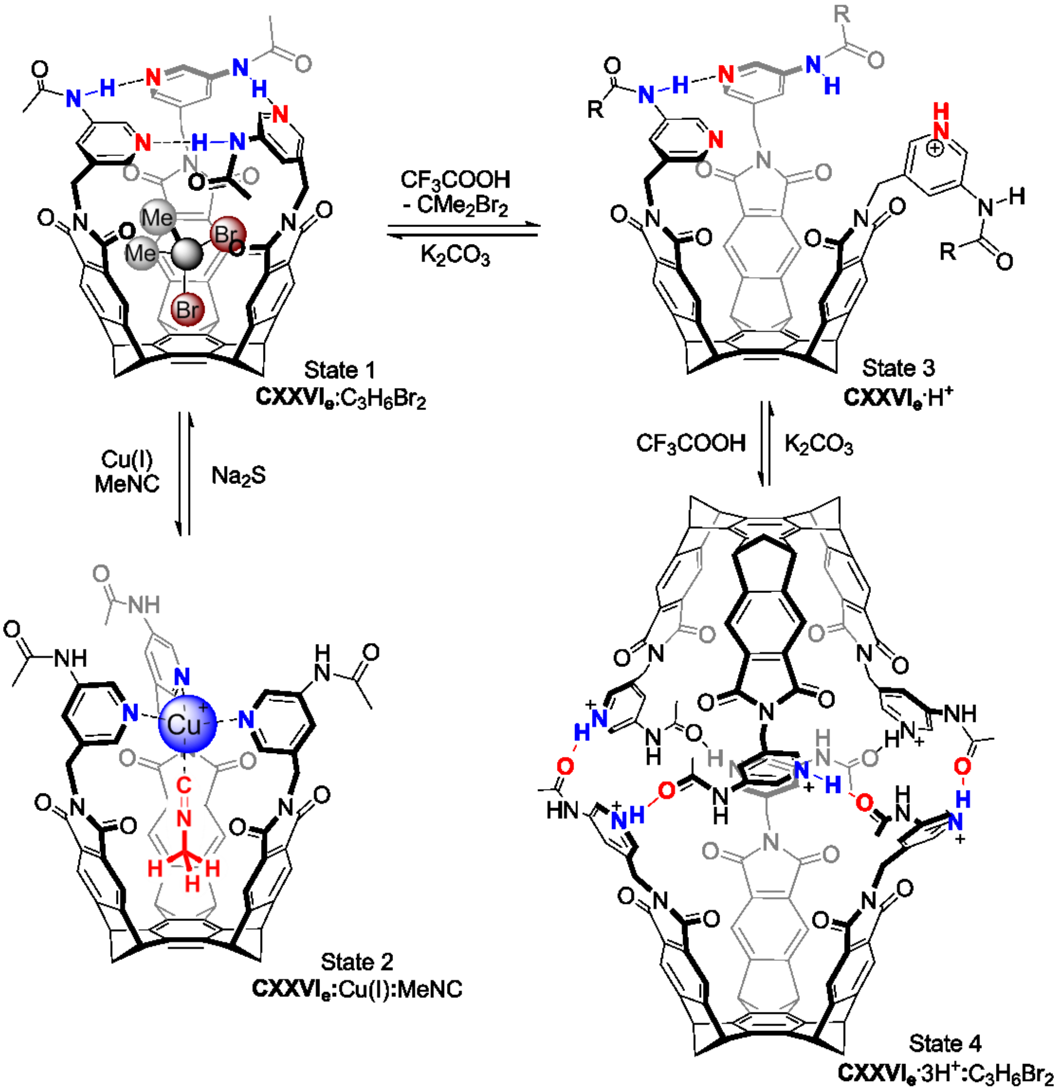
Thus, from these experiments, it is possible to conclude that simple host-guest chemistry is evolving to the control of guest trafficking by a fine regulation of the gate dynamics.

In addition, basket **CXXVIe** was found able to switch to several species by external stimulus. Starting from state 1, in which **CXXVIe** encapsulates CMe_2Br_2, a first mode of switching was achieved by the addition of $(CuOTf)_2PhMe$ in presence of CH_3NC. As the coordination of copper on the gates provides a strong interaction, the hydrogen bond network is consequently broken and the exchange of the two guests is observed.

The second mode of switching is based on the break of intramolecular H-bonding by the protonation of pyridines with CF_3COOH (acid stimulus), unfolding the basket and provoking the guest departure.

The third mode of switch is obtained by the full protonation of the pyridines, determining the association of **CXXVIe** into a dimeric capsule which is still able to host CMe_2Br_2.

The above acid stimulus is fully reversed upon addition of a base, reestablishing the original basket. Thus the guest exchange is reversibly controlled through various stimulus allowing a fully reversible switching folding basket.[40]



Scheme 2.23 Four state switching of molecular basket **CXXVI**$_{e}$.

The last study about molecular basket **CXXVI**$_{e}$ reported the investigation of the well-known chair-to-chair interconversion of encapsulated cyclohexane. By studying the interconversion kinetic of D11-cyclohexane at low temperatures, the interconversion rate inside the basket was demonstrated 5 times faster than in the bulk of a solvent. This was ascribed to a destabilization of the chair conformation inside the cavity of the basket, as supported by theoretical calculations, while the half-chair conformation, which is the transition state between the chair and boat conformations, is stabilized due to the complementarity with the internal morphology of this rigid host. Thus the activation barrier for interconversion is reduced, giving an explanation for the increased rate of chair-chair interconversion.[41]

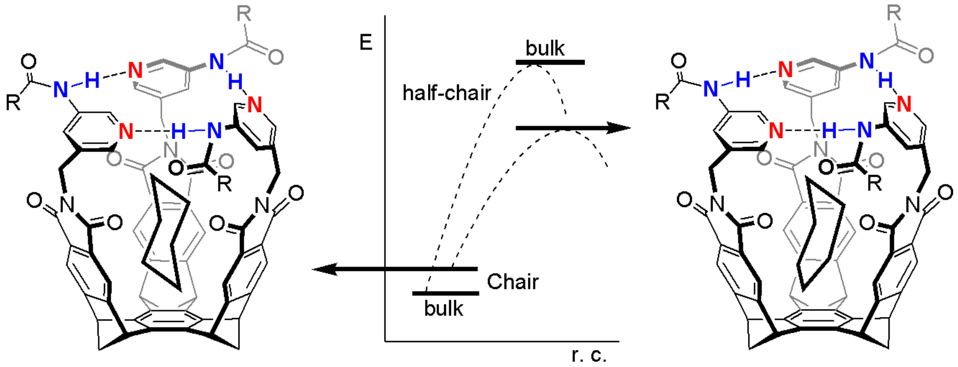


Fig. 2.10. Destabilization of chair (left) and stabilization of half-chair (right) conformers of cyclohexane inside molecular basket.

In conclusion, molecular baskets showed not only the ability to act as supramolecular hosts, but exhibited also important features such as the tunable gate dynamics and a multi-state switching through controlled external stimulus, therefore allowing a good control of the guest translocation.

Considering also the possibility to stabilize transition states, all these features are a proof of how elements of design on artificial hosts can enhance binding ability and selectivity, which are fundamental requrements for the rational design of supramolecular catalysts.

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CHAPTER 3

AIM AND STRUCTURE OF THE THESIS

Benzocyclotrimers are polycyclic compounds, usually prepared by cross-coupling reactions of bicyclic olefins. Two possible diastereoisomers are obtained: the C_3-symmetric *syn* and the *anti*, characterized by a lower degree of symmetry. As stated in Chapter 1, cyclotrimerization reactions are often affected by unfavorable *syn/anti* ratios and only in recent years highly diastereoselective methodologies have been reported. The availability of s*yn*-cyclotrimers in large amounts is the fundamental requirement to perform any research with the aim to develop new supramolecular systems and to study the related host-guest chemistry. In fact, s*yn*-benzocyclotrimers exhibit a cup-shaped structure that renders these molecules very promising scaffolds in supramolecular chemistry. Moreover, the recent research on the field is oriented toward the development of new self-assembling systems based on controlled dynamical gating phenomena.

Thus, the objectives of this thesis are:

- the development of new selective methods for the cyclotrimerization of bicyclic olefins;
- the functionalization of benzocyclotrimers for the preparation of supramolecular hosts;
- the investigation of the supramolecular properties of the new obtained cyclotrimeric structure.

Therefore the thesis is divided into 8 chapters, as outlined:

Chapter 1 and 2 give an overview on the research so far reported in the field of benzocyclotrimers derived from bicyclic olefins.

Chapter 4 describes the development of a new procedure for the synthesis of benzotricamphor in high yield and diastereoselectivity and reports the investigation of the most suitable functionalizations to convert this cyclotrimer into possible supramolecular hosts.

Chapter 5 reports on the supramolecular applications of covalent molecular cages obtained from benzotricamphor.

Chapter 6 describes the preparation of supramolecular aggregates by non-covalent forces using self-assembling cyclotrimers.

Chapter 7 reports new general findings in the field of acetylene chemistry resulted from the study of specific functionalization reactions for benzocyclotrimers.

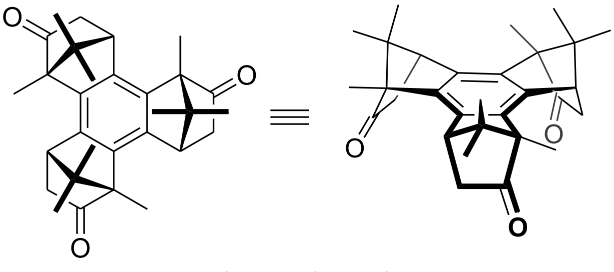
Chapter 8 reports the final conclusion of this work.

CHAPTER 4

BENZOTRICAMPHOR: A VERSATILE SCAFFOLD

As introduced in Chapter 2, benzotricamphor was already known at the beginning of the present project, although the possibilities offered by this benzocyclotrimer has been deeply investigated within this thesis.[1]

This compound presents three carbonyl groups at the rim of a cup-shaped and rigid structure, which may lead to a versatile scaffold in view of possible supramolecular applications.



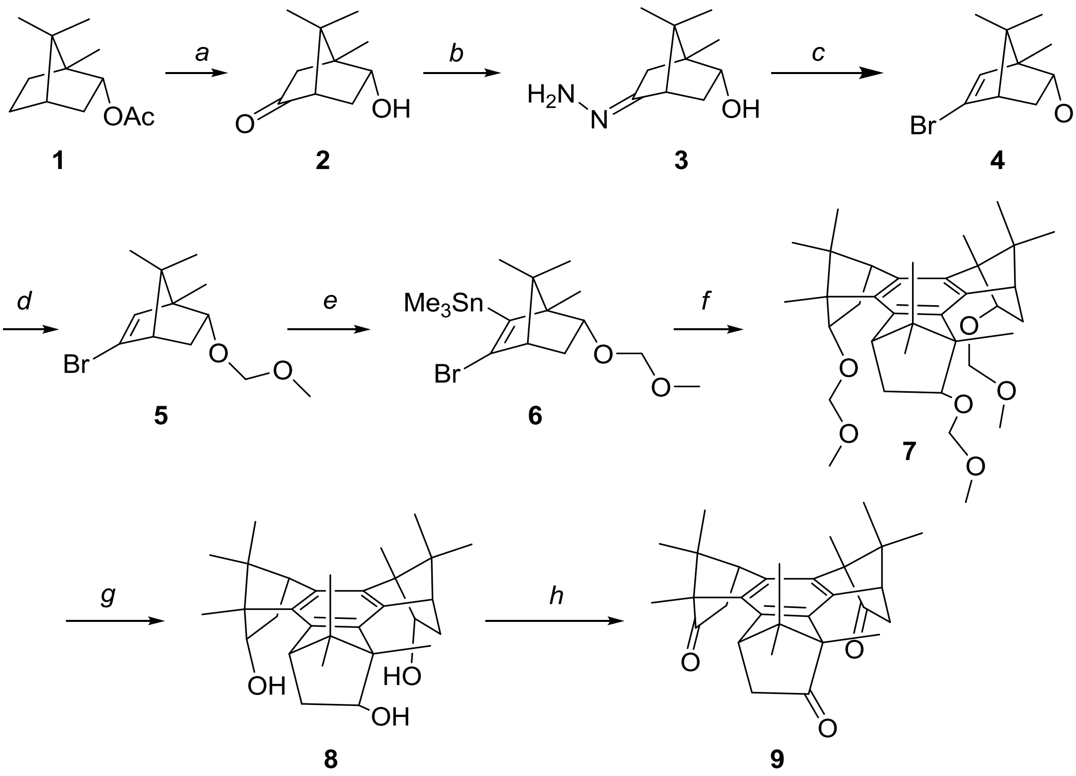
syn-benzotricamphor

Fig. 4.1 Top (left) and side (right) view of *syn*-benzotricamphor.

The synthetic routes to benzotricamphor which were reported before this project and the original methodology developed in the course of this thesis will be described in this Chapter.

4.1. *PREVIOUS METHODS*

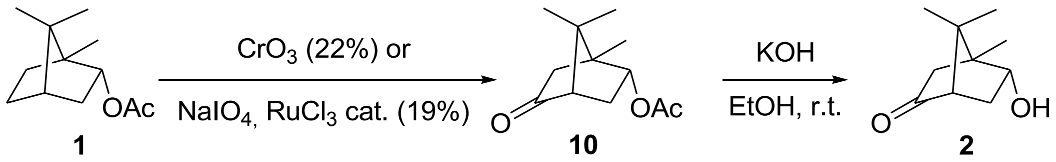
Benzotricamphor was obtained for the first time through the oxidation of benzotriborneol **8**,[2] which was prepared from the commercially available (-)-acetyl borneol through a seven-step synthesis (Scheme 4.1).



Scheme 4.1 Synthesis of benzotriborneol **8** and benzotricamphor **9**. Details of the reaction conditions are reported in the following text.

Step a: oxidation of acetil borneol

5-Oxoborneol **2** was obtained by the oxidation at the methylene carbon in position 5 of bornyl acetate **1**, followed by basic cleavage of the acetate ester (Scheme 4.2). The yield of the oxidation step was usually low (nearly 20%) using a large excess (5.0 eq.) of chromium(VI) oxide, in acetic acid at 140 °C, according to the procedure of Meinwald.[3]



Scheme 4.2 Oxidation of borneol acetate and basic hydrolysis.

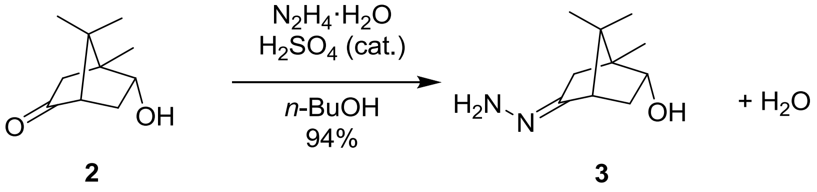
Bornyl acetate was chosen as starting material because it is susceptible of selective oxidation at the position 5, although in low yield. The selectivity in directing the oxidation process to the desired position of the bornane skeleton was ascribed to the acetate group, presumably through the coordination with the active oxidizing species. This hypothesis was supported by the fact that, under these conditions, other borneol derivatives were not susceptible to a selective oxidation at position 5. For example, borneol was oxidized at the alcoholic group to afford camphor, and the latter was slowly consumed to produce unrecoverable products, deriving from oxidation at position 3. Camphor ethanediol acetal was oxidized by chromium(VI) at methylenes moiety of the acetal, affording two unseparable diastereomers.

Alternatively, this oxidation was achieved with similar results using the less toxic oxidant sodium periodate (4.0 eq.), in presence of 2.0 mol% ruthenium(III) chloride at 60 °C in a acetic acid/acetonitrile/water mixture.

The saponification step was subsequently carried by treating 5-oxobornyl acetate **10** with potassium hydroxide in ethanol at room temperature in a few hours, allowing the recovery of the product in nearly quantitative yield.

Step b: synthesis of borneol-5-hydrazone

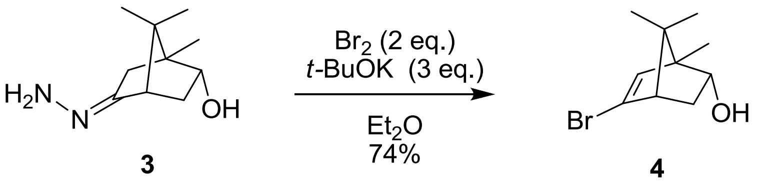
The conversion of 5-oxoborneol **2** into the corresponding hydrazone **3** was easily obtained in good yield, reacting **2** with a large excess of hydrazine hydrate and a catalytic amount of sulfuric acid in refluxing *n*-butanol. The water produced from the reaction was usually azeotropically removed and trapped by the use of 4 Å molecular sieves.



Scheme 4.3 Synthesis of borneol-5-hydrazone.

Step c: synthesis of 5-bromobornenol

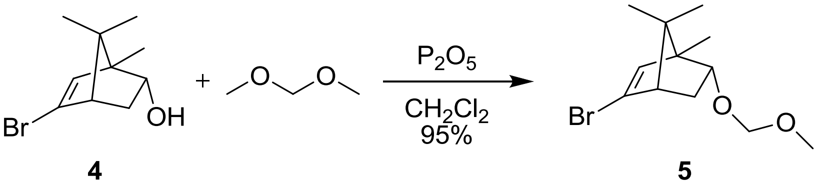
The transformation of hydrazone **3** into bromo-olefin **4** was performed with bromine and potassium *tert*-butoxide in diethyl ether under sonication. The crude product is conveniently purified by sublimation at reduced pressure, obtaining **4** in 74% yield (Scheme 4.4).



Scheme 4.4 Conversion of hydrazone **3** to vinyl bromide **4**.

Step d: protection of alcoholic group

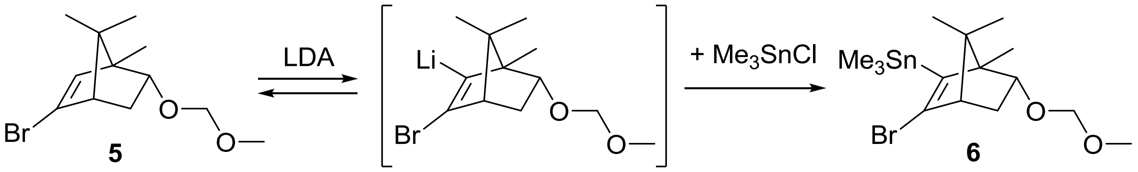
Since the next steps require strong bases or organometallic reagents, the hydroxy group of **4** must be protected. Several protecting groups were tested and the best choice resulted methoxymethylene (MOM) group. The protection of **4** was conveniently carried out with dimethoxymethane in dichloromethane and a large amount of phosphoric anhydride.[4]



Scheme 4.5 Protection of alcoholic moyety of **4**.

Step e: stannylation

Trimethylstannyl group was introduced in the protected bromobornenol **5** to prepare the substrate for the cyclotrimerization reaction. The stannylation was achieved by treatment with lithium diisopropylamide (LDA) in tetrahydrofuran and subsequent addition of trimethyltin chloride.

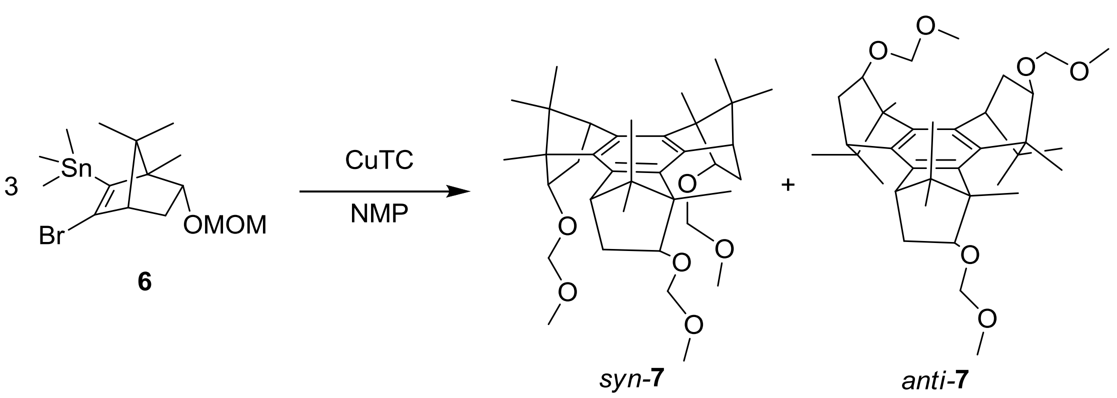


Scheme 4.6 Stannilation of **5**.

The product was obtained in 86% yield with a good level of purity after a simple work-up procedure.

Step f: cyclotrimerization

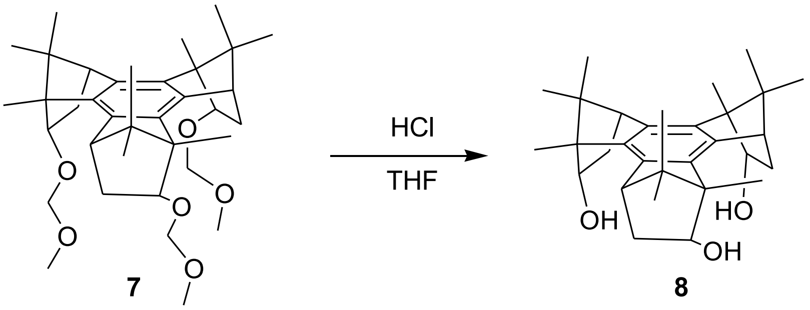
As mentioned in Chapter 1, the cyclotrimerization of bromostannyl olefins is carried in *N*-methylpyrrolidin-2-one (NMP) in presence of stoichiometric amount of copper(I) 2-thiophenecarboxylate (CuTC). In the case of substrate **6**, the reaction afforded a 5.5:1 *syn/anti* mixture of trimers in 69% overall yield.



Scheme 4.7 Cyclotrimerization of bromostannyl olefin **6**.

Step g: deprotection

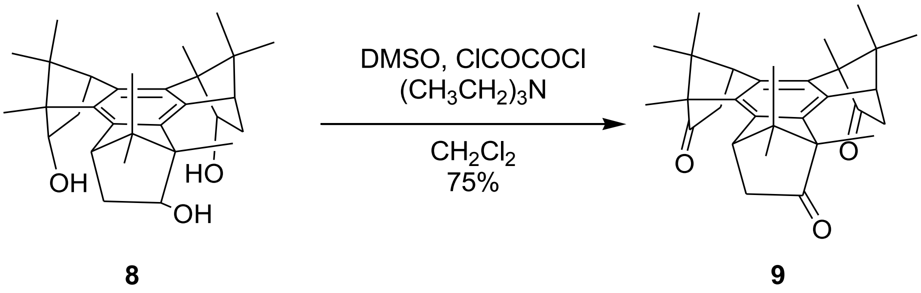
Isolated *syn*-**7** was deprotected with ease by acid treatment. Noticeably, *syn*-benzotriborneol **8** was the first reported enantiopure functionalized benzocyclotrimer and exhibited supramolecular properties, for example in recognition of chiral ammonium ions.[2c]



Scheme 4.8 Removal of MOM groups to obtain *syn*-benzotriborneol.

Step h: benzotricamphor synthesis

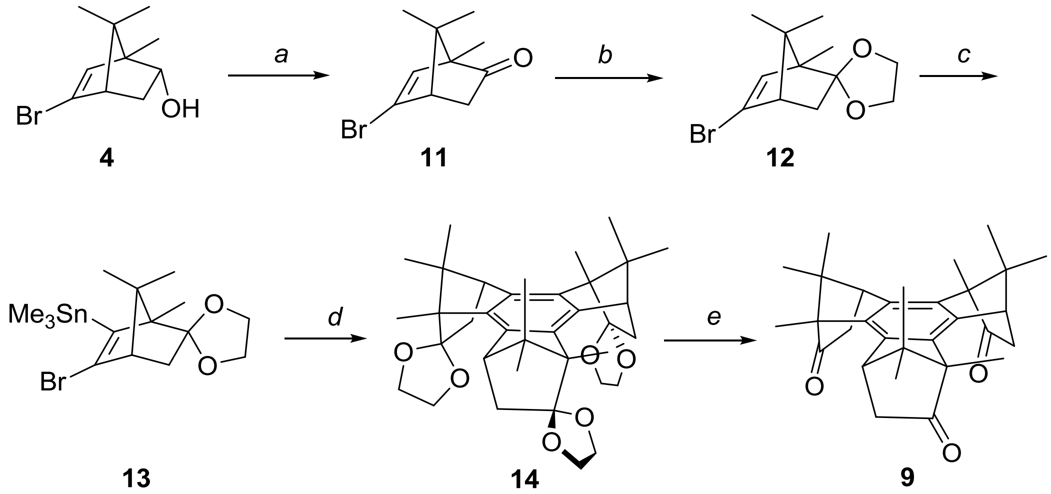
The oxidation of the hydroxyl groups of benzotriborneol **8** to afford the carbonyl moieties of benzotricamphor **9** was carried out using the Swern protocol (Scheme 4.9).[5]



Scheme 4.9 Preparation of benzotricamphor **9** from benzotriborneol **8**.

Finally, benzotricamphor **9** was obtained after eight synthetic steps, which afforded products in good yield, except for the first oxidation reaction (step *a*) which decreased the overall yield to 4%.

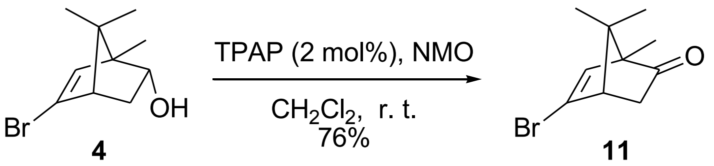
Benzotricamphor, was prepared also through a modification of the previous method from vinyl bromide **4**. This is briefly described in Scheme 4.10.



Scheme 4.10 Alternative synthesis of benzotricamphor. Reaction conditions are described in the following text.

Step a: oxidation of 4-bromobornenol

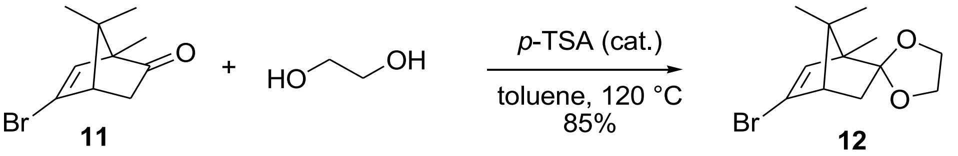
The oxidation of the hydroxyl group of **4** was carried out with *N*-methylmorpholine-*N*-oxide (NMO) and 2 mol% of tetrapropylammonium perrutenate (TPAP) in dichloromethane at room temperature,[6] affording the product in 76% yields.



Scheme 4.11 Oxidation of **4** to ketone **11**.

Step b: protection of ketone group

Ketone **11** needs a protective group before the stannylation step in order to avoid the possible reaction of LDA with acidic hydrogens in α-positions to the carbonyls. Ketone **11** was therefore transformed in the corresponding acetal **12** with ethylene glycol under azeotropic removal of water, affording the expected product in 85% yield.

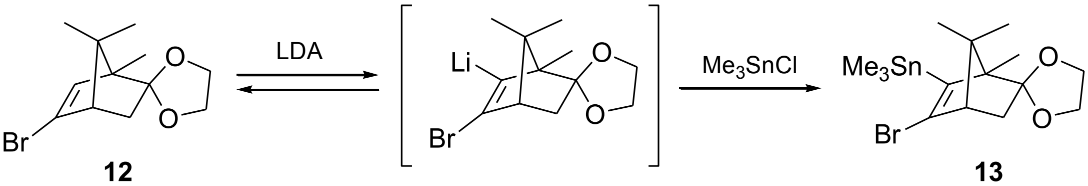


11 **12**

Scheme 4.12 Protection of the carbonyl group of **11**.

Step c: stannylation

The stannylation of **12** was carried out with LDA and trimethyltin chloride, in a similar fashion to **5**, obtaining the stannane **13** in 88% yield.

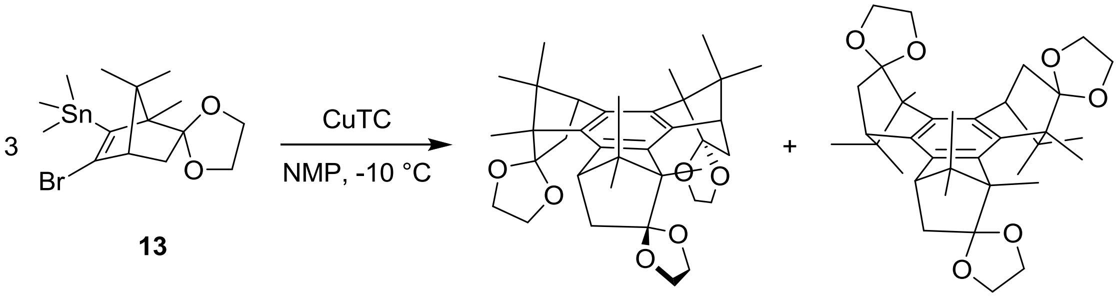


12 **13**

Scheme 4.13 Stannilation of **12**.

Step d: cyclotrimerization

The cyclotrimerization of **13** was carried in NMP at -10 °C in presence of a stoichiometric amount of CuTC. The benzocyclotrimers **14** were obtained in 27% overall yield in 6.5:1 *syn/anti* mixture.



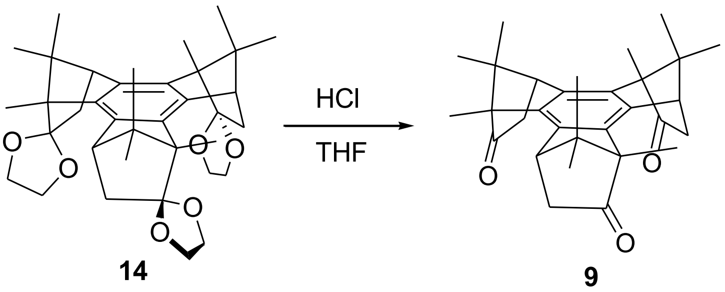
13

syn-**14** *anti*-**14**

Scheme 4.14 Cyclotrimerization of **13**.

Step g: deprotection

Protected *syn*-**14** was converted to benzotricamphor **9** by acid hydrolysis of the acetal groups, affording the tris-ketone in nearly quantitative yield after a simple crystallization from hot methanol.



Scheme 4.15 Deprotection of **14** to obtain benzotricamphor.

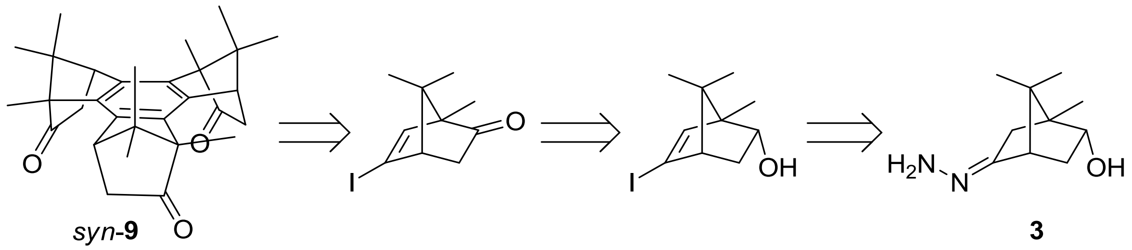
This synthetic route was similar to the first method in the number of synthetic step, but differed in the order in which the alcoholic oxidation to ketone step occurs. In the previous synthetic route this transformation was performed converting benzotriborneol **8** to benzotricamphor **9** in the last step, whereas in the second methodology the oxidation is carried in the early stage of the overall synthesis. In both cases, a protection and de-protection steps was required by the stannylation route, either for alcoholic or for carbonyl moieties. The overall yield was 1% (7% from borneol-5-one) thereby concluding that this procedure was less effective in the preparation of *syn*-**9**.

The cyclotrimerization step dramatically reduced the overall performance of the strategy. In fact, the analogue reaction in the synthesis of triol **8** provided the product in 69% yield, while the cyclotrimerization of **13**, afforded the protected benzotricamphor **14** in 27% yield. The only positive aspect was the 6.5: 1 *syn* to *anti* selectivity found in the cyclotrimerization of **13**, whereas the first method afforded triol **8** in 5.5:1 selectivity in favor of the *syn* isomer.

4.2. BENZOTRICAMPHOR FROM 5-IODOBORNENONE

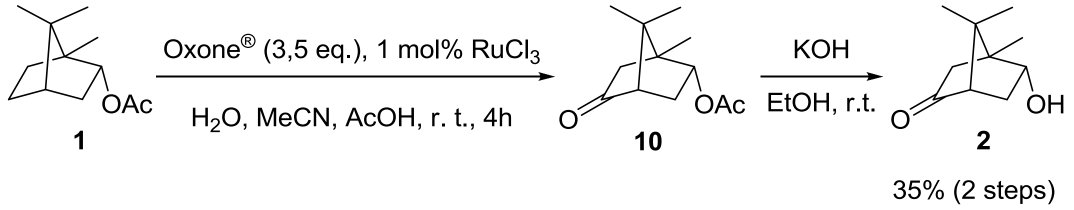
The low overall yields obtained with previous methodologies prompted us to study a new method for the synthesis of benzotricamphor. In order to obtain *syn*-**9** in amounts useful for practical applications, two goals must be pursued: 1) reduce synthetic steps, and 2) optimize the existing ones. In order to design a new procedure we followed the methodology implemented by Sakurai for cyclotrimerization of enantiopure iodobornenes under palladium catalysis.[7]

The new planned synthetic route was based on the cyclotrimerization of an enantiopure vinyl iodide derived from the known hydrazone **3**, in a similar fashion to the methodology to obtain bromide **4**. A method based on cyclotrimerization via Heck hetero-couplings offered the advantages to avoid the stannylation step and consequently the protection and de-protection reactions.



Scheme 4.16 Proposed retro-synthesis of benzotricamphor based on cyclotrimerization of an enantiopure iodobornene.

In order to increase the overall yield, the first ruthenium-catalyzed oxidation of bornyl acetate to 5-oxoborneol **2** was further investigated. Several efficient co-oxidants were tested in order to obtain the best conversion and selectivity (hydrogen peroxide *t*-BuOOH,[8] ozone,[9] calcium hypochlorite[10] and Oxone®[11]). Commercially available and inexpensive Oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) resulted the best oxidant, furnishing almost complete conversion of the starting material even in the presence of lower amounts of ruthenium catalyst (1 mol%).

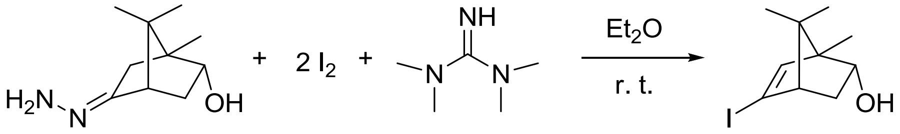


Scheme 4.17 Oxidation of acetyl borneol with oxone.

The reaction mixtures resulted essentially constituted by equimolar amounts of two main products: 5-oxoborneol acetate **10** and 6-oxoborneol acetate, as demonstrated by GC-MS and ^{1}H NMR. The purification of **10** was not necessary. Indeed, crude mixtures of the oxidation reaction submitted to saponification furnished the sole 5-oxoborneol **2**. The overall yield of these two steps resulted a reproducible 35%, which was higher than any previous methods. Moreover Oxone® was the most inexpensive and the safest oxidant(s) of all the reagent tested. Further investigations aimed at improving selectivity and yield, such as the addition of several ligands for the ruthenium catalyst or reduction of the reaction temperature did not improve selectivity and led to a general decrease of performances.

Synthesis of 5-iodobornenol

Hydrazone **3** was efficiently prepared through the procedure described above (Scheme 4.3). Compound **3** was converted to 5-iodobornen-2-ol **15** through a modification of a previously described procedure for the preparation of vinyl iodides from hydrazones.[12] Indeed, the reported addition of a solution of iodine in ether to a mixture of hydrazone **3** and *N*,*N*,*N*,*N*-tetramethyl guanidine (TMG) in ether afforded **15** in 66% yield, whereas reverse addition of a solution of hydrazone to the iodine solution furnished 84% yield of iodide.



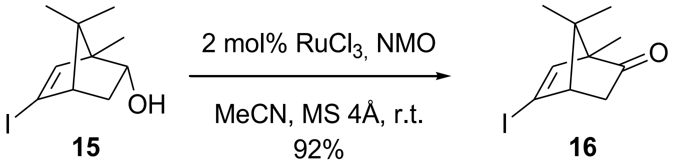
3

15

Scheme 4.18 Conversion of hydrazone **7** into vinyl iodide **15**.

Synthesis of 5-iodobornenone

The oxidation of hydroxyl group in **15** was carried out with *N*-methylmorpholine-*N*-oxide (NMO) and 2 mol% of tetrapropylammonium perrutenate (TPAP) in dichloromethane at room temperature,[6] affording the product in 70-90% yields. Nevertheless, it was found that better and more reproducible results could be obtained with the less expensive ruthenium(III) cloride (3 mol%) as catalyst in acetonitrile as solvent.



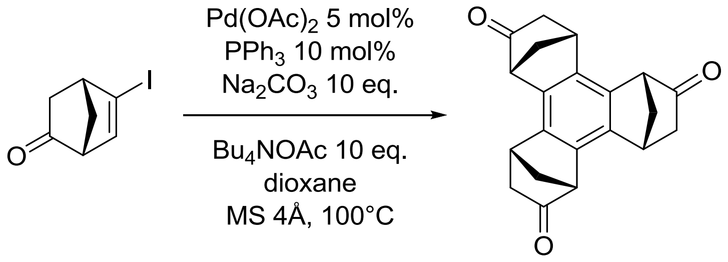
15

16

Scheme 4.19 Oxidation of **15** to ketone **16**.

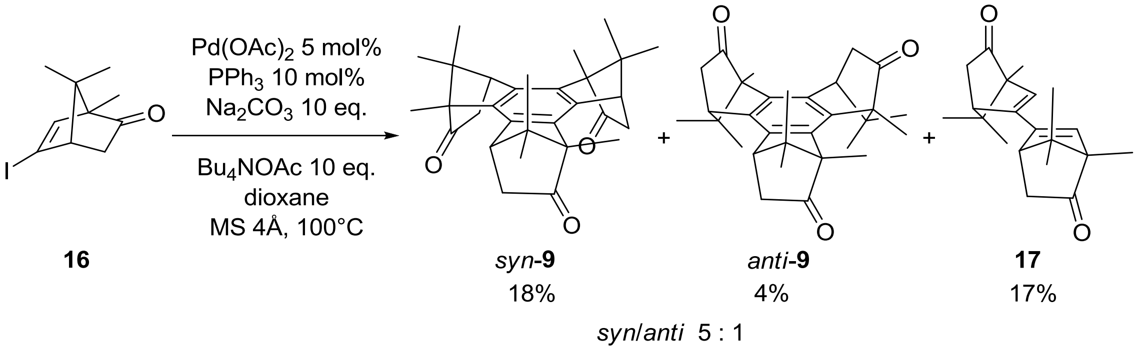
Cyclotrimerization

The palladium-catalyzed cyclotrimerization of 5-iodobornenone **16** to afford benzotricamphor was accomplished without any further use of protecting groups. In a preliminary stage, the reaction conditions reported for Heck-type cyclotrimerization of enantiopure iodobornenes were tested with our substrate. The conditions reported by Sakurai are herein reported (see Chapter 1 for more details).[7]



Scheme 4.20 General conditions for palladium catalyzed cyclotrimerization of enantiopure iodobornenes as reported by Sakurai.

Under these conditions, the cyclotrimerization of **16** afforded benzotricamphor **9** in 22% overall yield and a 5:1 *syn/anti* ratio, along with considerable amounts of the C_2-symmetric dimer **17**.



Scheme 4.21. Palladium catalyzed cyclotrimerization of **16**.

The method of Sakurai was not suitable to provide sufficient amounts of *syn*-benzotricamphor to further investigate its possible functionalization. Thus, the cyclotrimerization of **16** was screened varying all the reaction parameters in order to improve the final yields and selectivity.

As first, the conditions reported by Sakurai required large amounts of base and expensive tetrabutylammonium salt, which are prohibitive in case of a scale-up of the reaction. Thus the amounts of base and tetrabutylammonium salt were limited to five equivalents with respect to the substrate, for any set of reaction conditions. The results of the screening are summarized in Table 4.1.

Table 4.1 Effect of reagent and conditions on Heck-type cyclotrimerization of **8**.[a]

Entry	Base (5 eq.)	Solvent	*n*-Bu_4N^+ X^-[b] (5 eq.)	Pd (5 mol%)	Ligand[c]	Additive[d]	Temp. (°C)	*syn*-9 (%)[e]	17 (%)[e]
1	Na_2CO_3	dioxane	OAc	$Pd(OAc)_2$	PPh_3	_	100	12	48
2	K_2CO_3	dioxane	OAc	$Pd(OAc)_2$	PPh_3	_	100	16	59
3	Cs_2CO_3	dioxane	OAc	$Pd(OAc)_2$	PPh_3	_	100	0	24
4	KOAc	dioxane	OAc	$Pd(OAc)_2$	PPh_3	_	100	11	7
5	K_3PO_4	dioxane	OAc	$Pd(OAc)_2$	PPh_3	_	100	10	32
6	K_2CO_3	DMF	OAc	$Pd(OAc)_2$	PPh_3	_	100	8	29
7	K_2CO_3	dioxane	OAc	$Pd(OAc)_2$	$P(p\text{-}FPh)_3$	_	100	16	39
8	K_2CO_3	dioxane	OAc	$Pd(OAc)_2$	$P(p\text{-}OMePh)_3$	_	100	17	35
9	K_2CO_3	dioxane	OAc	$Pd(OAc)_2$	$P(o\text{-}tol)_3$	_	100	13	40
10	K_2CO_3	dioxane	OAc	$Pd(OAc)_2$	$P(tBu)_3HBF_4$	_	100	4	44
11	K_2CO_3	dioxane	OAc	$Pd(OAc)_2$	dppe	_	100	18	36
12	K_2CO_3	dioxane	OAc	$Pd(OAc)_2$	dppp	_	100	22	49
13	K_2CO_3	dioxane	OAc	$Pd(OAc)_2$	dppf	_	100	28	43
14	K_2CO_3	dioxane	OAc	$Pd(OAc)_2$	dppf	_	80	7	15
15	K_2CO_3	dioxane	Br	$Pd(OAc)_2$	dppf	_	100	0	13
16	K_2CO_3	dioxane	I	$Pd(OAc)_2$	dppf	_	100	0	4
17	K_2CO_3	toluene	OAc	$Pd(OAc)_2$	dppf	_	100	38	30
18	K_2CO_3	toluene	OAc	$Pd(acac)_2$	dppf	_	100	10	19
19	K_2CO_3	toluene	OAc	$Pd_2(dba)_3$	dppf	_	100	7	30
20	K_2CO_3	toluene	OAc	$PdCl_2$	dppf	_	100	30	19
21	K_2CO_3	toluene	OAc	$(PdallylCl)_2$	dppf	_	100	31	18
22	K_2CO_3	toluene	OAc	$Pd(OAc)_2$	dppf	AgOAc	100	7	5
23	K_2CO_3	toluene	OAc	$Pd(OAc)_2$	dppf	$AgNO_3$	100	0	6
24	K_2CO_3	toluene	OAc	$Pd(OAc)_2$	dppf	Ag_2CO_3	100	7	15
25	K_2CO_3	toluene	OAc	$Pd(OAc)_2$	dppf	18-Crown-6[f]	100	19	20
26	K_2CO_3	toluene	OAc	$Pd(OAc)_2$	dppf	NaOAc	100	53	17
27	K_2CO_3	toluene	OAc	$Pd(OAc)_2$	dppf	NaOAc[g]	100	41	16
28	K_2CO_3	toluene	OAc	$Pd(OAc)_2$	dppf	KOAc[h]	100	51	25
29	K_2CO_3	toluene	OAc	$Pd(OAc)_2$	dppf	KOAc	100	65	19

[a]All reactions were preformed in the presence of triturated 4 Å molecular sieves; reaction time: 4 h; [b] Bu_4NOAc was conveniently prepared from stochiometrical amounts of Bu_4NI and AgOAc; [c] 10 mol% for Entries 1-10 and 5 mol% for Entries 11-27; [d] 2 eq. for Entries 22-24 and 5 eq. for Entries 26, 29; [e] Yields were determined by GC on an average of two runs with tetradecane as an internal standard. [f] 10 mol%; [g] 3.5 eq. Bu_4NOAc, 7.5 eq NaOAc; [h] 2.5 eq.

Reducing the amount of base and Bu_4NOAc with respect to the reported conditions by Sakurai, resulted in a decrease of yield and selectivity (Entry 1), whereas the change of the base afforded better yields of *syn*-**9** and **17**. For example, potassium carbonate (Entry 2) was likely the most effective base to convert the substrate into detectable products rather than polymeric materials, which were observed with other bases.

The use of different ligands for palladium had also an effect on the reaction yields: monodentate phosphines (Entries 7-10) showed a limited efficiency in promoting the cyclotrimerization. Amongst bidentate ligands dppf showed higher efficiency and selectivity, compared to dppe and dppp (Entries 11-13).

Concerning the palladium source, $PdCl_2$ as well as $(PdClallyl)_2$ (Entries 20 and 21) displayed good efficacy, but $Pd(OAc)_2$ resulted the best metal precursor (Entry 17).

The influence of different solvents was also investigated, observing that DMF is the less suitable for the reaction (Entry 6). On the contrary, toluene had a positive effect by increasing the yield of *syn*-**9** and reducing the amount of dimer **17** (Entry 17) with respect to dioxane (Entry 13). This positive effect could be rationalized considering the special nature of this Heck reaction, in which the same olefin bears both the donor and the acceptor carbons of the coupling process. Because of the poor activation of the olefin exerted by the iodine atom, the insertion of the second vinyl iodide into the palladium-vinyl complex to is not particularly favored. In this scenario the homo-coupling mediated by Pd(IV)[13] species, leading to dimer **17**, is a seriously competitive reaction. Less polar solvents can stabilize less efficiently these palladium(IV) species, with beneficial effects for the cyclotrimerization process.

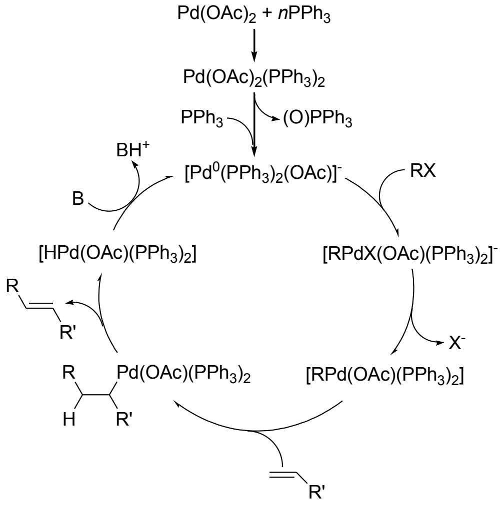
As stated by Sakurai, Bu_4NOAc resulted the sole tetrabutylammonium salt effective to promote the cyclotrimerizations of iodobornenes whereas Bu_4NBr or Bu_4NI (Entries 15 and 16 respectively) seemed to inhibit the reaction. This indicated that the presence of acetate ions played an active role in promoting the cyclotrimerization and not only in the stabilization of metal nanoparticles.

