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dissertation entitled

THE SYNTHESIS AND MODIFICATION OF
HOMOCALIXARENES

presented by

ALEXANDER V. PREDEUS

has been accepted towards fulfillment
of the requirements for the

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Major Professor's Signature

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Date

THE SYNTHESIS AND MODIFICATION OF HOMOCALIXARENES

By

Alexander V. Predeus

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ABSTRACT

THE SYNTHESIS AND MODIFICATION OF HOMOCALIXARENES

By

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A series of homocalixarenes was prepared using the "triple annulation" approach, that employs the benzannulation reaction between bis-Fischer carbene complexes and bis-alkynes to create three rings of the macrocycle simultaneously. Both homocalix[3]arenes and homocalix[4]arenes were prepared successfully. Furthermore, it was shown that this approach remains effective on a very broad spectrum of ring sizes, allowing the construction of macrocycles ranging from 15 to 56 carbon atoms. The method also afforded the synthesis of a pyrrole-containing macrocycle, proving its tolerance to numerous functional groups.

The method was applied to the synthesis of C_3-symmetrical homocalix[3]arenes, that were prepared using cyclization reactions with protected intermediates followed by appropriate deprotection. The latter reaction was shown to be useful for homocalix[3]arene preparation on a gram scale. A number of homocalix[3]arene triflates were prepared and characterized. A series of coupling reactions were tested on appropriate model compounds, and several low rim modification reactions were attempted with homocalixarene triflates.

Overall, efficient methods for the preparation of various homocalixarenes are developed. These methods are tolerant to many functional groups, allowing syntheses of a wide variety of ring sizes, and practical gram amounts of material, broadening the possibilities of homocalixarene use and applications.

ACKNOWLEDGEMENT

I would like to express my deep gratitude to Professor Wulff. His guidance gives an almost unbelievable amount of freedom to pursue things that truly fascinate and interest you, at the same time allowing you to face your challenges and grow personally and as a scientist. The doors of his office were always open, and he was always as helpful and as inspiring as advisor could be. This has been a life-changing experience for me.

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It is a pleasure to thank all of my current and former colleagues. From what I learned, Wulff group always had very friendly and professional atmosphere, and I am very happy to have had a chance to breath in it (this by no means is a reference to Dr. Zhensheng Ding's thiol reductions). I thank Dima Berbasov, Aman Desai, Zhensheng Ding, Wynter Gilson, Yong Guan, Anil Gupta, Li Huang, Keith Korthals, Nilanjana Majumdar, Munmun Mukherjee, Corey Newman, Victor Prutyanov, Hong Ren, James Woods, Andrei Vorogushin and many others for their friendship, and for creating truly inspiring and professional scientific environment in the group.

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ABBREVIATIONS

1,2-DCE	1,2-Dichloroethane
BTMA	Benzyltrimethylammonium
DME	1,2-Dimethoxyethane
DMF	N,N-Dimethylformamide
DMSO	Dimethyl sulfoxide
ESI/MS	Electrospray Ionisation Mass-Spectroscopy
EXSY	Chemical Exchange Spectroscopy
FAB/MS	Fast Atom Bombardment Mass-Spectroscopy
HMPA	Hexamethylphosphoramide
HPLC	High Performance Liquid Chromatography
LDA	Lithium Diisopropyl Amide
mCPBA	*meta*-Chloroperoxybenzoic acid
NMR	Nuclear Magnetic Resonance Spectroscopy
NOE	Nuclear Overhauser Effect
S-PHOS	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
TBS	*tert*-Butyl dimethylsilyl
THF	Tetrahydrofuran
TLC	Thin Lawyer Chromatography
TMM	Trimethylenemethane
TMS	Trimethylsilyl
TosMIC	(*para*-Toluenesulfonyl)methyl isocyanide
TPE	Tetraphenylethylene

CHAPTER ONE

SYNTHESIS AND PROPERTIES OF HOMOCALIXARENES

The Universe is full of magical things, patiently waiting for our wits to grow sharper.

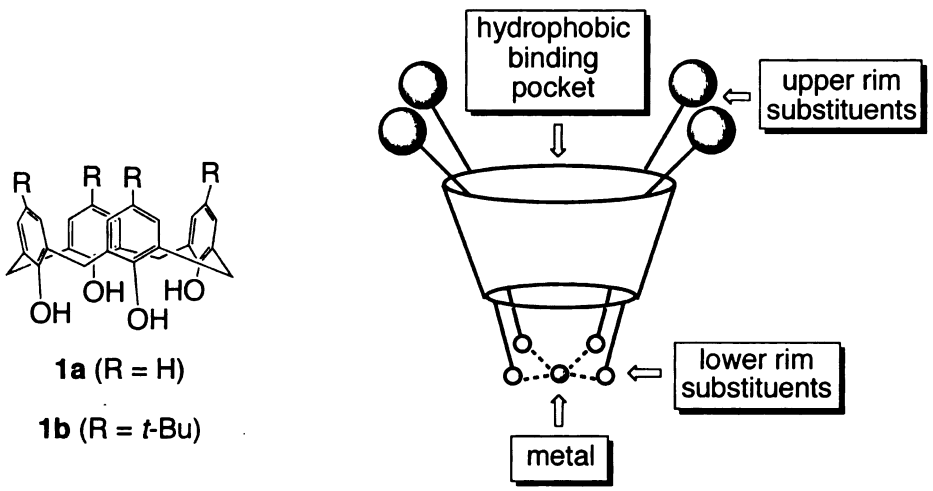
Eden Phillpotts

1. Relevant Terminology and the Importance of Homocalixarenes.

Calixarenes (from Latin *calix*, cup) are a popular and versatile class of macrocycle formed from the condensation of a *p*-substituted phenol (e.g. *p-tert*-butylphenol) with formaldehyde. Since they contain bridged aromatic rings, they are formally members of the cyclophane family. In cyclophane nomenclature, one of the simplest calixarenes **1a** (Figure 1.1) is termed [1.1.1.1]metacyclophane. The number of phenolic residues is denoted by a number in square brackets. Thus the most common cyclic tetramer with four *p-tert*-butyl substituents **1b** is termed *p-tert*-butyl-calix[4]arene[1].