However, to obtain a good yield of cyclotrimer a high concentration of acetate was not sufficient. Indeed the presence of tetrabutylammonium was strictly required, as the reduction of its concentration decreased the yield of *syn*-**9**, even in presence of an excess of acetate ions (Entry 27). This is in accordance with the hypothesis of Sakurai that the catalytic activity is correlated to the formation and stabilization of palladium nanoparticles.

Moreover, the use of different additives had a considerable effect in terms of yield and selectivity. The use of sodium or potassium acetate had the most beneficial effect in the formation of cyclotrimer *syn*-**9** (Entries 26-29).

This behaviour can be explained by a very efficient and stereoselective hetero-coupling and supports the hypothesis of the formation of anionic Pd(0) and Pd(II) active complexes, as suggested by C. Amatore (Scheme 4.22).[14] The presence of relevant amounts of acetate ions favors the formation of highly active tri-coordinate anionic species of palladium(0), which underwent oxidative addition with the vinyl halide. After the dissociation of the halide from the anionic complex, the insertion step (the recognized rate-determining step) occurs with enhanced speed and the product is released by β-hydride elimination.

To rationalize the cyclotrimerization process with vinyl halide **16**, two insertion steps likely occur to provide an open vinyl trimer. The formation of a 6 membered ring is therefore possible through a 6-π-electrocyclization reaction and the cyclotrimer is produced after aromatization of the system as mentioned in Chapter 1 (Scheme 1.28)



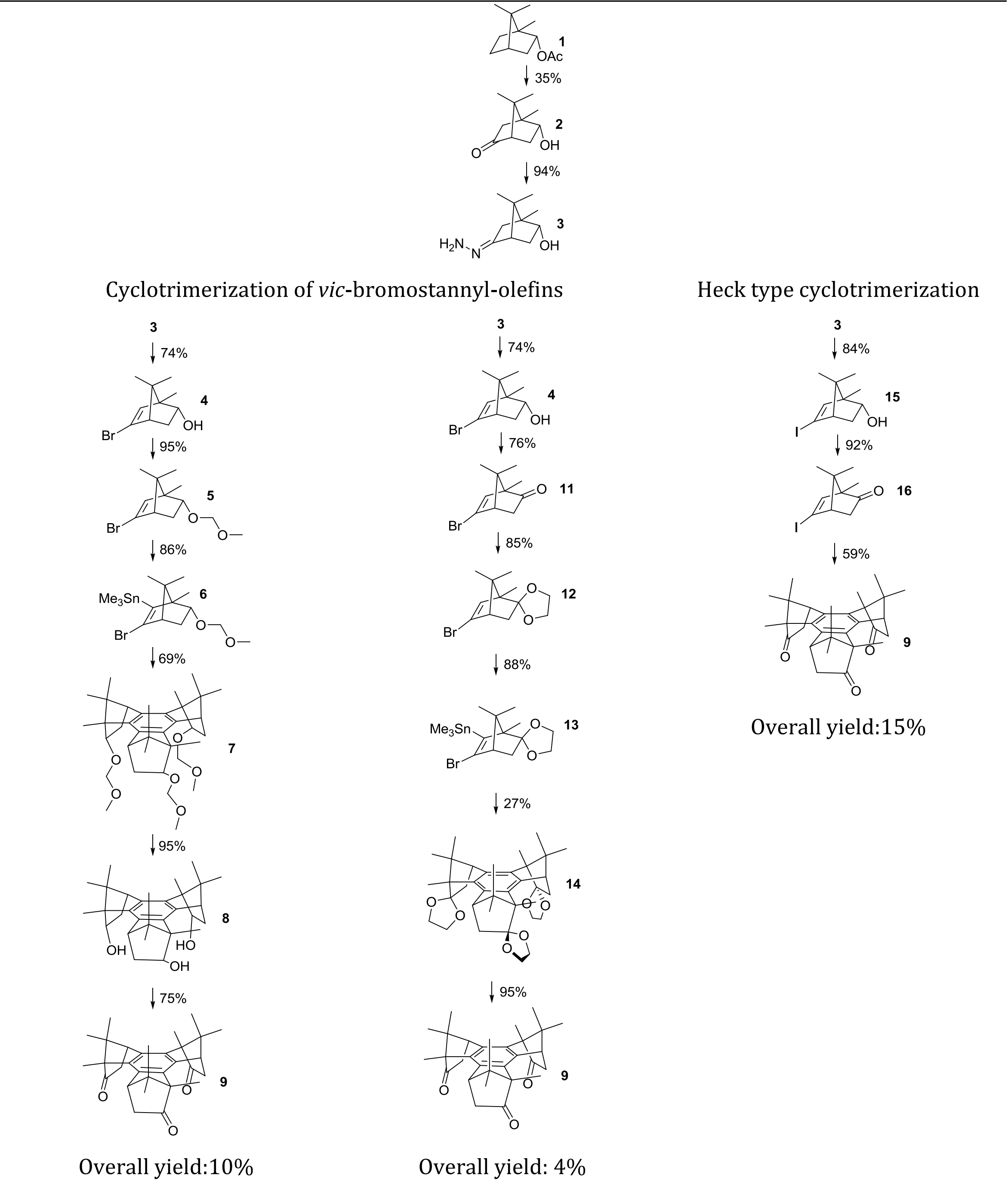
Scheme 4.22 Mechanism for palladium catalyzed Heck reaction as proposed by Amatore.[14]

On the other hand, the addition of silver salt, which was expected to force the iodine abstraction, led to the almost complete inhibition of the reaction (Entries 22-24). The detrimental effect of silver(I) can be rationalized invoking a redox interaction with palladium(II), which is prevented under these conditions to form the active palladium(0).

Although the formation of **17** could be ascribed to a palladium(IV)-mediated process,[13] the yields for this dimer were hardly related to the variation of experimental conditions (Table 4.1), and in general its minimization led to enhanced yields of the *syn*-trimer.

One hypothesis for the formation of **17** is the oxidative homo-coupling of the substrate, promoted by the presence of oxygen from molecular sieves in the reaction mixture. Unfortunately, all efforts to exclude oxygen from molecular sieves have so far failed in the attempt to avoid the formation of dimer **17**.

Finally, the reaction resulted reproducible in multi-gram scale, furnishing good amounts of *syn*-cyclotrimer. The overall yield of *syn*-**9** resulted 15% in five chemical transformations and was higher than any previous method (Scheme 4.23).

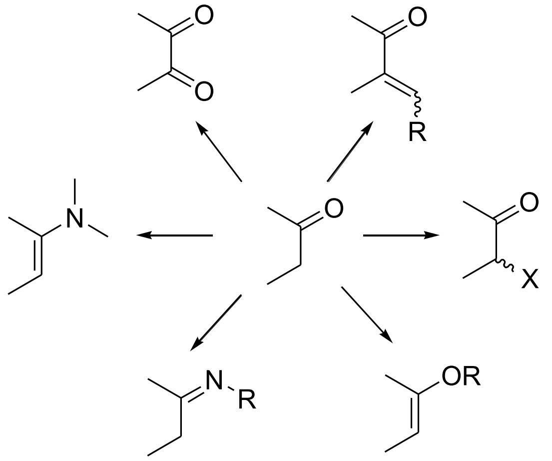


Scheme 4.23 Comparison of the synthetic routes for the synthesis of benzotricamphor.

4.3 MAIN ROUTES TO FUNCTIONALIZATION

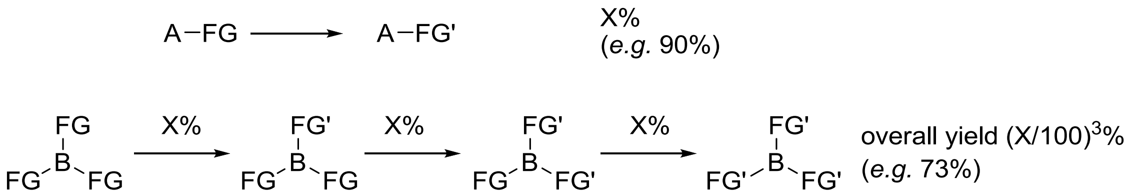
Benzotricamphor itself does not exhibit any recognition ability, but it is possible to prepare supramolecular hosts modifying its structure through opportune derivatizations. Condensation with hydroxylamine was the first reported functionalization inducing supramolecular behavior in benzotricamphor.[1]

The functionalization reactions, which were investigated with the aim to prepare derivatives of **9** exhibiting supramolecular properties, will be herein described. Benzotricamphor bears three carbonyl groups, so far many possible functionalizations are predictable and the most important ones are described below.



Scheme 4.24 Suitable functionalizations of carbonyl for the preparation of host compounds.

An important consideration must be bear in mind when dealing with multi-substituted scaffolds: the maximum yield expected for the whole transformation process is the yield of a single process raised to the n^th^ power, where n is the number of functional groups to be transformed. A practical example is reported in Scheme 4.25.



Scheme 4.25 Decrease of overall yield in a three-fold substituted substrates.

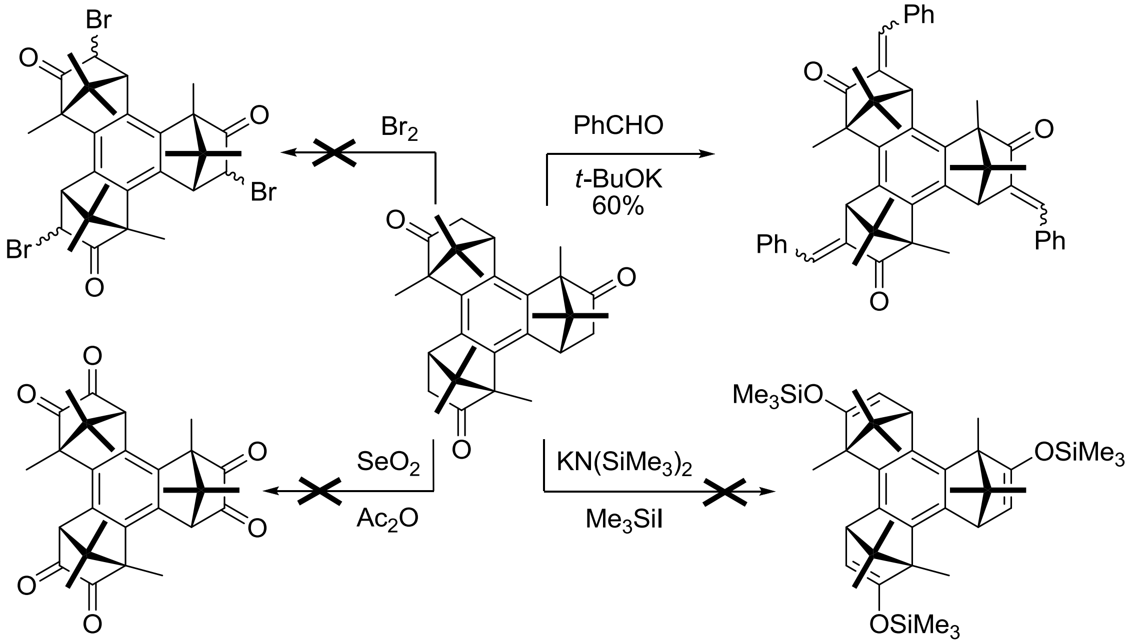
When we consider a reaction occurring on the monomer in 90% yield, the maximum yield expected for the whole transformation process in a trimer will be 72%. Moreover, during the reaction progress the substrate can also change its structure, sometimes increasing the steric hindrance in the proximity of the forthcoming reaction centers and therefore the yields of the subsequent steps is further decreasing. For these reasons it results crucial to find the very best conditions for the single transformation before applying the methodology to any trimer, in order to avoid deleterious waste of expensive materials.

Preliminary reactions

Early tests assessed the poor reactivity of *syn*-benzotricamphor **9** toward some common reactions which are highly efficient with camphor (Scheme 4.26). Surprisingly, benzotricamphor *syn*-**9** resulted completely unreactive to bromine[15] and to selenium dioxide.[16]

Furthermore, any attempt to convert the three carbonyls of *syn*-**9** into trimethylsilylenolethers with trimethylsilyl chloride (or iodide) failed to furnish reasonable yields of tris-trimethylsilylenolether derivative. Only inseparable mixture of mono-, di- and tri-silylated products were obtained. The poor reactivity could not be imputed to the inefficient conversion into the tris-enolate, since the same metalating procedure furnished good yields of tris-enolethers with other electrophiles (see next Paragraphs).

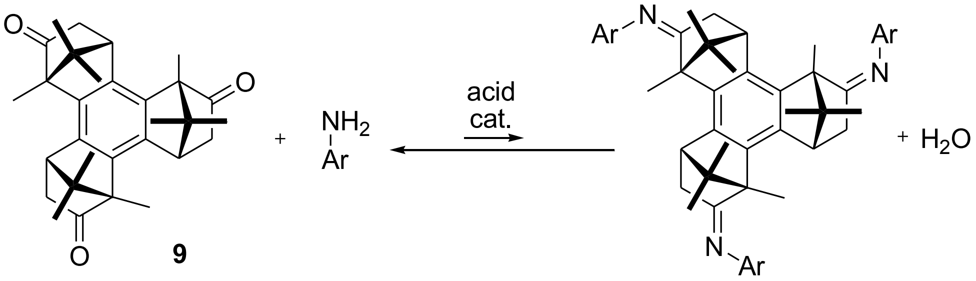
Finally, *syn*-**9** condensed with benzaldehyde, although it resulted inert towards formaldehyde or sterically hindered aromatic aldehydes such as mesitylaldehyde.



Scheme 4.26 Unfavored functionalizations for benzotricamphor.

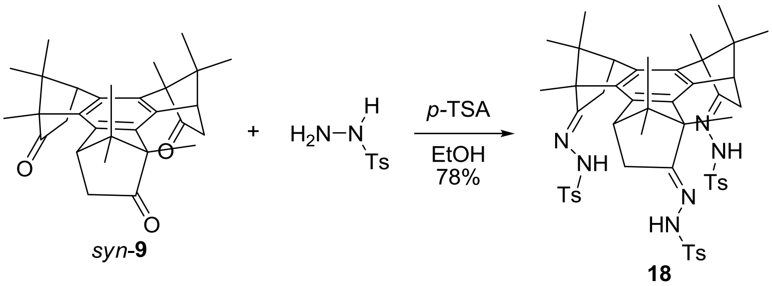
Condensation with nitrogen derivatives

The condensation with amines is one of the simplest reaction that can be carried on a ketone. Nevertheless, the condensation of benzotricamphor with aromatic amines, according to well established procedures,[17] did not afford the desired products, or in some cases the corresponding imines were too unstable to be isolated.



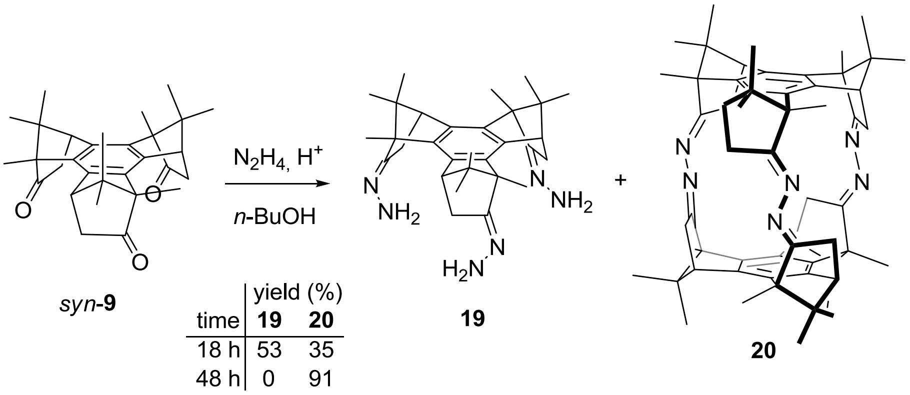
Scheme 4.27 Unfavored equilibrium in the condensation reaction of **9** with anilines.

The condensation product of *syn*-**9** with tosylhydrazide[18] was isolated in 78% yield, although it rapidly decomposed to benzotricamphor under very mild conditions.



Scheme 4.28 Synthesis of benzotricamphor tosylhydrazone **18**.

On the other hand, when **9** was reacted with hydrazine, the expected hydrazone **19** was isolated in 53% yield, concomitantly with the related azine **20** (35% yield). Coherently with the higher thermodynamic stability of azines with respect to hydrazones,[19] prolonged reaction times led to an almost complete conversion to **20**.



	yield (%)	
time	**19**	**20**
18 h	53	35
48 h	0	91

Scheme 4.29 Reaction of **9** with hydrazine. The tris-azine **20** is most stable product and is obtained selectively for longer reaction time.

Since molecular cages were considered potential supramolecular hosts, it was investigated the preparation of other molecular cages based on the condensation of aliphatic diamines with **9**.[20]

[redacted]

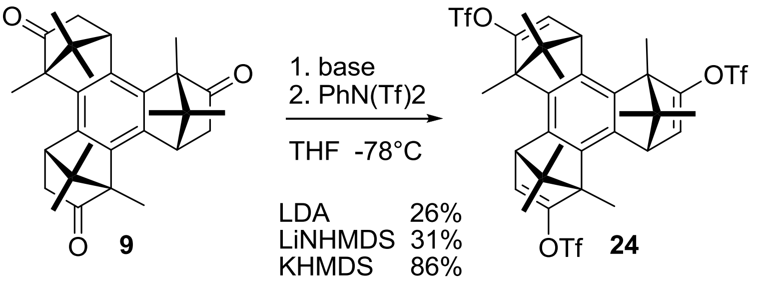
Product	n	Yield, %
20	0	91
21	2	39
22	3	0
23	4	25

Scheme 4.30 Synthesis of molecular cages from *syn*-**9** and aliphatic diamines.

The cages so far obtained were found relatively stable, but it was not possible to obtain larger cages using other diamines such as xililendiamines. In any case, the properties and supramolecular behavior of cages **20**-**23** has been investigated and will be described in the next Chapter.

Benzotricamphor triflate

Transformation of the carbonyl moieties of *syn*-**9** into three vinyl trifluoromethanesulphonic esters is a flexible and feasible methodology to access differently substituted benzotribornane through palladium-catalyzed cross-coupling reactions. The formation of the tris-enolester was accomplished by treatment of benzotricamphor with a strong base, followed by the addition of *N*-phenyl-bis(trifluoromethanesulfonimide).[21]

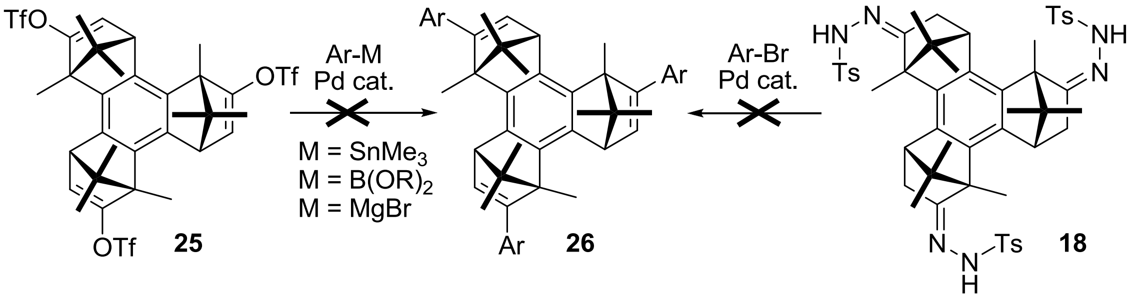


Scheme 4.31 Triflation of *syn*-**9**.

Cross-coupling reactions

Substitution of triflates at the vinylic positions with properly substituted aryl groups can produce a deeper cavity with stiff walls able to impose recognition properties to the overall structure.

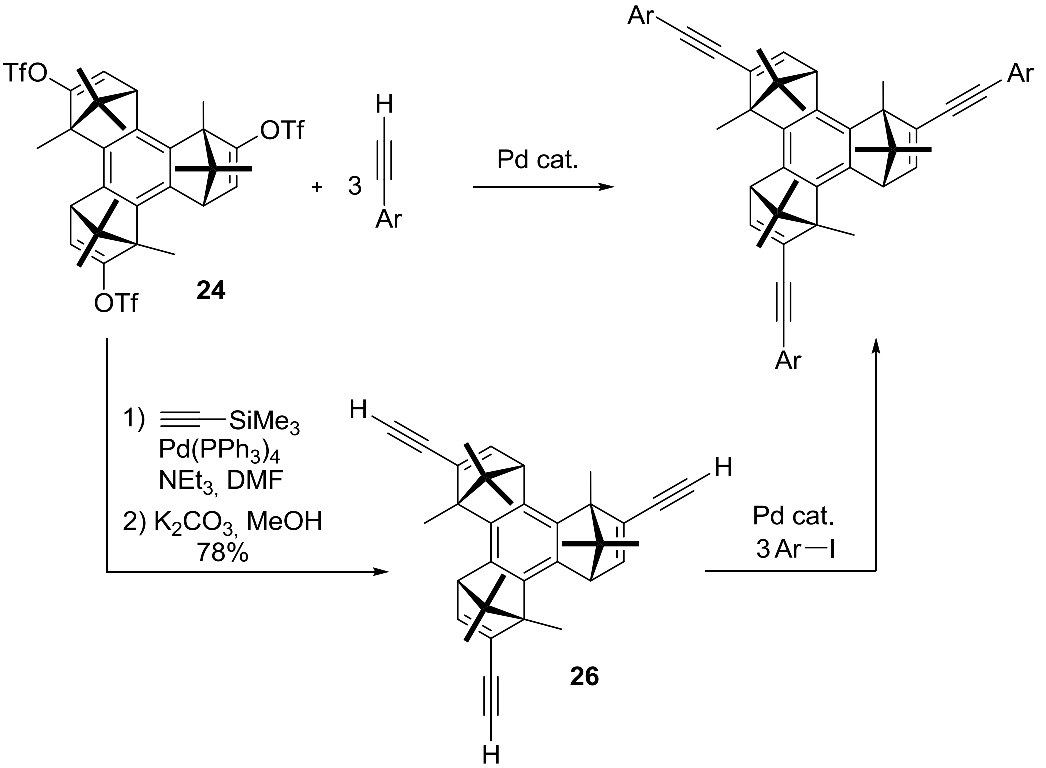
Several procedures were reported for the coupling of aryl groups with vinyl triflates.[22] In most cases when these reactions were applied to benzotricamphor triflate **24**, they failed to furnish the triple substituted products. Indeed, they afforded mixtures of mono- and di-substituted products, in addition to unreacted and decomposed material. The recently reported coupling of aryl bromides with tosyl hydrazones,[23] also failed when applied to the tosylhydrazone of benzotricamphor **18**.



Scheme 4.32 Unfavourable coupling reactions on benzotricamphor derivatives.

The failure of these procedures was imputed to the steric congestion exerted by the bridge-head methyls, that prevented an effective insertion of the arils. Therefore, in order to introduce these aromatic rings on the sterically congested positions of the benzotribornene scaffold, the presence of a stiff and slim spacer was speculated.

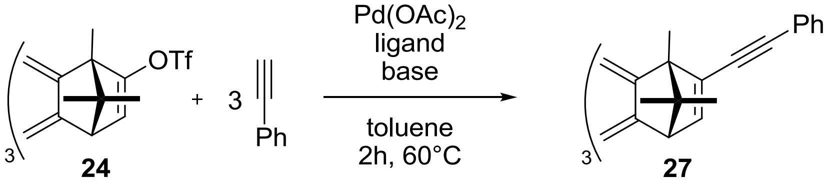
The functionalization of **24** by cross-coupling reactions was successful when Sonogashira-type couplings with terminal alkynes were applied. This procedure furnished good amounts of products either when terminal aryl-alkynes were coupled with **24**, or when aryl halides were coupled with the acetylene derivative **26**.[24]



Scheme 4.33 Sonogashira-type approaches to the functionalization of **24**.

The first approach was optimized after a screening of different bases and ligands[24] for the Pd-catalyzed coupling of **24** with phenylacetylene.

Table 4.2 Bases and ligands used for the coupling of phenylacetylene with **24**.[a]

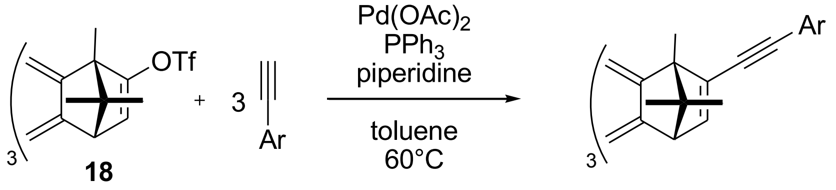


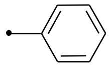
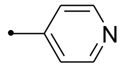
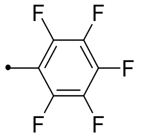
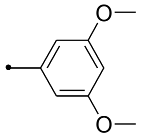
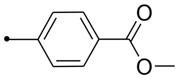
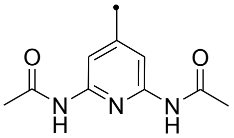
Entry	Base	Ligand	27 (%)[b]
1	piperidine	PPh_3	92
2	$HN(i\text{-}Pr)_2$	PPh_3	35
3	NEt_3	PPh_3	81
4	piperidine	$P(p\text{-tol})_3$	69
5	piperidine	$P(p\text{-OMe})_3$	41

[a] Reaction conditions: 3.3 eq. of phenylacetylene, 10 mol% of $Pd(OAc)_2$, 20 mol% of ligand, 10 eq. base. [b] Yields were determined by NMR using mesitylene as an internal standard.

The Sonogashira coupling of **24** with many aryl-acetylenes afforded six new differently substituted cyclotrimers (Table 4.3). The use of the related products as supramolecular hosts has been investigated and will be presented in Chapter 6.

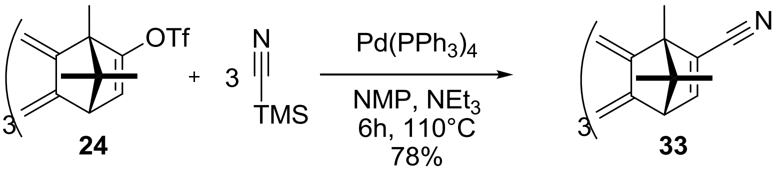
Table 4.3 Coupling of aryl-acetylenes on **24**.[a]



Entry	Ar	Ref.	Time (h)[b]	Product	Yield (%)[c]
1			2	**27**	85
2		24a	4	**28**	84
3		25	8	**29**	10
4		24b	6	**30**	62
5		26	6	**31**	82
6		27	6	**32**	40

[a] Reaction conditions: 4 eq. of arylacetylene, 10 mol% of $Pd(OAc)_2$, 20 mol% of PPh_3, 10 eq. of piperidine. [b] Reactions were followed by NMR and stopped after full consumption of **25**. [c] Isolated yields.

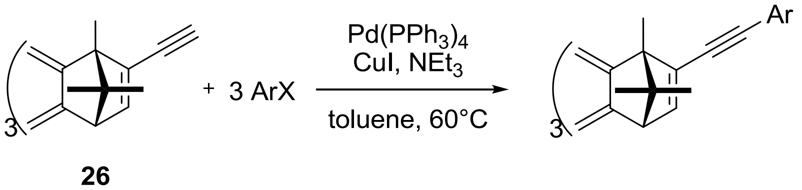
Similarly, triflate **24** reacted also with trimethylsilyl cyanide[28] to afford the corresponding benzotribornene nitrile **33** in good yield, which has been also investigated as possible supramolecular host (Chapter 6).



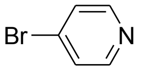
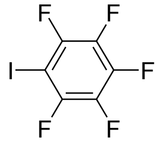
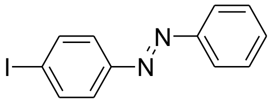
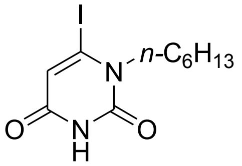
Scheme 4.34 Coupling of **25** with TMSCN.

The second approach for the functionalization of benzotricamphor triflate by Sonogashira couplings was based on the coupling of aryl halides with the acetylene derivative **26**. For this reaction literature conditions were employed.[29]

Table 4.4 Coupling of aryl-iodides with **26**.[a]



26

Entry	ArX	Ref.	Product	Yield (%)[b]
1		30	**28**	39
2			**29**	45
3		31	**34**	48
4		27	**35**	51

[a] Reaction conditions: 5 eq. of aryl halide, 10 mol% of $Pd(PPh_3)_4$, 10 eq. of NEt_3, overnight. [c] Isolated yields.

Although, this second approach led to the synthesis of new functionalized cyclotrimers in moderate yields, in one case it was possible to obtain the product in higher yield compared to the previous method (Table 4.3, Entry 3, compound **30**: 10%).

In conclusion, an optimized method for the cyclotrimerization of enantiopure iodobornenes based on the Heck self-coupling reaction was presented. The new cyclotrimerization protocol avoided the protection and de-protection steps and the use of toxic organostannyl compounds, therefore reducing the number of synthetic steps and leading to a general increase of the global yield with respect to the previous methodologies.

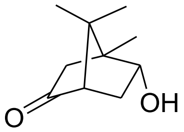
The screening of the possible derivatization reactions for benzotricamphor successfully led to the preparation of new differently functionalized benzocyclotrimers. The most suitable reactions to convert this C_3-symmetric scaffold into promising structures with supramolecular properties were the condensation with aliphatic diamines and the Sonogashira coupling of the trifluoromethanesulfonate derivative of benzotricamphor with terminal alkynes.

4.4 EXPERIMENTAL SECTION

GENERAL

All reactions were performed in flame-dried glassware blanketed with argon. Reagents purchased were used without further purifications. Solvents were eventually dried according procedures reported in Armarego, W. L. F. and Perrin, D. D. "Purification of Laboratory Chemicals", Fourth Ed., Butterworth-Heinemann Ed., 1996. The evolution of the reactions was monitored by TLC, GC-MS or 1H NMR. Flash-chromatography were performed with 230-400 mesh silica-gel. Melting points are uncorrected. Optical rotations were observed in a 10 cm cell. ^{1}H NMR and ^{13}C{1H} NMR spectra were recorded at 298 K, unless otherwise stated, on a Bruker AVANCE 300 spectrometer operating at 300.15 and 75.48 MHz respectively and the δ values in ppm are relative to TMS.

(1*S*,4*S*)-2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-5-one



2

A mixture of (-)-bornyl acetate (14 mL, 13.7 g, 70.0 mmol), oxone® (150.0 g, 244 mmol) and a 0.1 M aq. solution of RuO_4 (7 mL, 1mol % Ru)[1] in a solvent mixture of MeCN/AcOH/H_2O (1:1:1.4, 155 mL) were poured in a 500 mL screw-cap Pyrex bottle. The bottle was carefully sealed and placed in a water bath at rt. The slurry was maintained in vigorous stirring for 4 hours, during which heat evolved and pressure increased.[2] The end-point of the reaction was monitored by the change of colour from bright yellow to light green. The bottle was cautiously opened (dissolved oxygen in the liquid can cause foaming) and the resulting slurry was filtered, washing the inorganic salts with AcOEt (3×50 mL). The aqueous layer was diluted with H_2O (200 mL) and extracted with AcOEt (3×100 mL). Combined organic

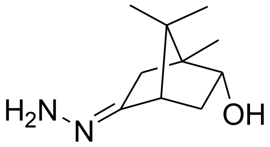
---

[1] The solution was obtained dissolving $RuCl_3 \cdot 2.5H_2O$ (1.26 g, 5.0 mmol) and $NaIO_4$ (2.14 g, 10.0 mmol) in H_2O (100 mL).

[2] CAUTION! In one case we reported a violent rupture of the bottle with splashing of the reaction mixture: the aluminium bucked was used to contain possible breaks, while water was used to remove the excess of heat produced by the reaction.

washing and extracts were placed into a 1 L beaker and cautiously neutralized adding solid Na_2CO_3. then the organic layer was separated from the aqueous phase, dried over $MgSO_4$ and concentrated at reduced pressure. The resulting oil was dissolved in EtOH (150 mL) and KOH (3.92 g, 70.0 mmol) was added. The resulting solution was stirred at r.t. under Ar for 5 hours, and concentrated at reduced pressure. The residue was diluted in satd. aq. NaCl and extracted with Et_2O (3×100 mL). Combined organic layers were washed with satd. aq. $Na_2S_2O_5$ sat (15 mL) and satd. aq. $NaHCO_3$ (15 mL), dried over $MgSO_4$ and concentrated in *vacuum*. The residue was purified by recrystallization from hot cyclohexane to afford 3.76 g (32% yield) of pale yellow crystals, m.p. = 235-237 °C; $[\alpha]_D^{22} = -86$ (*c* 1.1, CHC_3); ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 4.25 (1 H, d, *J* = 9.0 Hz), 2.64 (1 H, d, *J* = 18.7 Hz), 2.52 (1 H, m), 2.15 (1 H, d, *J* = 5.3 Hz), 1.91 (1 H, d, *J* = 18.7 Hz), 1.60 (1 H, br s), 1.31 (1 H, dd, *J* = 14.3 and 3.6 Hz), 1.03 (3 H, s), 0.98 (3 H, s), 0.95 (3 H, s).

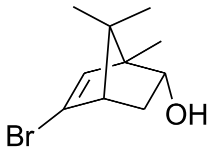
(1*S*,2*R*,4*S*)-2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-5-hydrazone



3

A mixture of 2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-5-one **2** (10.0 g, 59.5 mmol), hydrazine hydrate (25 mL, 520 mmol) and concd. H_2SO_4 (cat.) in *n*BuOH (80 mL) was heated at reflux using a Dean-Stark trap filled with molecular sieves (4 Å) for 18 h. The resulting solution was cooled, filtered and concentrated in *vacuum*. The resulting solid was washed with Et_2O to afford a white solid (10.2 g, 94% yield) pure enough for the next steps; m.p. = 145-147 °C; $[\alpha]_D^{22} = +6.8$ (*c* 2.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 4.68 (2 H, br s), 4.15 (1 H, d, *J* = 8.0 Hz), 2.52 (1 H, d, *J* = 16.9 Hz), 2.55-2.37 (1 H, m), 2.26 (1 H, d, *J* = 4.6 Hz), 1.84 (1 H, dd, *J* = 13.6, 3.5 Hz), 0.99 (3 H, s), 0.92 (3 H, s), 0.84 (3 H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm): 162.4, 75.6, 53.5, 50.4, 48.3, 36.2, 29.8, 20.3, 17.8, 13.0; IR (KBr) *v* 3323, 3152, 2950, 1679, 1628, 1449, 1386, 1339, 1106, 1047, 981, 894, 855, 654 cm^{-1}; *m/z* (EI, 70 eV):182 (M^+, 17), 164 (10), 149 (14), 123 (40), 79 (43), 55 (48), 41 (100%).

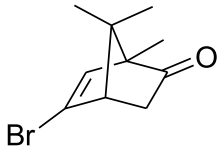
(1*S*,2*R*,4*S*)-3-Bromo-6-hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-ene



4

A flame-dried three-necked round-bottomed flask, equipped with a mechanical stirrer, an argon inlet with bubbler, and a dropping funnel, was placed in a sonication bath. Bromine (9.8 mL, 82.8 mmol) was added to a slurry of 2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-5-hydrazone **3** (6.10 g, 33.5 mmol) and *t*BuOK (15.0 g, 134 mmol) in dry Et_2O (350 mL) under sonication and vigorous stirring conditions over 1 h. During the addition evolution of gas (N_2) was observed. Water (100 mL) was added to the resulting mixture, the layers were separated, and the lower layer was extracted with Et_2O (3×50 mL). The combined organic extracts were dried with MgSO4, concentrated in vacuum, and the resulting red oil was purified by sublimation (110 °C at 7.5×10^{-2} Torr) to afford 5.7 g (74%) of **4** as colorless crystals. m.p. = 66-69 °C; $[\alpha]_D^{22}$ = +71.7 (*c* 2.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 5.78 (1 H, s), 4.61 (1 H, d, *J* = 7.6 Hz), 2.50-2.44 (2 H, m), 2.40 (1 H, s), 1.19 (3 H, s), 0.94 (3 H, s), 0.80 (3 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 133.8, 128.5, 79.4, 78.4, 60.3, 59.2, 37.7, 20.1, 18.8, 10.5; IR (KBr) *v* 3353, 2956, 2869, 1584, 1449, 1382, 1288, 1060, 1053 cm^{-1}; *m/z* (EI, 70 eV):186-188 (M^+ - C_2H_4O, 24),151 (10), 107 (99), 91 (100%).

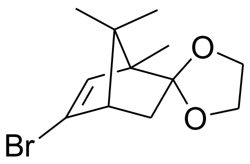
(1*S*,2*R*,4*S*)-5-Bromo-1,7,7-trimethylbicyclo[2.2.1]hept-5-en-2-one



11

A mixture of 5-bromo-6-hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-ene **4** (10.0 g, 43.3 mmol), *N*-methylmorpholine-*N*-oxide (7.6 g, 64.9 mmol), tetrapropylammonium perrutenate (300 mg, 0.87 mmol) and activated 4 Å molecular sieves (10 g) in dichloromethane (200 mL) was stirred at r.t. under Ar for 2 hours. The mixture was filtered on a celite pad, washing the solid with CH_2Cl_2 (50 mL) and the filtrate was concentrated at reduced pressure. The residue was diluted in 1M aq. HCl (150 mL) and the mixture was extracted with pentane (3×100 mL). Combined organic layers were washed with satd. aq. $NaHCO_3$ (50 mL), satd. aq. NaCl (50 mL), dried over $MgSO_4$ and concentrated in *vacuum*. The resulting oil was purified by flash-chromatography (eluant Et_2O/*n*-pentane in gradient from 0:10 to 1.5:8.5) to obtain 7.6 g (76% yield) as pale yellow oil; $[\alpha]_D^{22}$ = +508 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 5.64 (1 H, s), 2.67 (1 H, d, *J* = 3.4 Hz), 2.26 (1 H, dd, *J* = 16.8, 3.4 Hz), 2.04 (2 H, d, *J* = 16.8 Hz), 1.16 (3 H, s), 1.05 (3 H, s), 0.92 (3 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 213.5, 133.1, 131.1, 67.3, 60.3, 57.3, 35.2, 19.3, 19.1, 6.9; IR (film) *v* 2968, 2932, 2872, 1747, 1578, 1024 cm^{-1}; *m/z* (EI, 70 eV): 228-230 (M^+, 5), 186-188 (M^+ - C_2H_4O, 55), 107 (100%).

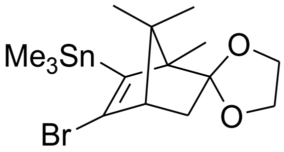
(1*S*,2*R*,4*S*)-5-Bromo-1,7,7-trimethylbicyclo[2.2.1]hept-5-en-2-ethanediol acetal



12

A mixture of 5-bromo-1,7,7-trimethylbicyclo[2.2.1]hept-5-en-2-one **11** (7.00 g, 30 mmol), ethylene glycol (4.00 mL, d 1.113 g/mL, 70 mmol) and *p*-toluenesulfonic acid (600 mg, 3.1 mmol) in toluene (300 mL) was heated at reflux using a Dean-Stark trap filled with molecular sieves (4 Å) for 18 h. The resulting solution was diluted with aqueous $NaHCO_3$ and extracted with Et_2O (4×50 mL). Combined organic layers were washed with satd. aq. $NaHCO_3$ (50 mL), satd. aq. NaCl (50 mL), dried over $MgSO_4$ and concentrated in *vacuum*. The resulting oil was purified by flash-chromatography (eluant Et_2O/*n*-hexane in gradient from 0:10 to 1.5:8.5) to obtain **12** (7.13 g, 85% yield) as pale yellow oil; $[\alpha]_D^{22}$ = +126 (*c* 1.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 5.84 (1 H, s), 4.00-3.75 (4 H, m), 2.40 (1 H, d, *J* = 3.7 Hz), 2.14-2.07 (2 H, dd, *J* = 12.8, 3.7 Hz), 1.63 (1 H, d, *J* = 12.8 Hz), 1.07 (3 H, s), 1.02 (3 H, s), 0.96 (3 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 137.1, 128.0, 119.5, 66.0, 64.4, 62.7, 59.9, 59.8, 40.1, 21.2, 20.4, 7.6; IR (film) *v* 2959, 2874, 1589, 1473, 1449, 1299, 1184, 1052, 988, 924, 874, 737 cm^{-1}; *m/z* (EI, 70 eV): 272-274 (M^+, 6), 186-188 (M^+ - C_2H_4O, 48), 107 (94), 86 (100%).

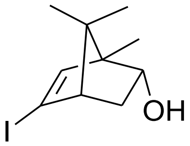
(1*S*,2*R*,4*S*)-5-Bromo-6-trimethylstannil-1,7,7-trimethylbicyclo[2.2.1]hept-5-en-2-ethanediol acetal



13

To a solution of dry diisopropylamine (7.70 mL, 54.9 mmol) in dry THF (60 mL), maintained at 0 °C under Ar, was added dropwise *n*-BuLi (2.5 M, 24 mL, 60 mmol), and the mixture was maintained at 0 °C for 15 min. 5-bromo-1,7,7-trimethylbicyclo[2.2.1]hept-5-en-2-ethanediol acetal **12** (6,47 g, 23.7 mmol) was added through a syringe, and the mixture was stirred for an additional 15 min. Trimethyltin chloride (5.28 g, 26.5 mmol) was added in one portion, and the mixture was allowed to warm to room temperature overnight. The resulting solution was poured into water (100 mL) and extracted with Et_2O (3×50 mL). The combined organic extracts were washed with H_2O (50 mL), saturated aqueous NaCl (50 mL), dried with MgSO4, and concentrated in vacuo to afford the product (9.09 g, 88% yield); m.p. = 40.9 °C; $[\alpha]_D^{22}$ = +86 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 3.97-3.71 (4 H, m), 2.39 (1 H, d, *J* = 3.7 Hz), 2.05-1.61 (2 H, dd, *J* = 12.2, 3.1 Hz), 1.05 (3 H, s), 1.00 (3 H, s), 0.98 (3 H, s), 0.24 (9 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 149.5, 139.9, 119.1, 67.1, 65.4, 63.8, 61.6, 58.9, 40.0, 20.9, 20.0, 9.4, -7.7; IR (KBr) *v* 2965, 1554, 1387, 1299, 1173, 1091, 1018, 769, 527 cm^{-1}; *m/z* (EI, 70 eV): 436 (M^+, 2), 421 (M^+ - CH_3, 3), 377 (8), 350 (28), 335 (85), 255 (70), 229 (72), 105 (100%).

(1*S*,2*R*,4*S*)-5-Iodo-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-5-ene

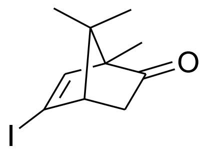


15

A solution of 2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-5-hydrazone **3** (11.20 g, 61.4 mmol) and TMG (48 mL, 382 mmol) in dry Et_2O (100 mL) was added in 30 min to a solution of I_2 (31.75 g, 125 mmol) and TMG (30 mL, 239 mmol) in dry Et_2O

(200 mL) at room temperature. The resulting slurry was concentrated at reduced pressure, H_2O (150 mL) was added and the mixture was extracted with hexane (5×100 mL). The combined organic layers were washed with 1M aq. HCl (50 mL), satd. aq. NaCl (50 mL), dried over $MgSO_4$ and concentrated in *vacuum*. The residue oil was purified by flash chromatography (eluant AcOEt/hexanes 3:7) to obtain 14.75 g (86% yield) of tan crystals; m.p. 55-56 °C. $[\alpha]_D^{22}$ = +76 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 6.14 (1 H, br s), 4.12 (1 H, br s), 2.48 (1 H, dd, *J* = 3.8, 1.0 Hz), 2.40 (1 H, ddd, *J* = 13.2, 3.8, 0.6 Hz), 1.13 (3 H, s), 1.07 (1 H, br s), 0.96 (1 H, dd, *J* = 13.2, 2.5 Hz), 0.95 (3 H, s), 0.82 (3 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 143.4, 100.0, 78.4, 63.4, 61.1, 59.5, 37.6, 20.3, 18.8, 10.2; IR (KBr) *v* 3369, 2957, 1567, 1448, 1287, 1059 cm^{-1}; *m/z* (EI, 70 eV): 234 (M^+-C_2H_4O, 53), 151 (57), 109 (52), 107 (100), 105 (54%).

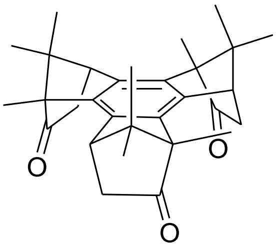
(1*S*,4*S*)-5-Iodo-1,7,7-trimethylbicyclo[2.2.1]hept-5-en-2-one



16

A mixture of 5-iodo-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-5-ene **15** (18.21 g, 65.5 mmol), *N*-methylmorpholine-*N*-oxide (13.00 g, 111 mmol), $RuCl_3 \cdot H_2O$ (0.44 g, 1.96 mmol, 3 mol% Ru) and activated 4 Å molecuar sieves (18 g) in acetonitrile (300 mL) was stirred at r.t. under Ar for 3 hours. The mixture was filtered on a celite pad, washing the solid with CH_2Cl_2 (50 mL) and the filtrate was concentrated at reduced pressure. The residue was diluted in 1M aq. HCl (150 mL) and the mixture was extracted with pentane (3×100 mL). Combined organic layers were washed with satd. aq. $NaHCO_3$ (50 mL), satd. aq. $Na_2S_2O_5$ (50 mL), satd. aq. NaCl (50 mL), dried over $MgSO_4$ and concentrated in *vacuum*. The resulting oil was purified by flash-chromatography (eluant Et_2O/*n*-pentane in gradient from 0:10 to 1.5:8.5) to obtain 15.78 g (87% yield) as pale yellow oil; $[\alpha]_D^{22}$ = +571 (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 5.97 (1 H, dd, *J* = 1.1, 1.0 Hz), 2.74 (1 H, dd, *J* = 3.5, 1.1 Hz), 2.18 (1 H, ddd, *J* = 16.9, 3.5, 1.0 Hz), 1.96 (1 H, d, *J* = 16.9 Hz), 1.14 (3 H, s), 1.04 (3 H, s), 0.92 (3 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 213.4, 139.8, 104.6, 68.2, 60.6, 60.2, 34.8, 19.4, 19.2, 6.6; IR (film) *v* 2961, 1744, 1561, 1023, 673 cm^{-1}; *m/z* (EI, 70 eV): 276 (M$^+$, 19), 234 (100), 107 (87), 91 (60), 79 (29), 77 (18%).

(+)-*syn*-(1*R*,4*S*,5*R*,8*S*,9*R*,12*S*)-3,4,7,8,11,12-hexahydro-1,5,9,13,13’,14,14’,15,15’-nonamethyl-1,4:5,8:9,12-trimethanotriphenylen-2,6,10-trione



syn-**9**

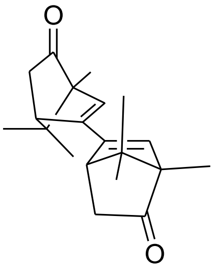
To a solution of 5-Bromo-6-trimethylstannil-1,7,7-trimethylbicyclo[2.2.1]hept-5-en-2-ethanediol acetal **13** (9.09 g, 20.8 mmol) in dry NMP (15 mL), maintained at –20 °C under Ar, copper(I)thiophenecarboxylate (5.96 g, 31.3 mmol) was added portionwise. The well-stirred mixture was allowed to warm to room temperature overnight. The resulting slurry was diluted with 20% aqueous NH_3 (50 mL) and extracted with AcOEt (3×50 mL). The combined organic extracts were washed with H_2O (50 mL) and saturated aqueous NaCl (50 mL), dried with $MgSO_4$ and concentrated in vacuo. The resulting oil was dissolved in a 1:1 mixture of THF and 1M HCl (20 mL) and the solution was stirred at room temperature for 24 hrs. Volatile materials were removed under *vacuum* and the resulting oil was purified by flash-chromatography (eluant Et_2O/cyclohexane in gradient from 1:9 to 5:5) to afford 880 mg (26% yield) of *syn*-**9** as colourless crystals.