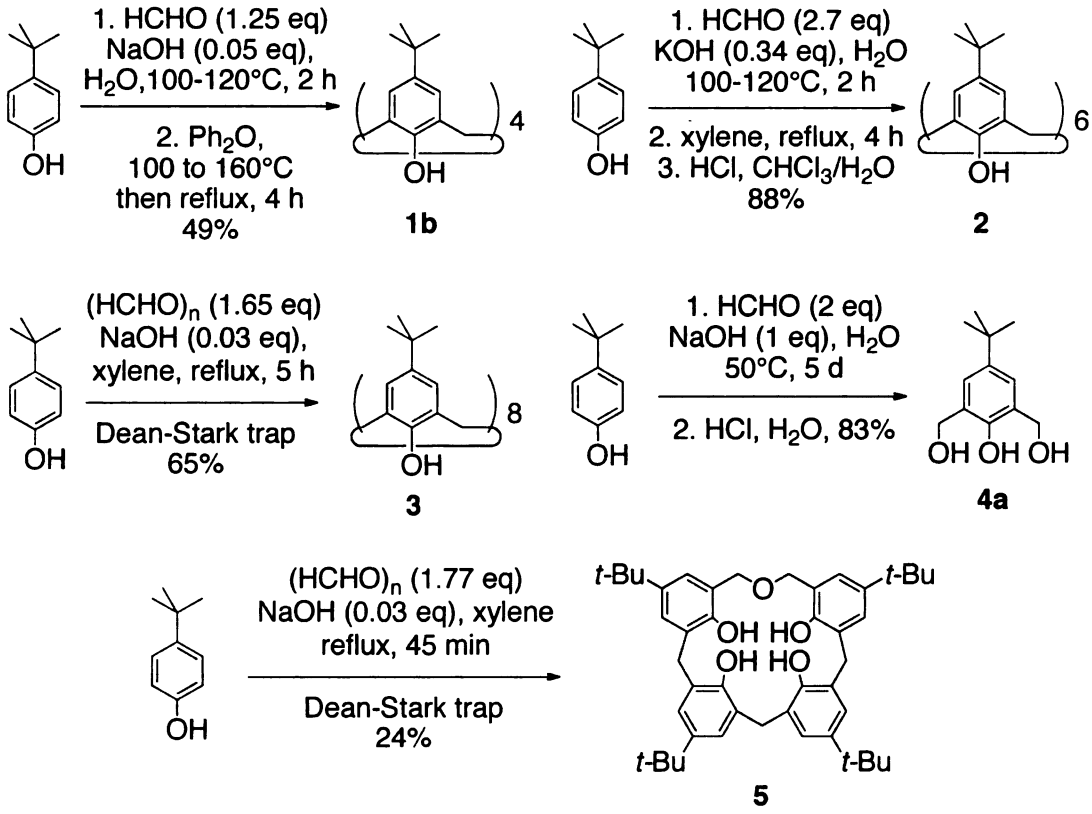
Calixarenes have attracted reseachers due to their easy preparation and unique structural features. In the *cone* conformer (all 4 OH groups on the same side) of classic calix[4]arene, one can single out the following structural elements: 1) a hyrophobic binding pocket; 2) upper rim with substituents; 3) lower rim with substituents; 4) cation binding site (Figure 1.1). While the original idea was to use calixarenes to imitate the enzyme binding pocket, eventually calixarenes became some of the most popular *host* compounds for *supramolecular* host-guest complexation, self-organized systems, as well as ligands for selective metal extraction, etc.

Figure 1. 1. Calix[4]arene structure elements.



The active research of calixarenes have started when individual compounds resulting from condensation of *p-tert*-butylphenol with formaldehyde were fully characterized by the laboratory of C. David Gutsche[2–4]. Among many other things, his research group was the first to find effective ways of selective calixarene preparation. At that point it became obvious that calixarene preparations are extremely sensitive to reaction conditions, such as substituents in organic substrate, dilution, presence of metal cations, and temperature. This can be illustrated by reactions in Scheme 1.1, when different conditions lead to 5 different main products[2–6] from the *same* starting materials. It is also worth noticing that preparation of calix[4]arene from *p*-methylphenol *completely fails* under the same conditions that afford **1b** from *p-tert*-butylphenol in 49% yield.

Scheme 1. 1. Various outcomes of base-catalyzed reaction of p-*tert*-butylphenol with formaldehyde.

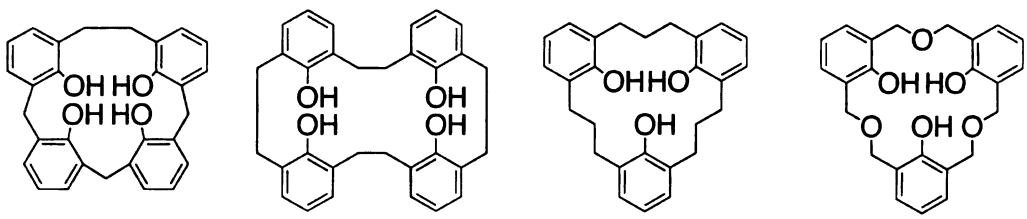


While calixarenes have got a lot of attention from almost any possible point of view, their analogues with more then one carbon atom in the linker bonding the aromatic rings – *homocalixarenes* – are a lot less studied. This is mostly due to significantly harder preparation; still, numerous researchers have been attracted by the possibilities that homocalixarenes offer, such as larger cavity size, binding sites in aliphatic chains, easier lower rim modification due to reduced steric hindrance, and many others.

There is a certain amount of ambiguity in homocalixarene naming today[7]. Some researchers only call compounds with *one* extra methylene group (like **6**) homocalixarene, while structure **7a** would be termed *all*-homocalixarene, structure **8a** –

all-(bis)homocalixarene, etc. The problems with this approach rise when larger rings or rings with different aliphatic linkers are considered. Another problem occurs when rings of the type **9a** are described. In literature, they are often referred to as homooxacalixarenes, but sometimes are still described as members of more general class of "homocalixarenes".

Figure 1. 2. Homocalixarenes and homooxacalixarenes.



6 **7a** **8a** **9a**

It seems unreasonable to enforce any kind of strict nomenclature now. The possible ambiguity in naming, if necessary, can be removed with the help of additional descriptors (i.e. structure **9a**, if needed, can be called hexahomotrioxacalix[3]arene, etc.). Also, many researchers avoid naming such structures at all.

2. Preparation of Homocalixarenes.

As it was mentioned before, most of the known homocalixarene preparation methods are inferior to ones used to prepare calixarenes. They often require high dilution and produce low yields of the target compounds; they also lack generality, and often give unpredictable results on non-standard substrates.