Tetrabutylammonium acetate was prepared by mixing stochiometric amounts of AgOAc and tetrabutylammonium iodide in methanol. Silver(I) bromide was filtered and the solution was concentrated in *vacuum* to afford an oil that was heated at 120 °C for 1 h under *vacuum*. Cooling to room temperature was followed by immediate solution in the desired solvent under Ar atmosphere.[32]

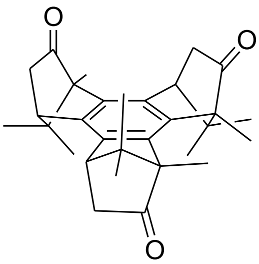
General procedure for cyclotrimerization screening (Table 4.1). An oven-dried Schlenk tube equipped with a magnetic stirring bar was charged with ligand (0.05

mmol), Pd source (0.025 mmol), base (2.5 mmol), additives, molecular sieves 4 Å (200 mg) and was closed with a septum. The vessel was evacuated and backfilled with argon (for a total of 3 times), then a degassed solution of anhydrous *n*-Bu$_4$NOAc (0.75 g, 2.5 mmol) in 3 mL of dry solvent was added via syringe. The solution was heated to 100 °C for 15 min and then a solution of (1*S*,4*S*)-5-iodo-1,7,7-trimethylbicyclo[2.2.1]hept-5-en-2-one **16** (138 mg, 0,5 mmol) in 1 mL of solvent was added via syringe. The mixture was stirred at 100 °C for 4 h, cooled to room temperature, diluted in Et$_2$O and washed with 1M HCl. Tetradecane (50 µL) was added to the solution as an internal standard and then the reaction mixture was analyzed via GC.

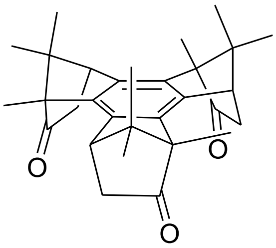
Scale-up procedure for cyclotrimerization of 5-iodo-1,7,7-trimethylbicyclo[2.2.1]hept-5-en-2-one



17



anti-**9**



syn-**9**

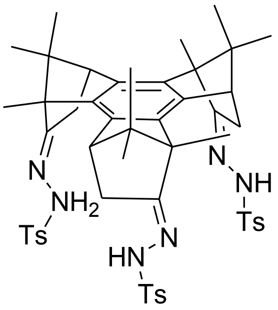
A mixture of KOAc (15.4 g, 147 mmol), K$_2$CO$_3$, (20,3 g, 147 mmol), activated 4 Å molecular sieves (16 g), Pd(OAc)$_2$ (328 mg, 1,46 mmol) and dppf (809 mg, 1.46 mmol) was evacuated and backfilled with argon (for a total of 3 times). Then a degassed solution of anhydrous *n*-Bu$_4$NOAc (44,3 g, 147 mmol) in 200 mL of toluene was added via syringe. The solution was heated to 100 °C for 15 min (the mixture turned to black). Then, a solution of (1*S*,4*S*)-5-iodo-1,7,7-trimethylbicyclo[2.2.1]hept-5-en-2-one **16** (8.10 g, 29.3 mmol) in dry toluene (50 mL) was added via syringe. The mixture was stirred at 100 °C for 8 hours, cooled to rt and filtered on a celite pad, washing the solid with AcOEt. Water (50 mL) was added to the filtrate and the resulting mixture was extracted with Et$_2$O (3×50 mL). The combined organic layers were washed with 1M HCl (2×50 mL), satd. aq. NaHCO$_3$ (50 mL), dried over MgSO$_4$ and concentrated at reduced pressure. The residue oil was purified by flash-chromatography (eluant Et$_2$O/cyclohexane in gradient from 1: 9 to 5:5).

First eluate: **1,7,7-trimethyl-5-(4,7,7-trimethyl-5-oxobicyclo[2.2.1]hept-2-en-2-yl)bicyclo[2.2.1]hept-5-en-2-one**, recristallized from cyclohexane, 0,70 g (16% yield) as colourless crystals; m.p. = 185 °C. $[\alpha]_D^{22}$ = +1509 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 5.41 (2 H, s), 2.68 (2 H, d, *J* = 3.1 Hz), 2.25 (2 H, dd, *J* = 16.7, 3.1 Hz), 1.63 (2 H, d, *J* = 16.8 Hz), 1.07 (6 H, s), 1.05 (6 H, s), 0.92 (6 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 214.4, 149.6, 127.3, 66.8, 59.1, 48.9, 36.2, 19.4, 19.1, 6.6; IR (KBr) *ν* 2962, 1737, 1442, 1030, 757 cm^{-1}; *m/z* (EI, 70 eV): 298 (M^+, 47), 214 (100), 199 (33), 91 (23%).

Second eluate: **(+)-*syn*-(1*R*,4*S*,5*R*,8*S*,9*R*,12*S*)-3,4,7,8,11,12-hexahydro-1,5,9,13,13',14,14',15,15'-nonamethyl-1,4:5,8:9,12-trimethanotriphenylen-2,6,10-trione**, recristallized from methanol, 2.56 g (59% yield) as colourless crystals; m.p. = 272-273 °C. $[\alpha]_D^{22}$ = +691 (*c* 1.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 3.36 (3 H, d, *J* = 4.0 Hz), 2.46 (3 H, dd, *J* = 17.6, 4.0 Hz), 1.80 (3 H, d, *J* = 17.6 Hz), 1.33 (9 H, s), 1.02 (9 H, s), 0.85 (9 H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 213.8, 143.6, 132.6, 65.1, 58.8, 46.1, 38.9, 20.0, 19.2, 8.0; IR (KBr) ν 2966, 1739, 1038 cm^{-1}; *m/z* (EI, 70 eV): 444 (M^+, 50), 402 (100), 374 (58), 360 (87), 346 (68), 331 (79%).

Third eluate: **(+)-*anti*-(1*S*,3*R*,4*R*,5*R*,6*R*,8*S*,9*R*,10*R*,12*S*)-1,2,7,8,11,12-hexahydro-4,5,9,13,13',14,14',15,15'-nonamethyl-1,4:5,8:9,12-trimethanotriphenylene-3,6,10-trione**, 0,48 g (11% yield) as colourless crystals; m.p. = 240 °C (dec). $[\alpha]_D^{22}$ = +753 (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 3.33 (1 H, d, *J* = 4.0 Hz), 3.15 (1 H, d, *J* = 3.8 Hz), 3.08 (1 H, d, *J* = 3.9 Hz), 2.58 (1 H, dd, *J* = 17.5, 3.9 Hz), 2.56 (1 H, dd, *J* = 17.4, 3.8 Hz), 2.46 (1 H, dd, *J* = 17.5, 3.9 Hz), 2.05 (1 H, d, *J* = 17.4 Hz), 1.96 (1 H, d, *J* = 17.5 Hz), 1.90 (1 H, d, *J* = 17.5 Hz), 1.36 (3 H, s), 1.33 (3 H, s), 1.32 (3 H, s), 1.05 (3 H, s), 0.98 (3 H, s), 0.96 (3 H, s), 0.81 (3 H, s), 0.66 (3 H, s), 0.59 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 214.4, 214.0, 213.5, 145.0, 141.8, 140.0, 138.4, 137.9, 131.9, 66.7, 66.4, 65.4, 60.0, 59.9, 59.5, 59.3, 46.7, 46.3, 45.4, 39.9, 39.6, 39.3, 20.2, 20.14, 20.10, 19.5, 19.38, 19.37, 9.8, 9.8, 8.2; IR (KBr) ν 2970, 1742, 1392, 1029 cm^{-1}; *m/z* (EI, 70 eV): 444 (M^+, 58), 402 (66), 374 (63), 360 (79), 345 (100), 331 (68), 207 (25%).

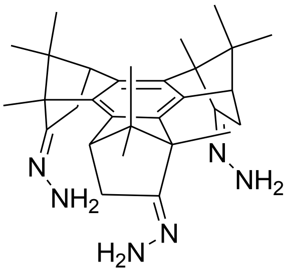
E,E,E-(1*R*,4*S*,5*R*,8*S*,9*R*,12*S*)-3,4,7,8,11,12-Hexahydro-1,5,9,13,13',14,14',15,15'-nonamethyl-1,4:5,8:9,12-trimethanotriphenylen-2,6,10-tri-tosylhydrazide



syn-**18**

In a round bottomed-flask fitted with a dropping funnel filled with activated 4 Å molecular sieves and topped with a condenser, a solution of *syn*-**9** (0.50 g, 1.12 mmol), tosylhydrazine (3.14 g, 16.9 mmol) and conc. H_2SO_4 (20 µL, 0.4 mmol) in EtOH (10 mL) was refluxed for 18 hours. Excess of tosylhydrazine was filtered out and volatile materials were removed in *vacuum*. The residue was purified by flash chromatography on basic alumina (eluant cyclohexane/AcOEt in gradient from 9:1 to 2:8) to afford colorless crystals (0.78 g, 74% yield). The product slowly decomposed to *syn*-**9**, even when stored at -20 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.86 (6 H, *J* = 8.1 Hz), 7.35 (6 H, *J* = 8.1 Hz), 6.90 (3 H, broad), 3.1 (3 H, *J* = 3.4 Hz), 2.47 (9 H, s), 2.05 (3 H, dd *J* = 15.9, 3.2 Hz), 1.29 (9 H, s), 1.23 (3 H, *J* = 16.1 Hz) 0.69 (9 H, s), 0.65 (9 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 144.3, 129.4, 128.9, 128.5, 128.0, 126.2, 109.6, 77.2, 47.0, 21.7, 19.9, 19.3, 18.8, 9.3.

E,E,E-(1*R*,4*S*,5*R*,8*S*,9*R*,12*S*)-3,4,7,8,11,12-Hexahydro-1,5,9,13,13',14,14',15,15'-nonamethyl-1,4:5,8:9,12-trimethanotriphenylen-2,6,10-trihydrazone

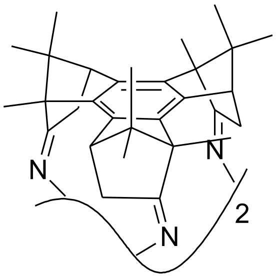


syn-**19**

In a round bottomed-flask fitted with a dropping funnel filled with activated 4 Å molecular sieves and topped with a condenser, a solution of *syn*-**9** (200 mg, 0.45 mmol), hydrazine hydrate (1.5 mL, 31.0 mmol) and conc. H_2SO_4 (2 µL, $4.0 \cdot 10^{-2}$

mmol) in *n*-BuOH (5 mL) was refluxed for 18 hours. Volatile materials were removed by suction and the residue was triturated with hexane, filtered and washed with hexane, to afford 117 mg (53% yield) of colourless crystals; m.p. = 300 °C (dec.); $[\alpha]_D^{22}$ = +165 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 4.73 (6 H, br s), 3.29 (3 H, d, *J* = 4.0 Hz), 2.44 (3 H, dd, *J* = 16.0, 4.0 Hz), 1.77 (3 H, d, *J* = 16.0 Hz), 1.42 (9 H, s), 0.91 (9 H, s), 0.73 (9 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 161.6, 138.9, 136.0, 58.8, 58.6, 47.1, 30.2, 19.6, 19.1, 10.0; IR (KBr) ν 2924, 1630, 1448, 1384, 872 cm^{-1}.

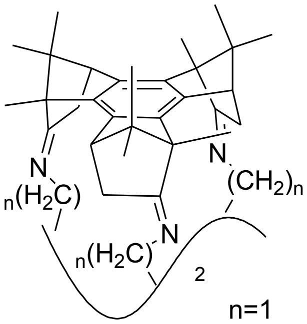
(+)-*syn*-(1*R*,4*S*,5*R*,8*S*,9*R*,12*S*)-3,4,7,8,11,12-Hexahydro-1,5,9,13,13',14,14',15,15'-nonamethyl-1,4:5,8:9,12-trimethanotriphenylen-2,6,10-trione Azine



syn-**20**

In a round bottomed-flask fitted with a dropping funnel filled with activated 4 Å molecular sieves and topped with a condenser, a solution of *syn*-**9** (90 mg, 0.20 mmol), hydrazine hydrate (0.75 mL, 15 mmol) and conc. H_2SO_4 (2 μL, $4.0\cdot10^{-2}$ mmol) in *n*-BuOH (3 mL) was refluxed for 64 hours. Volatile materials were removed by suction and the residue was purified by flash-chromatography (eluant AcOEt/hexane 4:6) to obtain 80 mg (91% yield) of colourless crystals; m.p. = 350 °C (dec.); $[\alpha]_D^{22}$ = +843 (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.14 (6 H, d, *J* = 3.9 Hz), 2.69 (6 H, dd, *J* = 16.9, 3.9 Hz), 1.43 (6 H, d, *J* = 16.9 Hz), 1.43 (18 H, s), 0.97 (18 H, s), 0.77 (18 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 173.6, 140.6, 135.2, 59.2, 57.1, 47.2, 33.0, 19.7, 19.2, 9.4; IR (KBr) ν 2975, 1662, 1444, 1385 cm^{-1}.

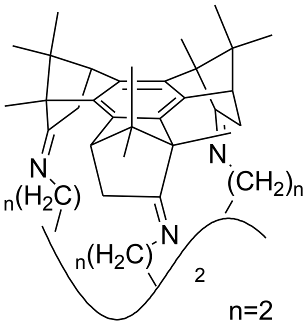
(+)-*syn*-(1*R*,4*S*,5*R*,8*S*,9*R*,12*S*)-3,4,7,8,11,12-Hexahydro-1,5,9,13,13',14,14',15,15'-nonamethyl-1,4:5,8:9,12-trimethanotriphenylen-2,6,10-trione Ethane Imine



syn-**21**

A mixture of *syn*-**9** (200 mg, 0.45 mmol), 1,2-diaminoethane (90 μL, 1.4 mmol), $BF_3 \cdot OEt_2$ (5 μL, $4.5 \cdot 10^{-2}$ mmol), pulverized activated 4 Å molecular sieves (800 mg) in dry toluene (5 mL) was heated at 130 °C for 64 hours in sealed tube. The resulting slurry was centrifuged and the liquid phase was concentrated in *vacuum*. The resulting solid material was purified by trituration with hexane and filtration, to afford 84 mg (39% yield) of colourless crystals; m.p. = 300 °C (dec.); $[\alpha]_D^{22}$ = +496 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.40 (6 H, m), 3.23 (3 H, d, *J* = 3.8 Hz), 2.60 (6 H, m), 2.37 (3 H, dd, *J* = 16.2, 3.8 Hz), 1.39 (3 H, d, *J* = 16.2 Hz), 1.36 (9 H, s), 0.88 (9 H, s), 0.81 (9 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 179.1, 140.9, 135.4, 60.6, 56.7, 54.1, 47.2, 32.6, 19.9, 19.1, 9.5; IR (KBr) ν 2975, 1662, 1444, 1385 cm^{-1}.

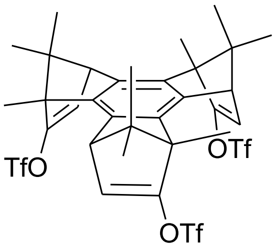
(+)-*syn*-(1*R*,4*S*,5*R*,8*S*,9*R*,12*S*)-3,4,7,8,11,12-Hexahydro-1,5,9,13,13',14,14',15,15'-nonamethyl-1,4:5,8:9,12-trimethanotriphenylen-2,6,10-trione Butane Imine



syn-**23**

A mixture of *syn*-**9** (100 mg, 0.22 mmol), 1,4-diaminobutane (200 μL, 2 mmol), PTSA (4.3 mg, 0.022 mmol), pulverized activated 4 Å molecular sieves (400 mg) in dry toluene (2.5 mL) was heated at 100 °C for 8 days in sealed tube. The resulting slurry was centrifuged, washing the solid with dichloromethane (2×5 mL) and the organic phases were concentrated in *vacuum*. The resulting solid material was extracted with ether (6×5 mL, with sonication for 3 min each), recovering the liquid by centrifugation. Ethereal extracts were concentrated in *vacuum* and the resulting solid was purified by trituration with ethyl acetate (2×0.5 mL), to affording 29 mg (25% yield) of colourless crystals, m.p. = 250 °C (dec.); $[\alpha]_D^{22}$ = +439 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.47 (6 H, m), 3.25 (3 H, d, *J* = 3.8 Hz), 2.83 (6 H, m), 2.42 (3 H, dd, *J* = 16.0, 3.8 Hz), 1.50 (3 H, d, *J* = 16.0 Hz), 1.37 (9 H, s), 1.25 (6 H, m), 0.90 (9 H, s), 0.81 (9 H, s), 0.59 (6 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 178.8, 140.4, 135.5, 60.6, 56.5, 52.9, 47.1, 31.8, 27.3, 19.9, 19.2, 9.6; IR (KBr) ν 2968, 2923, 1685, 1385, 1368 cm^{-1}.

***syn*-(1*R*,4*R*,5*R*,8*R*,9*R*,12*R*)-2,6,10-Tris(trifluoromethanesulfonate)-4,8,12-hexahydro-1,5,9,13,13',14,14',15,15'-nonamethyl-1,4:5,8:9,12-trimethanotriphenylene**



syn-**24**

To a solution of *syn*-**9** (2.10 g, 4.73 mmol) in dry THF (50 mL) maintained at -78 °C under Ar was added in 30 min. KHMDS in toluene (0.5 M, 42.6 mL, 21.3 mmol) and the mixture was maintained at the same temperature for 3 hours. *N*-phenyl-bis(trifluoromethanesulfonimide) (7.60 g, 21.3 mmol) in dry THF (20 mL) was added via syringe and the mixture was left to rise to r.t. overnight. The resulting solution was concentrated in *vacuum*, water (30 mL)was added and the mixture was extracted with Et_2O (3×30 mL). Combined organic extracts were washed with H_2O (30 mL), saturated aqueous NaCl (30 mL), dried over $MgSO_4$ and concentrated in *vacuum*. The resulting oil was purified by trituration with MeOH (3×5 mL) affording the product (3,30 g, 83% yield) as white solid, m.p. = 188 °C; $[\alpha]_D^{22}$ = -26 (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.18 (3 H, d, *J* = 3.9 Hz), 3.63 (3 H, d, *J* =

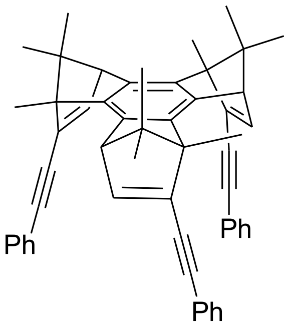
3.9 Hz), 1.39 (9 H, s), 1.23 (9 H, s), 0.76 (9 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 162.5, 139.0, 138.6, 122.5, 118.4 (q, *J* = 321.6 Hz), 74.1, 60.6, 53.0, 21.5, 19.6, 15.7, 8.5; IR (KBr) ν 2963, 1424, 1143, 1053 cm^{-1}; *m/z* (EI, 70 eV): 840 (M$^+$, 18), 707 (56), 691 (100), 574 (63), 557 (27), 540 (39), 532 (46), 515 (25).

General procedure for coupling reactions of *syn*-24 with phenylacetylene screening (Table 4.2). An oven-dried Schlenk tube equipped with a magnetic stirring bar was charged with ligand (20 mol %), $Pd(OAc)_2$ (1,2 mg, 5 µmol), *syn*-**24** (42 mg, 50 µmol) and was closed with a septum. The vessel was evacuated and backfilled with argon (for a total of 3 times) and degassed freshly distilled toluene (2 mL) was added via syringe. Base (30 eq.) and phenylacetylene (20 µl, 180 µmol) were added via syringe. The mixture was heated at 60 °C for 2 h, cooled to room temperature and concentrated in *vacuum*. Mesitylene (10 µL) was added as an internal standard and then the reaction mixture was analyzed via NMR.

General procedure for coupling reactions of *syn*-24 with arylacetylenes (Table 4.3). A mixture of $Pd(OAc)_2$ (5.4 mg, 23.8 µmol), PPh_3 (12.6 mg, 47.6 µmol), arylacetilene (0.95 mmol, 4 eq.) and *syn*-**24** (200 mg, 238 µmol) was evacuated and backfilled with argon (for a total of 3 times). Then degassed freshly distilled toluene (8 mL) and piperidine (0,72 mL, 7.2 mmol) was added via syringe. The mixture was heated to 60 °C and the evolution of the reaction was monitored by NMR. After full consumption of *syn*-**24**, the mixture was cooled to room temperature and concentrated in *vacuum*. The product was purified by Flash chromatography with appropriate eluant and stationary phase.

Product	Time (hrs)	Eluant	stationary phase	Yield (%)
Syn-**27**	2	cyclohexane	silica gel	85
Syn-**28**	4	AcOEt/EtOH from 10:0 to 7:3	basic alumina	84
Syn-**29**	8	pentane	silica gel	10
Syn-**30**	6	cyclohexane/CH_2Cl_2 from 10:0 to 7:3	silica gel	62
Syn-**31**	6	cyclohexane/Et_2O from 9:1 to 7:3	silica gel	82
Syn-**32**	6	AcOEt/EtOH from 10:0 to 7:3	basic alumina	40

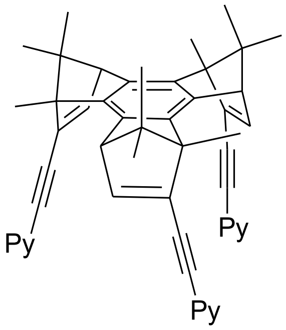
***syn*-(1*R*,4*R*,5*R*,8*R*,9*R*,12*R*)-2,6,10-Tris(2-phenylethynyl)-4,8,12-hexahydro-1,5,9,13,13',14,14',15,15'-nonamethyl-1,4:5,8:9,12-trimethanotriphenylene**



syn-**27**

Colorless crystals; m.p. 76-78 °C. $[\alpha]_D^{22}$ = + 1119 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 7.44-7.37 (6 H, series of m), 7.32-7.25 (9 H, series of m), 6.67 (3 H, d, *J* = 3.4 Hz), 3.73 (3 H, d, *J* = 3.4 Hz), 1.51 (9 H, s), 1.14 (9 H, s), 0.85 (9 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 144.8, 139.9, 137.7, 137.3, 131.3, 128.2, 127.8, 123.8, 85.8, 71.9, 62.8, 56.3, 29.7, 21.2, 19.8, 10.7; IR (KBr) *ν* 2925, 2193, 1487, 1384, 755 cm^{-1}.

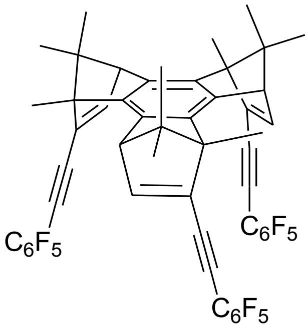
***syn*-(1*R*,4*R*,5*R*,8*R*,9*R*,12*R*)-2,6,10-Tris(2-ethynyl-4-pyridine)- 4, 8, 12-trihydro-1,5,9,13,13',14,14',15,15'-nonamethyl-1,4:5,8:9,12-trimethanotriphenylene**



syn-**28**

Orange crystals; m.p. 140-142 °C. $[\alpha]_D^{22}$ = + 1123 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.56 (6 H, br. s), 7.26 (6 H, d, *J* = 5.3 Hz), 6.80 (3 H, d, *J* = 3.4 Hz), 3.78 (3 H, d, *J* = 3.4 Hz), 1.52 (9 H, s), 1.14 (9 H, s), 0.86 (9 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 149.6, 147.6, 140.2, 137.6, 136.8, 131.8, 125.2, 95.3, 90.4, 72.6, 63.0, 56.5, 21.1, 19.7, 10.6; IR (KBr) *ν* 2956, 2929, 2187, 1599, 1386, 818 cm^{-1}.

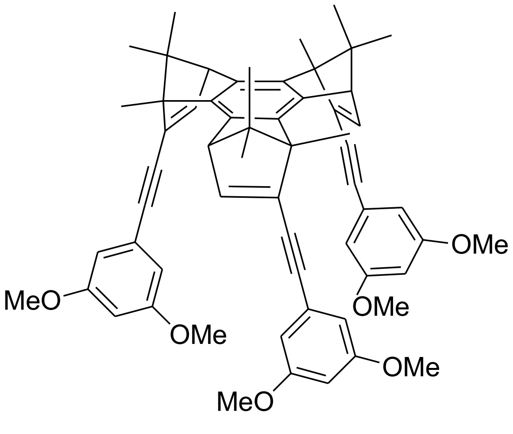
syn-(1*R*,4*R*,5*R*,8*R*,9*R*,12*R*)-2,6,10-Tris(2-(pentafluorophenyl)ethynyl)- 4, 8, 12-hexahydro-1,5,9,13,13’,14,14’,15,15’-nonamethyl-1,4:5,8:9,12-trimethanotriphenylene



syn-**29**

Colorless crystals; m.p. 130-132 °C. $[\alpha]_D^{22}$ = + 1124 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 6.85 (3 H, d, *J* = 3.2 Hz), 3.78 (3 H, d, *J* = 3.4 Hz), 1.50 (9 H, s), 1.13 (9 H, s), 0.84 (9 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 148.3, 146.5 (dm, *J* = 251.0 Hz), 141.1 (dm, *J* = 256.4 Hz), 140.2, 137.6 (dm, J = 250.7 Hz), 137.5(m), 136.4, 100.8 (td, *J* = 12.2 and 4.2 Hz), 98.2 (q, *J* = 2.7 Hz), 81.3 (q, *J* = 3.9 Hz), 72.6, 63.0, 56.6, 21.0, 19.6, 10.4; IR (KBr) *v* 2962, 2201, 1517, 1498, 989 cm^{-1}; *m/z* (EI, 70 eV): 967 (M^+, 100), 951 (27), 923 (24), 893 (39), 750 (20), 735 (16), 700 (18), 677 (22), 674 (24%).

syn-(1*R*,4*R*,5*R*,8*R*,9*R*,12*R*)-2,6,10-Tris(2-(3,5-dimetoxyphenyl)ethynyl)-4,8,12-trihydro-1,5,9,13,13’,14,14’,15,15’-nonamethyl-1,4:5,8:9,12-trimethanotriphenylene

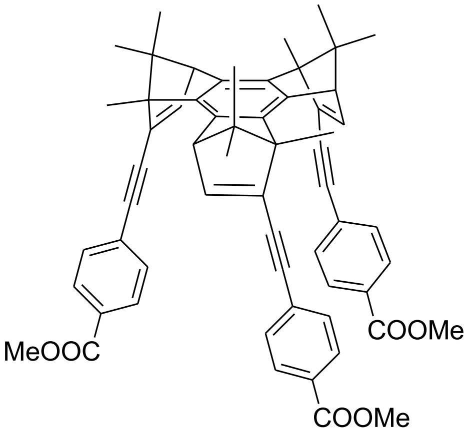


syn-**30**

Colourless solid; m.p. 115-117 °C. $[\alpha]_D^{22}$ = + 852 (*c* 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 6.67 (3 H, d, *J* = 3.4 Hz), 6.56 (6 H, d, *J* = 2.3 Hz), 6.40 (3 H, t, *J* = 2.2

Hz), 3.77 (18 H, s) 3.71 (3 H, d, *J* = 3.4 Hz), 1.49 (9 H, s), 1.12 (9 H, s), 0.83 (9 H, s); ^{13}C NMR (CDCl$_3$, 75 MHz) δ (ppm): 160.4, 145.2, 139.9, 137.7, 137.1, 125.1, 109.1, 101.4, 97.7, 85.4, 71.9, 62.9, 56.3, 55.4, 21.2, 19.7, 10.7; IR (KBr) *v* 2956, 2187, 1588, 1155 cm^{-1}.

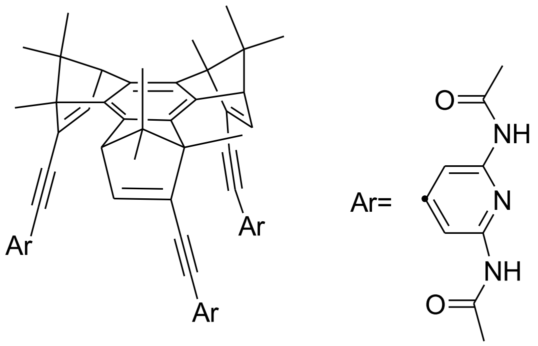
***syn*-(1*R*,4*R*,5*R*,8*R*,9*R*,12*R*)-2,6,10-Tris(2-(*p*-methylbenzoate)ethynyl)- 4,8,12-trihydro-1,5,9,13,13',14,14',15,15'-nonamethyl-1,4:5,8:9,12-trimethanotriphenylene**



syn-**31**

Colorless crystals; m.p. 125-126 °C. $[\alpha]_D^{22}$ = + 1815 (*c* 1.0, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ (ppm): 7.95 (6 H, d, *J* = 8.5 Hz), 7.44 (6 H, d, *J* = 8.7 Hz), 6.72 (3 H, d, *J* = 3.4 Hz), 3.91 (9 H, s), 3.75 (3 H, d, *J* = 3.4 Hz), 1.43 (9 H, s), 1.13 (9 H, s), 0.84 (9 H, s); ^{13}C NMR (CDCl$_3$, 75 MHz) δ (ppm): 166.6, 146.3, 140.1, 137.6, 137.1, 131.2, 129.4, 129.1, 128.5, 97.2, 88.8, 72.2, 62.9, 56.5, 52.1, 21.1, 19.7, 10.7; IR (KBr) *v* 2957, 2187, 1725, 1276 cm^{-1}.

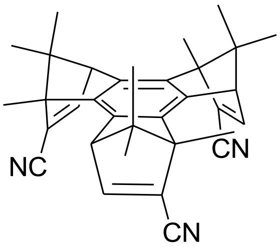
syn-(1*R*,4*R*,5*R*,8*R*,9*R*,12*R*)-2,6,10-Tris(2-(2,6-bisacetamido-*p*-pyridyl)ethynyl)-4,8,12-trihydro-1,5,9,13,13',14,14',15,15'-nonamethyl-1,4:5,8:9,12-trimethanotriphenylene



syn-**32**

The fractions from FC were concentrated and further purified dissolving the residue in CH_2Cl_2 and precipitating the product with Et_2O; m.p. 210 °C (dec); $[\alpha]_D^{22}$ = + 378 (*c* 0.3, $CHCl_3$); ^1H NMR (CD_3COCD_3, 300 MHz) δ (ppm): 9.13 (6 H, s), 7.88 (6 H, s), 6.92 (3 H, d, *J* = 3.2 Hz) 3.92 (3 H, d, *J* = 3.4 Hz), 2.12 (18 H, s), 1.58 (9 H, s), 1.17 (9 H, s), 0.92 (9 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 169.4, 149.8, 148.7, 140.6, 138.0, 137.0, 135.6, 110.7, 95.6, 89.8, 72.3, 62.9, 56.5, 24.0, 20.9, 19.4, 10.4; IR (KBr) *v* 2929, 2193, 1556, 1416 cm^{-1}.

syn-(1*R*,4*R*,5*R*,8*R*,9*R*,12*R*)-4,8,12-trihydro -1,5,9,13,13',14,14',15,15'-nonamethyl-1,4:5,8:9,12-trimethanotriphenylene-2,6,10-tricarbonitrile

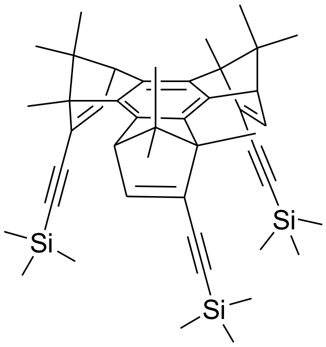


syn-**33**

To a solution of *syn*-**24** (160 mg, 0.19 mmol) in Et_3N (2 mL) and NMP (0.3 mL) maintained under Ar was added TMSCN (0.30 mL, 2.5 mmol) and $Pd(PPh_3)_4$ (24 mg, 0.021 mmol) and the resulting mixture was heated at 110 °C for 6 hours. The cooled solution was portioned between water (20 mL) and CH_2Cl_2 (3×20 mL) and the combined organic layers were washed with satd. aq. NaCl (30 mL), dried over $MgSO_4$ and concentrated in *vacuum*. The residue was purifed by FC (eluant CH_2Cl_2/hexane 3:7 in order to remove phosphorus by-products and AcOEt/hexane

3:7 to obtain the product) to afford *syn*-**33** (70 mg, 78% yield) as colourless solid, p.f. = 310 °C (dec.); $[\alpha]_D^{22}$ = +440 (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.34 (3 H, d, *J* = 3.5 Hz), 3.85 (3 H, d, *J* = 3.5 Hz), 1.55 (9 H, s), 1.13 (9 H, s), 0.83 (9 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):155.9, 140.6, 137.2, 128.3, 115.6, 74.6, 62.6, 56.9, 20.7, 19.4, 10.2; IR (KBr) ν 2975, 2208, 1466, 1392, 624 cm^{-1}.

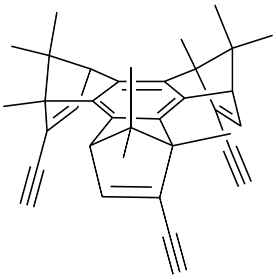
syn-(1*R*,4*R*,5*R*,8*R*,9*R*,12*R*)-2,6,10-Tris(2-(trimethylsilyl)ethynyl)-4,8,12-trihydro-1,5,9,13,13',14,14',15,15'-nonamethyl-1,4:5,8:9,12-trimethanotriphenylene



syn-**25**

A mixture of $Pd(PPh_3)_4$ (61.9 mg, 54 μmol) and *syn*-**24** (450 mg, 0.54 mmol) was evacuated and backfilled with argon (for a total of 3 times). Then degassed freshly distilled DMF (5 mL) and NEt_3 (1.2 mL) were added via syringe. Trimethylsilyl acetylene (0.8 mL, 5.7 mmol) was further added via syringe and the mixture was stirred at 60 °C overnight. Water (20 mL) was added and the resulting mixture was extracted with cyclohexane (3×20 mL). Combined organic extracts were washed with H_2O (20 mL), saturated aqueous NaCl (20 mL), dried over $MgSO_4$ and concentrated in *vacuum*. The resulting oil was purified by flash chromatography (eluant cyclohexane) and the product was further purified by trituration with methanol affording colorless crystals (330 mg, 89% yield). m.p. 211-213 °C; $[\alpha]_D^{22}$ = + 665 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 6.56 (3 H, d, *J* = 3.4 Hz), 3.62 (3 H, d, *J* = 3.4 Hz), 1.34 (9 H, s), 1.06 (9 H, s), 0.76 (9 H, s), 0.19 (27 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 145.1, 139.8, 137.4, 137.3, 102.8, 101.3, 71.9, 62.5, 56.1, 21.1, 19.7, 10.4, 0.2; IR (KBr) *ν* 2959, 2134, 1248, 843 cm^{-1}; *m/z* (EI, 70 eV): 684 (M^+, 100), 669 (25), 641 (15), 611 (9), 562 (12), 553 (10), 511 (7%).

syn-(1*R*,4*R*,5*R*,8*R*,9*R*,12*R*)-2,6,10-Triethynyl-4,8,12-trihydro-1,5,9,13,13’,14,14’,15,15’-nonamethyl-1,4:5,8:9,12-trimethanotriphenylene



syn-**26**

A mixture of TMS protected *syn*-**25** (300 mg, 0.44 mmol) and K_2CO_3 in MeOH/THF (1:1, 10 mL) was stirred at r. t. for 2 hours. The solvents were removed under *vacuum* and 1M HCl (20 mL) was added. The mixture was extracted with cyclohexane (3×20 mL) and combined organic extracts were washed with H_2O (20 mL), saturated aqueous NaCl (20 mL), dried over $MgSO_4$ and concentrated in *vacuum*. The resulting oil was purified by flash chromatography (eluant cyclohexane/Et_2O in gradient from 10:0 to 8:2) to afford colorless crystals (140 mg, 68% yield), m.p. 68 °C; $[\alpha]_D^{22}$ = + 534 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 6.73 (3 H, d, *J* = 3.2 Hz), 3.65 (3 H, d, *J* = 3.4 Hz), 1.43 (9 H, s), 1.09 (9 H, s), 0.79 (9 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 146.7, 139.9, 137.5, 136.6, 85.1, 79.9, 72.3, 62.4, 56.0, 21.1, 19.6, 10.4; IR (KBr) *v* 2929, 2083, 1630, 1386 cm^{-1}; *m/z* (EI, 70 eV): 468 (M^+, 100), 453 (26), 410(27), 395 (39), 207 (26%).

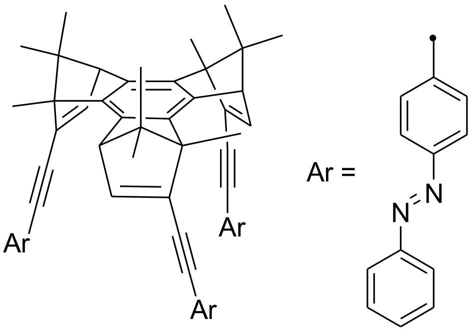
General procedure for coupling reactions of *syn*-26 with arylhalides (Table 4.4).

Method A: a mixture of $Pd(PPh_3)_4$ (12.3 mg, 10.7 μmol), CuI (4.1 mg, 21.4 μmol), arylhalide (0.48 mmol, 4.5 eq.) and *syn*-**26** (50 mg, 107 μmol) was evacuated and backfilled with argon (for a total of 3 times). Degassed freshly distilled toluene (4 mL) and NEt_3 (0,5 mL) were added via syringe. The mixture was stirred at 60 °C for 18 hours and concentrated in *vacuum*. The product was purified by silica gel chromatography.

Methd B: a mixture of $Pd(PPh_3)_4$ (12.3 mg, 10.7 μmol), CuI (4.1 mg, 21.4 μmol) and *syn*-**26** (50 mg, 107 μmol) was evacuated and backfilled with argon (for a total of 3 times). Degassed freshly distilled toluene (4 mL) and NEt_3 (0,5 mL) were added via syringe. Arylhalide (0.48 mmol, 4.5 eq.) was added via syringe and the mixture was stirred at 60 °C for 18 hours. Volatile materials were removed and the residue was purified by Flash chromatography with appropriate eluant and stationary phase.

Product	Method	Eluant	Stationary Phase	Yield (%)
Syn-**28**	A	AcOEt/EtOH from 10:0 to 7:3	basic alumina	39
Syn-**29**	A	Pentane	silica gel	45
Syn-**34**	B	hexane/CH_2Cl_2 from 10:0 to 7:3	silica gel	48
Syn-**35**	B	Cyclohexane/AcOEt from 7:3 to 0:10	silica gel	51

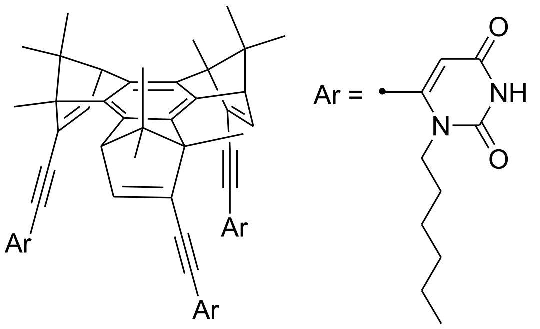
***syn*-(1*R*,4*R*,5*R*,8*R*,9*R*,12*R*)-2,6,10-Tris(2-(diphenyldiazene)ethynyl)-4,8,12-trihydro-1,5,9,13,13',14,14',15,15'-nonamethyl-1,4:5,8:9,12-trimethanotriphenylene**



syn-**34**

The fractions from FC were concentrated and further purified by trituration with MeOH to afford bright orange crystals, m.p. 163-165 °C. $[\alpha]_D^{22}$ = + 3566 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.93-7.85 (12 H, m), 7.45-7.36 (15 H, m), 6.76 (3 H, d, *J* = 3.2 Hz), 3.78 (3 H, d, *J* = 3.2 Hz), 1.55 (9 H, s), 1.15 (9 H, s), 0.87 (9 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 158.1, 152.7, 151.6, 145.9, 140.1, 137.7, 137.3, 132.1, 131.1, 129.1, 126.6, 122.9, 97.8, 88.6, 72.1, 62.9, 56.4, 21.2, 19.8, 10.7; IR (KBr) *v* 2959, 2182, 1498, 1493, 1385, 843 cm^{-1}.

***syn*-(1*R*,4*R*,5*R*,8*R*,9*R*,12*R*)-2,6,10-Tris(2-(*n*-hexil-uracil)ethynyl)-4,8,12-trihydro-1,5,9,13,13',14,14',15,15'-nonamethyl-1,4:5,8:9,12-trimethanotriphenylene**



syn-**35**

The fractions from FC were concentrated and further purified by dissolving the residue in Et_2O, filtering the solution and removing the solvent, m.p. 131 °C; $[\alpha]_D^{22}$ = + 1253 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.24 (3 H, s), 6.97 (3 H, d, *J* = 3.4 Hz), 5.84 (3 H, s), 3.94 (6 H, m), 3.79 (3 H, d, *J* = 3.6 Hz), 1.70 (6 H, broad), 1.57 (6 H, br, m), 1.49 (9 H, s), 1.31 (12 H, br, s), 1.13 (9 H, s), 0.83 (15 H, br, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 161.7, 151.1, 140.5, 138.6, 137.6, 135.8, 109.6, 106.4, 96.4, 89.2, 74.2, 63.4, 56.8, 46.6, 31.4, 28.8, 26.3, 22.5, 20.9, 19.6, 13.9, 10.81; IR (KBr) *v* 2930, 2193, 1690, 1451 cm^{-1}.

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CHAPTER 5

MOLECULAR CAGES

Since Cram, Pedersen and Lehn were awarded with the Nobel Prize in 1987 for their studies on supramolecular chemistry, this discipline has generated a multitude of growing opportunities in material science nano-technology, sensing, catalysis and other applications.[1]

5.1 INTRODUCTION

The successful building of molecular hosts is achieved when such molecules are able to estract efficiently smaller compounds from the surrounding media, usually a solvent,[2] and therefore separating two portions of space, in which the guest resides, as inner and outer.[3] From the development of supramolecular chemistry, usually defined as "*the chemistry beyond the molecules*",[4] a great number unimolecular and self-assembled host systems were properly designed to complement and bind a wide variety of guests through weak intermolecular forces.

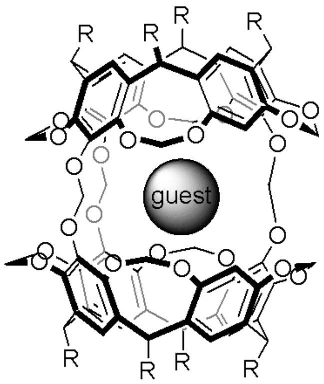
In particular, supramolecular recognition of gases and the study of the forces that bind gases are opening many potential applications. In biology, this discipline may offer some insight into the interaction mechanisms of gases with proteins and enzymes, for example the complexation of oxygen by hemoglobin or the atmospheric nitrogen fixation by plants as well as the carbon dioxide introduction into photosynthetic process. Moreover, the study of host-guest chemistry of gases can be used also for technological applications, for example in the development of novel materials and membranes for gas sensing, storage, and controlled release.

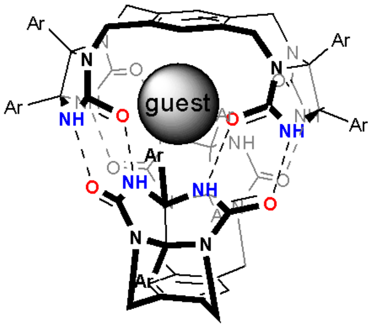
Finally, supramolecular chemistry is the most likely way to mimic enzymes in converting simple gases, at the appearance useless, into synthetically useful reagents.[5]

In general, the recognition of polar or charged compounds is usually achieved with a suitable supramolecular host that can interact through electrostatic forces, such as cation-anion, ion-dipole or H-bonding interactions. In contrast, the binding of neutral guests, small hydrocarbons for instance, is extremely difficult because these molecules require hosts characterized by concave surfaces in order to ensure large reciprocal van der Waals contacts. A remarkable exception to this is obtained with water soluble hosts, where the binding of apolar guests is driven by an entropic gain which is usually referred as hydrophobic effect.[6]

While gas hosting in solids is more common,[7] the same process is much more difficult to achieve in solution. In fact, in organic media the solvent does not aid the binding as water does, but on the contrary it competes for the host, thus the design of suitable hosting molecules must take into account the optimal complementarity between the cavity and the guest rather than with solvent molecules.

Neutral apolar hydrocarbon gases are intrinsically elusive guests. Nevertheless, the binding of such guests in solution has been investigated.[8] Analogously to common guests, which usually display packing coefficients[9] (PC) of about 55% inside the host,[10] gases usually require more space and consequently small PC of about 40%.[11] Example of efficient hosts for apolar gases are unimolecular receptors characterized by small volume cavities based on different scaffold such as cycloveratrylene[12] or resorcinarene.[8,13] Nevertheless, examples of sufficiently tight self-assembled capsules displaying suitable environments for hydrocarbon gas hosting are known based on resorcinarene[11,14] or aromatic glycouril[15] scaffolds.





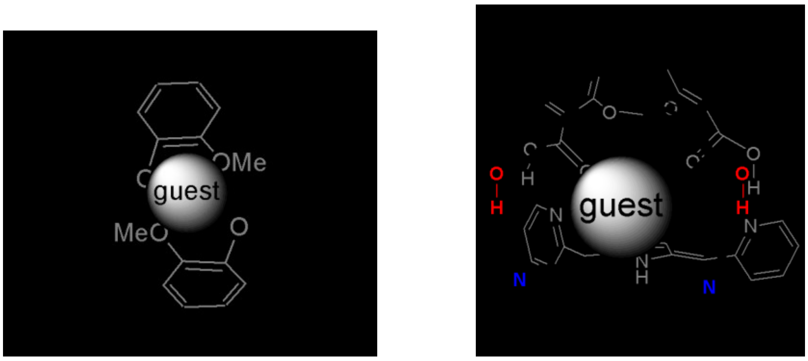
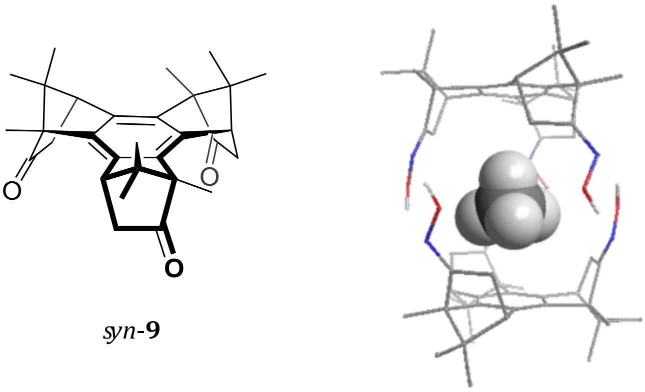


Fig. 5.1 Known supramolecular hosts able to bind gases in solution.

Benzocyclotrimers also showed binding properties for neutral guests, and benzotricamphor *syn*-**9** already exhibited supramolecular behavior with gaseous molecules after the functionalization to the corresponding oxime. [16]



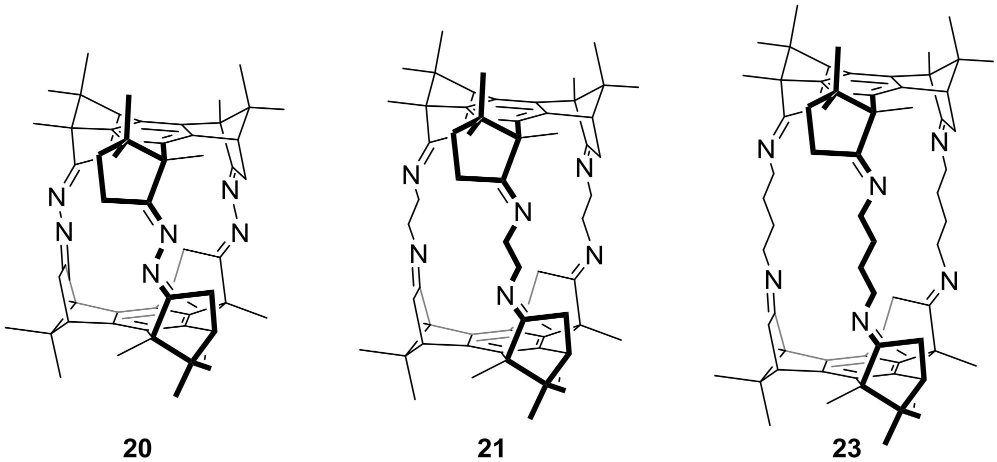
syn-**9**

Fig. 5.2 Benzotricamphor *syn*-**9** (left) and encapsulated methane into dimeric capsule of benzotricamphor-oxime (right).

Imine linkers, obtained by reactions between carbonyl compounds and primary anilines or amines, have been successfully employed to synthesize cage compounds.[17] Nevertheless such elaborated systems rarely reported host-guest properties often because of rather large structure and lack of suitable guests or proper experimental conditions.

5.2 SYNTHESIS OF THE CAGES

The reaction of *syn*-benzotricamphor with aliphatic diamines, as described in Chapter 4, led to the formation of unimolecular cages in which two benzocyclotrimeric units are linked by three di-imine bridges.



20 **21** **23**

Fig. 5.3 Molecular cages obtained from the condensation of *syn*-**9** with aliphatic diamines.

The formation of the cages resulted more favored than the mono-condensation of diamines with *syn*-**9** which should lead to open trimers. This was confirmed by analyzing the HMQC spectrum of alkyl chains of cage **21**, taken as representative example, which displays one carbon peak correlated with two proton signals.

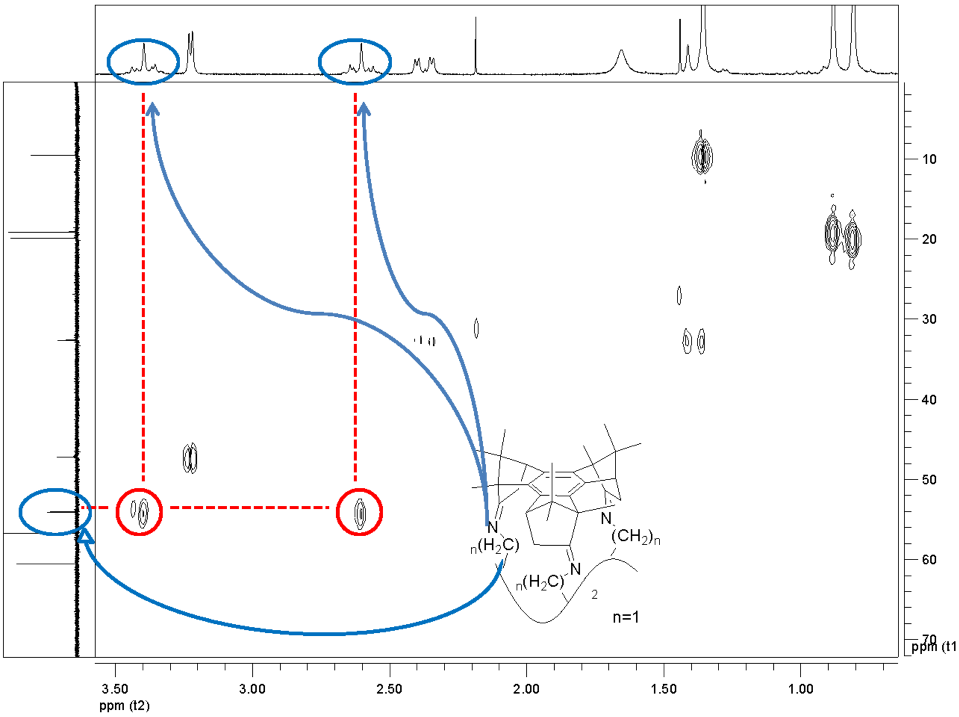


Fig. 5.4 HMQC spectra of cage **21**.

Moreover, proton and carbon NMR spectra of the cages showed unambiguously a highly symmetric structure of the cages, in which the imine double bonds are all in *Z* or in *E* fashion. Despite these compounds were relatively stable, single crystals suitable for X-ray diffraction could not be obtained for the determination of the geometrical isomerism, thus the most probable structure was determined by DFT calculations[18] and NOESY experiments. From computational results, the *E*-geometry of imine double bonds was predicted to be the most stabile for all molecular cages, is. In fact *syn-E,E,E*-**20** resulted 19.62 Kcal/mol more stable than *syn-Z,Z,Z*-**20**, *syn-E,E,E*-**21** resulted 5.23 Kcal/mol more stable than *syn-Z,Z,Z*-**21** and *syn-E,E,E*-**23** resulted 13.12 Kcal/mol more stable than *syn-Z,Z,Z*-**23.** These differences are probably due to steric hindrance caused by bridge-head methyls, that highly disfavors the *Z* conformation of every single bornene unit.

DFT calculations of the three cages **20**, **21** and **23**, which are represented in Fig. 5.5, allowed also to evaluate the internal volumes of the hosts.[19] Inner volumes increase from 16 Å^3 for *E,E,E*-**20**, to 56 and 88 Å^3 for *E,E,E*-**21** and *E,E,E*-**23** respectively.

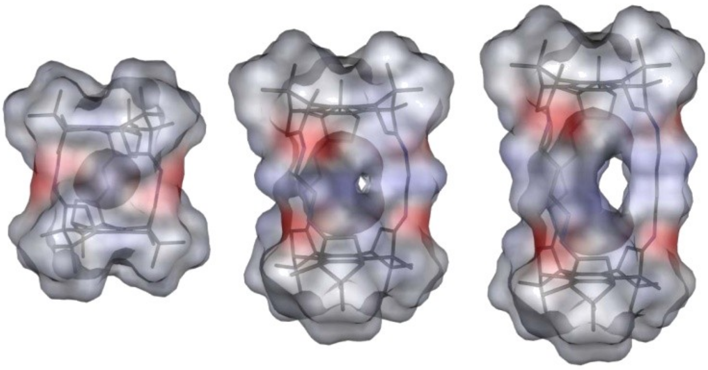
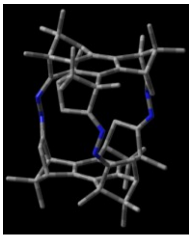
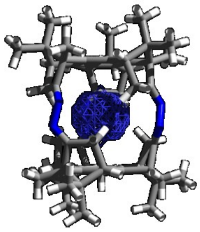
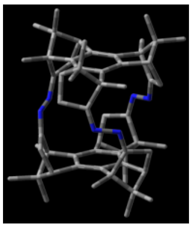
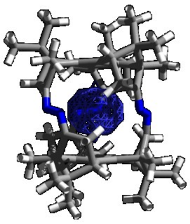
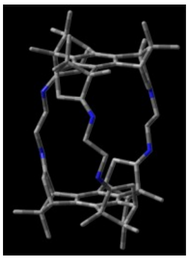
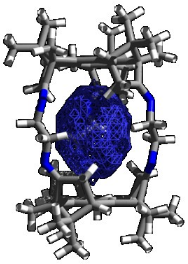
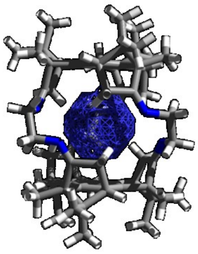
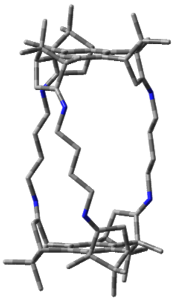
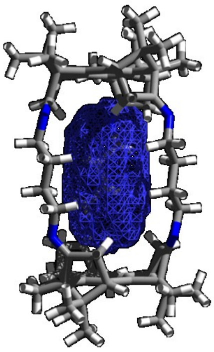
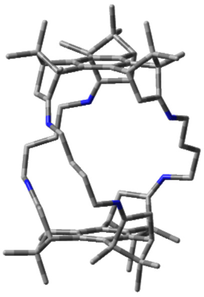
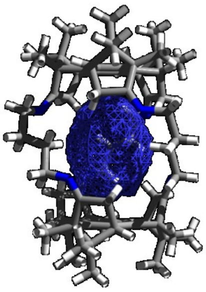


Fig. 5.5 Optimized structures of compounds *syn-E,E,E*-**20**, *syn-E,E,E*-**21** and *syn-E,E,E*-**23**.

Table 5.1 Energy and structural parameters for molecular cages **20**, **21**, **23**.

Cage	Structure	Inner surface	Heat of formation (Hartree)	Ar-Ar dist., Å	Cavity volume, Å^3
E,E,E-**20**			-2658.076884	16.24	16 Å^3
Z,Z,Z-**20**			-2658.045611	5.69	15 Å^3
E,E,E-**21**			-2894.009011	8.49	56 Å^3
Z,Z,Z-**21**			-2893.959410	6.95	31 Å^3
E,E,E-**23**			-3129.891201	10.89	88 Å^3
Z,Z,Z-**23**			-3129.794373	8.71	61 Å^3

5.3 INCLUSION EXPERIMENTS

The supramolecular behavior of cages **20**, **21** and **23** has been investigated by NMR measurements at variable temperatures in chloroform-d solutions, where low molecular hydrocarbons (methane, ethyne, ethene, ethane, propene, butane) and H_2 were bubbled. The experiments performed on **20** showed that was not possible to fill the cavity with H_2 or CH_4 as guests, as well as carrying the azine synthesis from **1** under H_2 atmosphere. Analogously, **23** provided no evidence of gas inclusion with all the above mentioned possible guests, even at low temperature. The reason for both negative results was ascribable to the unfavorable packing coefficients of guests inside the cages. Considering the calculated values of inner volumes, the internal cavity of **20** was too small and inaccessible to any guest from the outside. The opposite situation was verified for **23,** in which the internal volume was too big, therefore providing small PC (<0.47).[10] Moreover, the long chains which connect the two rigid cups in **23** have a certain degree of flexibility which may produce too wide apertures or the collapse of the chains into the cavity, thereby reducing in both cases any possibility to form stable host-guest complexes.

On the other hand, gas hosting was well observed in the case of cage **3**. Bubbling gases into solutions of cage **21** and recording NMR spectra at decreasing temperatures, made evident the inclusion phenomena by detecting an increase of intensity of the signal corresponding to the included gas molecule, usually up-field by nearly 2-4 ppm with respect to free solvated species.

The inclusion process for all guests was confirmed by NOESY experiments at low temperatures, which showed the exchange cross-peaks between free and bound guests, and in some case was well observable a scalar correlation between the hosted molecules and bridge-head hydrogens of the cyclotrimer.

Moreover, NMR spectra allowed to evaluate equilibrium constants by the quantitative determination of the species (host, included and free guest) at different temperatures. Therefore it was possible to calculate the relevant thermodynamic parameters ($\Delta H°$ and $\Delta S°$) for the in-out switch equilibrium by correlating $\ln K_{eq}$ with $1/T$ (van't Hoff plot).

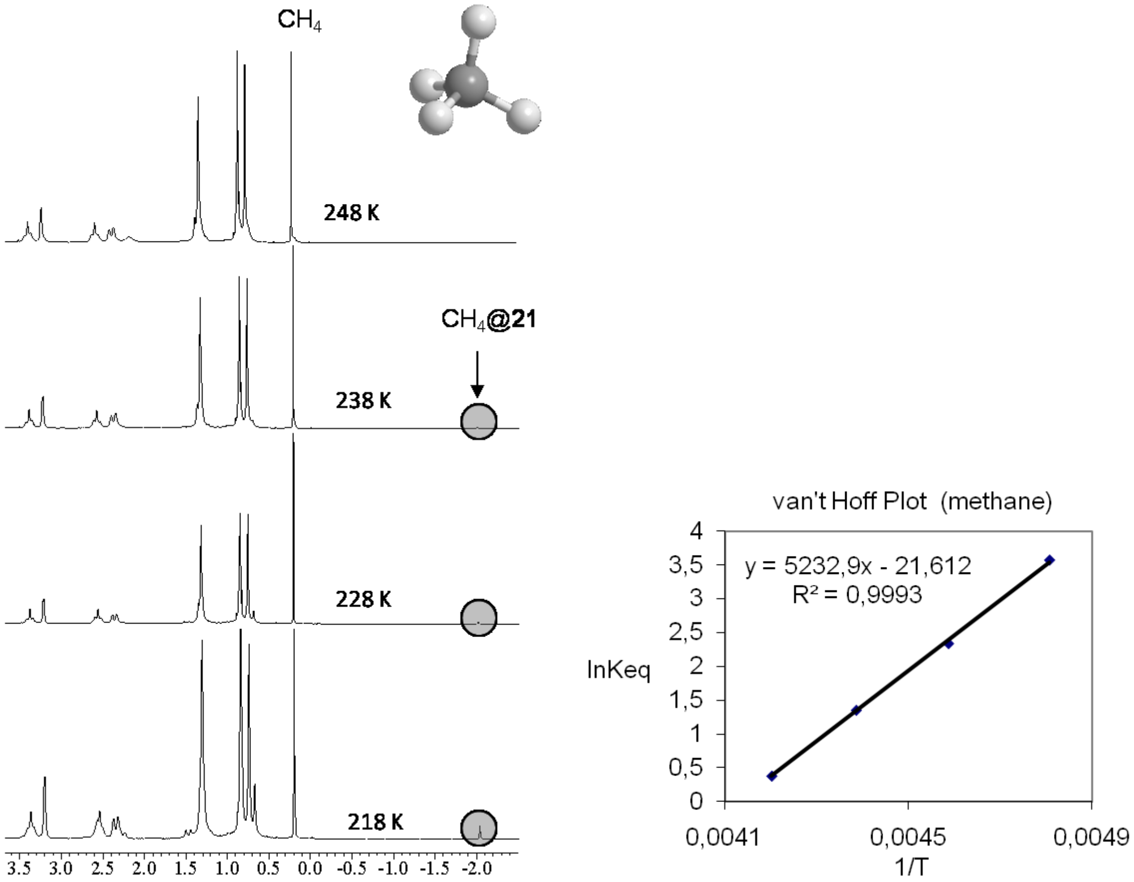


Fig. 5.6 1H NMR spectra of methane@**21** at different temperatures.

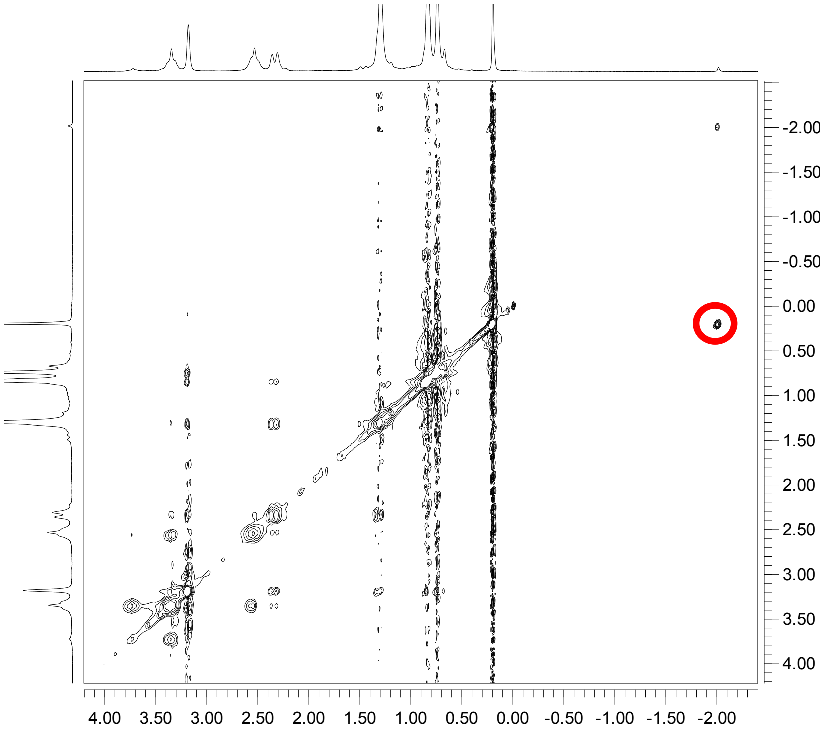


Fig. 5.7 NOESY of methane@**21** at 228 K. The cross peak between encapsulated and free methane is hooped in red.

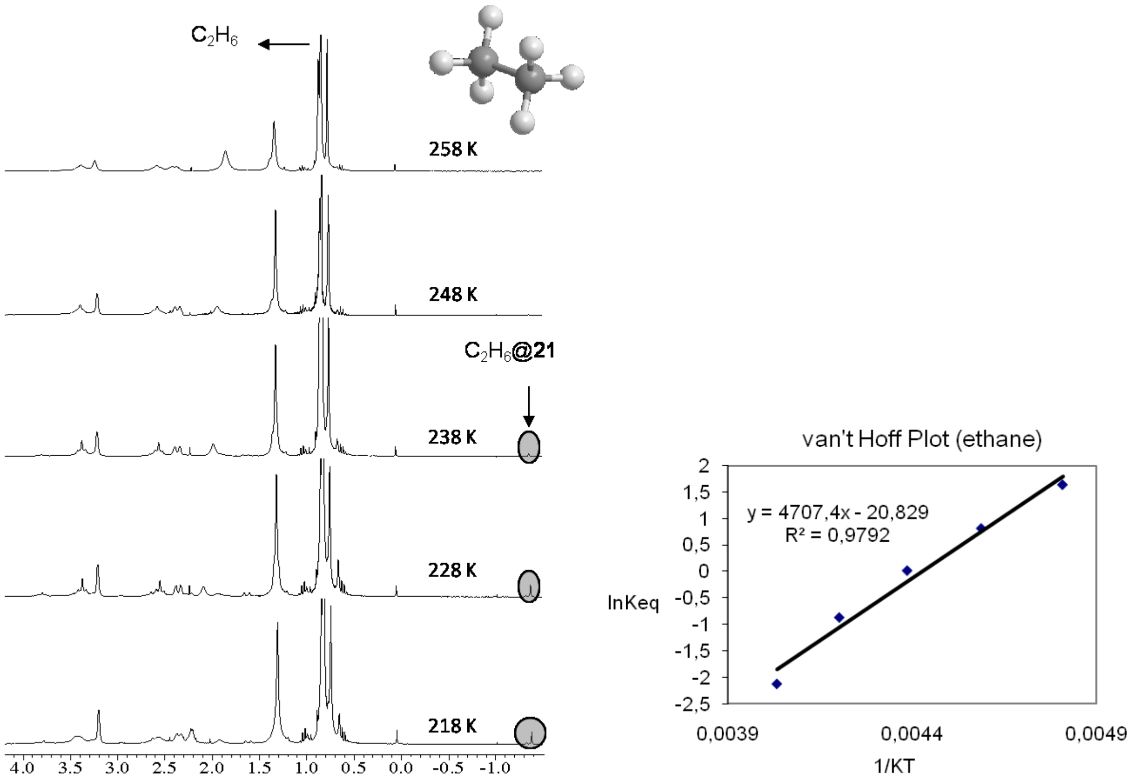


Fig. 5.8 1H NMR spectra of ethane@**21** at different temperatures.

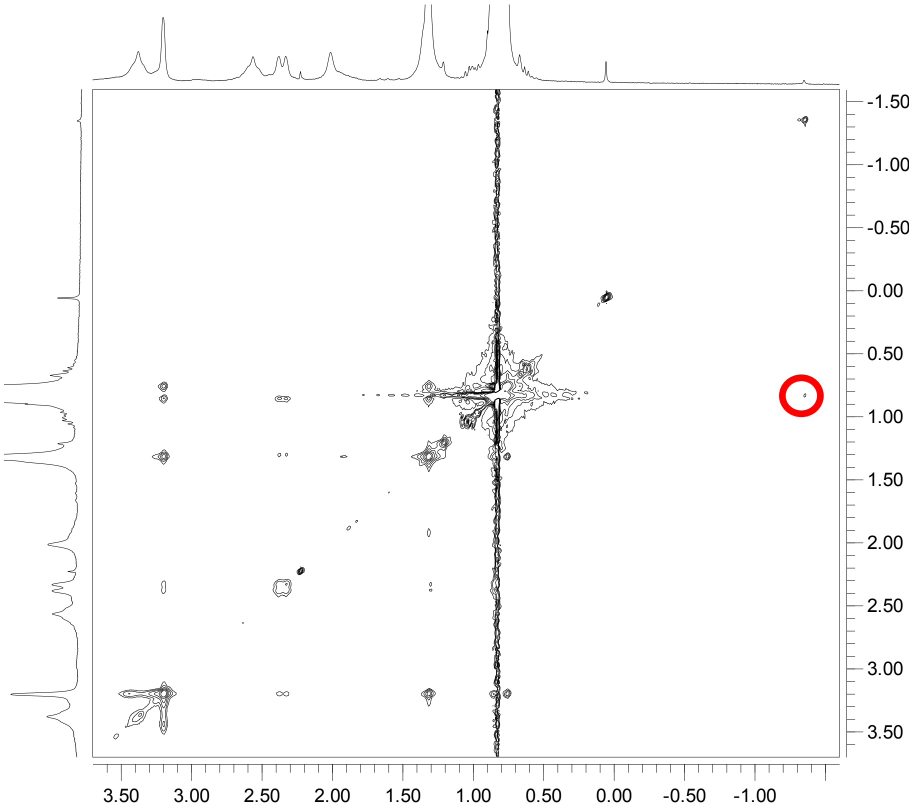


Fig. 5.9 NOESY of ethane@**21** at 228 K. The cross peak between encapsulated and free methane is hooped in red.

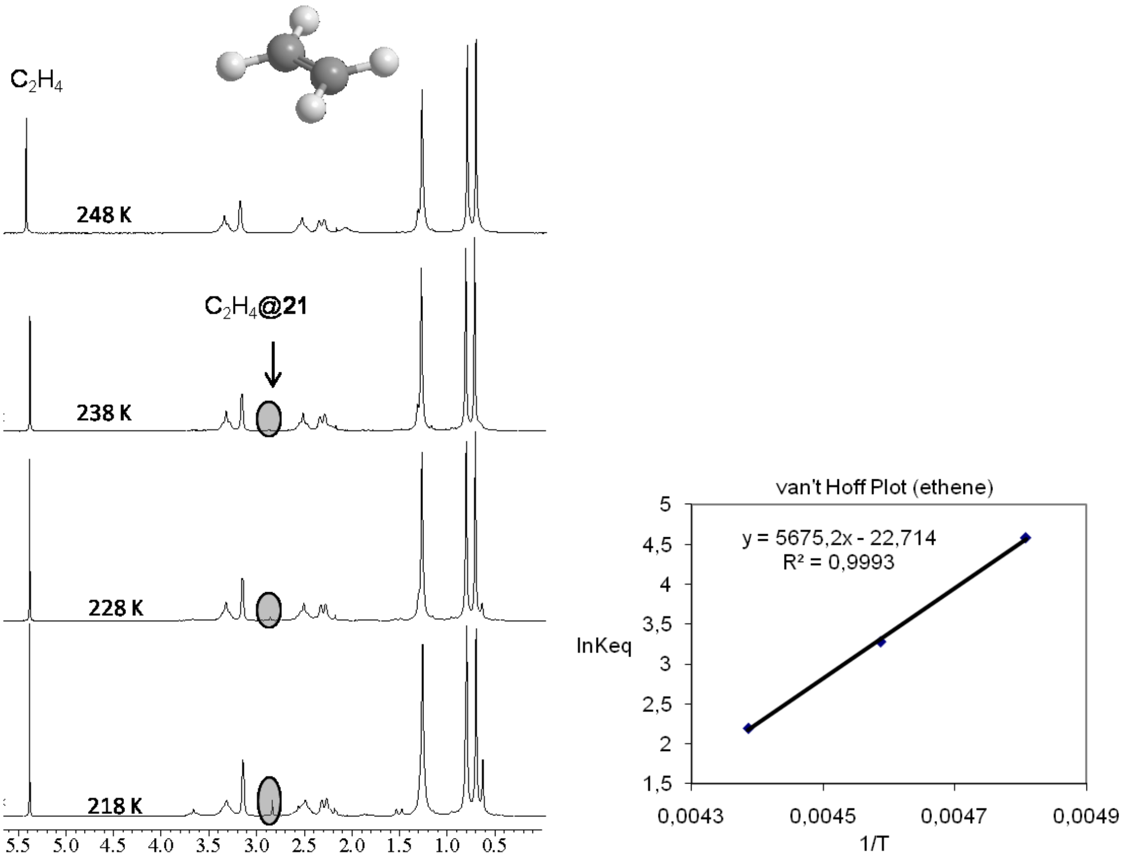


Fig. 5.10 1H NMR spectra of ethylene@**21** at different temperatures.

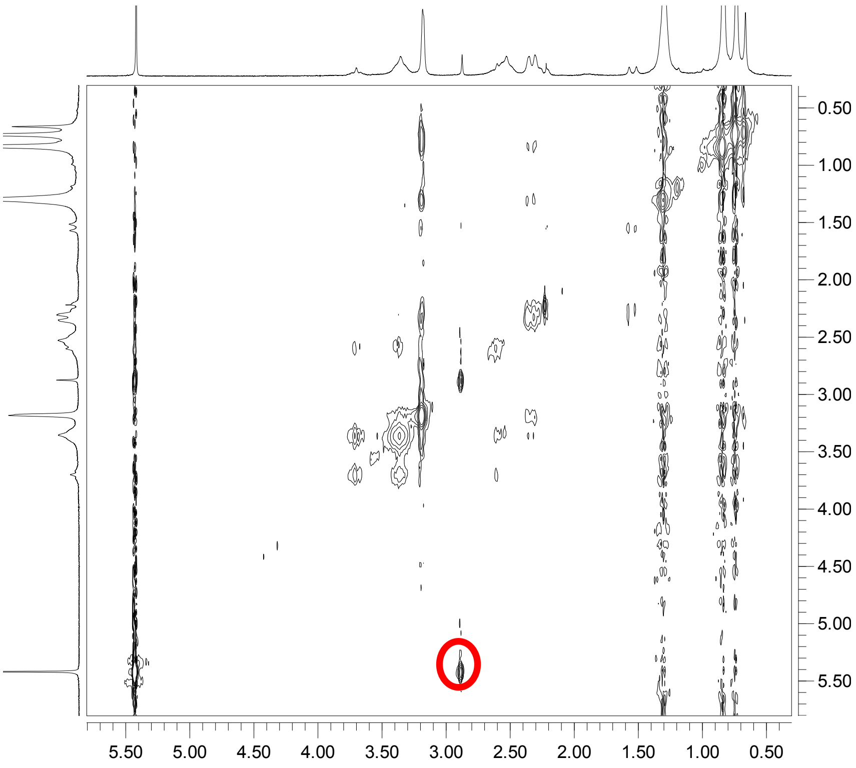


Fig. 5.11 NOESY of ethylene@**21** at 218 K. The cross peak between encapsulated and free methane is hooped in red.

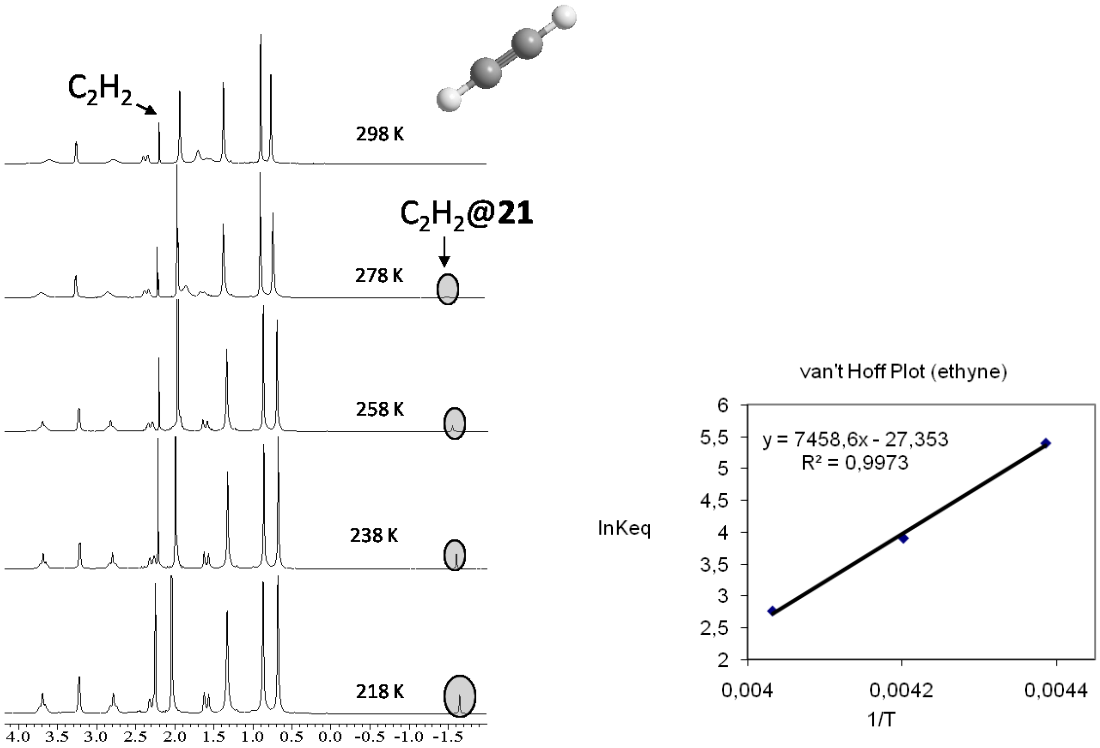


Fig. 5.12 1H NMR spectra of acetylene@**21** at different temperatures.

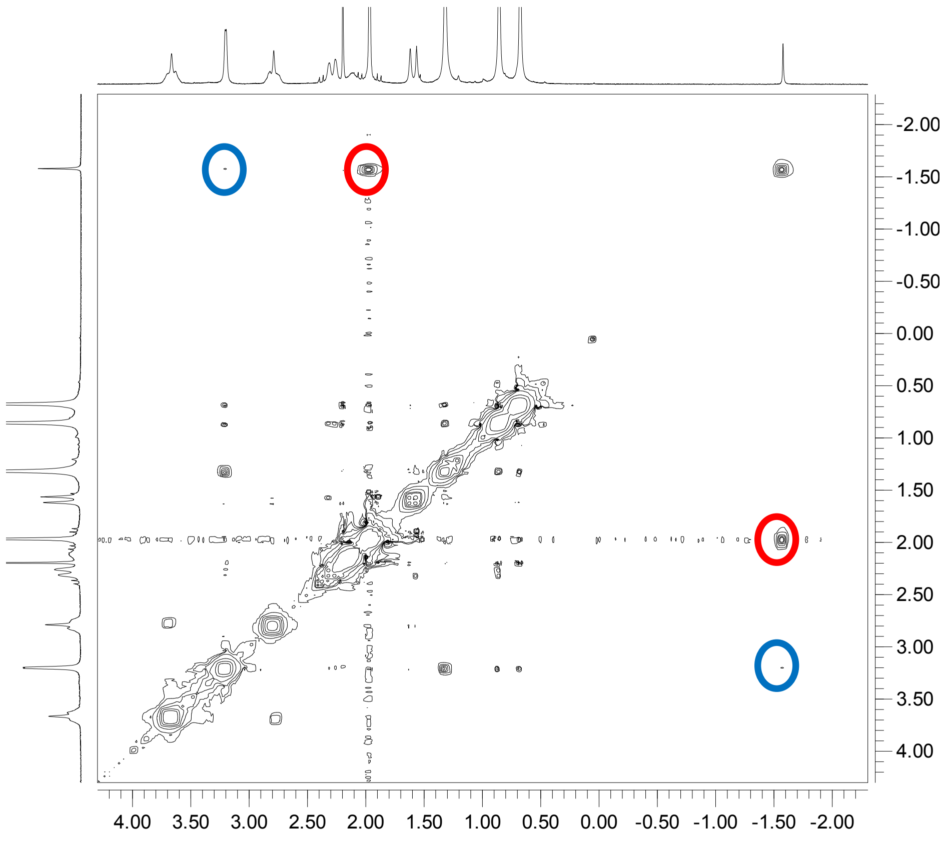


Fig. 5.13 NOESY of acetylene@**21** at 248 K. The cross peak between encapsulated and free methane is hooped in red. The interaction between acetylenic protons of the guest and bridge-head protons of the cageis hooped in blue.

The temperature at which the inclusion phenomenon starts and the position of the corresponding peaks in the spectra depends on the gas employed. The appearance of the signal of included species is possible when the permanence into the cavity is longer than seconds and guest exchange is relatively slow on the chemical shift timescale, therefore providing separate signals for free and encapsulated guest. For example, the encapsulation of CH_4 begins at 238 K and the signal of CH_4@**21** appears at -2.00 ppm. The negative chemical shift of included guests is due to shielding effects imparted by the two aromatic rings of **21**. Moreover, the degree of de-shielding on the resonances of the guests are correlated to the binding affinity of the gases for the host, as commonly observed in encapsulation phenomena.[20]

Larger guests (*i.e.* C_2H_4 and C_2H_6) were not bound efficiently, according to their large PC (Table 5.2). In fact, they were included only at very low temperatures, exhibiting low intensity peaks for C_2H_4@**21** and C_2H_6@**21** at 228 and 238 K, respectively. Gases with larger volumes (propene and butane) showed no encapsulation in **21** even at 208 K, as expected on the basis of their PC (>80%).
Ethyne showed the best affinity with the cavity of **21**, displaying the up-field shifted signal for encapsulated C_2H_2 at -1.51 ppm already at 278 K, the highest temperature of all guests (Fig. 5.8).

In order to better investigate affinity of host **21** for gaseous guests, thermodynamic parameters for the encapsulation process at low temperatures, were extrapolated from van't Hoff plots (Table 5.2).

Table 5.2. Chemical and thermodynamic data for encapsulation of gases@**21**.

Gas	Vol. (Å^3)	PC (%)[a]	Δδ (ppm)	K_{eq}[b]	ΔH[c]	ΔS[c]
CH_4	25	45	-2.16	3.40	-43	-0.18
H_3CCH_3	41	73	-2.19	1.13	-40	-0.18
H_2CCH_2	37	66	-2.55	8.99	-47	-0.19
HCCH	33	59	-3.67	221	-62	-0.23

[a] Packing coefficient = (guest volume)/(cavity volume); cavity volume: 56 Å^3; [b] L·mol^{-1}, determined at 228 K; [c] KJ·mol^{-1}; [e]KJ·mol^{-1}·K^{-1}

CH_4 and C_2H_6 displayed the smaller binding constants of the series, probably because they are both saturated hydrocarbons and could not complement well the cavity, being one too small and the other too big. On the other hand, PC of C_2H_4 and C_2H_2 are not too different, but geometries and chemical nature are quite different, thus their affinity for the cavity is also quite different.

Analyzing the calculated thermodynamic parameters, the binding of all the gaseous guests occurs with similar slightly negative entropic contribution, while negative $\Delta H°$ values allow to establish that the hosting phenomenon is enthalpically driven.

In particular, acetylene is characterized by the proper size and shape to properly fit the inner surface of the host and greatly takes advantage of the presence of strongly polarized C-H hydrogens which enables strong attractive CH-π interactions[21] with the electron rich aromatic rings of the benzocyclotrimer scaffold.

2D EXSY experiments at 228K allowed to calculate the activation energy both for the association and dissociation processes,[8] which for C_2H_2 are 52 and 61 $KJ\cdot mol^{-1}$, while for C_2H_4 are 48 and 55 $KJ\cdot mol^{-1}$, respectively. These values, in particular the activation barriers for guest release, are similar to those reported for other rigid hosts, such as cryptophanes,[8] because of the similitude existing between the two hosts in terms of size of the cavity and presence of three portals delimited by –CH_2CH_2- windows.

In conclusion, molecular cages based on *syn*-**9** scaffold provided suitable hosting structures for small neutral guests. The compromise between the volume and morphology of the cavities with the flexibility of the "bars" connecting the cyclotrimeric units determined the efficiency of the cages to bind gaseous molecules. The best hemi-carcerand **21** showed high complementarity in particular for acetylene because of attractive CH-π interactions.

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CHAPTER 6

MOLECULAR CAPSULES

6.1 INRODUCTION

Molecular recognition is based on weak intermolecular forces between two or more molecular units which manifest complementarities in size and shape, thereby providing stabile receptor-substrate complexes. Molecular recognition is often found in nature and governs the self-assembly of many biological systems such as the pairing of complementary nucleoside bases in the double helix of DNA and RNA structure and the substrate-enzymes recognition process.[1]

In the attempt to mimic biological processes, the principles that govern molecular recognition were extensively pursued[1a] and have paved the way to the origin of host-guest chemistry.[2] The design of synthetic receptors and the recognition of target guest molecules was therefore explored by taking advantage of a variety of noncovalent forces like hydrogen bonding, π-stacking, ionic, dipolar and van der Waals interactions.

Over the last decades the interest in the design and synthesis of nanoscale molecular containers and self-assembling molecular capsules increased. Since the pioneering work of Donald Cram,[3] synthetic capsules and cages of different sizes and shapes have been prepared through the self-assembly of different subunits into bigger architectures, as happens with natural systems, for examples in viruses and cell membranes.[4] Moreover, molecular capsules which exhibits an internal, limited space for the isolation of a molecule from the bulk solvent, exploited the concept of "molecule within molecule".

So far, the predominant interactions found in the assembly of molecular capsules were hydrogen bonds, metal ligand interactions, ionic forces and the hydrophobic effect. The importance of molecular capsules and containers resides not only in their fascinating design but also in their possible applications as molecular sensors, supramolecular catalysts and drug delivery systems.

The most representative examples of molecular capsules are herein briefly described. Noticeably, these supramolecular systems represent an alternative to the covalent approach of molecular cages in creating a closed space within a molecular framework[5] and the molecular association in capsules is reversible under relatively mild conditions.

In addition, the self-assembly process usually requires certain conditions due to the weakness of noncovalent interaction, such as a high degree of symmetry, the presence of a suitable guest molecule and a non competitive solvent. For example, hydrogen-bonded capsules are easily disrupted in polar solvents while capsules constructed through metal-ligand interactions disassembles in strongly coordinating solvents.

Hydrogen-bonded capsules

Hydrogen bonding is the most studied and one of the most important intermolecular force in self-assembling systems due to its directionality, specificity, and biological relevance. A representative example of this class are glycoluril-derived assemblies and cyclophane-derived capsules based on calixarene and resorcinarene scaffolds.

The first example of this series is represented by the so-called "tennisball", reported by Rebek and de Mendoza, consisting of two identical units in which the curvature of the structure promotes dimerization by H-bonding. Each unit is constituted by two diphenylglycoluril units linked by a durene spacer (Fig. 6.1). The assembly process is driven by the formation of eight hydrogen bonds and the capsule has a cavity with a volume of about 50 Å^3, suitable to host guests like benzene, adamantane and ferrocene derivatives.[6] The same authors reported also a series of molecular capsules based on glycoluril groups with variable shape and inner volume, in which three glycoluril moieties were appended to central a hexamethybenzene core. The resulting capsules resembles the appearance of a "jelly doughnut".[7]

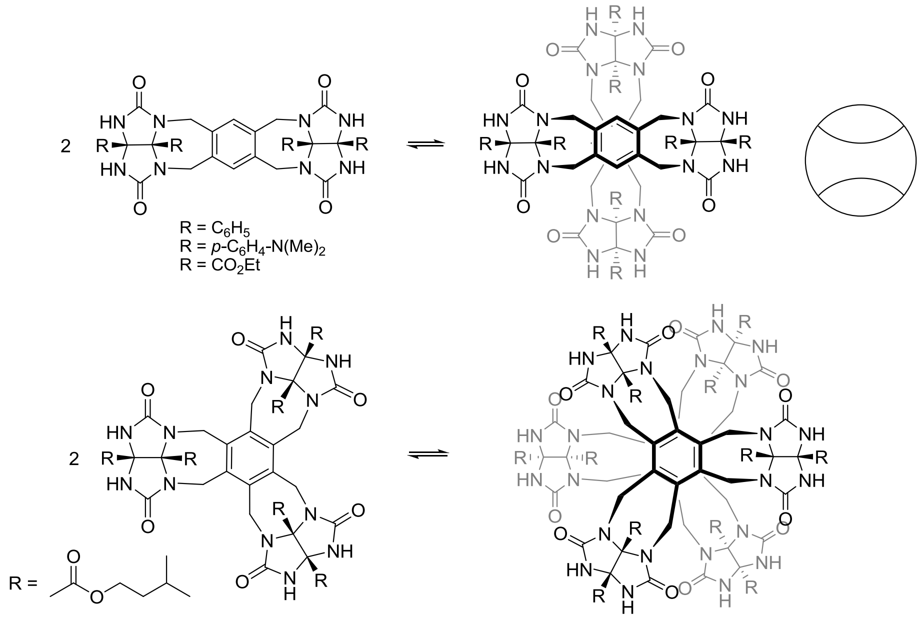


Fig. 6.1 Two identical molecules give a closed shell "tennis-ball" and structure of the "jelly doughnut".

Calix[4]arenes were also extensively used as possible scaffolds for H-bonded capsules. These molecules are self-complementary and able to associate via hydrogen bonds, upon introduction of the opportune functional groups, thereby providing a closed capsule by dimerization (Fig. 6.2).[8]

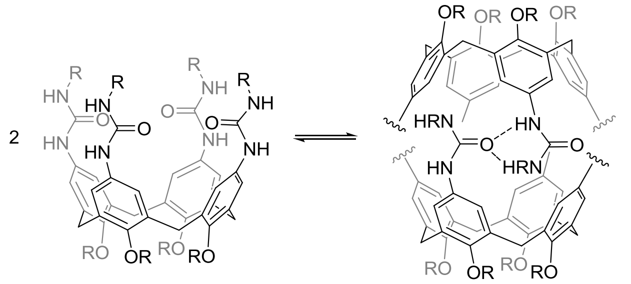


Fig. 6.2 Dimerization of an urea-substituted calix[4]arene through the formation of intermolecular hydrogen bonds.

Resorcin[4]arenes have been also investigated as scaffold for molecular capsules based on H-bonds. Kobayashi reported a molecular capsule based on a resorcinarene bearing carboxylic groups which dimerized in presence of 2-aminopyrimidine providing a structure where six molecules self assemble in the proper orientation and geometry (Fig. 6.3 a).[9] Other examples of H-bonded capsules based on a resorcinarene scaffold were reported by Rebek (Fig. 6.3 b).[10]

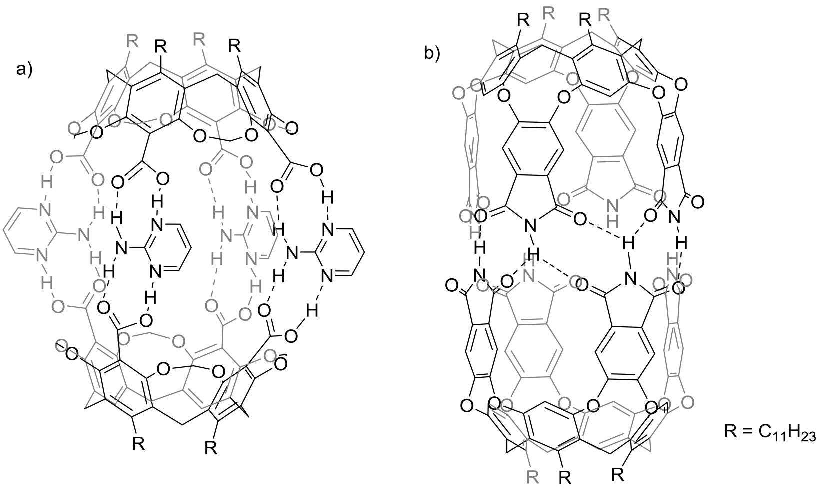


Fig. 6.3 Molecular capsules based on resorcinarene scaffolds. a) Kobayashi's capsule. b) dimer of a self-folding resorcinarine.

Capsules by Metal-ligand interactions

The assembly of molecular capsules by metal-ligand interactions is based on the great variety of coordination geometries offered by many transition metals.[11] Thus, coordinating groups on a cup-shaped scaffolds may lead to the closure of molecular cages with a variety of sizes and shapes by the coordination of metal linkers. Noticeably, unlike hydrogen-bonded capsules, the strength of the metal ligand interactions and the charge of the metal corners allowed many of these systems to aggregate in aqueous solutions.

The scaffolds used for preparing molecular capsules based on metal-ligand coordination has been calixarenes, resorcinarenes and porphyrines opportunely functionalized. For example, in those reported by Dalcanale[12] and Shinkai[13], resorcinarene and calixarene scaffold have been functionalized with nitrile and pyridyl groups which closed the cages upon the coordination of metals. In particular the most used precursor are usually Pd and Pt with square planar geometry and two labile ligands in *cis* positions (Fig. 6.4).

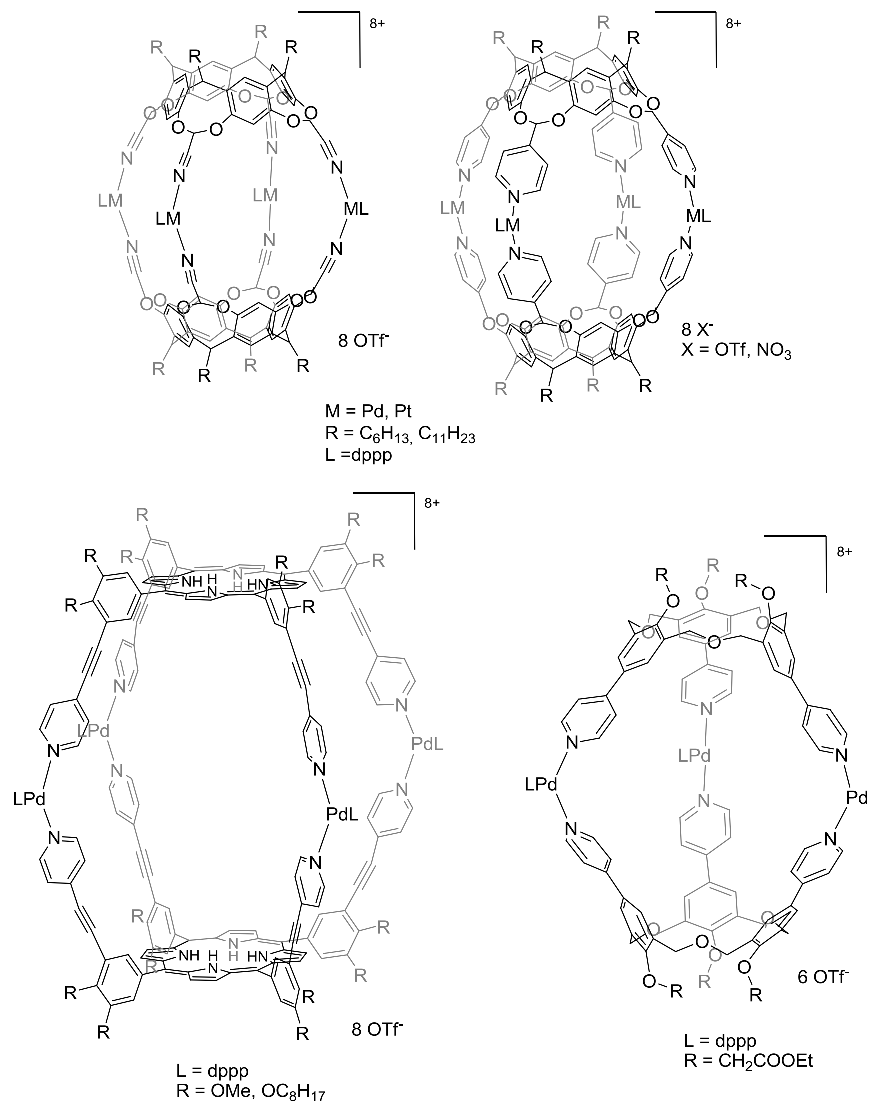


Fig. 6.4 Dalcanale's and Shinkai's cages.