Many of the synthetic methods used for homocalixarene preparation were borrowed from cyclophane chemistry. Even though metacyclophanes can be viewed as homocalix[2]arenes, for the following overview we will not mention cyclophane

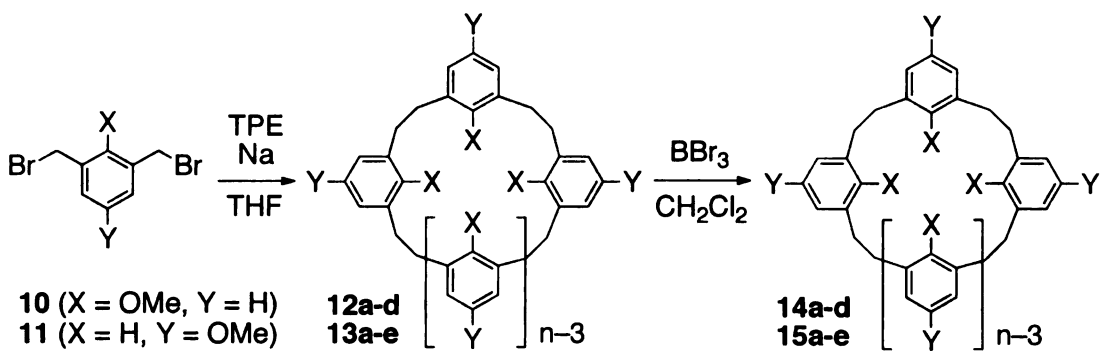
synthesis, and will concentrate our attention on substances with 3 or more aromatic rings in the molecule.

2.1. All-carbon Macrocyclic Cores.

A. Two-carbon Linkers (All-Homocalixarenes).

One of the earliest known ways to prepare *all*-homocalixarenes was the Müller-Röscheisen cyclization, a variation of the Wurtz coupling, which is carried out at –70 to –90°C using powdered sodium and tetraphenylethene (TPE) as a catalyst[8]. The resulting mixtures of products were separated by chromatography, and can be demethylated to obtain phenolic compounds:

Scheme 1. 2. Preparation of homocalixarenes by Müller-Röscheisen cyclization.



10 (X = OMe, Y = H)
11 (X = H, Y = OMe)

12a-d
13a-e

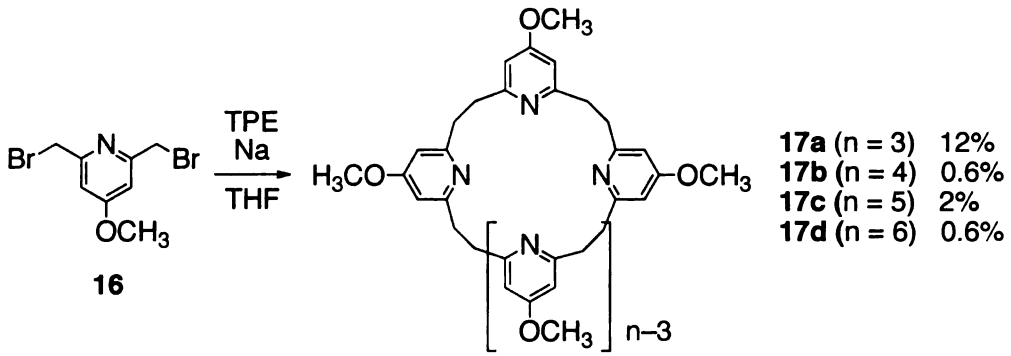
14a-d
15a-e

n	X = OMe Y = H	X = H Y = OMe
2	–	**13a** (21%)
3	–	**13b** (10%)
4	(trace)	**13c** (11%)
5	**12a** (6%)	**13d** (3%)
6	**12b** (8%)	**13e** (2%)
7	**12c** (4%)	–
8	**12d** (2%)	–

n	X = OH Y = H	X = H Y = OH
2	–	**15a** (93%)
3	–	**15b** (97%)
4	–	**15c** (99%)
5	**14a** (67%)	**15d** (87%)
6	**14b** (93%)	**15e** (93%)
7	**14c** (84%)	–
8	**14d** (74%)	–

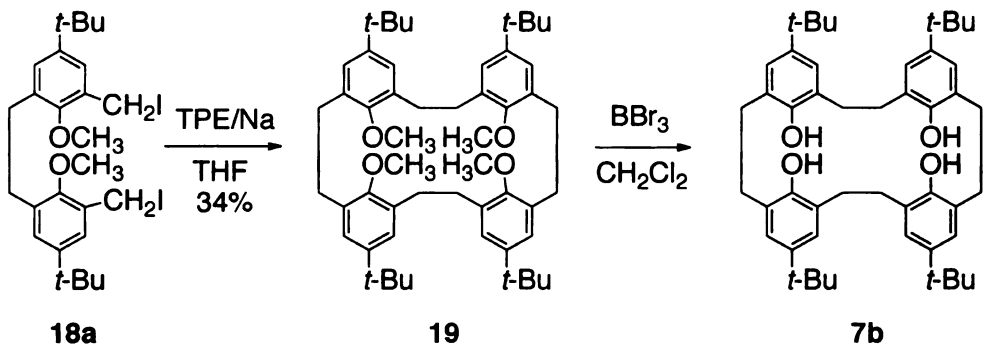
The method was also applied to pyridine derivatives[9]:

Scheme 1. 3. Preparation of homocalixpyridines by Müller-Röscheisen cyclization.



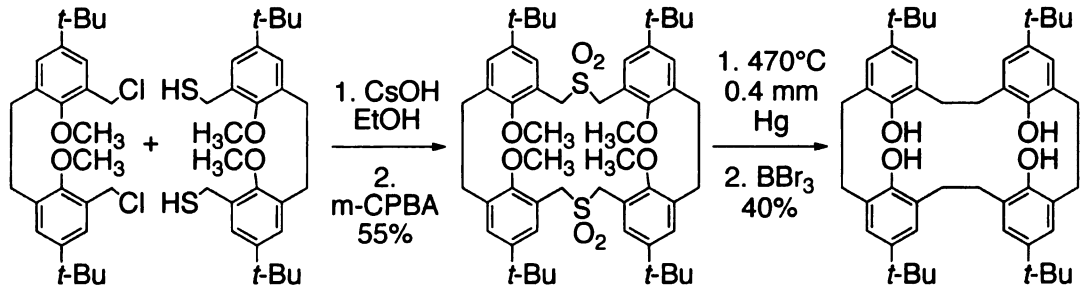
Another option, making Müller-Röscheisen cyclization more predictable, consists of making more complex precursors, followed by the coupling itself[10]:

Scheme 1. 4. Preparation of homocalixarene from a dimeric precursor.



Sulfur extrusion method also allows to access *all*-homocalix[4]arene **7b** in a more controllable way[11]. This method allows the macrocycle preparation by nucleophilic substitution under relatively mild conditions, due to high nucleophilicity of sulfur. After the oxidation into sulfone **21** by mCPBA, sulfur can be eliminated by vacuum pyrolysis (Scheme 1.5).

Scheme 1. 5. Preparation of homocalix[4]arene by sulfur extrusion method.

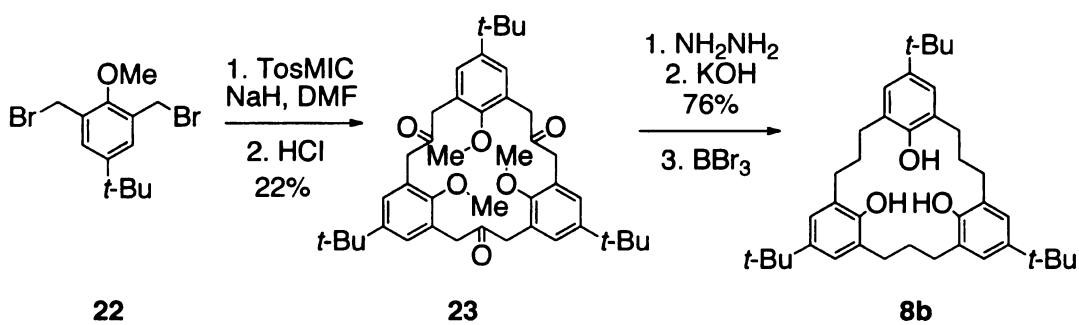


B. Three-carbon Linkers (All-bishomocalixarenes).

Several methods are known to work the best (or only) for making homocalixarenes with three carbons in the bridge between aromatic rings.

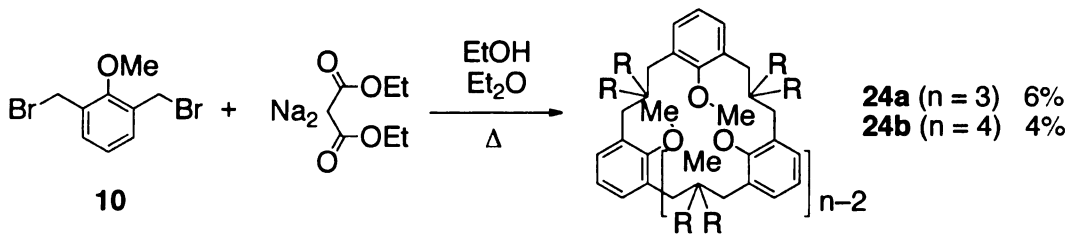
Cyclization with TosMIC ((p-toluenesulfonyl)methyl isocyanide) has been frequently employed in cyclophane and homocalixarene synthesis. Thus, triketone **23** was prepared using this reaction. Following Wolff-Kishner reduction and demethylation with BBr_3 gives homocalix[3]arene **8b**[12]:

Scheme 1. 6. Homocalix[3]arene preparation by trimerization of dibromide **22**.



Homocalixarenes **24a** and **24b** (as well as many others) were prepared using condensation of diethylmalonate dianion with **10**[13]. One drawback of this method is the necessity to get rid of carboxyethyl groups in the linkers if unsubstituted ring is desired.

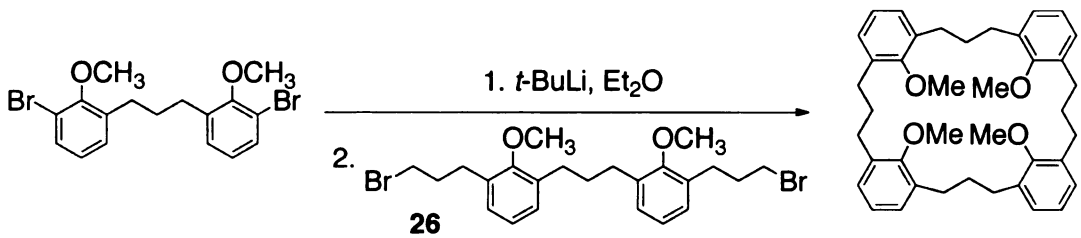
Scheme 1. 7. Malonate alkylation applied to homocalixarene preparation.



10

The cross-coupling reaction of the dianion of **25**, generated by *tert*-butyllithium, with **26** yielded homocalix[4]arene **27** along with several linear byproducts[14].

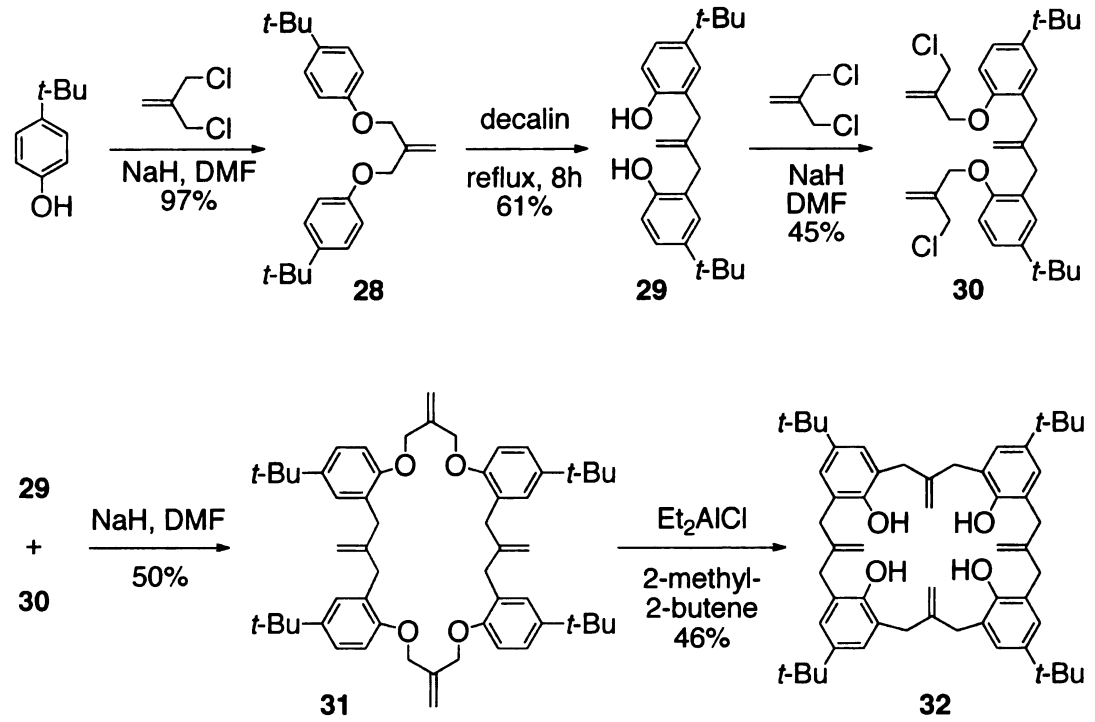
Scheme 1. 8. Cross-coupling of bis-aryllithium with alkyl bromide.