In this field, a significant contribute was provided by Fujita, which reported molecular cages based on the coordination of planar multidentate organic ligands (molecular panels) into large three-dimensional cages through the coordination with *cis*-protected square planar metals, [(en)Pd^{2+} or (en)Pt^{2+} (en = ethylenediamine)] (Fig 6.5).[14]

Molecular capsules based on metal-ligand interactions have found applications in supramolecular catalysis. In fact the cavities can be regarded as a "safe" closed space where otherwise unstable molecules, sequestered from the bulk solvent, are protected and stabilized. Moreover reactions which take place inside molecular capsules may beneficiate of a selectivity induced by the inner shape of the host, usually different from the bulk of a solvent.

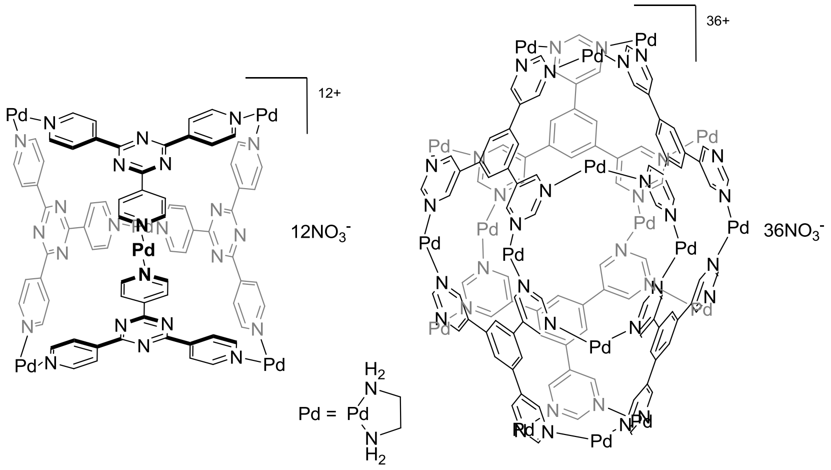
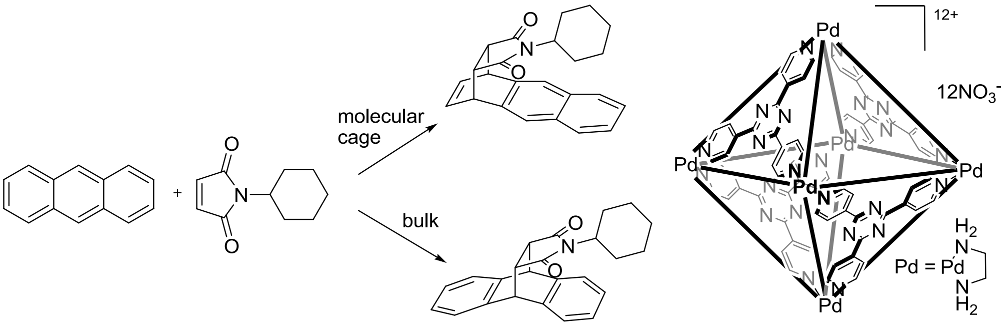


Fig. 6.5 Examples of Fujita's cages.

For example, Fujita reported the Diels-Alder reaction, in the presence of a coordination cage, of several anthracenes with *N*-phenylphthalimide (Scheme 6.1) and found a completely different selectivity (1,4 adduct) than that of the reaction carried without the cage (9,10 adduct).[15]



Scheme 6.1 Opposite selectivity in Diels Alder reactions carried out with and without molecular cages.

Capsules by ionic interactions

The previous examples of molecular capsules were characterized by a self-assembly process driven by strong and directional interactions, but several examples of stable cage-like complexes using multiple ionic interactions are also reported. The following examples are based on bearing cationic and anionic groups on calixarene[16] and porphyrin[17] based scaffolds, where the assembly is caused by strong electrostatic forces (Fig. 6.6).

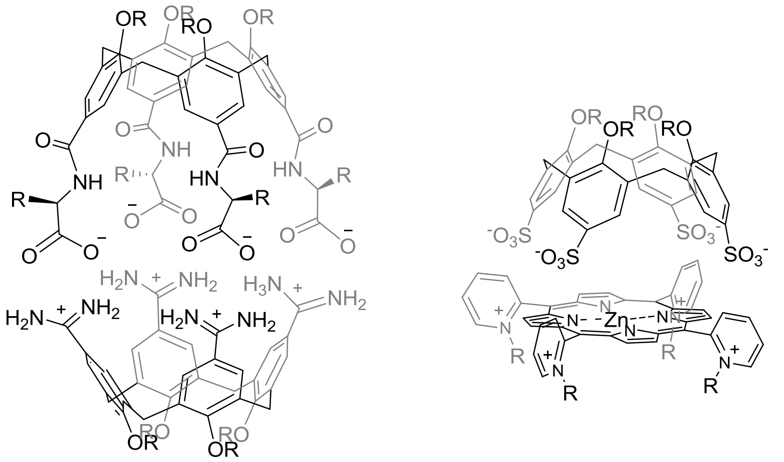


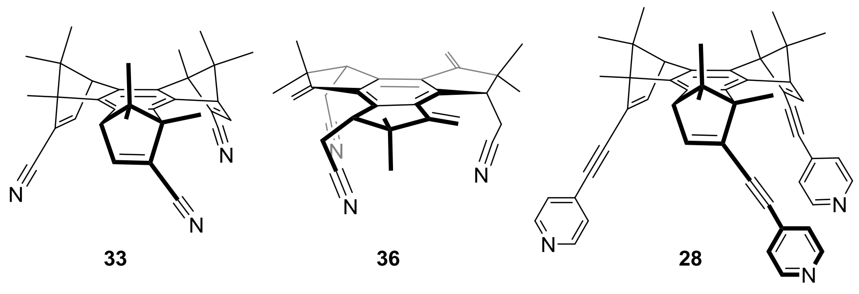
Fig. 6.6 Examples of capsules assembled through electrostatic interactions.

Hydrophobic effect

Finally, hydrophobic effect is widely used to facilitate both assembly process and guest encapsulation. Water soluble capsules, such as those based on resorcinarenes and the previously cited Fujita cages, provided encapsulation in water of non polar guests, which are pushed inside the hydrophobic cavities of molecular capsules by unfavorable entropies when they resides in the outer space.[18]

6.2 Molecular Capsules by Metal-Ligand Interactions

The most suitable benzocyclotrimers for the building of molecular assemblies by metal-ligand interactions are the structures **28**, **33**, **37**,[19] in which functional groups able to coordinate transition metals are placed at the rim of benzocyclotrimeric structures (Fig. 6.7). The nitrile and pyridil ligand groups have been often used in the preparation of molecular capsules based on metal-ligand interactions because they offer a suitable geometry, when they coordinate to metals, to close supramolecular assemblies.



33 **36** **28**

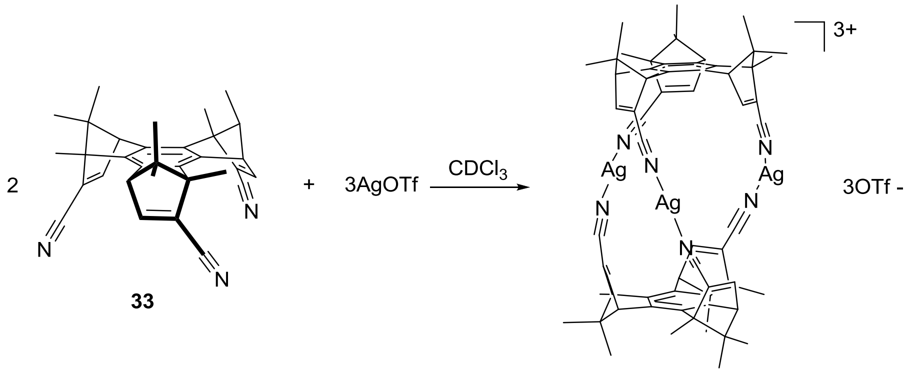
Fig. 6.7 Cyclotrimers bearing nitrile and pyridyl groups as coordinating groups.

The coordination properties of these compounds were demonstrated by titration experiments with silver and platinum and are described below. The formation of complexes was followed by titration experiments, performed by adding known amounts of a solution of the metal to a solution of the ligand in chloroform-d or acetone-d_6. After each addition of the metal, NMR spectra were recorded and the equivalent point was determined.

*Coordination experiments of nitrile **33***

The rigid trinitrile **33** was prepared through the coupling of benzotricamphor triflate with trimethylsilyl cyanide (Chapter 4, par. 4.3) and was used for the formation of a coordination cage by complexation with silver.

The addition of AgOTf to a solution of **33** in $CDCl_3$, caused the shift of the vinyl proton in the NMR spectra from 7.4 to 7.8 ppm when the [**33**]/[Ag] ratio reached the value of 2/3. This value is consistent with the formation of a complex in which two trimeric units are linked together with three metal units



Scheme 6.2 Formation of the coordination cage between nitrile **33** and Ag.

The down-field shift of the vinyl proton of **33** in the NMR spectra is consequence of the coordination of the nitrile groups on the metal. Moreover the progression of a single signal, which shifted from the position of the free ligand to a "maximum" value of chemical shift, means that the formation of the complex is a fast equilibrium process.[20] Thus, the association/dissociation of the complex is fast on the NMR time-scale and the observed signal is a weight average of free and coordinated ligand in rapid exchange.

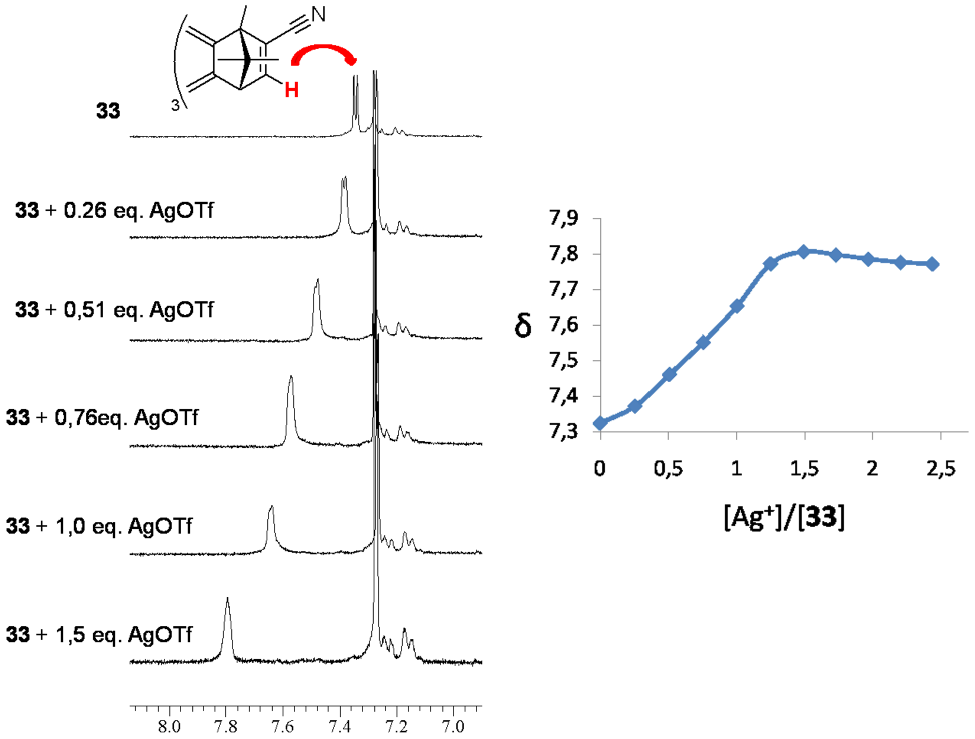


Fig. 6.8 NMR titration of trinitrile **33** with AgOTf.

The formation of the complex was finally demonstrated by ESI-MS measurements, which clearly displayed the peaks at *m/z* 1565.6 and 707.3 corresponding to mono $[\mathbf{33}_2\mathrm{Ag}_3(\mathrm{OTf})_2]^{+}$and bis-cationic $[\mathbf{33}_2\mathrm{Ag}_3(\mathrm{OTf})]^{2+}$, together with peaks at 1307.3 and 580.4 (respectively mono- and bis-cationic species of $\mathbf{33}_2\mathrm{Ag}_2$) related to the same capsule with only two Ag corners (Fig. 6.9).

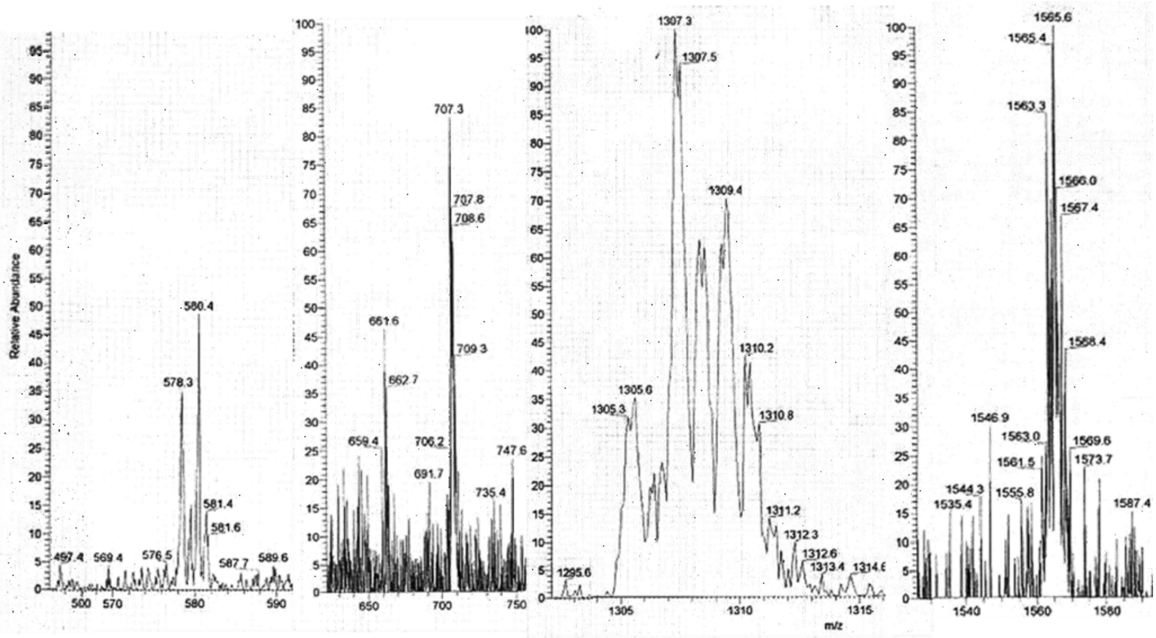
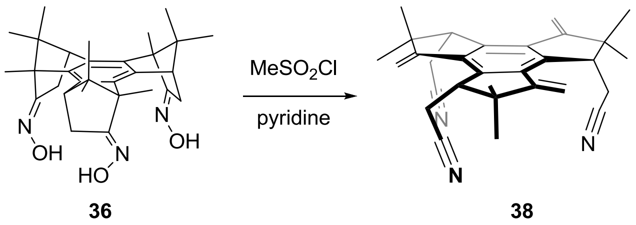


Fig. 6.9 ESI-MS of the coordination cage between nitrile **33** and Ag.

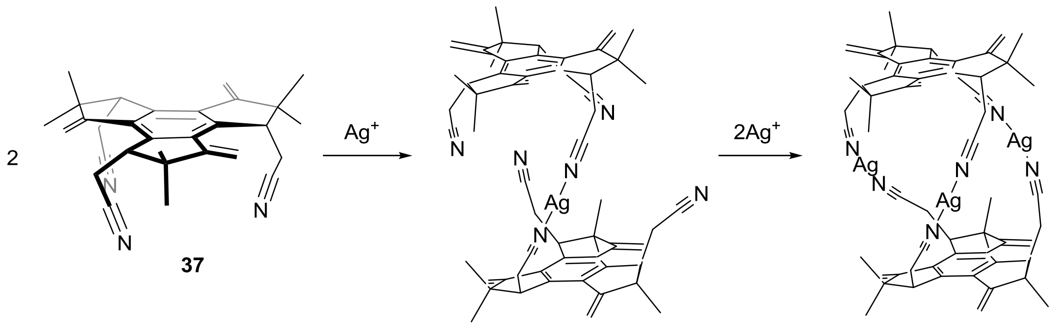
*Coordination experiments of nitrile **37***

The trimeric structure **37** was obtained in the attempt to perform the Beckman rearrangement to the trioxime **36** which rearranged to afford the new trimer bearing three flexible nitrile groups, instead of providing the amide.



Scheme 6.3 Reaction of trioxime **36** with mesyl chloride.

The possibility to prepare coordination cages with the flexible tridentate ligand **37** was studied by coordination experiments with silver. Taking advantage of the linear coordination geometry of Ag, it was expected the formation of a dimeric aggregate by coordination of two cyclotrimers with three Ag$^+$ ions. The NMR titration of **37** with AgOTf clearly showed the progressive down-field shift of the diastereotopic methylene protons during the additions of the metal, meaning that the coordination process occurred. The maximum shift was achieved after the addition of 1.5 equivalents of silver salt, thus the formation of a complex with a stochiometric ratio of 3/2 between [Ag] and [**37**] was evidenced. Moreover, the trend observed for the variation of the chemical shift during the titration had a low slope until [Ag]/[**37**] was 0.5, whereas further addition of the metal increased the slope of the titration curve (Fig. 6.9). A possible association mechanism that could account this trend is the initial formation of a monomeric specie with two ligands coordinated to one Ag and the further addition of the metal ends with the complete formation of the cage (Scheme 6.4).



Scheme 6.4 Possible cage formation by metal-ligand interactions between nitrile **37** and Ag$^+$.

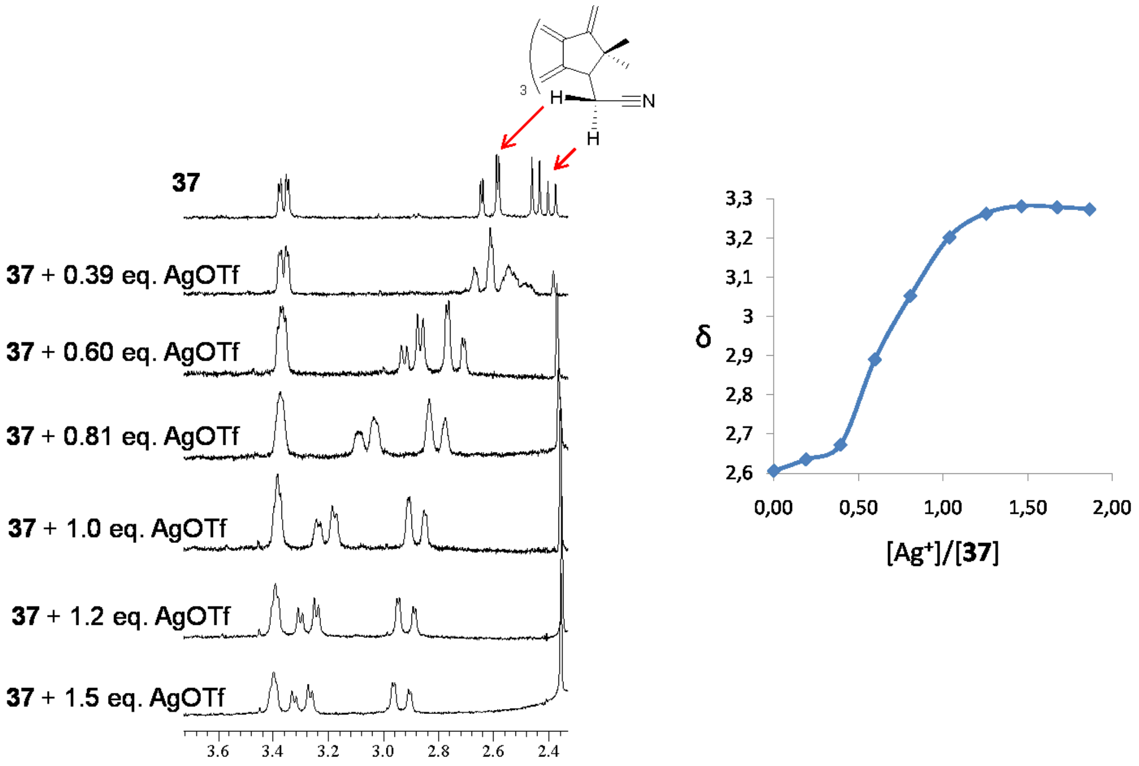


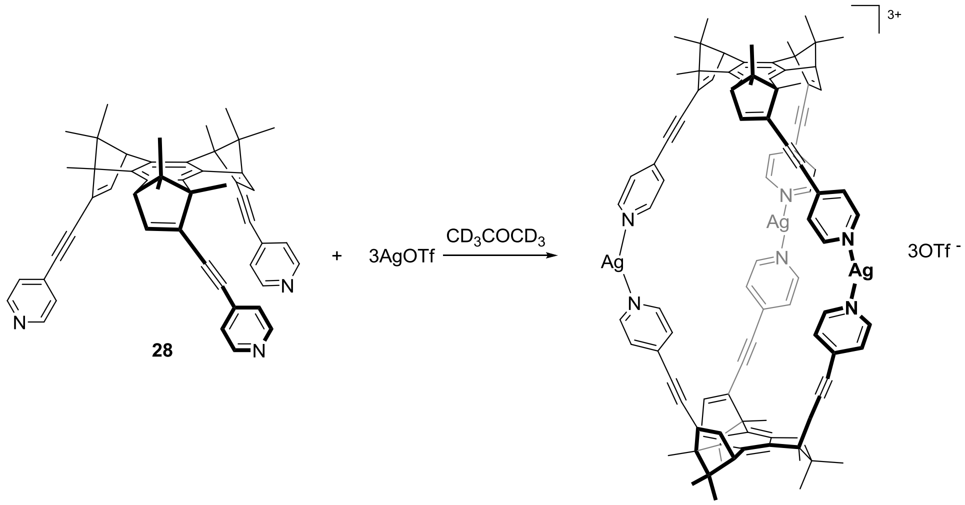
Fig. 6.10 NMR titration of trinitrile **37** with AgOTf.

Unfortunately, the formation of the complexes between trinitrile **37** and AgOTf were not confirmed by mass spectra, because the complex is likely too labile to survive during ionization processes.

*Coordination experiments of pyridine **28***

Pyridine is a more efficient coordinating ligand than nitrile. Trispyridine **28** was threfore used in coordination experiments with silver and platinum.

The coordination of silver was demonstrated by NMR titrations of **28** with AgOTf, observing the down-field shift of the signals assessed to the protons of vinyl and pyridine until a 3/2 ratio between the metal and the ligand was achieved (Fig. 6.11). As well as with nitriles **33** and **37**, this is consistent with the formation of a complex in which two cyclotrimeric units are linked with three metal units (Scheme 6.5), as confirmed by ESI-MS. Peaks at *m/z* 2022.0, 936.6 and 575.0 are associated to $[\mathbf{3}_2Ag_3(OTf)_2]^+$, $[\mathbf{28}_2Ag_3(OTf)]^{2+}$ and $[\mathbf{28}_2Ag_3]^{3+}$ respectively, as well as $[\mathbf{28}_2Ag_2(OTf)]^+$ to 1764.1 and $[\mathbf{28}_2Ag]^+$ to 1506.5 (Fig. 6.12).



Scheme 6.5 Formation of the coordination cage between trispyridine **28** and AgOTf.

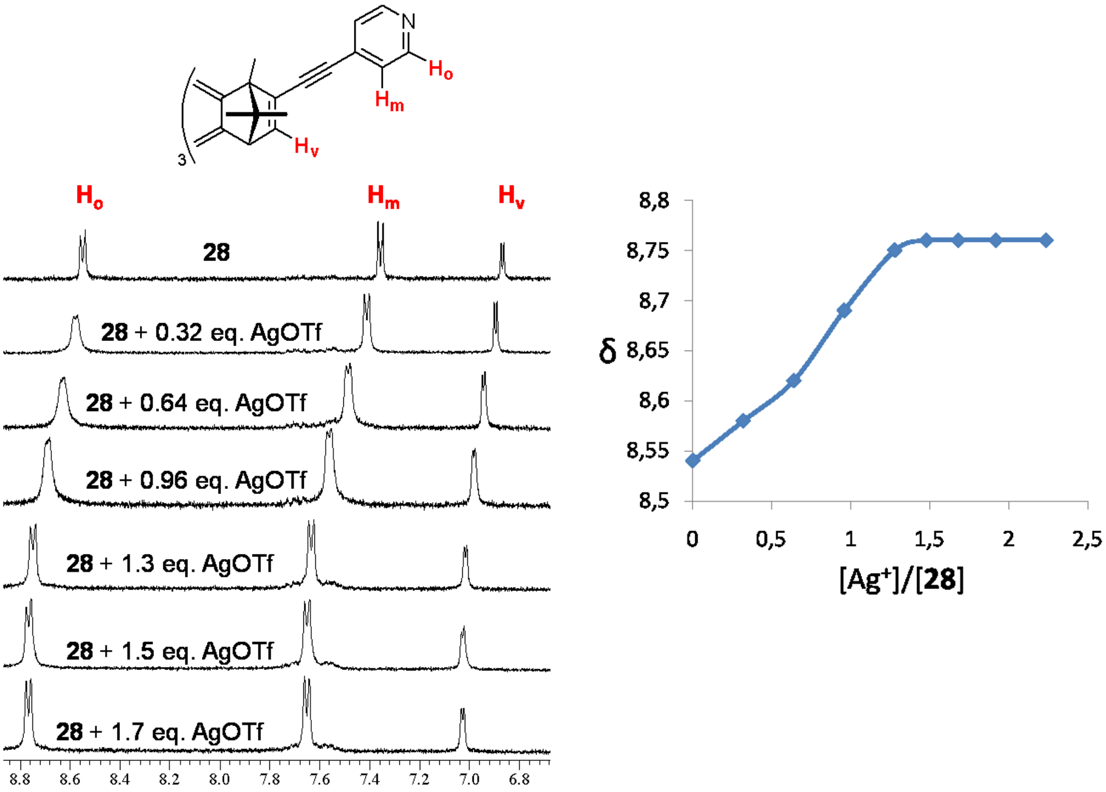


Fig. 6.11 NMR titration of tripyridine **28** with AgOTf.

The progression of the chemical shift value from free to complexed ligand was indicative of the formation of more species in fast equilibrium and therefore the observed NMR signal was the average of free and coordinated tripyridine, as well as was found for nitriles **33** and **37**.

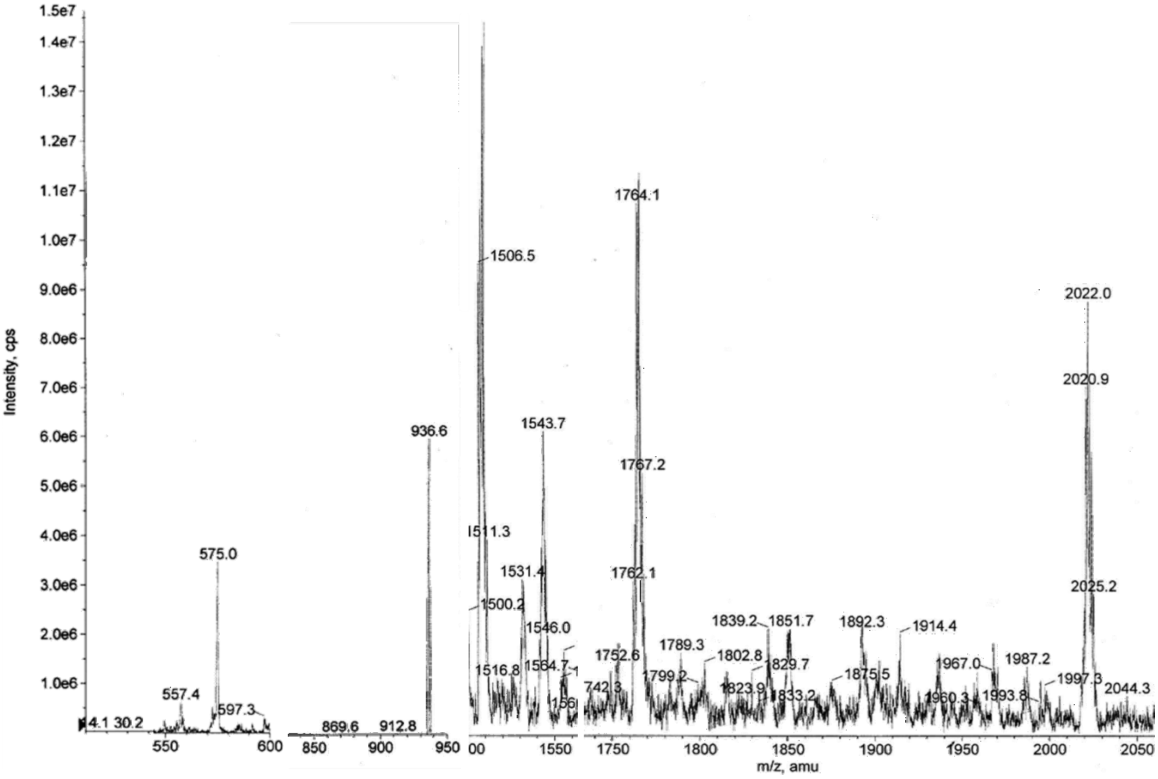
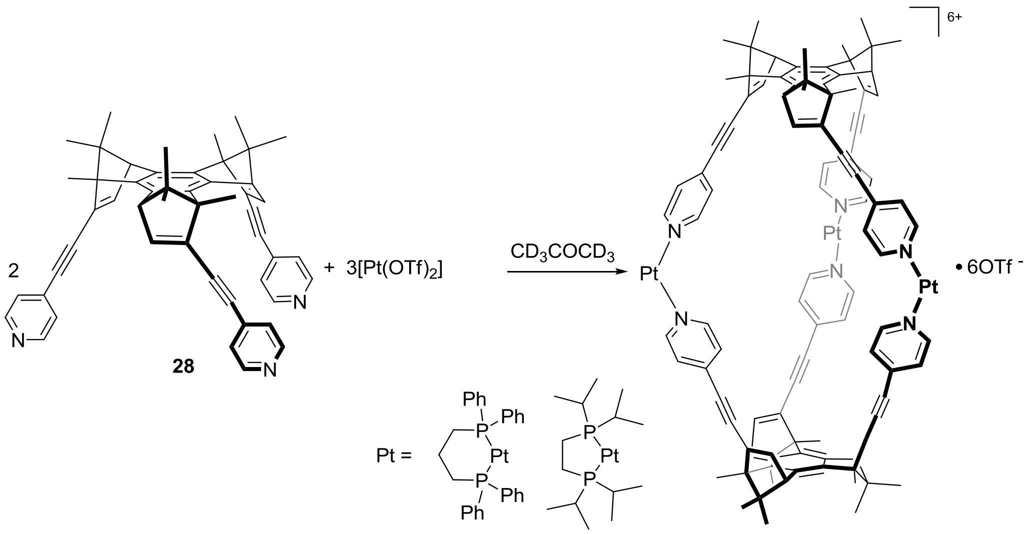


Fig. 6.12 ESI-MS of the coordination cage between trispyridine **28** and AgOTf.

Unlike nitriles **33** and **37** the more effective ligating properties of pyridine moiety offer the opportunity to obtain coordination compounds with platinum(II) complexes.

During the titration of **28** with Pt(dppp)OTf$_2$ and Pt(dippe)OTf$_2$ in acetone-d$_6$, new signals appeared in the NMR spectra, whose relative intensity increased while the signals of **28** decreased. The latter finally disappeared in correspondence of a 3/2 stoichiometric ratio between the metal and **28.** This behavior was consistent with the formation of the coordinating cage shown in Scheme 6.6, and it was confirmed by ESI-MS. Mass analysis of a 2:3 molar ratio solution of **28** and (dippe)Pt(OTf)$_2$ showed the formation of the dimeric capsule by the presence of the peaks at 1684.5, 1073.1, 768.5 and 584.1 *m/z*, attributed to [**28**$_2$[(dippe)Pt]$_3$(OTf)$_4$]$^{2+}$, [**28**$_2$[(dippe)Pt]$_3$(OTf)$_3$]$^{3+}$, [**28**$_2$[(dippe)Pt]$_3$(OTf)$_2$]$^{4+}$ and [**28**$_2$[(dippe)Pt]$_3$(OTf)]$^{5+}$ respectively. In the MS spectra are present peaks related to the capsule held together by two and even only one Pt corner, as evidenced by peaks at m/z 1305.4, 822.1 and 579.2 associated to [**28**$_2$[(dippe)Pt]$_2$(OTf)$_2$]$^{2+}$, [**28**$_2$[(dippe)Pt]$_2$(OTf)]$^{3+}$ and [**28**$_2$[(dippe)Pt]$_2$]$^{4+}$ as well as 929.4 related to [**28**$_2$[(dippe)Pt]]$^{2+}$ (Fig. 6.15).



Scheme 6.6 Formation of the coordination cage between trispyridine **28** and [Ptdppp](OTf)$_2$

The appearance of NMR signals for both free and coordinated ligand during the titration is related to slower exchange on the NMR timescale between free and coordinated ligand which is a typical property of Pt species (Fig. 6.13).[20] The second aspect is that the new signals are ascribable to a C_3-symmetric complex, meaning that the association process is fast and the formation of the closed cage is preferred to the mono- or bis-coordinated complexes.

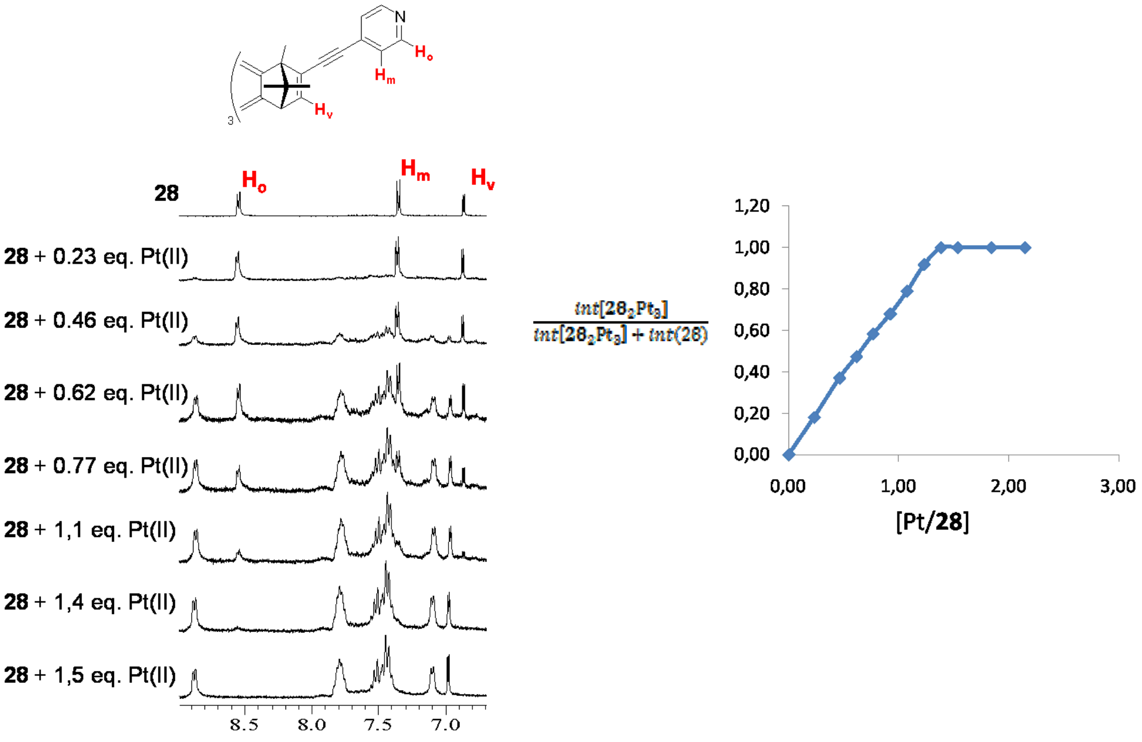


Fig. 6.13 NMR titration of tripyridine **28** with [Ptdppp](OTf)$_2$.

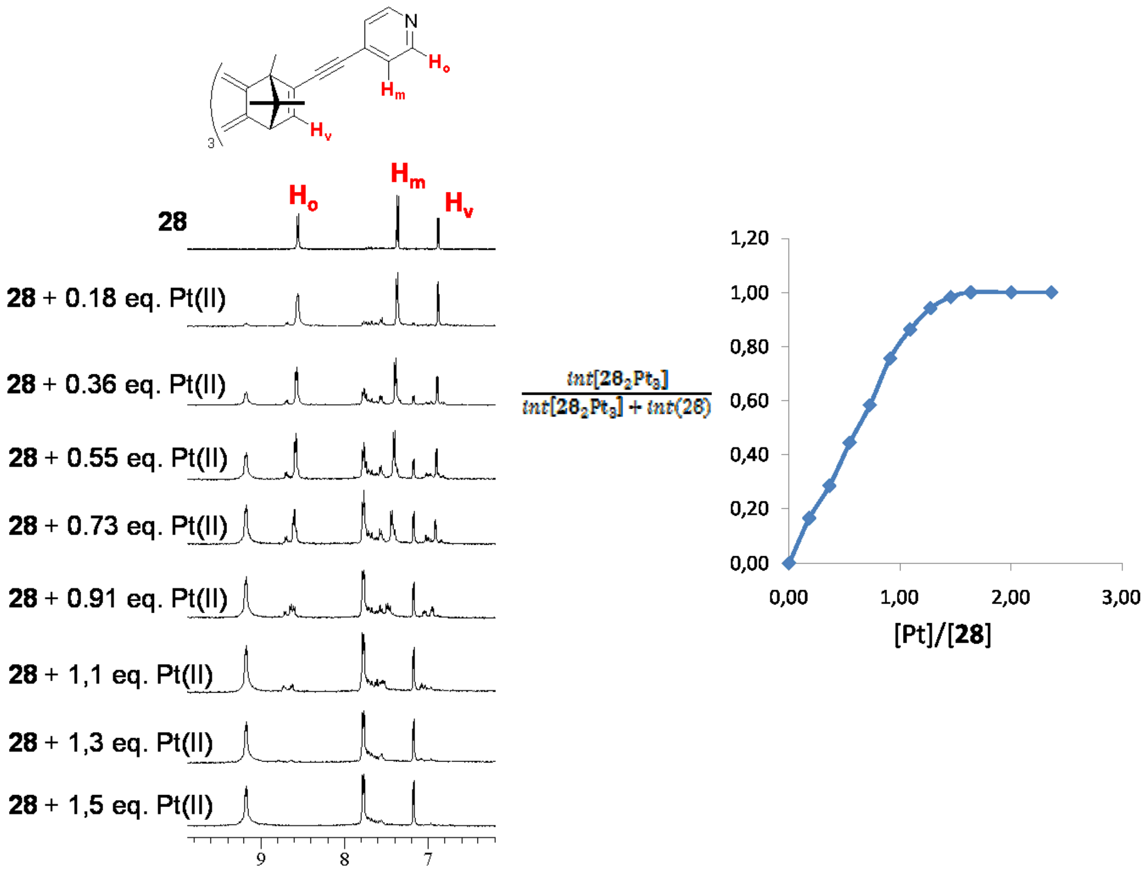


Fig. 6.14 NMR titration of tripyridine **28** with [Ptdippe](OTf)$_2$.

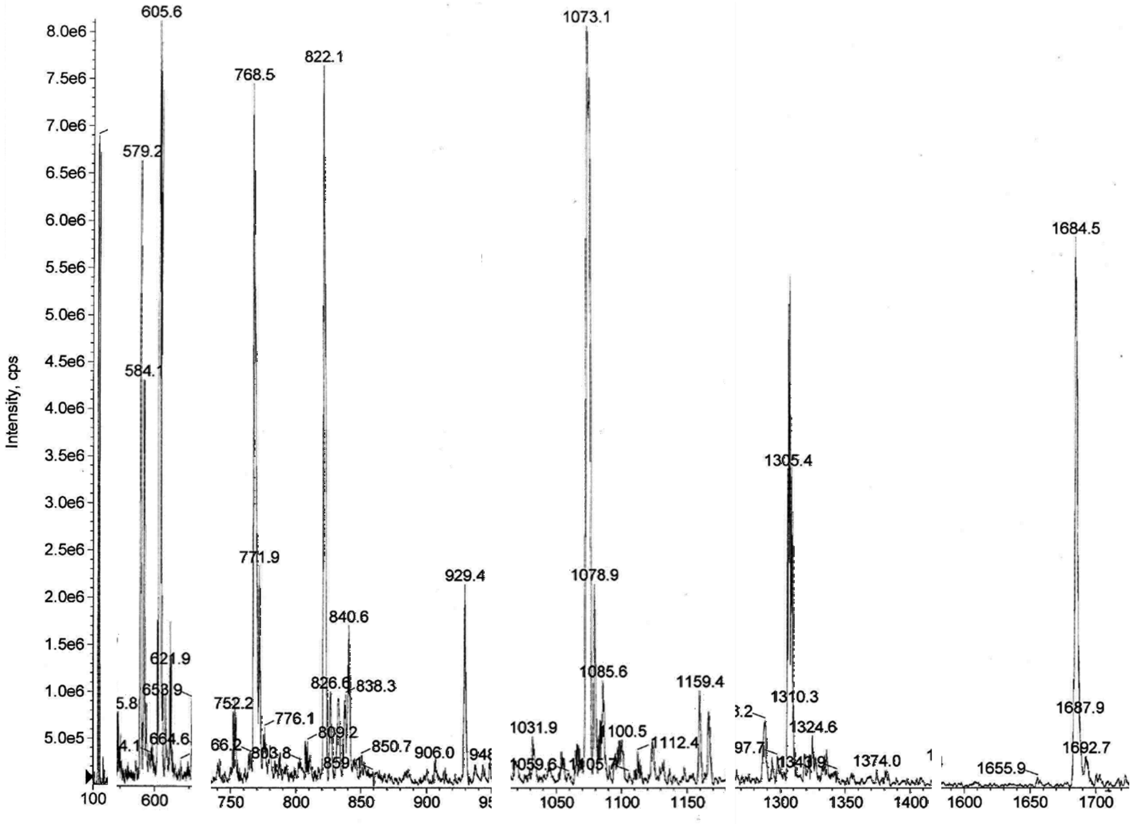


Fig. 6.15 ESI-MS of tripyridine **28** with [Ptdippe](OTf)$_2$.

The formation of the complexes was further demonstrated by 2D NMR. The NOESY spectra of the [**28**$_2$(Ptdppp)$_3$](OTf)$_6$ complex clearly displayed the interaction between the pyridines of the cyclotrimeric unit and the phenyls of the dppp coordinated to Pt, meaning that the two ligands are in close proximity (Fig. 6.16). Moreover, DOSY experiments provided estimated hydrodynamic radii both for the tripyridine alone (3.15 Å) and for the complex (6.29 Å), which are (again) consistent with the formation of a trinuclear complex capped by two cyclotrimeric units.

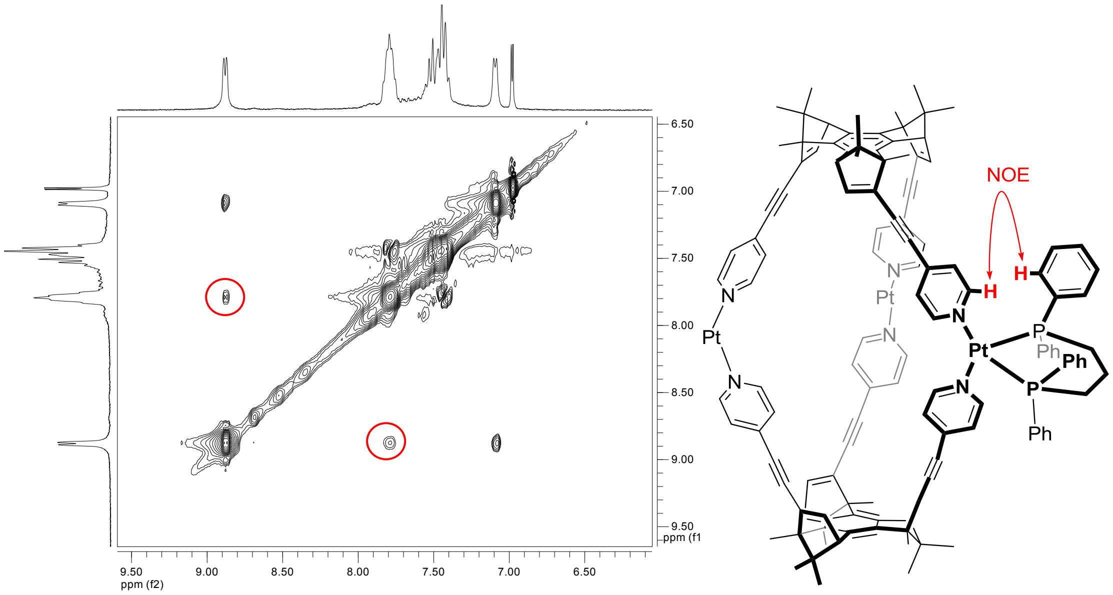
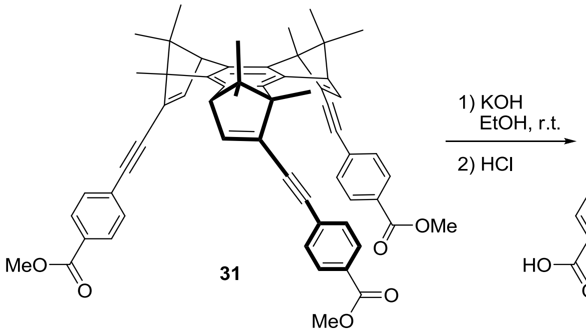


Fig. 6.16 NOESY spectra of the complex [**28**$_2$(Ptdppp)$_3$](OTf)$_6$. The interaction between ligand groups coordinated on Pt is hooped In red.