25 **26** 15–20% **27**

Claisen rearrangement was used to prepare homocalix[4]arene **32**, with double bonds in its bridges. Interestingly, transformation of **31** into **32** gives a very poor yield unless 2-methyl-2-butene is used solvent (Scheme 1.9)[15].

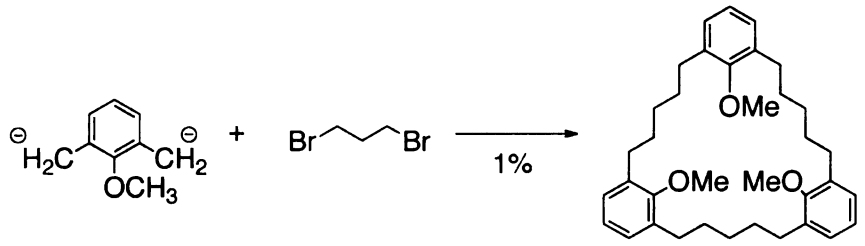
Scheme 1. 9. Claisen rearrangement used to prepare homocalixarenes.



C. Homocalixarenes With Larger (n ≥ 4) Linkers.

Dianion coupling was also used to prepare [5.5.5]metacyclophane **33** in 1% yield, but from simple precursors[16]:

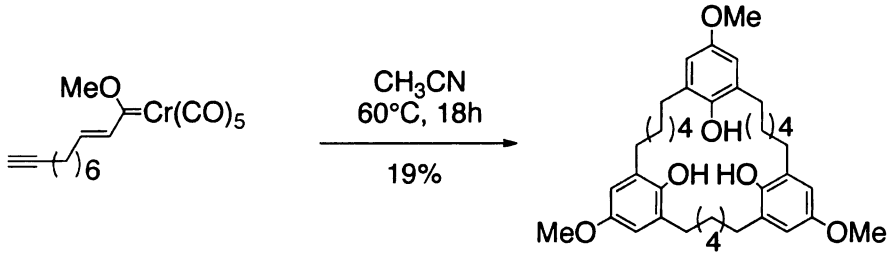
Scheme 1. 10. Benzylic dianion cross-coupling for homocalix[3]arene preparation.



33

Another example involves benzannulation reaction, that is discussed in greater detail in Chapter 2 of this work. Using this approach, Wang was able to prepare [6.6.6]metacyclophane **35** in 19% yield[17]:

Scheme 1. 11. Fischer carbene complex trimerization.



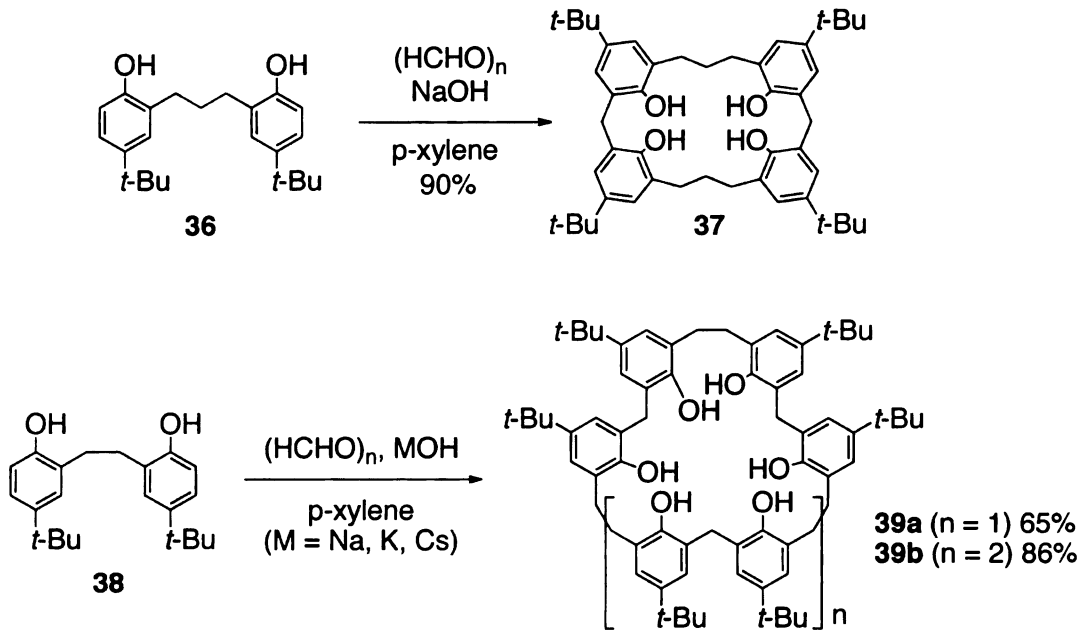
34 **35**

D. Homocalixarenes With Mixed Size Linkers.

As one can envisage, the adjustability of ring size and conformations by changing the linkers size can add a great deal of possibilities to homocalixarene host properties. The existing methods are never general, and reserchers often rely on increasing of aromatic rings number to prepare bigger rings (such as, making calix[6]arene instead calix[4]arene, etc.).

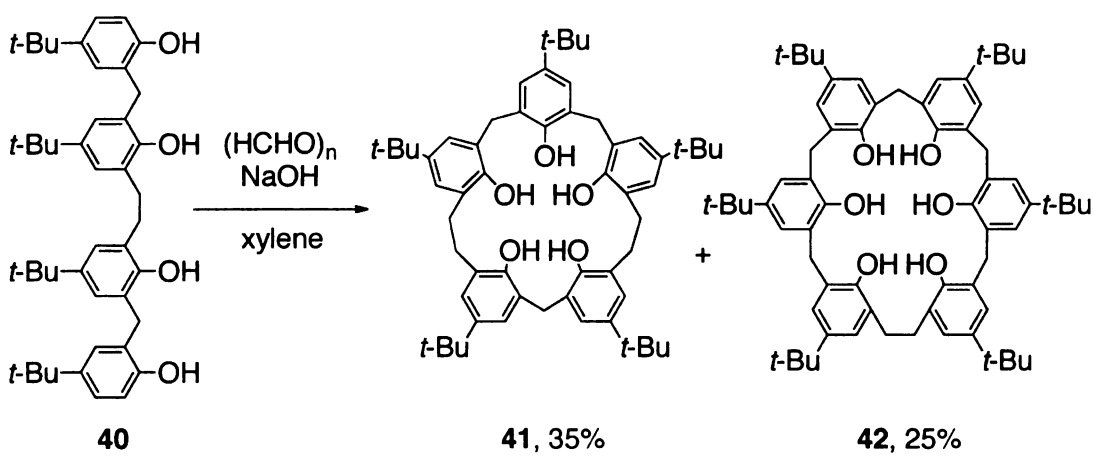
Often, the original calixarene preparation reaction – condensation with formaldehyde and other aldehydes – can be used for mixed homocalixarene preparation. Examples are given in Scheme 1.12[18,19]:

Scheme 1. 12. Base-catalyzed condensation of oligophenols with paraform.



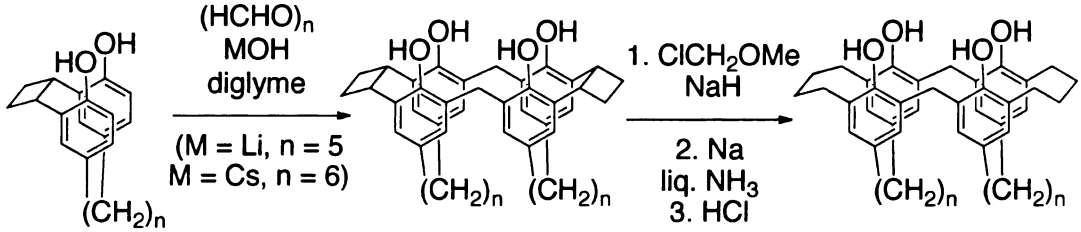
Despite looking predictable, even these simple reactions can be very surprising. For example, condensation of **40** with paraformaldehyde in xylene in the presence of NaOH unexpectedly gave compounds **41** and **42**. The mechanism of these transformations is not yet fully elucidated (Scheme 1.13)[20].

Scheme 1. 13. The unexpected formation of homocalixarenes **41** and **42**.



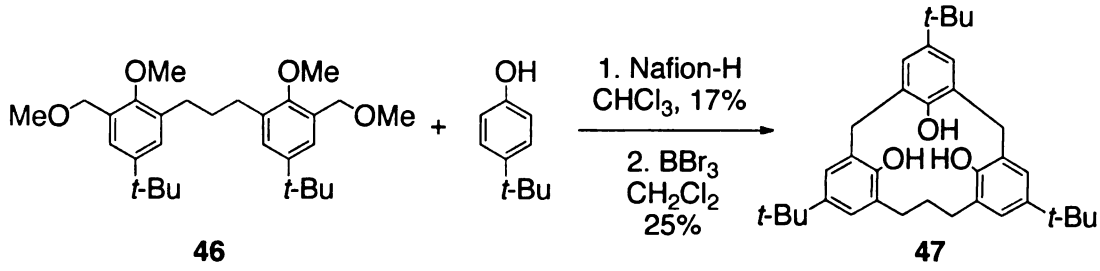
Using even this simple transformation, quite complicated frameworks were assembled. Thus, condensation of phenols **43** with formaldehyde and following Birch-type reduction afforded [4.1.4.1]metacyclophanes **45a** and **45b**, with pairs of aromatic rings linked for additional conformational rigidity[21]:

Scheme 1. 14. Preparation of cross-linked [4.1.4.1]metacyclophanes.



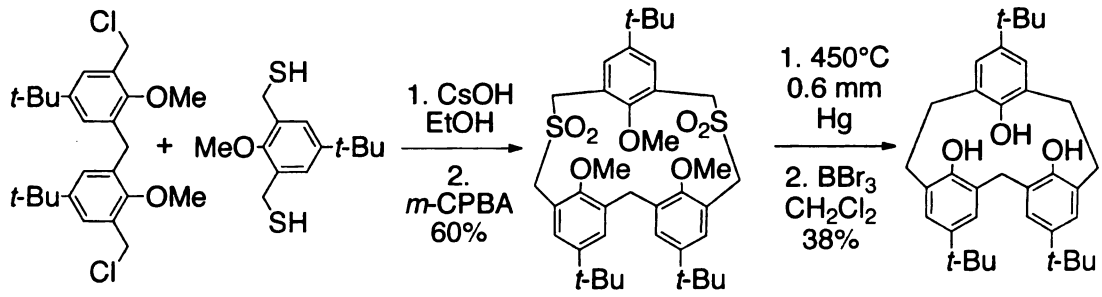
In a somewhat analogous reaction, Nafion-H (acidic Teflon-based resin) catalyzed cyclobenzylation was used to obtain [3.1.1]metacyclophane[22]:

Scheme 1. 15. Acid-catalyzed homocalixarene preparation.



Variations of earlier mentioned sulfone extrusion method also allow preparation of several types of homocalix[3]- and [4]arenes[23].

Scheme 1. 16. Preparation of [2.2.1]metacyclophane by sulfur extrusion method.