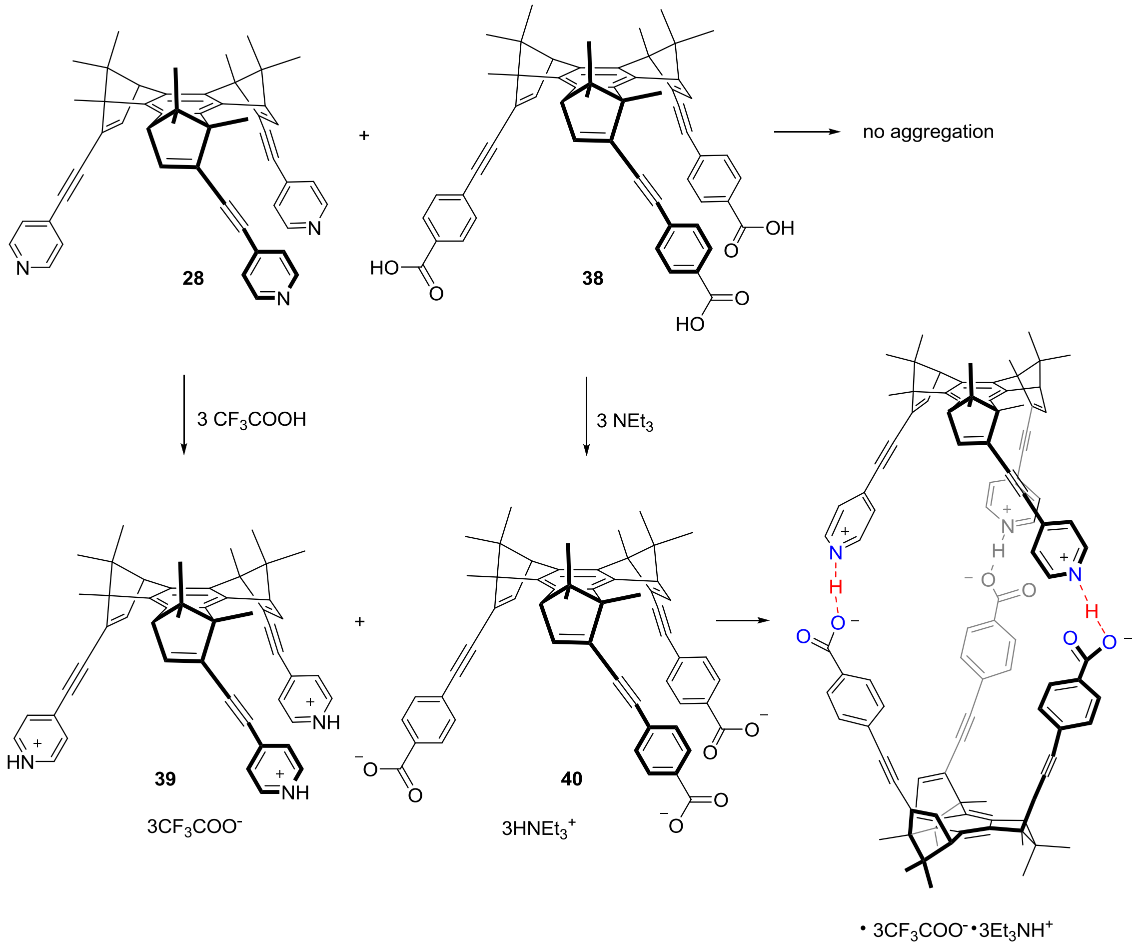
6.3 MOLECULAR CAPSULES BY IONIC INTERACTIONS

Tripyridine **28** was also used for the preparation of a self-assembling capsule based on ionic interactions with triacid **38**, obtained from the corresponding methyl ester **31** (Chapter 4, Paragraph 4.3, Table 4.3) by basic hydrolysis (Scheme 6.7). When **28** was mixed with **38** in $CDCl_3$ in the attempt to prepare an H-bonded capsule, no significative evidence of aggregation was observed. Thus suitable salts of **28** and **38** were prepared to stimulate the formation of a capsule by strong electrostatic interactions. The counter-ions were hydrophobic with the aim to render the salts of **28** and **38** soluble in organic solvents. Thus tripyridine **28** was protonated with CF_3COOH and the triacid **38** was converted to the corresponding tribenzoate **40** with triethylamine (Scheme 6.8).

The positions of ^{1}H-NMR signals did not change significatively during the titration of tribenzoate **40** with the trispyridinium **39**, except for the appearance of a new peak at 12 ppm which was not present in the spectra of **39** or **40** alone (Fig. 6.13). Thus a correlation between the variation of δ with the ratio of the two trimers, as in the case of metal-ligand cages, was not found.



Scheme 6.7 Synthesis of triacid **38.**



Scheme 6.8 Preparation of an ionic capsule based on a cyclotrimer scaffold by ionic/H-bond interactions

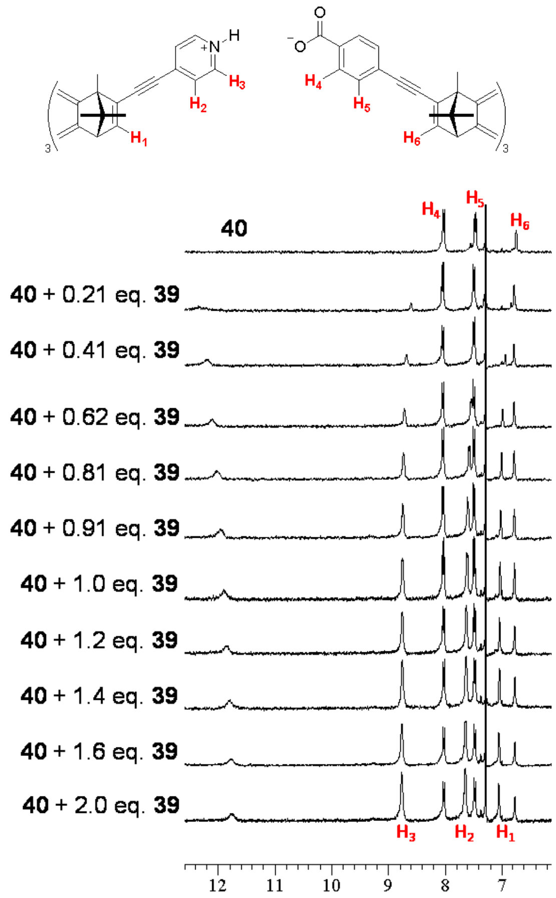


Fig. 6.17 NMR titrations of tribenzoate **40** with tripyridinium **39**

However, the appearance of the new peak at 12 ppm is consistent with the formation of an aggregate in which an hydrogen is “trapped” between the nitrogen atom on the pyridine of **39** and the carboxylic groups of **40.**[21]

The sharpens and highly symmetric appearance of the titration spectra suggest to exclude disordered forms of aggregation.

With the aim to prove the formation of a capsule, NOESY and DOSY experiments were carried out. The NOESY spectra clearly showed the NOE interaction between protons in *orto* to nitrogen in **39** and hydrogens in *orto* to carboxylate in **40** (Fig. 6.14). Moreover, DOSY measurements showed that **39** and **40** have the same diffusion coefficient when they were mixed in equimolar amount and confirmed the existence of a larger aggregate (hydrodynamic radii estimated in 5.78 Å) than **39** and **40** alone (4.51 and 4.41 Å respectively), that is indicative of a 1:1 complex. Since there was no aggregation between the neutral pyridine **28** and acid **38**, this suggested that ionic interactions, in association with H-bond formation, strongly influenced the assembly process. However, the scant variation of NMR spectra of both **39** and **40** during the titration might suggest the formation of a quite labile ionic capsule.

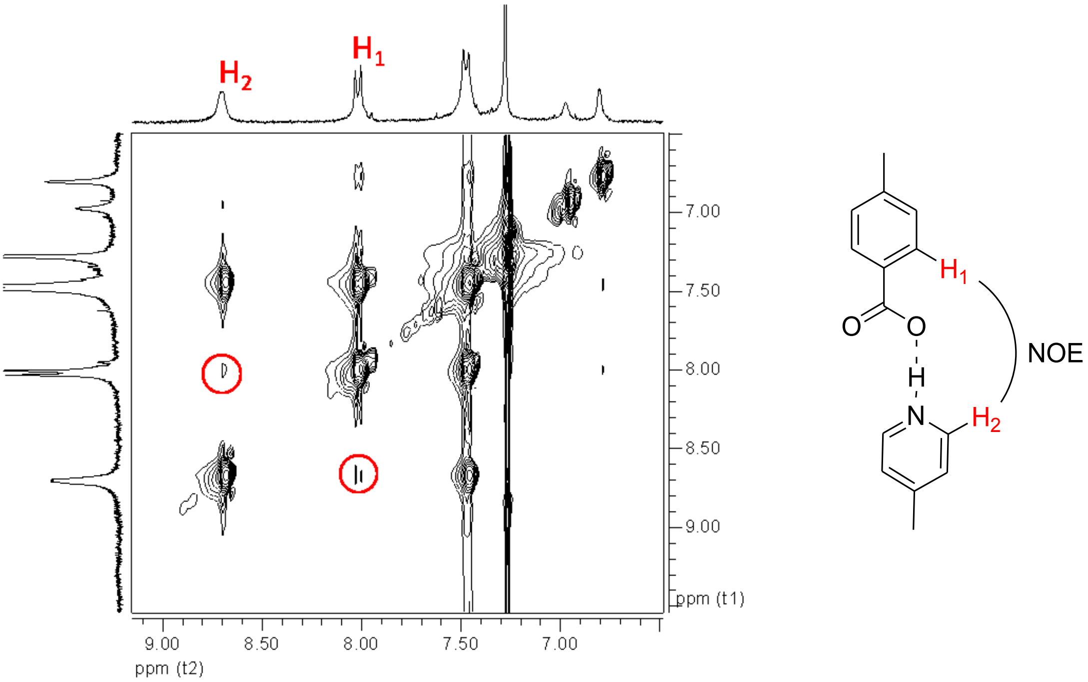


Fig. 6.18 NOESY spectra of a mixture 1:1 of tripyridinium **39** and tribenzoate **40**.

6.4 MOLECULAR CAPSULES BY H-BOND INTERACTIONS

The interaction between trimers **39** and **40** was an example in which the assembly process is driven by strong electrostatic forces. To achieve the assembly through purely H-bond interactions, compounds **32** and **35** were prepared by connecting molecular units able to provide an extended H-bond network to a benzocyclotrimeric scaffold (Fig. 6.20).[19] These groups are bis(acetamido)pyridine and an uracil derivative (Fig. 6.19), which mimic the H-bond interactions between adenine and uracil in RNA.

NMR titration of trimer **32** with **35**, clearly displayed the down-field shift of the *N*-H signal of the uracil, whereas the remaining signals were scarcely affected. This behavior can be assessed to the formation of H-bonds between the bis(acetamido)pyridin and the uracil moieties and it was indicative of the formation of the capsule (Fig. 6.21).

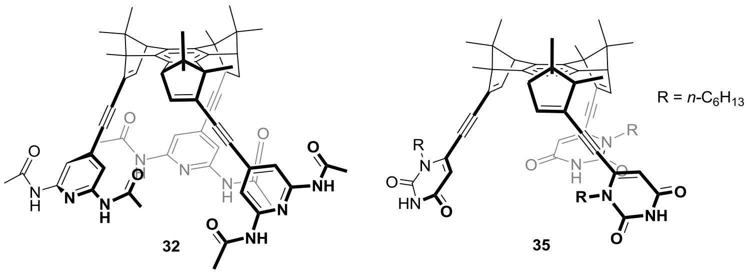


Fig. 6.19 Trimers bearing complementary H-bond donors and acceptors.

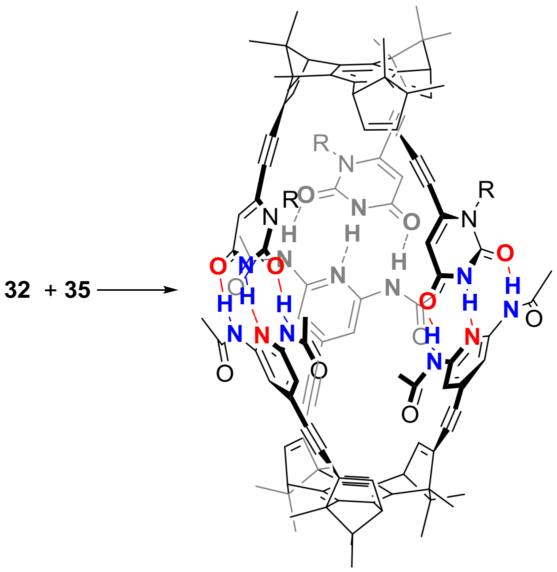


Fig. 6.20 Capsule formation by H-bond interactions.

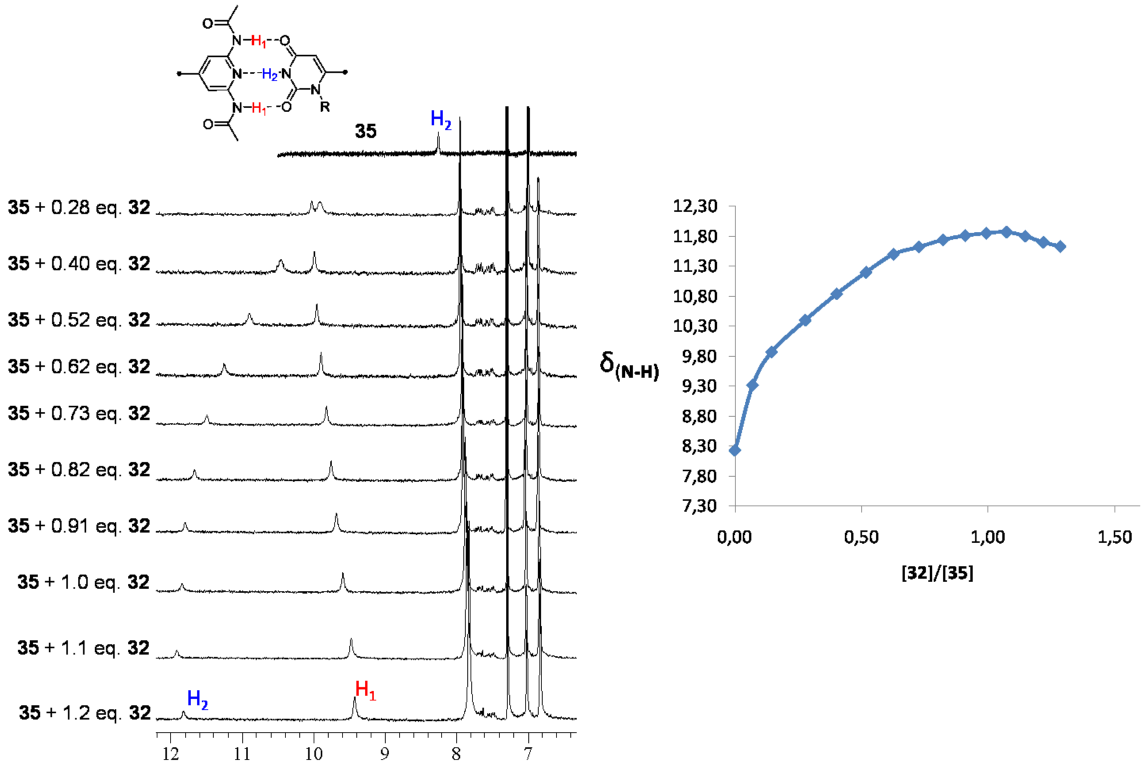


Fig. 6.21 NMR titration of **35** with **32**.

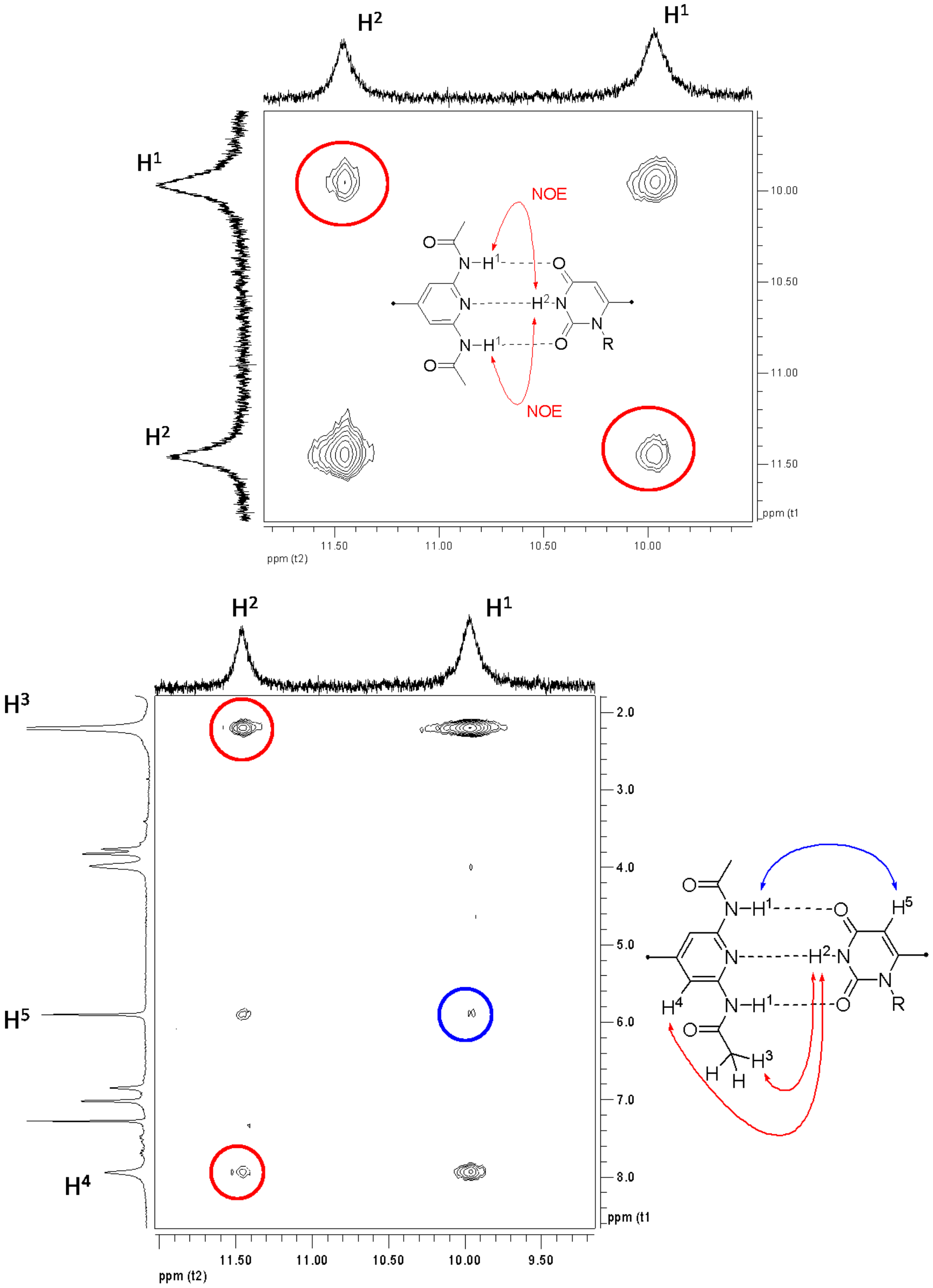


Fig. 6.22 Particulars of the NOESY spectra of an equimolar mixture of **32** and **35.**

In conclusion, different functional groups placed at the rim of a benzocyclotrimeric scaffold led to different derivatives which exhibited self-assembling abilities. Derivatives of benzotricamphor were used in the preparation of supramolecular aggregates by using the more common self-assembly interactions.

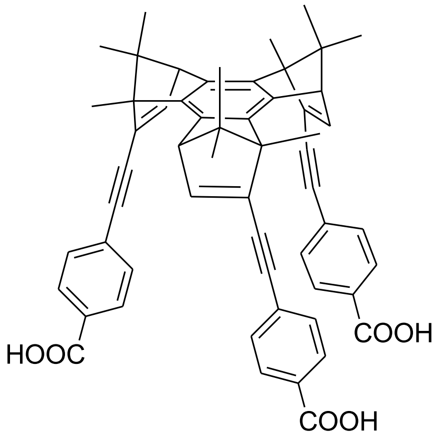
Thus trimers **28**, **33**, **37** allowed the preparation of coordination cages with transition metals, **39** and **40** showed attractive interactions through anion-cation pairing and finally trimers **32** and **35** assembled by the formation of a large H-bond network.

6.5 EXPERIMENTAL SECTION

GENERAL

All reactions were performed in flame-dried glassware blanketed with argon. Reagents purchased were used without further purifications. Solvents were eventually dried according procedures reported in Armarego, W. L. F. and Perrin, D. D. "Purification of Laboratory Chemicals", Fourth Ed., Butterworth-Heinemann Ed., 1996. The evolution of the reactions was monitored by TLC or ^{1}H NMR. ^{1}H NMR and ^{13}C{^{1}H} NMR spectra were recorded at 298 K, unless otherwise stated, on a Bruker AVANCE 300 spectrometer operating at 300.15 and 75.48 MHz respectively and the δ values in ppm are relative to TMS.

syn-(1*R*,4*R*,5*R*,8*R*,9*R*,12*R*)-2,6,10-Tris(2-(*p*-benzoate)ethynyl)-4,8,12-trihydro-1,5,9,13,13',14,14',15,15'-nonamethyl-1,4:5,8:9,12-trimethanotriphenylene

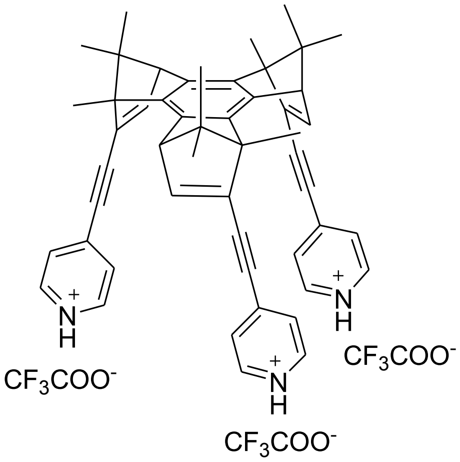


syn-**38**

A mixture of *syn*-(1*R*,4*R*,5*R*,8*R*,9*R*,12*R*)-2,6,10-tris(2-(*p*-methylbenzoate)ethynyl)-1,4,5,8,9,12-hexahydro-1,5,9,13,13',14,14',15,15'-nonamethyltrimethano-triphenylene (40.0 mg, 46 μmol) and KOH (151 mg, 2.70 mmol) in ethanol (10 mL) was stirred at room temperature for 6 hours. Solvent was removed under *vacuum* and HCl 1M (15 mL) was added. The mixture was extracted with Et_2O (3×15 mL) and combined organic extracts were washed with H_2O (15 mL), saturated aqueous NaCl (15 mL), dried over $MgSO_4$ and concentrated in *vacuum*. The residue was dissolved in chloroform and the solution was filtrated. The removal of the solvent under *vacuum* afforded the product (34.5 mg, 91% yield) as colorless crystals; m.p.

160°C; $[\alpha]_D^{22}$ = + 1317 (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 11.30 (3, H, br, s), 8.01 (6 H, d, *J* = 8.3 Hz), 7.56 (6 H, d, *J* = 8.6 Hz), 6.80 (3 H, d, *J* = 3.3 Hz), 3.90 (3 H, d, *J* = 3.3 Hz), 1.59 (9 H, s), 1.16 (9 H, s), 0.92 (9 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 167.9, 148.2, 142.1, 139.8, 139.3, 133.1, 131.6, 131.2, 130.0, 99.1, 90.1, 73.8, 64.9, 58.3, 22.4, 20.9, 12.0; IR (KBr) ν 2924, 2193, 1693, 1608, 1279 cm^{-1}.

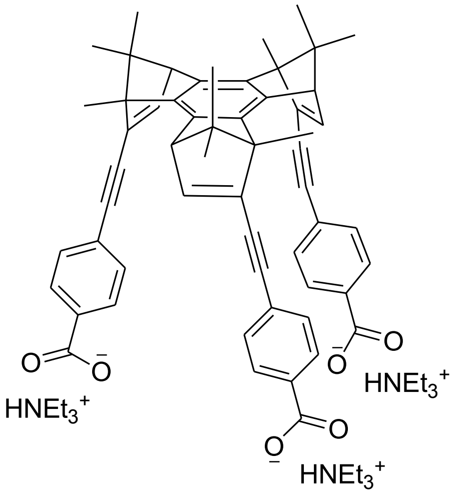
***Syn*-(1*R*,4*R*,5*R*,8*R*,9*R*,12*R*)-2,6,10-Tris(2-ethynyl-4-pyridinium)-4,8,12-trihydro-1,5,9,13,13',14,14',15,15'-nonamethyl-1,4:5,8:9,12-trimethanotriphenylene. Trifluoroacetate salt**



syn-**6**

A mixture of tripyridine *syn*-**28** (12.0 mg, 17.1 μmol) and trifluoroacetic acid (4.8 μL, 62.7 μmol) in $CHCl_3$ was dried in *vacuum* for 4 hours to afford quantitatively the salt as orange crystals, m.p. 63 °C; $[\alpha]_D^{22}$ = + 527 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.72 (6 H, d, *J* = 6.7 Hz), 7.61 (6 H, d, *J* = 6.4 Hz), 7.02 (3 H, d, *J* = 3.3 Hz), 4.93 (3 H, broad), 3.85 (3 H, d, *J* = 3.6 Hz), 1.55 (9 H, s), 1.15 (9 H, s), 0.87 (9 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 161.7 (q, *J* = 37.8 Hz), 152.5, 142.4, 140.6, 139.9, 137.5, 136.1, 127.5, 116.0 (q, *J* = 290 Hz), 98.5, 94.1, 73.9, 62.8, 57.2, 21.0, 19.6, 10.6; IR (KBr) ν 2929, 2187, 1605, 1383, 1172 cm^{-1}.

syn-(1*R*,4*R*,5*R*,8*R*,9*R*,12*R*)-2,6,10-Tris(2-(*p*-benzoate)ethynyl)-4,8,12-trihydro-1,5,9,13,13',14,14',15,15'-nonamethyl-1,4:5,8:9,12-trimethanotriphenylene. Triethylammonium salt



syn-**40**

A solution of triacid *syn*-**38** (12.0 mg, 14.5 μmol) and freshly distilled NEt_3 (7.2 μL, 50.6 μmol) in $CHCl_3$ was dried in *vacuum* for 4 hours to afford quantitatively the salt as colorless crystals, m.p. 69 °C; $[\alpha]_D^{22}$ = + 872 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.98 (6 H, d, *J* = 8.2 Hz), 7.41 (6 H, d, *J* = 8.2 Hz), 6.68 (3 H, d, *J* = 3.3 Hz), 3.72 (3 H, d, *J* = 3.3 Hz), 3.06 (18 H, q, *J* = 7.4 Hz), 1.50 (9 H, s), 1.27 (27 H, t, *J* = 7.2 Hz) 1.11 (9 H, s), 0.83 (9 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 171.3, 145.3, 139.9, 137.6, 137.2, 134.3, 130.8, 129.4, 126.3, 97.9, 87.5, 71.9, 62.8, 56.3, 45.1, 21.1, 19.7, 10.7, 8.6; IR (KBr) ν 2962, 2193, 1679, 1633, 1191 cm^{-1}.

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CHAPTER 7

PROPIOLIC ACID COUPLINGS

7.1 PREFACE

A fundamental requirement in the design of self-assembling systems is the presence of complementary recognition sites to provide relatively strong interactions during the formation of supramolecular aggregates. A functional group well exhibiting this behavior is the carboxylic group, demonstrated by the tendency of carboxylic acids to “self-associate in dimeric pairs by H-bond interactions.

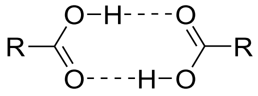
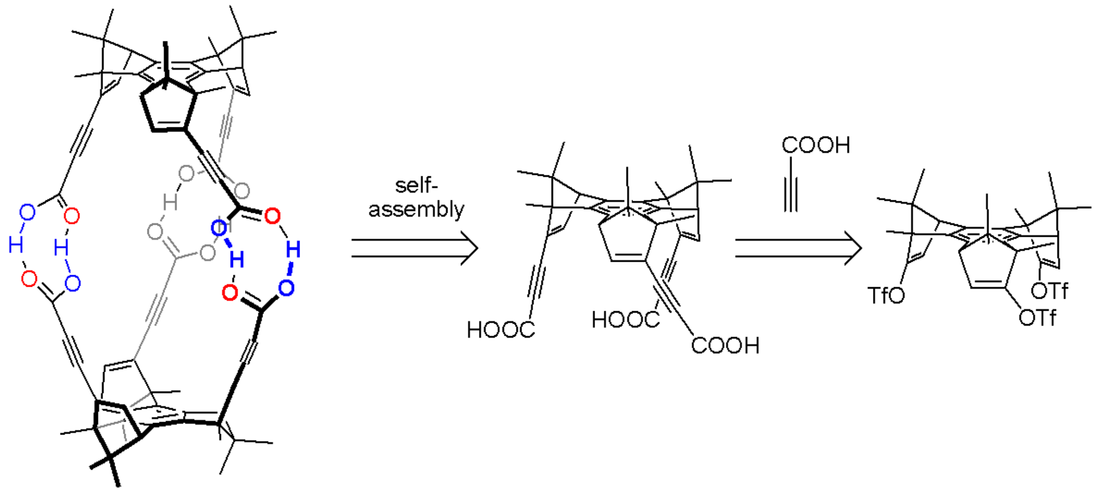


Fig. 7.1 dimerization of carboxylic acids by H-bonding.

This behavior raised the idea to achieve the self-assembly of a suitable cup-shaped structure into a supramolecular capsule through the self-recognition of carboxylic groups placed at the rim of this structure.

Self-assembling derivatives of benzotricamphor were successfully prepared through the coupling of terminal alkynes on benzotricamphor triflate **24** (Chapter 4). Thus, a possible self-assembling derivative could be prepared by replacing triflates at the vinyl positions with acetylene-carboxylic acid.

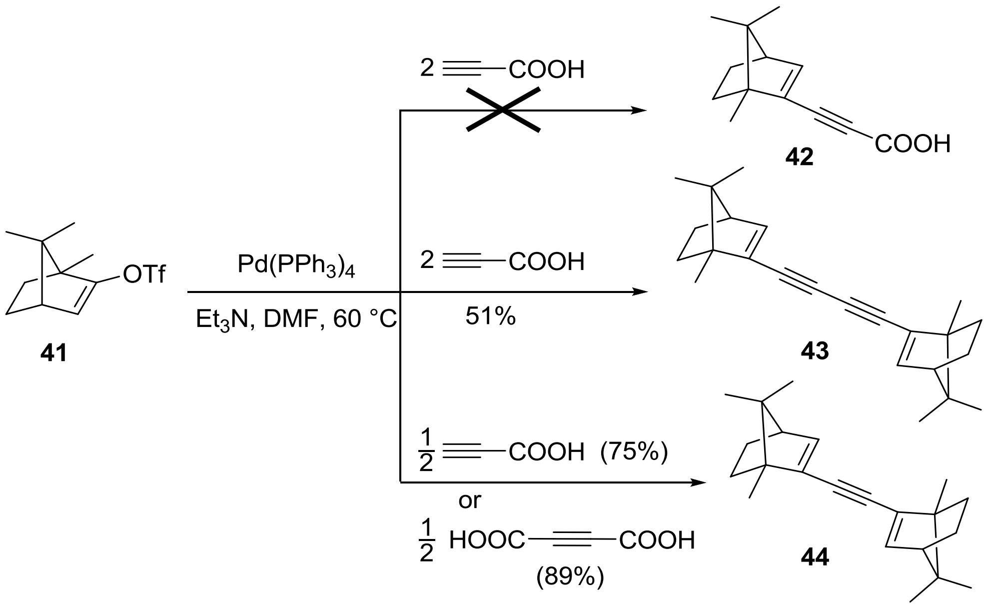


Scheme 7.1 Proposed retro-synthesis of a self-assembling cyclotrimer bearing carboxylic groups from triflate **24**.

Early tests were carried on camphor triflate **41**, which represented a simple model, accessible in large amount, to study the reactivity of benzotricamphor triflate **24** in cross coupling reactions with propiolic acid. At the beginning of our investigation, the known coupling reactions of vinyl triflates with respect of propiolic acid derivatives was only the functionalization of steroids with methyl and ethyl propiolates.[1]

Thus we attempted a preliminary reaction by treating **41** with an excess of propiolic acid in DMF at 60 °C and in presence of $Pd(PPh_3)_4$. Surprisingly, the reaction did not afford the expected acid **42**, and the symmetric diacetylene **43** was isolated in 51% yield. This unexpected result was ascribed to a decarboxylative oxidative coupling process related to the use of propiolic acid in the coupling reaction. Further experiments, in which the triflate **41** was reacted with half equivalents of propiolic acid or acetylene dicarboxylic acid, led in both cases to the formation of the symmetrical acetylene **44** in good yield (Scheme **7.2**).

These preliminary experiments have shown that propiolic acid, as well as acetylene dicarboxylic acid, represent two possible alkyne sources for cross coupling reactions. Thus, a more in depth study on the reactivity of camphor triflate with propiolic acid derivatives, using methyl propiolate, phenylpropiolic acid and propiolic acid itself, was performed.



Scheme 7.2 Preliminary reactions of camphor triflate with propiolic acid.

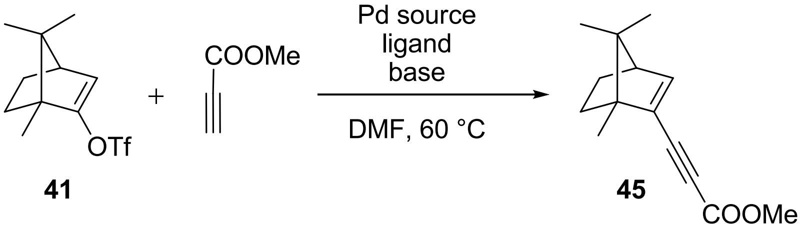
At the difference of previous chapters, mainly focused to the synthesis and the functionalization of benzocyclotrimers. this chapter describes the investigation of new methods for the synthesis of acetylenic compounds by the use of propiolic acid and its derivatives as triple bond source.

7.2 PROPIOLIC ACID COUPLINGS WITH CAMPHOR TRIFLATE

Methyl propiolate

Methyl propiolate represents a derivative in which the carboxylic group of propiolic acid is protected and decarboxylation is inhibited. The study of this substrate in conventional Sonogashira coupling reactions, is therefore possible. The investigation of this reaction was based on reported conditions for the coupling of enol triflates, derived from steroids, with ethyl propiolate in DMF at 60 °C, using NaOAc as base and $Pd(OAc)_2(PPh_3)_2$ as catalyst.[1] Under these conditions, the reaction carried on **41** afforded a low yield of product (10%), thus the reaction conditions were optimized by screening different bases, ligands and palladium sources. The results are summarized in Table 7.1.

Table 7.1 Effects of different bases, Pd sources and ligands on the synthesis of **45.**[a]



Entry	Base	Pd	Ligand	45, %[b]
1	NaOAc	$Pd(OAc)_2$	PPh_3	10
2	KOAc	$Pd(OAc)_2$	PPh_3	43
3	Na_2CO_3	$Pd(OAc)_2$	PPh_3	8
4	$\mathbf{K_2CO_3}$	$Pd(OAc)_2$	PPh_3	**63**
5	K_3PO_4	$Pd(OAc)_2$	PPh_3	52
6	K_2CO_3	$PdCl_2(PPh_3)_2$	PPh_3	38
7	K_2CO_3	$PdCl_2(MeCN)_2$	PPh_3	67
8	K_2CO_3	(allylPdCl)$_2$	PPh_3	37
9	K_2CO_3	$PdBr_2$	PPh_3	17
10	K_2CO_3	$Pd(OAc)_2$	PPh_3	65
11	K_2CO_3	$Pd(CF_3CO_2)_2$	PPh_3	56
12	K_2CO_3	Pd(acac)$_2$	PPh_3	87
13	K_2CO_3	**Pd(acac-F$_6$)$_2$**	PPh_3	**89**
14	K_2CO_3	$Pd(PPh_3)_4$	PPh_3	67
15	K_2CO_3	$Pd_2(dba)_3$	PPh_3	12
16	K_2CO_3	Pd(acac)$_2$	P(p-F-Ph)$_3$	26
17	K_2CO_3	Pd(acac)$_2$	$\mathbf{PPh_3}$	**88**
18	K_2CO_3	Pd(acac)$_2$	P(o-tol)$_3$	0
19	K_2CO_3	Pd(acac)$_2$	P(m-tol)$_3$	27
20	K_2CO_3	Pd(acac)$_2$	P(p-tol)$_3$	24
21	K_2CO_3	Pd(acac)$_2$	P(p-MeO-Ph)$_3$	12
22	K_2CO_3	Pd(acac)$_2$	PPh(Cy)$_2$	3
23	K_2CO_3	Pd(acac)$_2$	P(Cy)$_3$	5
24	K_2CO_3	Pd(acac)$_2$	dppe	0
25	K_2CO_3	Pd(acac)$_2$	dppb	5

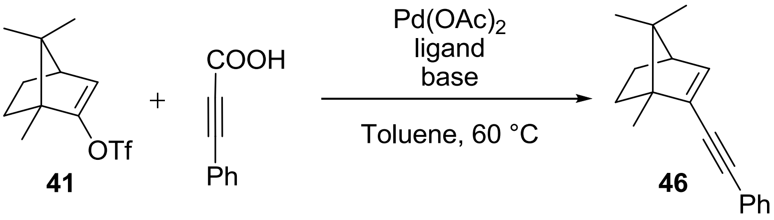
[a] Reaction conditions: 0.5 mmol scale, 1,5 eq. Methyl propiolate, 2.5% Pd source, 5% ligand, 4eq. base, 2h. [b] Yields determined by GC with undecane as an internal standard.

From the screening of the reaction, the best result, in terms of yield, was obtained using K_2CO_3 as a base and a catalytic system based on Pd(acac-F$_6$)$_2$/PPh_3 mixture (Entry 13). However the use of Pd(acac)$_2$ instead of the most expensive Pd(acac-F$_6$)$_2$ allowed the synthesis of **6** with almost the same yield (Entry 17). Indeed, under these conditions the product was obtained in 88% yield.

Phenylpropiolic acid

The reactivity of the carboxylic group of propiolic acid in cross-coupling reactions with the triflate **41** was explored by using a derivative in which only the carboxylic group is available for the reaction, while the terminal alkyne proton is replaced by another group. Thus, we chosen phenylpropiolic acid as cheap and simple reagent to study the decarboxylative coupling with vinyl triflate **41**.

Table 7.2 Effects of different bases and ligands on the synthesis of **46**.[a]



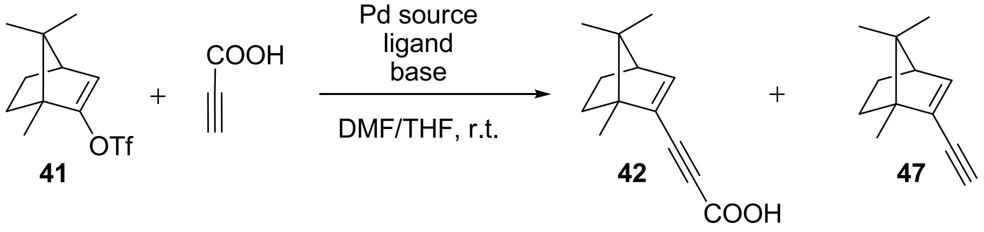
Entry	Base	Ligand	46, %[b]
1	4-Me-pyridine	PPh_3	6
2	lutidine	PPh_3	5
3	DMAP	PPh_3	2
4	imidazol	PPh_3	0
5	morpholine	PPh_3	33
6	piperidine	PPh_3	88
7	**4-Me-piperidine**	PPh_3	**93**
8	$NHEt_2$	PPh_3	25
9	$NH(i\text{Pr})_2$	PPh_3	71
10	chinuclidin	PPh_3	54
11	DABCO	PPh_3	70
12	DBU	PPh_3	55
13	NEt_3	PPh_3	49
14	$NEt(i\text{Pr})_2$	PPh_3	68
15	K_2CO_3	PPh_3	75
16	4-Me-piperidine	-	0
17	4-Me-piperidine	$P(p\text{-F-Ph})_3$	68
18	4-Me-piperidine	PPh_3	93
19	4-Me-piperidine	$P(o\text{-tol})_3$	18
20	4-Me-piperidine	$P(p\text{-tol})_3$	91
21	4-Me-piperidine	$P(p\text{-MeOPh})_3$	94
22	4-Me-piperidine	John-phos	12
23	4-Me-piperidine	$P(Cy)_3$	3
24	4-Me-piperidine	dppe	34
25	4-Me-piperidine	**dppf**	**95**

[a] Reaction conditions: 0.5 mmol scale, 2.5% $Pd(OAc)_2$, 5% PPh_3, 1.1 eq. Ph-propiolic acid, 10 eq. base, 4h. [b] Yields determined by GC with benzylacetone as an internal standard..

The reactivity of phenylpropiolic acid toward the coupling reaction with camphor triflate **41** could be justified taking into account a decarboxylative process. According to counter-experiments of Pd-catalyzed and thermal-induced protodecarboxylation of phenylpropiolic acid, the first process resulted dominant The best conditions for the formation of the coupling product between **41** and phenylpropiolic acid resulted by the use of 4-Me-piperidine as base and $Pd(OAc)_2$/dppf mixture as precursors of the catalytic system to obtain **46** in 95% yield (Entry 25).

Propiolic acid

The reactivity of propiolic acid was more difficult to investigate, since both alkyne hydrogen and carboxylic group were reactive in coupling reactions. Thus, the synthesis of camphor-propiolic acid **42** was studied at room temperature, in the attempt to avoid decarboxylative processes. However, this could not be completely inhibited, as a certain amount of the terminal alkyne **43** was often found as by-product.



Scheme 7.3 Coupling reaction between camphor triflate and propiolic acid at room temperature.

From screening experiments, the highest yield of **42** was obtained using $Pd(OAc)_2$ and PPh_3 as catalyst precursors and 4-methyl-piperidine as base (Table 7.3, Entry 28). The use of a solvent mixture DMF/THF in a 1:1 ratio was also fundamental to obtain good selectivity in the desired product.

Although optimization experiments revealed that in no cases product **42** was obtained with complete suppression of the formation of camphor-acetylene **47**, the amount of this byproduct was particularly appreciable when $(p\text{-FPh})_3$ was used as ligand and NEt_3 as base. Moreover, increase of **47** was observed decreasing the amount of base (Table 7.3, Entries 36-41), but at room temperature the yield did not exceed 60% even by extending reaction times.

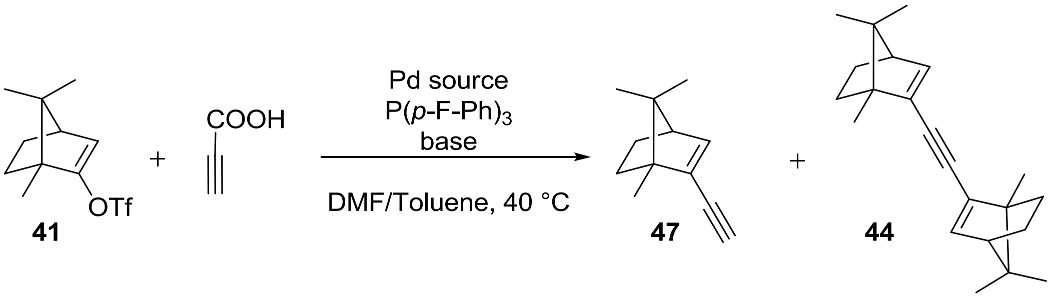
Table 7.3 Effects of different Pd sources ligands and bases on the synthesis of **42**.[a]

Entry	Pd	Ligand	Base (eq.)	42, %[b]	47, %[b]
1	$PdCl_2$	PPh_3	NEt_3 (10)	16	0
2	$PdBr_2$	PPh_3	NEt_3 (10)	19	0
3	$PdCl_2(MeCN)_2$	PPh_3	NEt_3 (10)	23	0
4	$PdCl_2(PPh_3)_2$	PPh_3	NEt_3 (10)	15	0
5	$(allylPdCl)_2$	PPh_3	NEt_3 (10)	71	10
6	**$Pd(OAc)_2$**	PPh_3	NEt_3 (10)	**83**	10
7	$Pd(CF_3CO_2)_2$	PPh_3	NEt_3 (10)	77	20
8	$Pd(acac)_2$	PPh_3	NEt_3 (10)	17	0
9	$Pd(acac\text{-}F_6)_2$	PPh_3	NEt_3 (10)	68	16
10	$Pd_2(dba)_3$	PPh_3	NEt_3 (10)	37	0
11	$Pd(OAc)_2$	$P(p\text{-}FPh)_3$	NEt_3 (10)	69	28
12	$Pd(OAc)_2$	**PPh_3**	NEt_3 (10)	**83**	13
13	$Pd(OAc)_2$	$P(o\text{-}tol)_3$	NEt_3 (10)	0	0
14	$Pd(OAc)_2$	$P(p\text{-}MeOPh)_3$	NEt_3 (10)	4	0
15	$Pd(OAc)_2$	$PPh(Cy)_2$	NEt_3 (10)	0	0
16	$Pd(OAc)_2$	John-phos	NEt_3 (10)	0	0
17	$Pd(OAc)_2$	$P(Cy)_3$	NEt_3 (10)	0	0
18	$Pd(OAc)_2$	$P(tBu)_3$	NEt_3 (10)	0	0
19	$Pd(OAc)_2$	dppe	NEt_3 (10)	1	0
20	$Pd(OAc)_2$	dppf	NEt_3 (10)	2	0
21	$Pd(OAc)_2$	-	NEt_3 (10)	0	0
22	$Pd(OAc)_2$	PPh_3	4-Me-pyridine (10)	3	0
23	$Pd(OAc)_2$	PPh_3	lutidine (10)	0	0
24	$Pd(OAc)_2$	PPh_3	DMAP (10)	0	0
25	$Pd(OAc)_2$	PPh_3	imidazol (10)	0	0
26	$Pd(OAc)_2$	PPh_3	morpholine (10)	32	8
27	$Pd(OAc)_2$	PPh_3	piperidine (10)	61	5
28	$Pd(OAc)_2$	PPh_3	**4-Me-piperidine (10)**	**88**	7
29	$Pd(OAc)_2$	PPh_3	$NHEt_2$ (10)	64	4
30	$Pd(OAc)_2$	PPh_3	$NH(iPr)_2$ (10)	19	0
31	$Pd(OAc)_2$	PPh_3	chinuclidin (10)	8	0
32	$Pd(OAc)_2$	PPh_3	DABCO (10)	4	0
33	$Pd(OAc)_2$	PPh_3	DBU (10)	72	2
34	$Pd(OAc)_2$	PPh_3	NEt_3 (10)	83	14
35	$Pd(OAc)_2$	PPh_3	$NEt(iPr)_2$ (10)	34	17
35	$Pd(OAc)_2$	PPh_3	K_2CO_3 (10)	5	3
36	$Pd(OAc)_2$	PPh_3	NEt_3 (10)	83	14
37	$Pd(OAc)_2$	PPh_3	NEt_3 (7.5)	76	20
38	$Pd(OAc)_2$	PPh_3	NEt_3 (5)	58	34
39	$Pd(OAc)_2$	PPh_3	NEt_3 (3)	39	58
40	$Pd(OAc)_2$	PPh_3	NEt_3 (2)	27	59
41	$Pd(OAc)_2$	PPh_3	NEt_3 (1.5)	36	15

[a] Reaction conditions: 0.5 mmol scale, 3% Pd source, 6% ligand, 1.2 eq. propiolic acid, 4h.[b] Yields determined by HPLC with acetophenone as an internal standard.