48 **49** **50** **51**

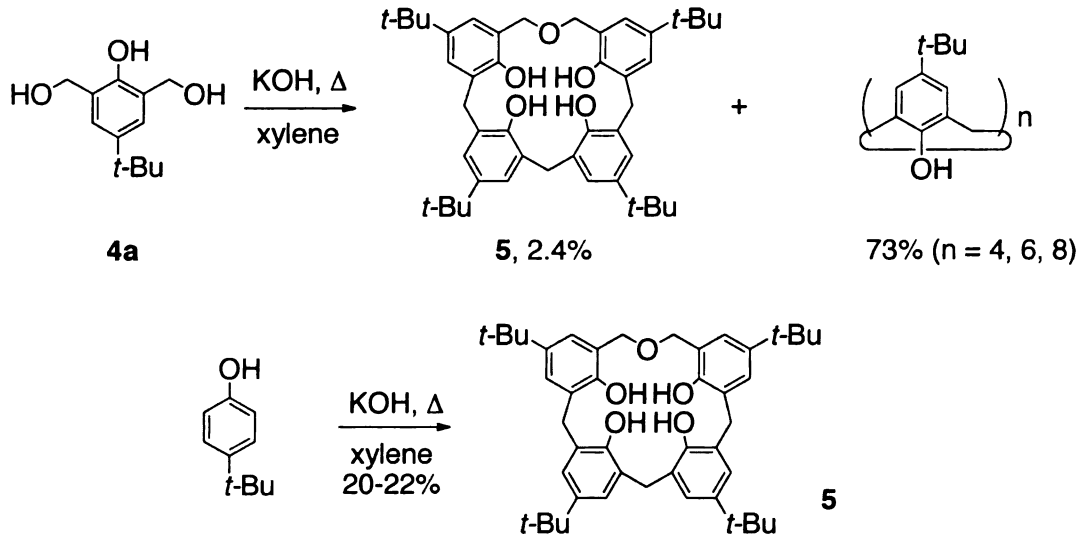
Altogether, the known methods rarely offer the control and choice of the size of the macrocycle.

2.2. Homooxacalixarenes.

A. Three-member Linkers.

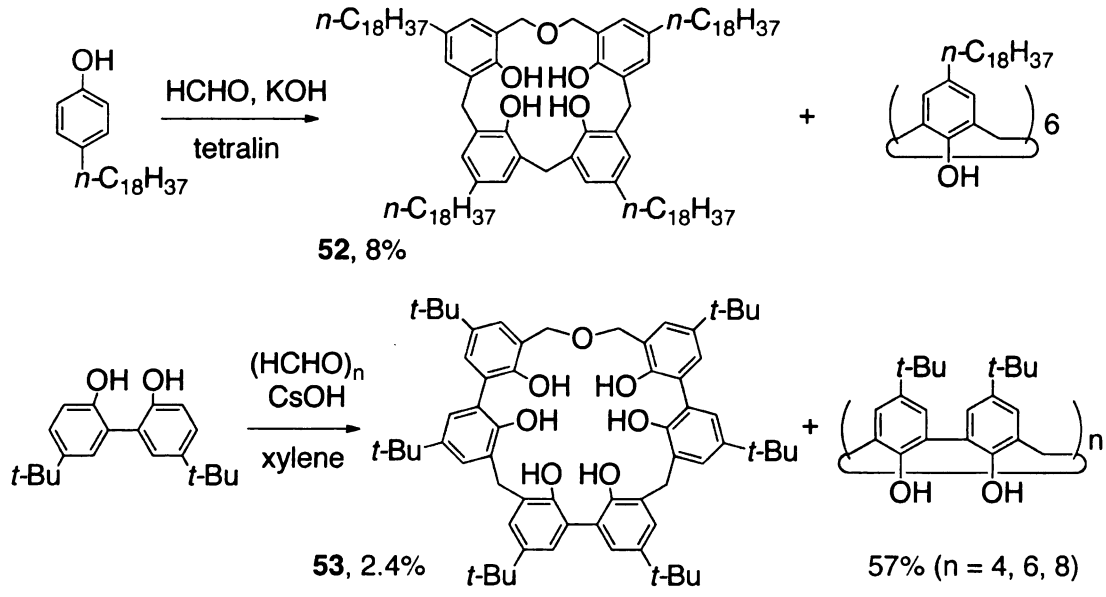
During the development of one-pot procedures for calix[n]arene preparation, Gutsche *et al.* discovered that condensation of 4-*tert*-butylphenol with formaldehyde in the presence of a base gives, in addition to the expected 4-*tert*-butylcalix[4]-, [6]- and [8]arenes, a fourth product – 4-*tert*-butylbishomooxacalix[4]arene **5**[24]. If the abovementioned condensation is carried out in xylene with KOH the yield of **5** rises to 20 – 22%, and the combined yield of calixarenes drops to 63%[24,25] (Scheme 1.17). A special preparative method for **5** starting from 4-*tert*-butylphenol has also been described[26].

Scheme 1. 17. Preparation of bishomooxacalix[4]arene **5**.



Similarly, compounds **52** and **53**, as well as several other ones with the same $-CH_2OCH_2-$ linker were prepared in low yields[27,28]:

Scheme 1. 18. Monooxacalixarene preparation.

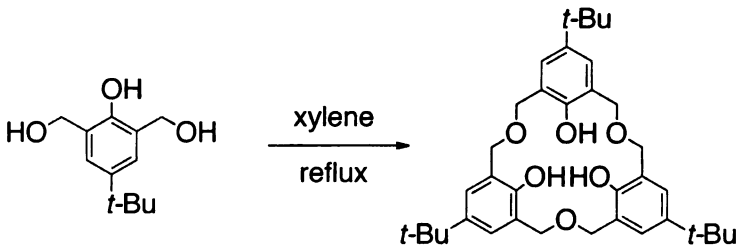


Fully symmetrical homooxacalix[3]arenes were attractive synthetic targets for several reasons:

- C_3 symmetry of the molecule, which can possibly be very useful for binding to primary ammonium cations, etc;
- Limited number of possible conformers. Fully symmetrical **9a** (Figure 1.2) can only exist in two conformations, *cone* and *partial cone* (*paco*);
- The presence of oxygen atoms in the linkers. Ether oxygen can possibly coordinate to metals or participate in hydrogen bonding;
- The cavity size (18 carbons) of **9a** is in between of calix[4]arene (16 carbons) and calix[6]arene (24 carbons).

Despite the interest towards these molecules, the applications of homooxacalixarenes really only began when Gutsche *et al.* have published their study on thermal degradation of phenols and polyphenols containing CH_2OH groups[29]. The methods of thermal and acid-catalyzed trimerization of inexpensive 2,6-bis(hydroxymethyl)phenols **4** have proven to be very effective in preparation of homooxacalix[3]arenes on gram and larger scale.

Scheme 1. 19. Thermal trimerization of triol **4a**.