These preliminary results prompted us to study a new procedure for the synthesis of camphor-acetylene **47** from triflate **41** in higher yield. This would lead to the development of a new method for the synthesis of terminal alkynes with several advantages compared to the traditional procedures employing expensive alkyne sources (typically trimethylsilylacetylene, TMSA).

The first significant increase in the yield of **47** was observed when the temperature was increased to 40°C and using a mixture of toluene and DMF as solvent. Nevertheless, selectivity problems emerged because product **47** coupled with the reagent **41**, with formation of the symmetrical acetylene **44**.



Scheme 7.4 Coupling reaction between camphor triflate and propiolic acid at 40°C.

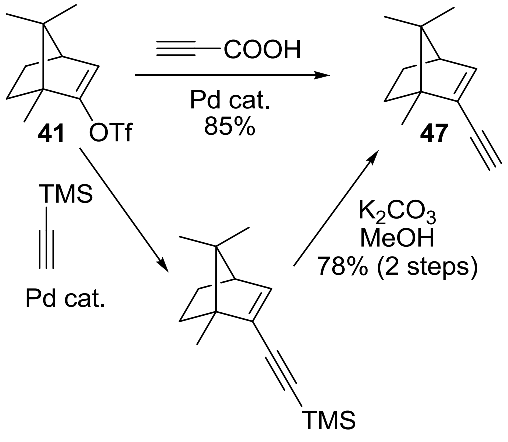
The reaction provided the alkyne **47** in high yield by the use of (allylPdCl)$_2$ as Pd source and NEt$_3$ as base (Table 7.4, Entry 16). The full selectivity to alkyne **47** was achieved when the amount of propiolic acid was increased to 3 equivalents with respect to the reagent **41** (Table 7.4, Entry 26, 92% yield of **47**).

The synthesis of the alkyne **47** with this method offered two main advantages with respect to the coupling with TMSA. The first is that propiolic acid is an inexpensive alkyne source. The second is the possibility to obtain the terminal alkyne **47** in a single step, while the use of TMSA requires a two steps process (to isolate the final product): the coupling reaction and the cleavage of the TMS group (Scheme **7.5**).

Table 7.4 Effects of different bases and Pd sources on the synthesis of **47**.[a]

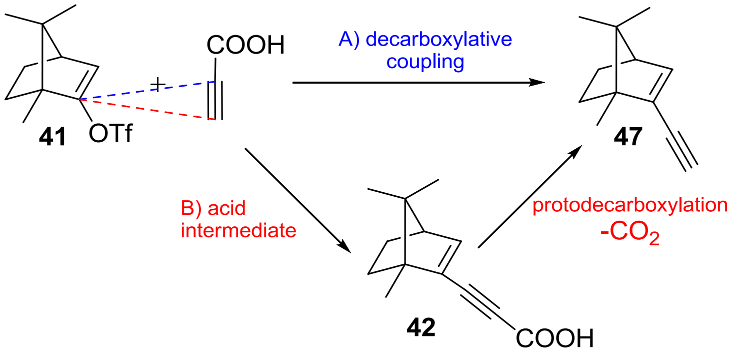
Entry	Pd	Base	Eq. base	Eq. acid	47, %[b]	44, %[b]
1	$Pd(OAc)_2$	4-Me-pyridine	1.45	1.4	4	2
2	$Pd(OAc)_2$	lutidine	1.45	1.4	0	0
3	$Pd(OAc)_2$	DMAP	1.45	1.4	0	0
4	$Pd(OAc)_2$	imidazole	1.45	1.4	0	0
5	$Pd(OAc)_2$	morpholine	1.45	1.4	33	41
6	$Pd(OAc)_2$	piperidine	1.45	1.4	43	21
7	$Pd(OAc)_2$	4-Me-piperidine	1.45	1.4	56	27
8	$Pd(OAc)_2$	$NHEt_2$	1.45	1.4	61	30
9	$Pd(OAc)_2$	$NH(iPr)_2$	1.45	1.4	71	28
10	$Pd(OAc)_2$	chinuclidin	1.45	1.4	40	26
11	$Pd(OAc)_2$	DBU	1.45	1.4	38	16
12	$Pd(OAc)_2$	**NEt_3**	1.45	1.4	**85**	6
13	$Pd(OAc)_2$	$NEt(iPr)_2$	1.45	1.4	49	18
14	$Pd(OAc)_2$	K_2CO_3	1.45	1.4	6	71
15	$PdCl_2$	NEt_3	1.45	1.4	0	0
16	**$(allylPdCl)_2$**	NEt_3	1.45	1.4	**88**	3
17	$Pd(OAc)_2$	NEt_3	1.45	1.4	84	5
18	$Pd(CF_3CO_2)_2$	NEt_3	1.45	1.4	61	25
19	$Pd(acac)_2$	NEt_3	1.45	1.4	47	7
20	$Pd(acac\text{-}F_6)_2$	NEt_3	1.45	1.4	74	19
21	$Pd(PPh_3)_4$	NEt_3	1.45	1.4	31	5
22	$Pd(dba)_2$	NEt_3	1.45	1.4	28	4
23	$Pd_2(dba)_3$	NEt_3	1.45	1.4	20	1
24	$(allylPdCl)_2$	NEt_3	1.45	1.4	88	3
25	$(allylPdCl)_2$	NEt_3	2	2	90	<1%
26	$(allylPdCl)_2$	NEt_3	**3**	**3**	**92**	<1%

[a] Reaction conditions: 0.5 mmol scale, 3% Pd, 6% $P(pF\text{-}Ph)_3$, 4h. [b] Yields determined by GC with tetradecane as an internal standard.



Scheme 7.5 Synthesis of camphor acetylene **47**. Comparison of isolated yield between the conventional method with TMSA and the coupling with propiolic acid.

The formation of the alkyne **47** may follow two processes. The first is the direct decarboxylative coupling between the triflate **41** and propiolic acid by the reaction of propiolic acid on the side of the carboxylic group (path A Scheme 7.6). The second hypothesis takes into account a two step overall process. In the first camphorpropiolic acid **42** is produced as an intermediate, then the proto-decarboxylation provides the alkyne **47** (path B Scheme 7.6).



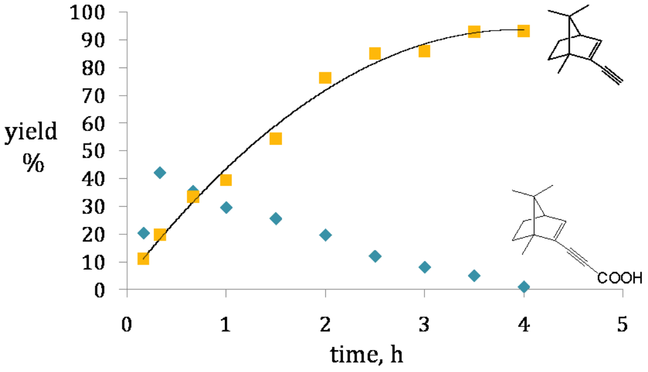
Scheme 7.6 Possible pathways in the formation of **9**.

The analysis of the reaction mixture at different times answered the question. If the reaction proceeds through the direct decarboxylative coupling of propiolic acid on **41**, the product **47** should increase with reaction time and acid intermediate **42** should not be detected. Instead, if the reaction proceeds through path B, then the presence of both species should be observed with the concentration of **42** that reaches a maximum and then decreases to zero, while **47** increases to a plateau. The following chart clearly confirms the latter pathway. In fact both **42** and **47** were detected in the reaction mixture and their amounts change as is expected from path B.

Table 7.5 Products distribution at different reaction times.[a]

Time	**42**, %[b]	**47**, %[b]
10 min	20	11
20 min	42	20
40 min	36	33
1 h	30	41
1.5 h	26	54
2 h	20	76
2.5 h	12	85
3 h	8	86
3.5 h	5	93
4 h	1	93

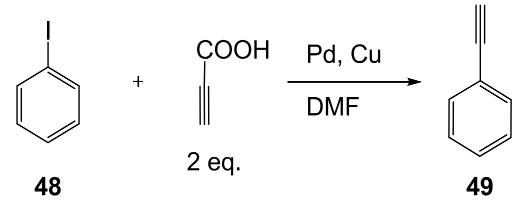
[a] Conditions: 0.5 mmol scale, 1.5% $(PdClallyl)_2$,, 6% $P(p\text{-}F\text{-}Ph)_3$, 3 eq. propiolic acid, 3 eq. NEt_3. [b] Yields determined by HPLC with acetophenone as an internal standard.



7.3 PROPIOLIC ACID COUPLINGS WITH ARYL HALIDES

To extend the scope of the reaction, the possibility to prepare terminal alkynes from aromatic halides by using propiolic acid as alkyne source was also investigated. The study was performed on phenyl iodide, varying all the reaction parameters, such as Pd and Cu sources, ligands, additives for copper, temperature and reaction time. The results are summarized in Table 7.6.

Table 7.6 Effect of different reaction parameters on yield of phenylacetylene **49**.[a]



Entry	Pd (3%)	Ligand (6%)	Cu[b]	Base, (eq.)	Additive	Time, h	49, %[c]
1	Pd(OAc)$_2$	PPh$_3$	CuI	HN(iPr)$_2$ (3)		4	42
2	Pd(OAc)$_2$	PPh$_3$	CuI	HN(iPr)$_2$ (4)		4	58
3	Pd(OAc)$_2$	PPh$_3$	CuI	HN(iPr)$_2$ (5)		4	55
4	Pd(OAc)$_2$	PPh$_3$	CuI	HN(iPr)$_2$ (6)		4	63
5	Pd(OAc)$_2$	PPh$_3$	CuI[d]	HN(iPr)$_2$ (6)		4	**76**
6	Pd(OAc)$_2$	PPh$_3$	CuI	HN(iPr)$_2$ (7)		4	51
7	Pd(OAc)$_2$	PPh$_3$	CuI	HN(iPr)$_2$ (8)		4	58
8	Pd(OAc)$_2$	PPh$_3$	CuI	HN(iPr)$_2$ (6)		4	63
9	Pd(OAc)$_2$	PPh$_3$	CuI	HN(iPr)$_2$ (6)		**5**	**75**
10	Pd(OAc)$_2$	PPh$_3$	CuI	HN(iPr)$_2$ (6)		6	58
13	Pd(OAc)$_2$	PPh$_3$	CuI	Pyridine (6)		5	7
14	Pd(OAc)$_2$	PPh$_3$	CuI	4-Me-pyridine (6)		5	16
15	Pd(OAc)$_2$	PPh$_3$	CuI	lutidine (6)		5	11
17	Pd(OAc)$_2$	PPh$_3$	CuI	DMAP (6)		5	7
18	Pd(OAc)$_2$	PPh$_3$	CuI	quinoline (6)		5	5
20	Pd(OAc)$_2$	PPh$_3$	CuI	imidazole (6)		5	5
21	Pd(OAc)$_2$	PPh$_3$	CuI	iIndole (6)		5	0
23	Pd(OAc)$_2$	PPh$_3$	CuI	NHEt$_2$ (6)		5	60
24	Pd(OAc)$_2$	PPh$_3$	CuI	morpholine (6)		5	20
25	Pd(OAc)$_2$	PPh$_3$	CuI	piperidine (6)		5	73
26	Pd(OAc)$_2$	PPh$_3$	CuI	4-Me-piperidin (6)		5	59
27	Pd(OAc)$_2$	PPh$_3$	CuI	NEt$_3$ (6)		5	32
28	Pd(OAc)$_2$	PPh$_3$	CuI	NEt(iPr)$_2$ (6)		5	20
29	Pd(OAc)$_2$	PPh$_3$	CuI	DABCO (6)		5	51
30	Pd(OAc)$_2$	PPh$_3$	CuI	DBU (6)		5	35
31	Pd(OAc)$_2$	PPh$_3$	CuI	K$_2$CO$_3$ (6)	18-crown-6	5	19

Table 7.6 Effect of different reaction parameters on yield of phenylacetylene **49**.[a]

Entry	Pd (3%)	Ligand (6%)	Cu[b]	Base, (eq.)	Additive	Time, h	49, %[c]
32	PdCl$_2$	PPh$_3$	CuI	HN(iPr)$_2$ (6)		5	55
33	PdCl$_2$(PPh$_3$)$_2$	PPh$_3$	CuI	HN(iPr)$_2$ (6)		5	58
34	PdBr$_2$	PPh$_3$	CuI	HN(iPr)$_2$ (6)		5	44
35	(allylPdCl)$_2$	PPh$_3$	CuI	HN(iPr)$_2$ (6)		5	54
36	Pd(OAc)$_2$	PPh$_3$	CuI	HN(iPr)$_2$ (6)		5	67
37	Pd(CF$_3$CO$_2$)$_2$	PPh$_3$	CuI	HN(iPr)$_2$ (6)		5	72
38	Pd(acac)$_2$	PPh$_3$	CuI	HN(iPr)$_2$ (6)		5	60
39	Pd(acac-F$_6$)$_2$	PPh$_3$	CuI	HN(iPr)$_2$ (6)		5	58
40	Pd(PPh$_3$)$_4$	PPh$_3$	CuI	HN(iPr)$_2$ (6)		5	48
41	Pd$_2$(dba)$_3$	PPh$_3$	CuI	HN(iPr)$_2$ (6)		5	52
42	Pd(OAc)$_2$	P(p-F-Ph)$_3$	CuI	HN(iPr)$_2$ (6)		5	53
43	Pd(OAc)$_2$	PPh$_3$	CuI	HN(iPr)$_2$ (6)		5	71
44	Pd(OAc)$_2$	P(o-tol)$_3$	CuI	HN(iPr)$_2$ (6)		5	4
45	Pd(OAc)$_2$	P(p-tol)$_3$	CuI	HN(iPr)$_2$ (6)		5	55
46	Pd(OAc)$_2$	P(p-MeO-Ph)$_3$	CuI	HN(iPr)$_2$ (6)		5	60
47	Pd(OAc)$_2$	PPh(Cy)$_2$	CuI	HN(iPr)$_2$ (6)		5	19
48	Pd(OAc)$_2$	John-phos	CuI	HN(iPr)$_2$ (6)		5	20
49	Pd(OAc)$_2$	P(Cy)$_3$	CuI	HN(iPr)$_2$ (6)		5	4
50	Pd(OAc)$_2$	dppe	CuI	HN(iPr)$_2$ (6)		5	7
51	Pd(OAc)$_2$	dppf	CuI	HN(iPr)$_2$ (6)		5	45
52	Pd(OAc)$_2$		CuI	HN(iPr)$_2$ (6)		5	0
53	Pd(OAc)$_2$	PPh$_3$	-	HN(iPr)$_2$ (6)		5	7
54	Pd(OAc)$_2$	PPh$_3$	CuI	HN(iPr)$_2$ (6)	Bu$_4$NBr	5	16
55	Pd(OAc)$_2$	PPh$_3$	CuI	HN(iPr)$_2$ (6)	Bu$_4$NI	5	11
56	Pd(OAc)$_2$	PPh$_3$	CuI	HN(iPr)$_2$ (6)	1,10-phenanthroline (10%)	5	41
57	Pd(OAc)$_2$	PPh$_3$	CuI	HN(iPr)$_2$ (6)	batophenanthrolin (10%)	5	31
58	Pd(OAc)$_2$	PPh$_3$	CuI	HN(iPr)$_2$ (6)	neocuproin (10%)	5	26
59	Pd(OAc)$_2$	PPh$_3$	CuI	HN(iPr)$_2$ (6)	TMEDA (10%)	5	62
60	Pd(OAc)$_2$	PPh$_3$	CuI	HN(iPr)$_2$ (6)	O-TMEDA (10%)	5	71
61	Pd(OAc)$_2$	PPh$_3$	CuBr	HN(iPr)$_2$ (6)	O-TMEDA (10%)	5	64
62	Pd(OAc)$_2$	PPh$_3$	CuCl	HN(iPr)$_2$ (6)	O-TMEDA (10%)	5	58
63	Pd(OAc)$_2$	PPh$_3$	Cu$_2$O	HN(iPr)$_2$ (6)	O-TMEDA (10%)	5	45
64	-	-	CuI	HN(iPr)$_2$ (6)	O-TMEDA (10%)	5	0
65	Pd(OAc)$_2$	PPh$_3$	CuI	HN(iPr)$_2$ (6)	O-TMEDA (10%)	3	54
66	Pd(OAc)$_2$	PPh$_3$	CuI	HN(iPr)$_2$ (6)	O-TMEDA (10%)	4	66
67	Pd(OAc)$_2$	PPh$_3$	CuI	HN(iPr)$_2$ (6)	O-TMEDA (10%)	5	59
68	Pd(OAc)$_2$	PPh$_3$	CuI	HN(iPr)$_2$ (6)	O-TMEDA (10%)	6	52
69	Pd(OAc)$_2$	PPh$_3$	CuI	HN(iPr)$_2$ (6)	O-TMEDA (20%)	3	44
70	Pd(OAc)$_2$	PPh$_3$	CuI	HN(iPr)$_2$ (6)	O-TMEDA (20%)	4	60
71	Pd(OAc)$_2$	PPh$_3$	CuI	HN(iPr)$_2$ (6)	O-TMEDA (20%)	5	63
72	Pd(OAc)$_2$	PPh$_3$	CuI	HN(iPr)$_2$ (6)	O-TMEDA (20%)	6	54

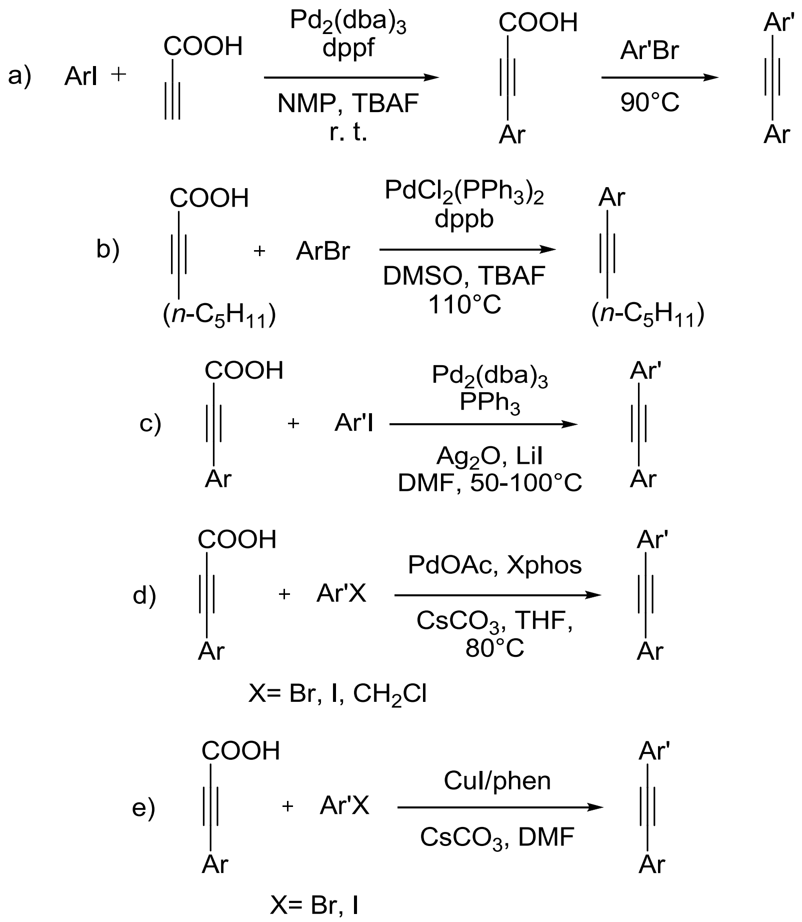
[a] Reaction conditions: 1 mmol iodobenzene, 2 mmol propiolic acid, 3 mL DMF, 60 °C. [b] 10 mol%. [c] Yields determined by GC with undecane as an internal standard. [d] 17 mol%.

The reaction of phenyl iodide with propiolic acid afforded the desired phenylacetylene, with yields that never exceeded 75%. This value likely represented a limit caused by the decomposition of the product under the reaction conditions. Similar reactions carried on bromobenzene demonstrated the poor applicability of the method providing even worse results with a maximum of 5% yield.

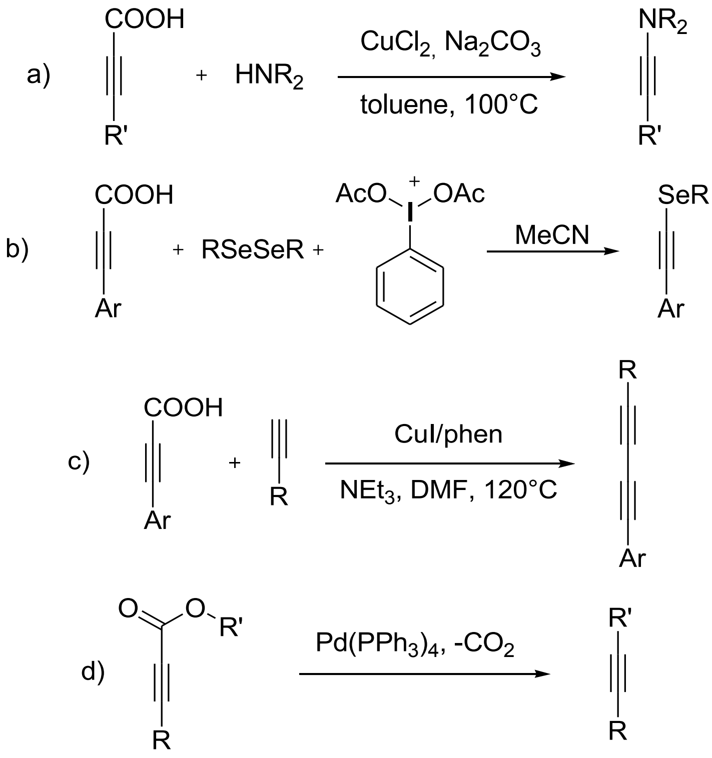
Thus the strategy was changed. The new target was the preparation of arylpropiolic acids from aryl bromides and propiolic acid, which may replace aryl acetylenes in coupling reactions.

The use of arylpropiolic acids for the preparation of substituted alkynes through decarboxylative coupling reactions was found in recent literature with examples leading to diaryl- (sp-sp^2 coupling), arylalkyl- (sp-sp^3 coupling) and diaryl di-acetylenes (sp-sp coupling) as well.[2-9] In the very first report by Lee and coworkers, propiolic acid was firstly coupled with an aryl iodide through a Sonogashira reaction to produce the corresponding arylpropiolic acid, that was subsequently submitted to the decarboxylative coupling with an aryl bromide to produce the non symmetric acetylene (Scheme 7.5 a).[2] The same authors reported also decarboxylative reactions employing phenylpropiolic and 2-octynoic acid (Scheme 7.5 b).[3] A different procedure for decarboxylative coupling of aryl propiolic acids with aryl bromides, iodides and triflates, was reported by Kim using silver and lithium salt as additives (Scheme 7.5 c).[4] More recently, two optimized protocols for decarboxylative couplings of alkynyl carboxylic acids with aryl and benzyl halides with low catalyst loading[5] (Scheme 7.5 d) and Pd-free decarboxylative cross-couplings catalyzed by copper[6] (Scheme 7.5 e) were reported.

Arylpropiolic acids were also employed in other decarboxylative transformations, for example in the synthesis of alkynyl selenides (Scheme 7.6 a),[7] in Cu-catalyzed oxidative amidations (Scheme 7.6 b)[8] and decarboxylative cross-coupling with terminal alkynes (Scheme 7.6 c).[9] Esters of alkynyl carboxylic acids have found also applications in decarboxylative reactions (Scheme 7.6 d).[10]



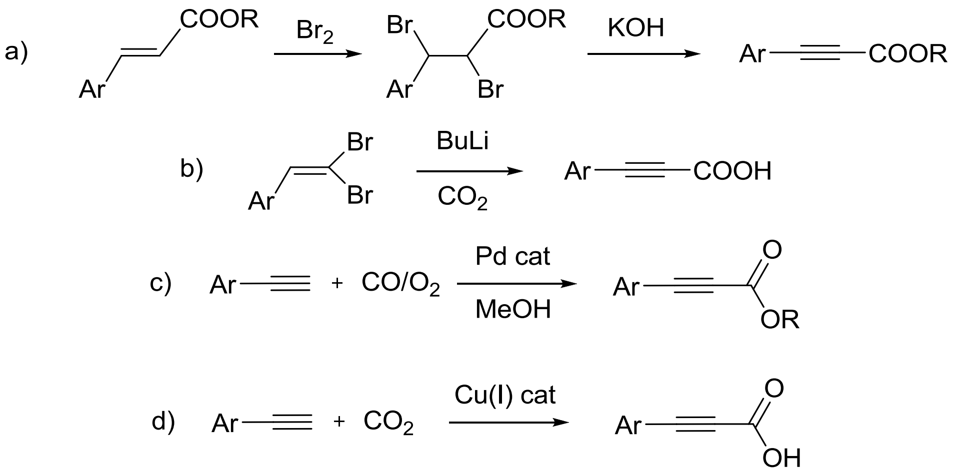
Scheme 7.7 Decarboxylative couplings of arylpropiolic acids.



Scheme 7.8 Decarboxylative reactions of propiolic acid derivatives.

As anticipated with the case of camphor triflate, the use of propiolic acid derivatives in coupling reactions presents several advantages over other terminal alkynes (TMSA) both in terms of atom economy and cost. In fact, propiolic acid is a less expensive reagent than TMSA and its use causes the release of the sole CO_2 as byproduct.

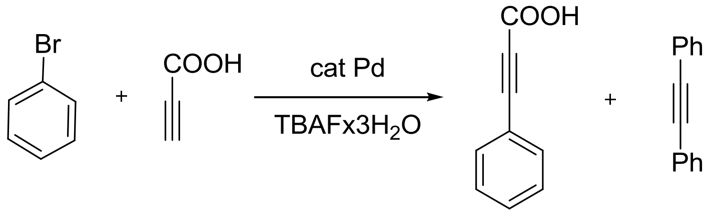
However, aryl propiolic acids often require an additional step for their preparation, as well as terminal alkynes. They can be obtained from the bromination of the corresponding cynnamic acids followed by a basic dehydrobromination (Scheme 7.7 a)[11] or they can be prepared by the reaction of 1,1-dibromoolefins with *n*-BuLi and CO_2 (Scheme 7.7 b).[7] Carbonylation[12] and very efficient carboxylation[13] reactions of terminal alkynes have been also reported (Scheme 7.7 c and d). In general these procedures provide the corresponding acids in 50 to 99% yields.



Scheme 7.9 Preparation of arylpropiolic acids.

The first reported coupling of propiolic acid with aryl iodides was carried in DMF/NEt_3 using a simple Pd/Cu catalyst.[14] In 2008 Lee presented a Pd catalized Cu-free protocol for the synthesis of arylpropiolic acids from aryl iodides which were coupled with a second aryl bromide to produce unsymmetrical acetylenes (Scheme 7.5 a) in one pot synthesis.[2] This approach for the synthesis of disubstituted acetylenes represents a convenient route because propiolic acid is an inexpensive alkyne source and a double coupling step is possible in the same reaction mixture. Herein, a new protocol for the one pot synthesis of disubstituted acetylenes from aryl bromides and propiolic acid is described.

At the outset, the reaction of Scheme 7.8 was investigated in the aim to maximize the yield in acid **51** with respect to tolane **52**.



50 **51** **52**

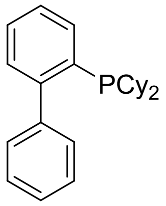
Scheme 7.10 Synthesis of phenylpropiolic acid from bromobenzene.

Screening

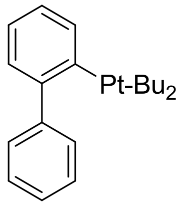
The conditions reported by Lee for the Sonogashira coupling with aryl iodides (TBAF as base in NMP as solvent and 5 mol% Pd_2dba_3/dppf as catalyst) were varied to promote the reaction with the less reactive bromide **50**. Table 7.7 reports the results obtained by varying ligands, Pd sources, temperature and reaction time. The activation of bromobenzene toward the coupling with propiolic acid required the increase of temperature to 60 °C, whereas PhI reacted at room temperature.[2] A decisive improvement with respect to conditions reported for PhI was found employing ligands L1-L4: accordingly, the conversion of **50** increased up to 99% within 4h in the case of **L4** (Xphos) (Entry 8). Ligand **L3** (Sphos) afforded almost full conversion of PhBr but afforded a better yield of **51** than **L4** and a lower amount of tolane **52** (Entry 9).

Under the same conditions of time and temperatures, a similar result in terms of yields and conversion was obtained by decreasing the amount of Pd in 5 mol% with respect to the substrate (Entry 12), but a decisive increase of the yield of **51** was achieved by reducing the reaction temperature to 50 °C and increasing the reaction time. At 50 °C the full conversion of the substrate was achieved after 16 hours and the yield of product increased to 71 % (Entry 15). The change of the palladium source to $(allylPdCl)_2$ led to a further increase of the final yield of phenylpropiolic acid (Entry 18), but the presence of diphenylacetylene as byproduct could not be prevented.

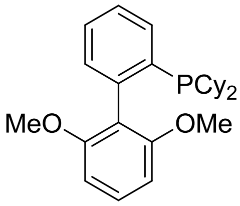
Table 7.7 Effect of different reaction parameters in the Palladium-Catalyzed Coupling Reaction of Propiolic Acid and Bromobenzene.[a]



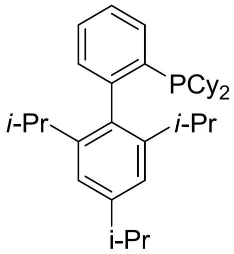
L1



L2



L3 (Sphos)



L4

Entry	ligand	Pd	% Pd (Pd:L)	time, h	T, °C	convn 50 (%)^{b}	51, (%)^{b,c}	52, (%)^{b}
1	P(*p*F-Ph)$_3$	Pd$_2$dba$_3$	10 (1:2)	4	60	33	19	0
2	PPh$_3$	Pd$_2$dba$_3$	10 (1:2)	4	60	25	17	0
3	P(*o*-tol)$_3$	Pd$_2$dba$_3$	10 (1:2)	4	60	57	38	0
4	P(*p*-tol)$_3$	Pd$_2$dba$_3$	10 (1:2)	4	60	37	14	0
5	P(*p*MeOPh)$_3$	Pd$_2$dba$_3$	10 (1:2)	4	60	29	10	0
6	dppe	Pd$_2$dba$_3$	10 (1:1)	4	60	2	0	0
7	dppf	Pd$_2$dba$_3$	10 (1:1)	4	60	33	26	0
8	L4	Pd$_2$dba$_3$	10 (1:1.5)	4	60	99	45	23
9	L3	Pd$_2$dba$_3$	10 (1:1.5)	4	60	97	54	6
10	L1	Pd$_2$dba$_3$	10 (1:1.5)	4	60	76	43	4
11	L2	Pd$_2$dba$_3$	10 (1:1.5)	4	60	92	49	6
12	L3	Pd$_2$dba$_3$	5 (1:1.5)	4	60	95	51	4
13	L3	Pd$_2$dba$_3$	5 (1:1.5)	4	50	67	42	0
14	L3	Pd$_2$dba$_3$	5 (1:1.5)	10	50	88	59	2
15	L3	Pd$_2$dba$_3$	5 (1:1.5)	16	50	100	71	7
16	L3	Pd$_2$dba$_3$	5 (1:1.5)	16	40	85	61	5
17	L3	Pd(OAc)$_2$	5 (1:1.5)	16	50	45	40	4
18	L3	(PdClallyl)$_2$	5 (1:1.5)	16	50	100	79	6
19	L3	PdCl$_2$	5 (1:1.5)	16	50	100	47	14
20	L3	PdBr$_2$	5 (1:1.5)	16	50	100	49	9
21	L3	Pd(F$_6$OAc)$_2$	5 (1:1.5)	16	50	92	68	3
22	L3	Pd(acac)$_2$	5 (1:1.5)	16	50	39	20	8

[a] Reaction conditions; 0.5 mmol bromobenzene, 0.55 mmol propiolic acid, 3.0 mmol TBAF·3H$_2$O, 1.5 mL NMP. [b] Conversion of PhBr and yields of products were determined by GC with tetradecane as an internal standard. [c] **51** was converted to the methyl ester using MeOTf and K$_2$CO$_3$.

In order to increase the final yield of phenylpropiolic acid, different bases and additives were used (Table 7.8), but the best result has been obtained using 10% of H$_2$O as co-solvent, leading to a 92% of product (Table 7.8, Entry 10).

Table 7.8 Effect of different bases, additives and co-solvents on the synthesis of **51**.[a]

Entry	(Pd:L)	time, h	T, °C	base (eq.)	additive	Solvent (co-solvent, %)	convn 50 (%)[b]	51, (%)[b,c]	52, (%)[b]
1	(1:1.5)	16	50	TBAF (6)		THF	35	11	1
2	(1:1.5)	16	50	TBAF (6)		DMSO	45	0	0
3	(1:1.5)	16	50	CsF (6)		NMP	32	4	8
4	(1:1.5)	16	50	TBAF (6)		NMP	41	24	3
5	(1:1.5)	16	50	TBAF (6)	CuI (10%)	NMP	80	32	3
6	(1:1.5)	16	50	TBAF (6)	Zn (10%)	NMP	35	24	0
7	(1:1.5)	16	50	NEt_3 (6)		NMP	74	traces	0
8	(1:1.5)	16	50	Cs_2CO_3 (6)		NMP	56	traces	0
9	(1:1.5)	16	50	TBAF (6)		NMP (H_2O, 5%)	100	84	3
10	(1:1.5)	16	50	TBAF (6)		NMP (H_2O, 10%)	99	92	5
11	(1:1.5)	16	50	TBAF (6)		NMP (H_2O, 15%)	92	58	5
12	(1:1.5)	16	50	TBAF (6)		NMP (MeOH, 10%)	88	62	12
13	(1:1.5)	16	50	TBAF (6)		NMP (*i*PrOH, 10%)	78	53	11
14	(1:1.5)	16	50	TBAF (6)		NMP (AcOH, 10%)	54	34	8
15	(1:2)	16	50	TBAF (6)		NMP (H_2O, 10%)	100	78	9
16	(1:1.5)	16	50	TBAF (4)		NMP (H_2O, 10%)	94	36	6
17	(1:1.5)	16	50	TBAF (2)		NMP (H_2O, 10%)	75	12	2
18	(1:1.5)	16	40	TBAF (6)		NMP (H_2O, 10%)	91	76	6
19	(1:1.5)	5	60	TBAF (6)		NMP (H_2O, 10%)	100	72	6

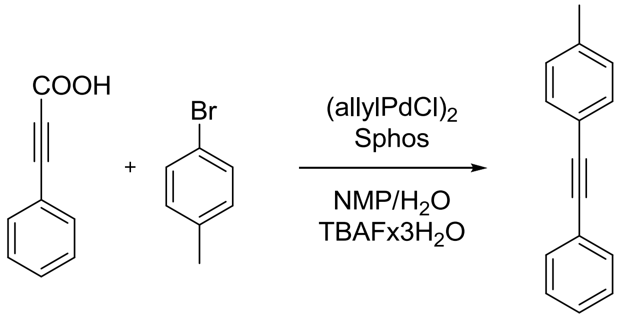
[a] Reaction conditions; 0.5 mmol bromobenzene, 0.55 mmol propiolic acid, 3.0 mmol $TBAF{\cdot}3H_2O$, 2.5 mol% $(PdClallyl)_2$, 7.5 mol% Sphos, 1.5 mL solvent. [b] Conversion of PhBr and yields were determined by GC with tetradecane as an internal standard. [c] **51** was converted to the methyl ester using MeOTf and K_2CO_3.

Noticeably, TBAF was the only base which efficiently promoted this reaction, while other organic and inorganic bases, commonly used in Sonogashira couplings, led to low yields (Entries 7 and 8). The activity of TBAF was likely not related to the single role of tetrabutylammonium or fluoride ions, since when CsF was used the yield of product was 4% (Entry 3) and other tetrabutylammonium salts were not prone to promote the reaction as well.[2]

The use of tetrabutylammonium fluoride has been already reported in coupling reactions of terminal alkynes with aryl halides,[15] however, there is a remarkable difference in reactivity between vinyl triflates, which reacted with propiolic acid using organic amines, and aryl halides, which were converted only in presence of TBAF.

In the aim of determining the conditions for preparing a disubstituited unsymmetrical acetylene, we investigated the reaction between phenylpropiolic acid and *p*-bromotoluene **53** in NMP/H_2O in presence of Sphos/(allylPdCl)$_2$ as catalyst and TBAF (6 eq.) at different temperatures (Table 7.9). Under these conditions the maximum yield was found at 80°C after 14 h. The increase of reaction time did not improve the yield of product **54a**.

Table 7.9 Palladium-Catalyzed Decarboxylative Coupling Reaction of Phenylpropiolic Acid and 4-bromotoluene.[*a*]



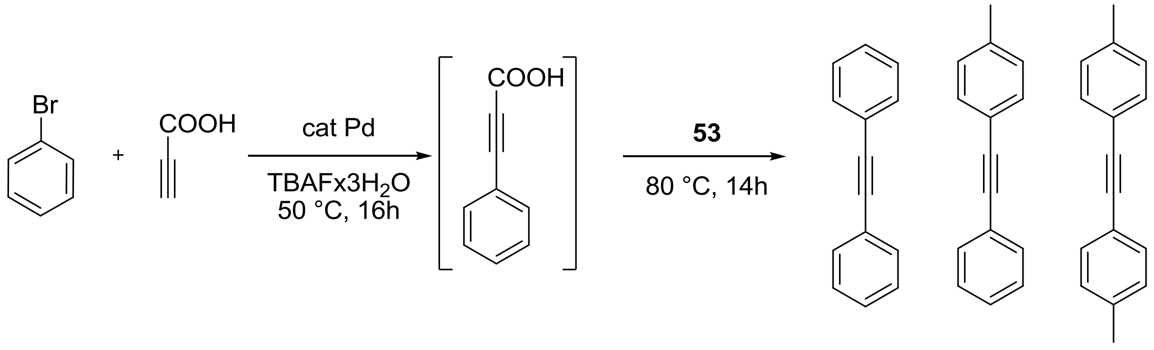
51 **53** **54a**

Entry	Temp, °C	Time, h	Convn. 53, %[b]	54a, %[b]
1	70	10	69	45
2	80	10	82	71
3	90	10	91	55
4	80	14	92	84

[a] Reaction conditions: 0.5 mmol phenylpropiolic acid, 0.5 mmol *p*-bromotoluene, 3.0 mmol TBAF·3H_2O, 2 mL NMP/H2O 9:1, 2,5 mol % (allylPdCl)$_2$, 7,5 mol % **L3**, [b] Conversion of **53** and yield of **54a** were determined by GC with tetradecane as an internal standard.

Further screening experiments were performed in order to determine the overall performance of the one-pot synthesis of unsymmetrical acetylenes using aryl bromides. After the first step, in which PhBr was reacted with propiolic acid at 50 °C for 16 h, *p*-bromotoluene was added into the reaction mixture and the temperature was raised to 80 °C. The final yield of the product **54a** followed the trend of values obtained for the synthesis of **51**. Thus, the best result was obtained using Sphos/(allylPdCl)$_2$ as precursor of the catalytic system and a solvent mixture NMP/H_2O (Entry 3).

Table 7.10 One-pot synthesis of unsymmetrical acetylene **54b**.[a]



50 **51** **52** **54a** **55**

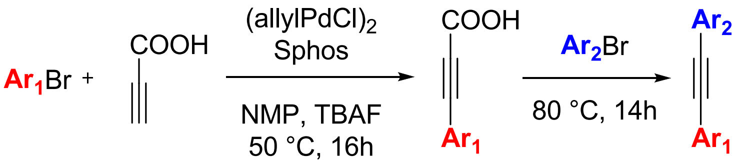
Entry	Ligand	Pd	(Pd:L)	Solvent (cosolvent, %)	convn 50, (%)[b]	convn 53, (%)[b]	52, (%)[b]	54a, (%)[b]	55, (%)[b]
1	Sphos	(PdClallyl)$_2$	(1:1.5)	NMP	91	90	7	48	3
2	Sphos	(PdClallyl)$_2$	(1:1.5)	NMP (H_2O 5%)	97	84	36	64	18
3	Sphos	(PdClallyl)$_2$	(1:1.5)	NMP (H_2O 10%)	100	98	7	76	5
4	Sphos	(PdClallyl)$_2$	(1:2)	NMP (H_2O 10%)	100	100	9	72	7
5	Xphos	(PdClallyl)$_2$	(1:1.5)	NMP (H_2O 10%)	100	92	26	39	19
6	Sphos	$PdCl_2$	(1:1.5)	NMP (H_2O 10%)	99	95	13	37	1
7	Sphos	$PdBr_2$	(1:1.5)	NMP (H_2O 10%)	99	87	22	58	1
8	Sphos	Pd(OAc)$_2$	(1:1.5)	NMP (H_2O 10%)	100	88	14	59	0
9	Sphos	Pd(F_6OAc)$_2$	(1:1.5)	NMP (H_2O 10%)	100	92	6	70	4
10	Sphos	Pd(acac)$_2$	(1:1.5)	NMP (H_2O 10%)	99	96	35	45	19
11	Sphos	Pd_2dba_3	(1:1.5)	NMP (H_2O 10%)	99	94	26	39	14

[a] Reaction conditions; 0.5 mmol bromobenzene, 0.55 mmol propiolic acid, 3.0 mmol TBAF·3H_2O, 1.5 mL solvent, 0,5 mmol bromotoluene. [b] Conversion and yield values were determined by GC with tetradecane as an internal standard.

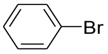
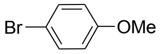
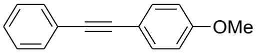
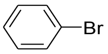
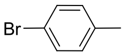
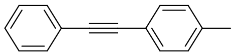
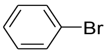
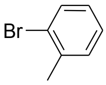
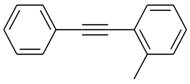
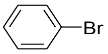
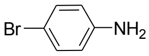
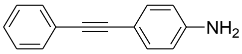
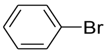
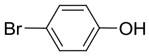
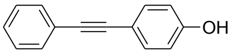
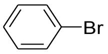
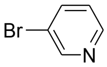
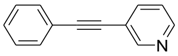
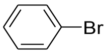
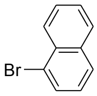
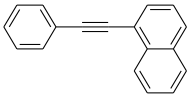
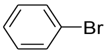
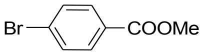
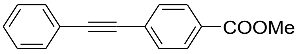
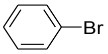
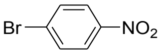
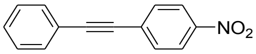
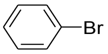
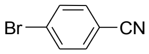
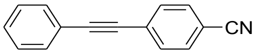
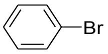
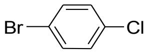
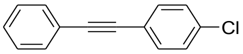
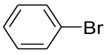
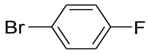
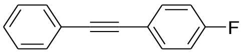
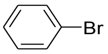
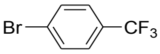
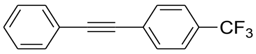
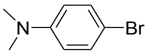
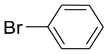
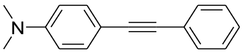
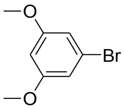
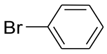
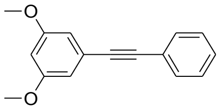
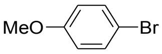
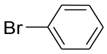
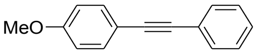
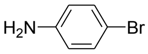
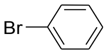
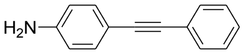
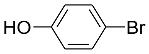
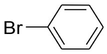
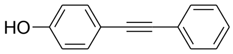
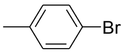
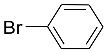
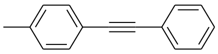
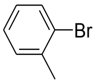
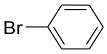
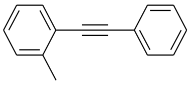
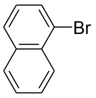
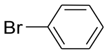
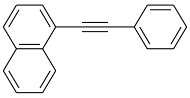
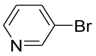
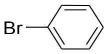
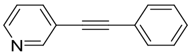
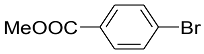
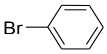
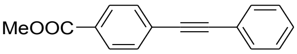
Scope

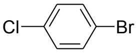
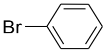
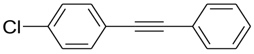
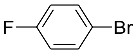
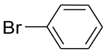
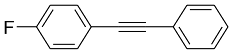
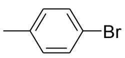
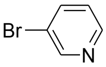
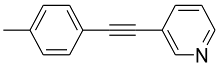
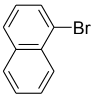
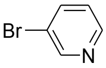
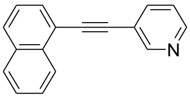
Starting from the data so far reported several disubstituted non symmetric acetylenes were prepared. Table 7.11 reports the one pot synthesis of unsymmetrical acetylenes starting from propiolic acid, finding a fair compatibility with different functional groups and electron-donating, and –withdrawing substituents. The coupling of different aryl bromides with propiolic acid also seems to provide the corresponding arylpropiolic acids, with best results obtained using electron rich substituents over electron-withdrawing groups.

Table 7.11 Synthesis of disobstituted diaryl alkynes.[a]



54

Entry	Ar_1Br	Ar_2Br	Product		Yield (%)[b]
1				**54b**	45
2				**54a**	71
3				**54c**	67
4				**54d**	43
5				**54e**	64
6				**54f**	70
7				**54g**	83
8				**54h**	72
9				**54i**	34
10				**54j**	31
11				**54k**	49
12				**54m**	69
13				**54n**	77
14				**54o**	71
15				**54p**	63
16				**54b**	51
17				**54d**	50
18				**54e**	32
19				**54a**	73
20				**54c**	22
21				**54g**	82
22				**54f**	45
23				**54h**	34

Entry	**Ar$_1$Br**	**Ar$_2$Br**	**Product**		**Yield (%)**[b]
24				**54k**	55
25				**54m**	39
26				**54q**	78
27				**54r**	56

[a]Reaction conditions: aryl bromide 1 (0.5 mmol), propiolic acid (0.55 mmol), 2.5 mol % (allylPdCl)$_2$, 7.5 mol % L3, TBAF·3H$_2$O 3.3 mmol, NMP(2 mL) at 50°C for 16 h and 0.5 mmol of aryl bromide 2 at 80 °C for 14 h. [b]Yield of isolated product.

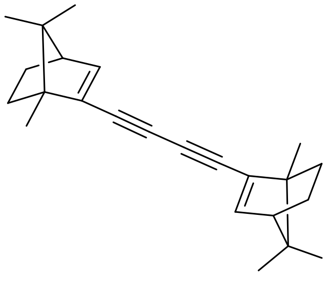
In conclusion, a protocol for the synthesis of disubstituited aryl acetylenes employing aryl bromides was developed. The activation of bromobenzene towards the coupling with propiolic acid is possible using **L3** (Sphos) as ligand in combination with (allylPdCl)$_2$. These conditions are also compatible with further functionalization, in particular decarboxylative couplings with aryl bromides which provide the corresponding disubstituted acetylenes in moderate to good yields for a range of differently substituted aryl bromides.

7.4 EXPERIMENTAL SECTION

GENERAL

All reactions were performed in flame-dried glassware blanketed with argon. Reagents purchased were used without further purifications. Solvents were eventually dried according to procedures reported in Armarego, W. L. F. and Perrin, D. D. "Purification of Laboratory Chemicals", Fourth Ed., Butterworth-Heinemann Ed., 1996. The evolution of the reactions was monitored by TLC, GC-MS or ^{1}H NMR. GC analyses were carried out using an HP-5 capillary column (Phenyl Methyl Siloxane 30 m x 320 x 0.25, 100/2.3-30-300/3). HPLC analyses were carried out using a standard HPLC C18 inverse phase. Flash-chromatography were performed with 230-400 mesh silica-gel. Optical rotations were observed in a 10 cm cell. ^{1}H NMR and ^{13}C{^{1}H} NMR spectra were recorded at 298 K, unless otherwise stated, on a Bruker AVANCE 300 spectrometer operating at 300.15 and 75.48 MHz respectively and the δ values in ppm are relative to TMS.

1,4-Bis(1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl)buta-1,3-diyne



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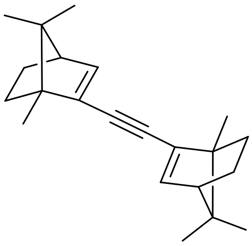
An oven-dried vessel equipped with a magnetic stirring bar was charged with $Pd(PPh_3)_4$ (40 mg, 0.035 mmol) and (+)-camphor triflate (200 mg, 0.70 mmol). After purging the vessel with alternating *vacuum* and argon cycles, degassed DMF (4 mL) and NEt_3 (1 mL) were added via syringe. Propiolic acid (90 μL, 1.44 mmol) was added via syringe and the mixture was stirred overnight at 60 °C. The resulting mixture was diluted with 1M HCl (30 mL) and extracted with cyclohexane (3×20 mL). The combined organic layers were washed with 1M HCl (20 mL), satd. aq. NaCl (20 mL), dried over $MgSO_4$ and concentrated in *vacuum*. The residue was purified by flash chromatography (cyclohexane) to obtain 57 mg (51% yield) of colorless crystals, m.p. 94 °C; $[\alpha]_D^{22}$ = - 131 (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 6.44 (2 H, d, *J* = 3.0 Hz), 2.37 (2 H, t, *J* = 3.7 Hz), 1.95-1.83 (2 H, m), 1.63-1.52 (2 H, m), 1.19-0.99 (4 H, m), 1.09 (6 H, s), 0.79 (12 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm):144.7, 136.2, 103.3, 95.0, 56.7, 56.3, 52.3, 31.0, 24.7, 19.5, 11.8, 10.0; IR (KBr) *v* 2962, 2182, 1715, 1627 cm^{-1}; *m/z* (EI, 70 eV): 320 (90), 277 (78), 207 (96), 91 (59), 44 (57), 41 (62), 40 (100%).

1,2-Bis(1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl)ethyne



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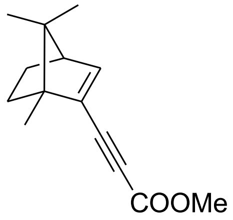
Metod A: an oven-dried vessel equipped with a magnetic stirring bar was charged with $Pd(PPh_3)_4$ (20 mg, 0.017 mmol), acetylenedicarboxylic acid (23 mg, 0.2 mmol) and (+)-camphor triflate (100 mg, 0.35 mmol). After purging the vessel with alternating *vacuum* and argon cycles, degassed DMF (2 mL) and NEt_3 (0.5 mL) were added via syringe. The mixture was stirred overnight at 60 °C. The resulting mixture was diluted with 1M HCl (30 mL) and extracted with cyclohexane (3×20 mL). The combined organic layers were washed with 1M HCl (20 mL), satd. aq. NaCl (20 mL), dried over $MgSO_4$ and concentrated in *vacuum*. The residue was purified by flash chromatography (hexane) to obtain 48 mg (94% yield) of white crystals.

Metod B: an oven-dried vessel equipped with a magnetic stirring bar was charged with $Pd(PPh_3)_4$ (40 mg, 0.035 mmol) and (+)-camphor triflate (200 mg, 0.70 mmol). After purging the vessel with alternating *vacuum* and argon cycles, degassed DMF (4 mL) and NEt_3 (1 mL) were added via syringe. Propiolic acid (25 μL, 0.40 mmol) was added via syringe and the mixture was stirred overnight at 60 °C. The resulting mixture was diluted with 1M HCl (30 mL) and extracted with cyclohexane (3×20 mL). The combined organic layers were washed with 1M HCl (20 mL), satd. aq. NaCl (20 mL), dried over $MgSO_4$ and concentrated in *vacuum*. The residue was purified by flash chromatography (hexane) to obtain 65 mg (75% yield) of white crystals; m.p. 73 °C; $[\alpha]_D^{22}$ = - 89 (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 6.23 (2 H, d, *J* =

3.7 Hz), 2.35 (2 H, t, *J* = 3.7 Hz), 1.95–1.83 (2 H, m), 1.62-1.52 (2 H, m), 1.19-0.97 (4 H, m), 1.09 (6 H, s), 0.82 (6 H, s), 0.80 (6 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm):139.7, 132.5, 89.4, 56.7, 56.3, 55.7, 52.1, 31.2, 25.0, 19.7, 12.0; IR (KBr) *ν* 2958, 1721, 1455 cm^{-1}; *m/z* (EI, 70 eV): 295 (86), 267 (93), 252 (75), 239 (100), 224 (47), 210 (26), 196 (23%).

General procedure for screening the coupling reactions of camphor triflate with methyl propiolate (Table 7.1) An oven-dried vessel equipped with a magnetic stir bar was charged with ligand (0.025 mmol), Pd source (0.012 mmol), base (2 mmol) and camphor triflate (143 mg, 0.5 mmol). After purging the vessel with alternating *vacuum* and nitrogen cycles, degassed DMF (2 mL) was added via syringe. Methyl propiolate (54 μL, 0.60 mmol) was added via syringe and the mixture was stirred at 60 °C for 2 hours, cooled to room temperature, diluted with AcOEt and washed with 1M HCl. A known amount of undecane was added to the solution as an internal standard and then the reaction mixture was analyzed via GC.

3-(1,7,7-Trimethylbicyclo[2.2.1]hept-2-en-2-yl)propiolic acid methylester



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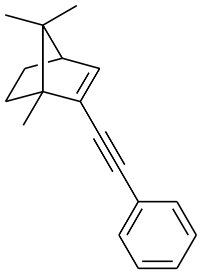
Collected screening reaction mixtures were poured into 1M HCl (30 mL) and extracted with Et_2O (3×20 mL). The combined organic layers were washed with 1M HCl (20 mL), satd. aq. NaCl (20 mL), dried over $MgSO_4$ and concentrated in *vacuum*. The residue was purified by flash chromatography (hexane/AcOEt in gradient from 9:1 to 7:3) to obtain **45** as colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.26 (1 H, d, *J* = 3.5 Hz), 3.78 (3 H, s), 2.43 (1 H, t, *J* = 3.5 Hz), 1.94-1.88 (1 H, m), 1.63-1.57 (1 H, m), 1.12-0.99 (2 H, m), 1.10 (3 H, s), 0.80 (3 H, s), 0.78 (3 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):154.8, 148.8, 129.3, 84.3, 83.8, 57.1, 56.1, 52.7, 52.6, 30.9, 24.3, 19.4, 19.3, 11.6.

General procedure for screening the coupling reaction of camphor triflate with phenylpropiolic acid (Table 7.2). An oven-dried vessel equipped with a magnetic stirring bar was charged with ligand (5 mol%), $Pd(OAc)_2$ (3.4 mg, 15.1 µmol, 2.5 mol %), phenylpropiolic acid (82.3 mg, 0,55 mmol) and camphor triflate (143 mg, 0.5 mmol). After purging the vessel with alternating *vacuum* and nitrogen cycles, degassed toluene (2 mL) and base (10 eq.) were added via syringe. The mixture was stirred at 60 °C for 4 hours, cooled to room temperature, diluted with hexanes and washed with 1M HCl. A known amount of benzylacetone was added to the solution as an internal standard and then the reaction mixture was analyzed via GC.

1,7,7-Trimethyl-2-(2-phenylethynyl)bicyclo[2.2.1]hept-2-ene



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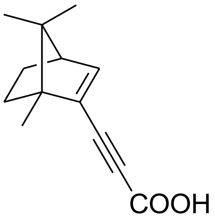
Collected screening reaction mixtures were poured into 1M HCl (30 mL) and were extracted with Et_2O (3×20 mL). Combined organic layers were washed with 1M HCl (20 mL), satd. aq. NaCl (20 mL), dried over $MgSO_4$ and concentrated in *vacuum*. The residue was purified by flash chromatography (hexane) to obtain **46** as colourless oil, $[\alpha]_D^{22}$ = - 75 (*c* 1.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.45 (2 H, dd, J = 8.1, 1.7Hz), 7.31–7.27 (3 H, m), 6.35 (1 H, d, *J* = 3.4 Hz), 2.40 (1 H, t, *J* = 3.4 Hz), 1.95-1.90 (1 H, m), 1.63-1.59 (1 H, m), 1.18-1.14 (1 H, m), 1.15 (3 H, s), 1.09-1.05 (1 H, m), 0.85 (3 H, s), 0.83 (3 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):140.7, 132.1, 131.5, 128.2, 127.8, 123.8, 93.2, 85.9, 56.5, 55.8, 52.2, 31.2, 24.9, 19.7, 19.6, 12.0; IR (KBr) *v* 2956, 2198, 1723, 1449, 1268 cm^{-1}; *m/z* (EI, 70 eV): 236 (99), 221 (71), 208 (99), 193 (100), 192 (45), 178 (86), 115 (59%).

General procedure for screening the coupling reaction of camphor triflate with propiolic acid (Table 7.3). An oven-dried vessel equipped with a magnetic stirring bar was charged with ligand (6 mol%), Pd source (3 mol %) and camphor triflate (143 mg, 0.5 mmol). After purging the vessel with alternating *vacuum* and nitrogen cycles, degassed THF (1 mL), DMF (1 mL), base (5 mmol, 10 eq.) and propiolic acid (39 µL, 0.6 mmol) were added via syringe. The mixture was stirred at r.t. for 4 hours, diluted with AcOEt and washed with 1M HCl. A known amount of acetophenone was added to the solution as an internal standard and the reaction mixture was analyzed via HPLC.

3-(1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl)propiolic acid



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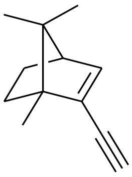
Combined screening reaction mixtures were poured into 1M HCl (30 mL) and were extracted with hexane (3×20 mL). Combined organic layers were washed with 1M HCl (20 mL), satd. aq. NaCl (20 mL), dried over $MgSO_4$ and concentrated in *vacuum*. The residue was purified by flash chromatography (hexane/AcOEt in gradient from 9:1 to 7:3) to obtain **42** as colourless crystals, m.p. 85 °C; $[\alpha]_D^{22}$ = - 180 (*c* 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.60 (1 H, br s) 6.75 (1 H, d, *J* = 3.1 Hz), 2.46 (1 H, t, *J* = 3.7 Hz), 1.97-1.90 (1 H, m), 1.65-1.59 (1 H, m), 1.14–1.02 (2 H, m), 1.12 (3 H, s), 0.81 (3 H, s), 0.79 (3 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):158.7, 150.4, 129.1, 86.5, 84.1, 57.2, 56.2, 52.8, 30.9, 24.2, 19.3, 19.3, 11.6; IR (KBr) *ν* 2954, 2194, 1676, 1415, 1281 cm^{-1}; *m/z* (EI, 70 eV): 160 (M^+ -CO_2, 53), 145 (76), 132 (30), 131 (31), 117 (100), 115 (91), 91 (45%).

General procedure for screening the coupling reaction of camphor triflate with propiolic acid (Table 7.4). An oven-dried vessel equipped with a magnetic stirring bar was charged with P(*p*F-Ph)$_3$ (9.4 mg, 29.7 µmol, 6 mol%), Pd source (3 mol %) and camphor triflate (143 mg, 0.5 mmol). After purging the vessel with alternating *vacuum* and nitrogen cycles, degassed toluene (1.5 mL), DMF (0.5 mL), base (1.4 eq.) and propiolic acid (47 µL, 0.72 mmol) were added via syringe. The mixture was stirred at 40 °C for 4 hours, diluted with AcOEt and washed with 1M HCl. A known amount of tetradecane was added to the solution as an internal standard and the reaction mixture was analyzed via GC.

2-Ethynyl-1,7,7-trimethylbicyclo[2.2.1]hept-2-ene



47

An oven-dried vessel equipped with a magnetic stirring bar was charged with P(*p*F-Ph)$_3$ (9.4 mg, 29.7 µmol), (allylPdCl)$_2$ (2.7 mg, 7.4 µmol) and camphor triflate (143 mg, 0.5 mmol). After purging the vessel with alternating *vacuum* and nitrogen cycles, degassed toluene (1.5 mL), DMF (0.5 mL), NEt$_3$ (0.21 mL, 1.5 mmol) and propiolic acid (98 µL, 1.5 mmol) were added via syringe. The mixture was stirred at 40 °C for 4 hours, then poured into 1M HCl (30 mL) and extracted with pentane (3×20 mL). Combined organic layers were washed with 1M HCl (20 mL), satd. aq. NaCl (20 mL), dried over MgSO$_4$ and concentrated in *vacuum*. The residue was purified by flash chromatography (pentane) to obtain **47** (66 mg, 85% yield) as colourless oil, $[\alpha]_D^{22}$ = - 129 (*c* 1.2, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 6.35 (1 H, d, *J* = 3.4 Hz), 3.10 (1 H, s), 2.35 (1 H, t, *J* = 3.6 Hz), 1.93-1.84 (1 H, m), 1.60-1.53 (1 H, m), 1.13-0.98 (2 H, m), 1.07 (3 H, s), 0.78 (6 H, s); ^{13}C NMR (CDCl$_3$, 100 MHz) δ (ppm): 142.4, 131.1, 80.6, 80.2, 56.6, 55.4, 52.0, 31.0, 24.7, 19.5, 19.4, 11.7; IR (KBr) *v* 2957, 2088, 1633, 1457, 1386 cm^{-1}; *m/z* (EI, 70 eV): 160 (M$^+$, 65), 145 (76), 132 (31), 131 (29), 117 (100), 115 (89), 91 (41).

General procedure for screening the coupling reaction of phenyl iodide with propiolic acid (Table 7.6). An oven-dried vessel equipped with a magnetic stirring bar was charged with ligand (60 µmol, 6 mol%), Pd source (30 µmol, 3 mol %) and Cu source (0.1 mmol, 10 mol%). After purging the vessel with alternating *vacuum* and nitrogen cycles, degassed DMF (2 mL), base, propiolic acid (130 µL, 2 mmol) and phenyl iodide (110 µL, 1 mmol) were added via syringe. The mixture was stirred at 60 °C for 5 hours, diluted with hexane and washed with 1M HCl. A known amount of undecane was added to the solution as an internal standard and then the reaction mixture was analyzed via GC.

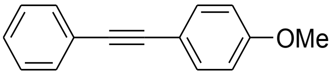
General procedure for screening the coupling reaction of phenyl bromide with propiolic acid (Table 7.8 and 7.9). An oven-dried vessel equipped with a magnetic stirring bar was charged with ligand and Pd source. After purging the vessel with alternating *vacuum* and nitrogen cycles, a degassed solution of TBAFx3H_2O (0,95 g, 3 mmol) in NMP/co-solvent mixture (2 mL) was added. Propiolic acid (36 µL, 0,55 mmol) and phenyl bromide (53 µL, 0,5 mmol) were added via syringe and the mixture was stirred at different temperatures at the given time. After cooling to 0°C, K_2CO_3 (0.2 g, 1,5 mmol) and methyl triflate (0,4 mL, 3,5 mmol) were added and the mixture was stirred at 0 °C for 3 hours. Then diethylether (2 mL) was added and the mixture was washed with H_2O. A known amount of tetradecane was added to the solution as an internal standard and then the reaction mixture was analyzed via GC.

General procedure for screening of the one-pot synthesis of unsymmetrical acetylene (Table 7.10). An oven-dried vessel equipped with a magnetic stirring bar was charged with Sphos (15.4 mg, 37.5 µmol) and Pd source (25 µmol). After purging the vessel with alternating *vacuum* and nitrogen cycles, a degassed solution of TBAFx3H_2O (0,95 g, 3 mmol) in NMP/co-solvent mixture (2 mL) was added. Propiolic acid (36 µL, 0,55 mmol) and phenyl bromide (53 µL, 0,5 mmol) were added via syringe and the mixture was stirred at 50 °C for 16 h. *p*-Bromotoluene (62µL, 0,5 mmol) was added and the mixture was stirred at 80 °C for 14 hours. After cooling to r.t. Et_2O was added and the mixture was washed with 1M HCl. A known amount of tetradecane was added to the solution as an internal standard and then the reaction mixture was analyzed via GC.

General procedure for the one-pot synthesis of unsymmetrical acetylene from aryl bromides(Table 7.11). An oven-dried vessel equipped with a magnetic stirring bar was charged with Sphos (15.4 mg, 37.5 µmol) and $(allylPdCl)_2$ (4.6 mg, 25 µmol). After purging the vessel with alternating *vacuum* and nitrogen cycles, a degassed solution of TBAFx3H_2O (0,95 g, 3 mmol) in NMP/H_2O (9:1, 2 mL) was added. Propiolic acid (36 µL, 0,55 mmol) and aryl bromide **1** (0,5 mmol) were added via syringe and the mixture was stirred at 50 °C for 16 h. Aryl bromide **2** (0,5 mmol) was added and the mixture was stirred at 80 °C for 14 hours. After cooling to r.t. the mixture was diluted with saturated aqueous NH_4Cl (20 mL), extracted with Et_2O

(3×20 mL). Combined organic extracts were washed with H_2O (20 mL), saturated aqueous NaCl (20 mL), dried over $MgSO_4$ and concentrated in *vacuum*. The crude product was purified by silica gel chromatography (eluant cyclohexane/Et_2O).

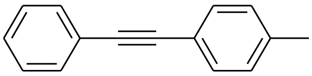
1-Methoxy-4-(2-phenylethynyl)benzene[4]



54b

^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 7.54-7.49 (2 H, m), 7.48 (2 H, d, *J* = 9.1 Hz), 7.37-7.31 (3 H, m), 6.88 (2 H, d, *J* = 9.1 Hz), 3.83 (3 H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 159.6, 133.0, 131.4, 128.3, 127.9, 123.6, 115.4, 114.0, 89.4, 88.1, 55.3.

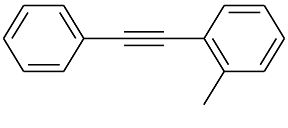
1-Methyl-4-(2-phenylethynyl)benzene[2]



54a

^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 7.56-7.51 (2 H, m), 7.44 (2 H, d, *J* = 8.5 Hz), 7.38-7.32 (3 H, m), 7.16 (2 H, d, *J* = 8.0 Hz), 2.38 (3 H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 138.4, 131.6, 131.5, 129.1, 128.3, 128.0, 123.5, 120.2, 89.5, 88.7, 21.5.

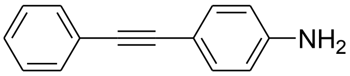
1-Methyl-2-(2-phenylethynyl)benzene[2]



54c

^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 7.57-7.49(3 H, m), 7.38-7.33 (3 H, m), 7.25-7.15 (3 H, m), 2.53 (3 H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 140.2, 131.8, 131.5, 129.4, 128.3, 128.3, 128.1, 125.6, 123.5, 123.0, 93.3, 88.3, 20.7.

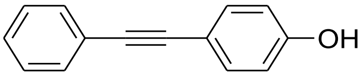
4-(2-phenylethynyl)aniline[6]



54d

^{1}H NMR (200 MHz, CDCl$_3$) δ (ppm): 7.51-7.47 (2, H m) 7.36-7.29 (5 H, m), 6.63 (2 H, d, *J* = 8.5 Hz), 3.81 (2 H, br, s); ^{13}C NMR (50 MHz, CDCl$_3$) δ (ppm): 146.6, 132.9, 131.3, 128.2, 127.6, 123.9, 114.7, 112.7, 90.1, 87.3.

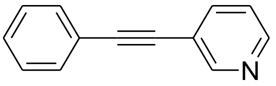
4-(2-phenylethynyl)phenol[16]



54e

^{1}H NMR (200 MHz, CDCl$_3$) δ (ppm): 7.54-7.49 (2 H, m), 7.43 (2 H, d, *J* = 8.5 Hz), 7.35-7.31 (3 H, m), 6.81 (2 H, d, *J* = 9.1 Hz), 4.85 (1 H, br, s); ^{13}C NMR (50 MHz, CDCl$_3$) δ (ppm): 155.6, 133.3, 131.4, 128.3, 128.0, 123.5, 115.7, 115.5, 89.1, 88.0.

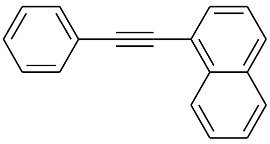
3-(2-phenylethynyl)pyridine[2]



54f

^{1}H NMR (200 MHz, CDCl$_3$) δ (ppm): 8.77 (1 H, d, *J* = 1.8 Hz), 8.55 (1 H, dd, *J* = 4.9, 1.2), 7.81 (1 H, dt, *J* = 7.9, 1.8 Hz), 7.58-7.53 (2 H, m), 7.39-7.35 (3 H, m), 7.31-7.25 (1 H, m); ^{13}C NMR (50 MHz, CDCl$_3$) δ (ppm): 152.2, 148.5, 138.4, 131.7, 128.8, 128.4, 123.0, 122.5, 120.4, 92.6, 85.9.

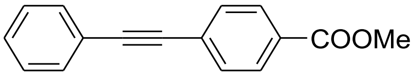
1-(2-Phenylethynyl)naphthalene[2]



54g

^{1}H NMR (200 MHz, CDCl$_3$) δ (ppm): 8.47 (1 H, d, *J* = 7.9 Hz), 7.90-7.77 (3 H, m), 7.70-7.39 (8 H, m); ^{13}C NMR (50 MHz, CDCl$_3$) δ (ppm): 133.3, 133.2, 131.6, 130.3, 128.7, 128.4, 128.4, 128.3, 126.7, 126.4, 126.2, 125.3, 123.4, 120.9, 94.3, 87.5.

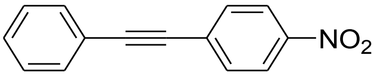
Methyl 4-(2-phenylethynyl)benzoate[17]



54h

^{1}H NMR (200 MHz, CDCl$_3$) δ (ppm): 8.02 (2 H, d, *J* = 8.5 Hz), 7.59 (2 H, d, *J* = 8.5 Hz), 7.57-7.52 (2 H, m), 7.39-7.35 (3 H, m), 3.93 (3 H, s); ^{13}C NMR (50 MHz, CDCl$_3$) δ (ppm): 166.6, 131.7, 131.4, 129.5, 129.4, 128.7, 128.4, 128.0, 122.7, 92.3, 88.6, 52.2.

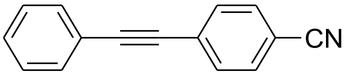
1-Nitro-4-(2-phenylethynyl)benzene[2]



54i

^{1}H NMR (200 MHz, CDCl$_3$) δ (ppm): 8.22 (2 H, d, *J* = 9.1 Hz), 7.67 (2 H, d, *J* = 8.5 Hz), 7.59-7.54 (2 H, m), 7.43-7.37 (3 H, m); ^{13}C NMR (50 MHz, CDCl$_3$) δ (ppm): 147.0, 132.2, 131.8, 130.2, 129.2, 128.5, 123.6, 121.1, 94.7, 87.5.

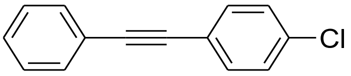
4-(2-Phenylethynyl)benzonitrile[4]



54j

^{1}H NMR (200 MHz, CDCl3) δ (ppm): 7.67-7.61 (4 H, m), 7.57-7.52 (2 H, m), 7.40-7.36 (3 H m); ^{13}C NMR (50 MHz, CDCl$_3$) δ (ppm): 132.0, 132.0, 131.8, 129.1, 128.5, 128.2 122.2, 118.5, 111.5, 93.8, 87.7.

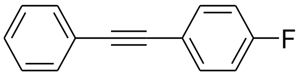
1-Chloro-4-(2-phenylethynyl)benzene[6]



54k

^{1}H NMR (200 MHz, CDCl$_3$) δ (ppm): 7.55-7.50 (2 H, m), 7.46 (2 H, d, *J* = 8.5 Hz), 7.36-7.30 (5 H m); ^{13}C NMR (50 MHz, CDCl$_3$) δ (ppm): 134.2, 132.8, 131.6, 128.7, 128.4, 128.4, 122.9, 121.8, 90.3, 88.2.

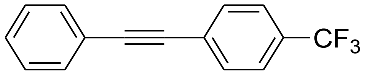
1-Fluoro-4-(2-phenylethynyl)benzene[18]



54m

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 7.55-7.48 (4 H, m), 7.38-7.33 (3 H, m), 7.09-7.00 (2 H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 162.5 (d, *J* = 249.8 Hz), 133.4 (d, *J* = 8.8 Hz), 131.5, 128.3, 128.3, 123.1, 119.4 (d, *J* = 3.2 Hz), 115.6 (d, *J* = 21.7 Hz), 89.0, 88.3 ppm.

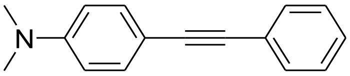
1-(2-phenylethynyl)-4-(trifluoromethyl)benzene[18]



54n

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 7.67–7.61 (4 H, m), 7.58–7.53 (2 H, m), 7.39–7.35 (3 H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 131.8, 131.7, 128.8, 128.4, 127.1 (q, *J* = 1.6 Hz), 125.2 (q, *J* = 4.0 Hz), 123.9 (q, *J* = 271.4 Hz), 122.5, 91.7, 87.9.

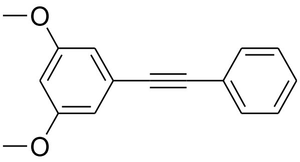
4-N,N-dimethyl-4-(2-phenylethynyl)aniline[6]



54o

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 7.53-7.48 (2 H, m), 7.41 (2 H, d, *J* = 9.1 Hz), 7.35-7.29 (3 H, m), 6.66 (2 H, d, *J* = 9.1 Hz), 2.99 (6 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm):150.1, 132.7, 131.2, 128.2, 127.4, 124.1, 111.8, 110.0, 90.6, 87.3, 40.2.

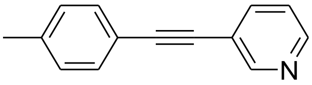
1,3-dimethoxy-5-(2-phenylethynyl)benzene[19]



54p

^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 7.57-7.52 (2 H, m) 7.38-7.33 (3 H, m), 6.71 (2 H, d, *J* = 2.1 Hz), 6.47 (1 H, t, *J* = 2.4 Hz), 3.81 (6 H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm): 160.5, 131.6, 128.3, 128.0, 124.5, 123.1, 109.3, 101.8, 89.3, 88.9, 55.4.

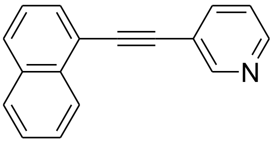
3-[2-(4-methylphenyl)ethynyl]pyridine[2]



54q

^{1}H NMR (200 MHz, CDCl$_3$) δ (ppm): 8.75 (1 H, d, *J* = 1.2 Hz), 8.53 (1 H, dd, *J* = 5.1, 1.8 Hz), 7.79 (1 H, m), 7.44 (2 H, d, *J* = 7.8 Hz), 7.23-7.20 (1 H, m), 7.17 (1 H, d, *J* = 7.8Hz), 2.38; ^{13}C NMR (50 MHz, CDCl$_3$) δ (ppm): 152.2, 148.4, 139.0, 138.3, 131.5, 129.2, 123.0, 120.7, 119.4, 92.8, 85.3, 21.5.

3-[2-(Naphthalen-1-yl)ethynyl]pyridine[2]



54r

^{1}H NMR (200 MHz, CDCl$_3$) δ (ppm): 8.89 (1 H, d, *J* = 1.2 Hz), 8.59 (1 H, dd, *J* = 4.9, 1.8 Hz), 8.41 (1 H, d, *J* = 7.9 Hz), 7.94-7.86 (3 H, m), 7.80 (1 H, dd, *J* = 7.3, 1.2 Hz), 7.67–7.44 (3 H, m), 7.36-7.30 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ (ppm): 152.2, 148.6, 138.4, 133.1, 133.1, 130.7, 129.3, 128.4, 127.0, 126.5, 126.0, 125.2, 123.1, 120.6, 120.1, 90.8, 90.7.

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CHAPTER 8

CONCLUSIONS

The work presented in this thesis well satisfied the objectives planned at the beginning of the project. Moreover, the results so far obtained give an important contribution to the knowledge of benzocyclotrimers chemistry.

Concerning the synthetic aspects, a new protocol for palladium catalyzed cyclotrimerization of enantiopure iodobornenes was developed and optimized for the synthesis of benzotricamphor in a multi-gram scale. The new method for the preparation of this cyclotrimer, described in Chapter 4, reduced the number of synthetic step than previous methodologies and led to the increase of global yield. Moreover, the new cyclotrimerization protocol, based on the Heck self-coupling reaction of enantiopure iodobornenes, avoids protection/deprotection steps and the use of toxic organo-tin compounds, extensively used in copper promoted cyclotrimerizations.

The screening of possible functionalization reactions for benzotricamphor successfully led to the preparation of new differently functionalized benzocyclotrimers. The most suitable reactions, to convert this C_3-symmetric scaffold into promising structures with supramolecular properties, are the condensation with aliphatic diamines and the Sonogashira coupling reactions with therminal alkynes. In particular, the first approach allowed the preparation of covalent molecular cages and the second led to self-assembling derivatives.

Inclusion experiments with molecular cages derived from benzotricamphor were performed and demonstrated hosting properties with regard to small neutral guests (Chapter 5).

In particular, the efficiency of the cages to bind gaseus molecules was determined by the compromise between the inner volume and morphology of the cages with the size and shape of the guests in association with weak attractive forces.

Moreover, the trifluoromethanesulfonate derivative of benzotricamphor constituted a versatile scaffold for the preparation of several self-assembling molecules. Indeed, coupling reactions with terminal alkynes allowed the preparation of differently substituted cyclotrimers, which were able to form supramolecular aggregates by using the more common self-assembly interactions. In Chapter 6 the preparation of coordination cages by metal-ligand interactions and capsules by ionic or H-bonding interactions are described as well.

An interesting side result emerged during the investigation of functionalization reactions of benzotricamphor triflate with propiolic acid derivatives (Chapter 7). In particular, acetylene carboxylic acid revealed an alternative alkyne source in the synthesis of acetylenic compounds, with respect to the commonly used trimethylsilyl acetilene both in terms of cost and atom economy. Moreover, from our study a new and advantageous protocol for the synthesis of unsymmetrical disubstituted alkynes from aryl bromides was developed and optimized.

Finally, the work presented in this thesis reports a series of positive findings that do not close any possible future development. In particular, the perspectives of this project will be in the field of supramolecular catalysis and drug delivery systems. Moreover, the preparation of new self-assembling systems is always possible by using at least one of the infinite existing synthetic methods and the introduction of recognition binding sites is also possible. In general, the future development of supramolecular chemistry will introduce engineering aspects that would transform simple molecular boxes into powerful nanotechnological objects.

Thus, the rational design of new molecular containers, assisted by the tools of organic synthesis, would and will provide new supramolecular systems that will overcome the simple concept of host-guest chemistry and will enter deeply into the molecular modification through highly controlled chemical transformations.

RIASSUNTO

BENZOCICLOTRIMERI FUNZIONALIZZATI: SINTESI STEREO CONTROLLATA E APPLICAZIONI SUPRAMOLECOLARI

I benzociclotrimeri sono composti policiclici che possono essere ottenuti mediante reazioni di accoppiamento di olefine bicicliche. Le reazioni di ciclotrimerizzazione hanno subito una notevole evoluzione a partire dalla prima sintesi dell'epticene nel 1970. I primi metodi per la sintesi di benzociclotrimeri si basavano sulla ciclotrimerizzazione di intermedi acetilenici altamente tensionati, i quali potevano essere generati dalla reazione di alogenuri vinilici con reagenti litio-organici. Tuttavia, questo metodo porta a rese modeste e può venir applicato solamente ad una limitata gamma di substrati.

A partire dal 1996, l'utilizzo di sali di rame quali promotori delle reazioni di ciclotrimerizzazione ha notevolmente incrementato la possibilità di preparare ciclotrimeri funzionalizzati e ha permesso un generale aumento delle rese.

Un ulteriore miglioramento nelle reazioni di ciclotrimerizzazione di substrati vinilici è stato ottenuto mediante l'uso di catalizzatori a base di palladio. In particolare questo approccio ha condotto alla sintesi di benzociclotrimeri a partire da reattivi Grignard e bromo-stannil olefine. Tuttavia la più recente evoluzione di questo metodo, basata sulla reazione di accoppiamento di Heck, ha permesso di condurre efficacemente la ciclotrimerizzazione di iodobicicloolefine enantiopure variamente funzionalizzate con elevate rese e diastereoselettività.

In generale, dalla ciclotrimerizzazione di olefine bicicliche si possono ottenere due diastereoisomeri: il *sin*,che possiede simmetria C_3 e una struttura concava, e l'*anti*, dotato di un minore grado di simmetria e solitamente meno utile per ulteriori impieghi.

L'ottenimento di *sin*-ciclotrimeri in grandi quantità è dunque un requisito fondamentale per lo studio delle possibili applicazioni di questi composti nel campo della chimica supramolecolare.

Nell'ambito specifico di questa tesi è stata messa a punto una metodica originale per la sintesi di ciclotrimeri funzionalizzati sulla base della ciclotrimerizzazione palladio-catalizzata di iodoborneni enantiopuri. Questa metodologia ha permesso di ridurre il numero di passaggi sintetici (da otto a cinque) rispetto alle precedenti metodologie basate sulla ciclotrimerizzazione di *vic*-bromo-stannilolefine mediante promotori a base di rame, con un conseguente aumento delle rese globali (da 4% a 15%).

La metodologia messa a punto ha consentito di ottenere elevate quantità di sin-ciclotrimero enantiopuro ed ha permesso di evitare l'uso di reagenti tossici, quali gli organostannili.

Il benzociclotrimero su cui è stato incentrato lo studio è un composto tricarbonilico (benzotricanfora) che è stato ottenuto a partire dall'acetilborneolo, un composto enantiopuro di origine naturale e di basso costo. Oltre all'ottimizzazione della procedura per la sintesi della benzotricanfora, sono state studiate le possibili vie di funzionalizzazione per la preparazione di complesse strutture molecolari in base alle più comuni reazioni di derivatizzazione della canfora. In particolare, le reazioni di condensazione con ammine si sono rivelate estremamente proficue per la preparazione di gabbie molecolari in grado di includere piccole molecole neutre.

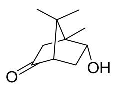
L'efficienza del processo di inclusione è stata determinata dal compromesso tra il volume e morfologia delle cavità, con la flessibilità delle catene alchiliche che collegano le unità ciclotrimeriche.

È stata inoltre ottimizzata la reazione di preparazione del tris-triflato della benzotricanfora sul quale sono state applicate le più comuni reazioni accoppiamento palladio-catalizzate al fine di funzionalizzare ulteriormente la benzotricanfora. I primi tentativi di accoppiamento sp^2-sp^2 con substrati arilici hanno condotto a scarsi risultati impiegando acidi boronici, organostannili e reattivi di Grignard. La preparazione di derivati della benzotricanfora ha invece avuto successo mediante reazioni di accoppiamento tra carboni sp^2-sp (reazione di Sonogashira) con aril acetileni. I nuovi composti ottenuti sono quindi costituiti da una unità policiclica a simmetria C_3 la cui funzionalizzazione ai bordi determina una struttura concava. La cavità è ulteriormente arricchita dalla presenza di varie funzionalizzazioni sui gruppi arilici terminali.

Tali gruppi hanno permesso di preparare aggregati supramolecolari attraverso l'interazione di più unità ciclotrimeriche sfruttando le più comuni interazioni utilizzate nella preparazione di supramolecole. Nello specifico, sono state ottenute gabbie di coordinazione con metalli di transizione quali l'argento e il platino e capsule basate su interazioni di tipo ionico e legami a idrogeno. La formazione di questi aggregati è stata dimostrata mediante misure NMR e tecniche di spettrometria di massa.

Infine, dallo studio specifico delle possibili reazioni di funzionalizzazione di benzociclotrimeri, è risultato un nuovo metodo generale per la sintesi di aril-acetileni disostituiti, il quale si basa sulle reazioni di accoppiamento decarbossilativo degli acidi acetilen-carbossilici. Lo studio volto a valutare la reattività dei derivati dell'acido propiolico nelle reazioni di accoppiamento con triflati vinilici, ha rivelato alcuni vantaggi in termini sia di economia monetaria che atomica rispetto all'uso di precursori "tradizionali" nella sintesi di composti acetilenici.

List of synthesized compounds



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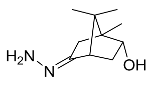

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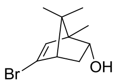

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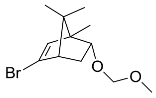

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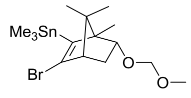

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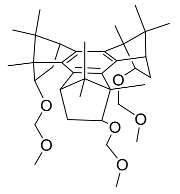

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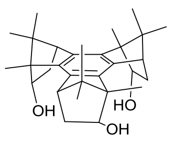

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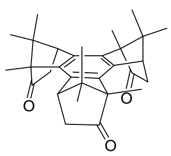

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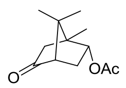

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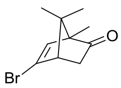

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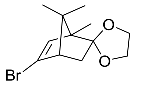

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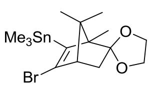

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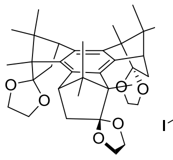

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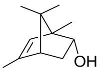

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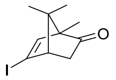

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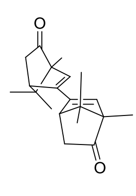

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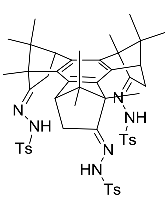

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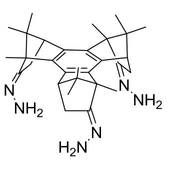

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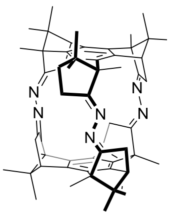

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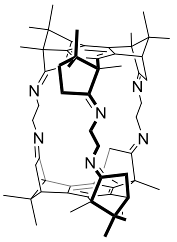

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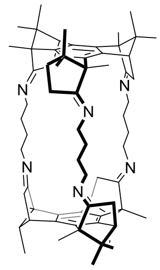

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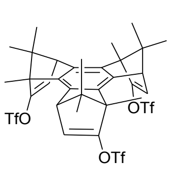

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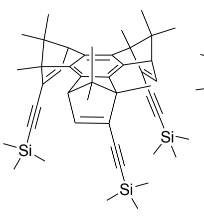

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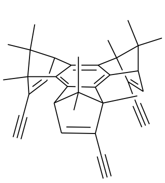

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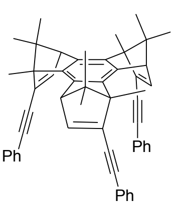

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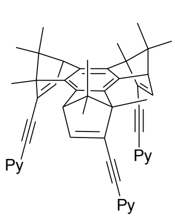

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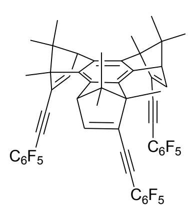

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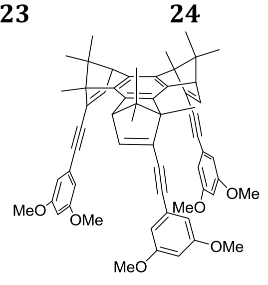

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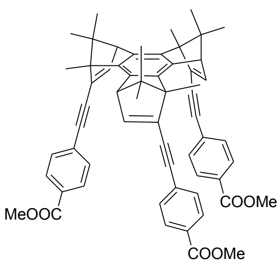

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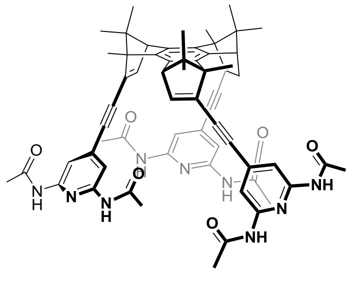

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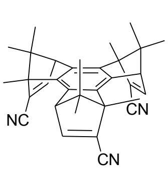

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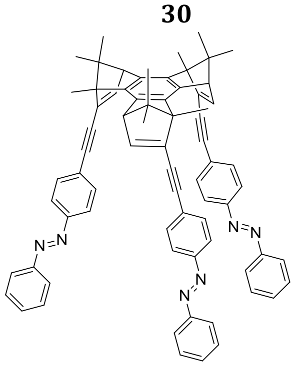

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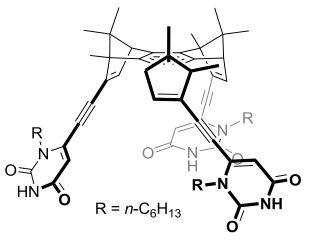

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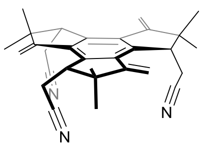

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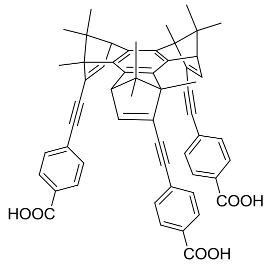

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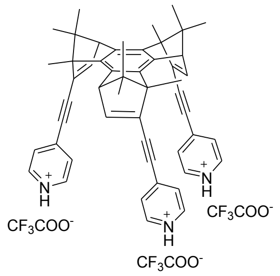

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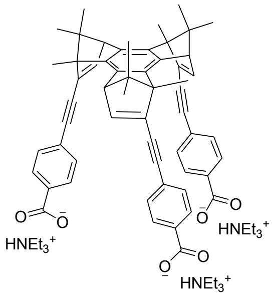

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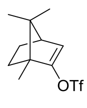

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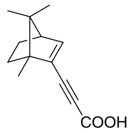

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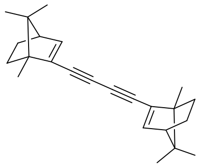

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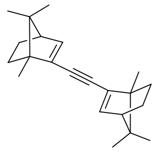

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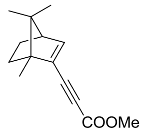

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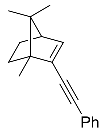

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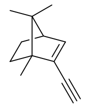

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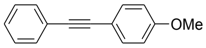

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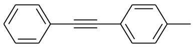

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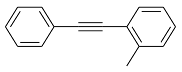

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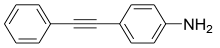

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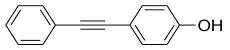

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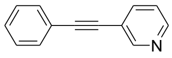

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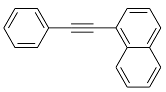

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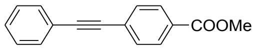

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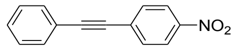

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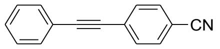

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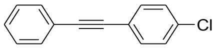

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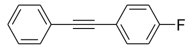

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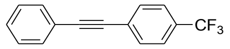

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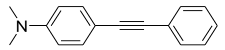

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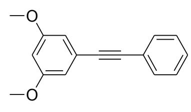

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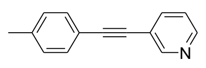

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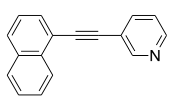

54r

Estratto per riassunto della tesi di dottorato

L'estratto (max. 1000 battute) deve essere redatto sia in lingua italiana che in lingua inglese e nella lingua straniera eventualmente indicata dal Collegio dei docenti.

L'estratto va firmato e rilegato come ultimo foglio della tesi.

Studente: Stefano Tartaggia matricola: 955477

Dottorato: Scienze Chimiche

Ciclo: XXIII

Titolo della tesi[1]: Benzociclotrimeri Funzionalizzati: Sintesi Stereo Controllata e Applicazioni Supramolecolari

Abstract:

I benzociclotrimeri sono composti policiclici che possono essere ottenuti da olefine bicicliche mediante reazioni di accoppiamento. In questa tesi viene presentata l'ottimizzazione di un nuovo metodo per la ciclotrimerizzazione di iodoborneni enantiopuri basato sulla reazione di Heck. L'ottimizzazione delle possibili reazioni di funzionalizzazione dei ciclotrimeri ottenuti ha permesso la sintesi di derivati in grado di esibire proprietà supramolecolari. In particolare, le reazioni di condensazione della benzotricanfora con diammine alifatiche hanno condotto verso gabbie molecolari in grado di ospitare piccole molecole neutre. Inoltre le reazioni di accoppiamento del trilfato della benzotricanfora con alchini terminali hanno portato a nuovi ciclotrimeri con proprietà auto-assemblanti, basate sulla formazione di legami di coordinazione, legame a idrogeno e interazioni ioniche. Infine, dallo studio delle funzionalizzazioni di benzociclotrimeri, è stato ottimizzato un nuovo metodo generale per la sintesi di aril-acetileni disostituiti basato sulle reazioni di accoppiamento decarbossilativo dell' acido acetilen-carbossilico.

Firma dello studente

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[1] Il titolo deve essere quello definitivo, uguale a quello che risulta stampato sulla copertina dell'elaborato consegnato.

Estratto per riassunto della tesi di dottorato

L'estratto (max. 1000 battute) deve essere redatto sia in lingua italiana che in lingua inglese e nella lingua straniera eventualmente indicata dal Collegio dei docenti.

L'estratto va firmato e rilegato come ultimo foglio della tesi.

Studente: Stefano Tartaggia matricola: 955477

Dottorato: Scienze Chimiche

Ciclo: XXIII

Titolo della tesi[2]: Functionalized Benzocyclotrimers: Stereo Controlled synthesis and Supramolecular Applications

Abstract:

Benzocyclotrimers are polycyclic compounds which can be obtained through self-coupling reactions of bicyclic olefins. This work presents the optimization of a new method for the synthesis of cyclotrimers using a feasible procedure based on the Heck-type self-coupling reaction of enantiopure iodobornenes. The screening and the optimization of several functionalization reactions led to the preparation of covalent supramolecular hosts and self-assembling derivatives. In particular, the condensation of benzotricamphor with aliphatic diamines provided imine-linked molecular cages which exhibited hosting properties for small neutral guests. On the other hand, coupling reactions of benzotricamphor triflate with terminal alkynes provided new self-assembling derivatives based on metal-ligand, H-bonding and ionic interactions. The research of other functionalization reactions for benzocyclotrimers helpfully led to a new general method for the synthesis of disubstituted arylacetylenes from aryl bromides based on decarboxylative coupling reactions of acetylene carboxylic acid.

Firma dello studente

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[2] Il titolo deve essere quello definitivo, uguale a quello che risulta stampato sulla copertina dell'elaborato consegnato.