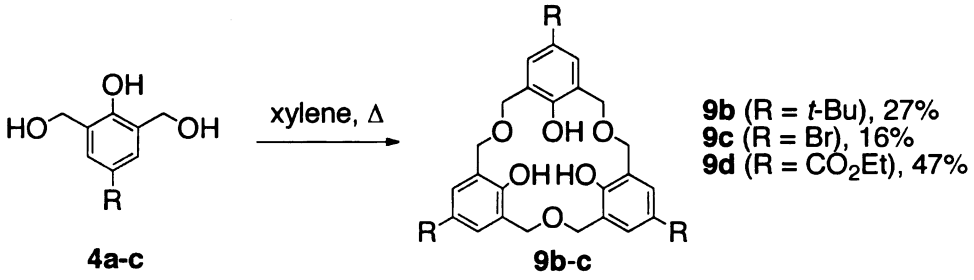


4a **9b**, 30%

Many researchers have found this thermal trimerization to be poorly reproducible. Later it was reported[30] that traces of acid in starting material **4a** were responsible for the

cyclization, and pure recrystallized **4a** gave only traces of target product upon heating in xylene. Despite this, several more groups have used the thermal acid-free process and obtained homooxacalixarenes **9b**[31], **9c**[32], **9d**[33], and others.

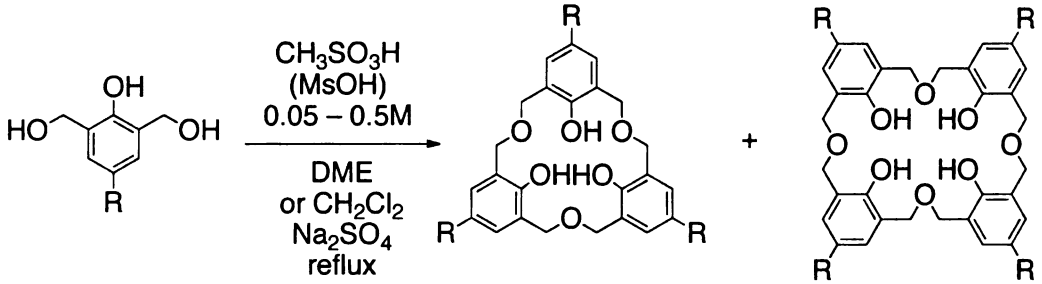
Scheme 1. 20. Homooxacalix[3]arenes by thermal decomposition of triols.



4a-c **9b-c**

The role of acid was studied and resulted in a detailed report by Daitch *et al.*[34] (Scheme 1.21). His method applied sodium sulfate to bind the produced water, and cyclizations were carried out at a high dilution of **4**, in 1,2-dimethoxyethane (DME) or dichloromethane.

Scheme 1. 21. Acid-catalyzed cyclization of triols **4**.

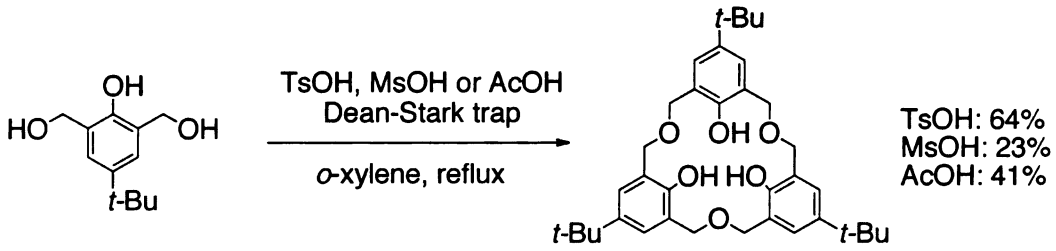


4a-e, 0.05M **9b, 9e-h** **54b, 54e-h**

Compound	R	solvent	**9**:**54** ratio	Yield of **9**, %
9b	*t*-Bu	DME	5:1	32
9e	*i*-Pr	DME	12:1	30
9f	Et	DME	14:1	21
9g	Cl	DME	5:1	12
9h	Me	DME	16:1	21

Alternatively, trimerization of **4a** in *o*-xylene with different acids was studied, and *p*-toluenesulfonic acid was found to be the most effective, giving 64% yield[30]:

Scheme 1. 22. Acid-catalyzed preparation of **9b** in xylene.

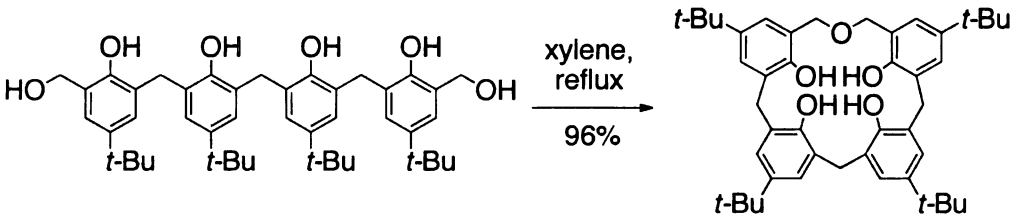


4a **9b**

It is important to notice that these preparations are limited only to homooxacalix[3]arenes with all the same substituents in the *para* position, that some substituents work significantly worse than the others, and there seems to be no way to predict which one will work better.

Homooxacalixarenes have also been prepared from various bis(hyroxymethyl)polyphenols. Thus, abovementioned monooxacalix[4]arene **5** was obtained in nearly quantitative yield by intramolecular dehydration of tetramer **55**, which in turn was obtained from *p-tert*-butylphenol in 3 steps[29].

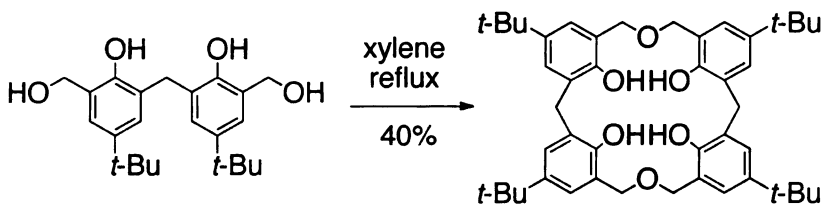
Scheme 1. 23. Preparation of monooxacalixarene **5** from advanced precursor **55**.



55 **5**

Dioxacalixarene **57** was the product of similar dehydration starting from dimer **56**. Interestingly, homooxacalixarene **5** was also obtained in the cyclization of **56** in less then 1% yield[29].

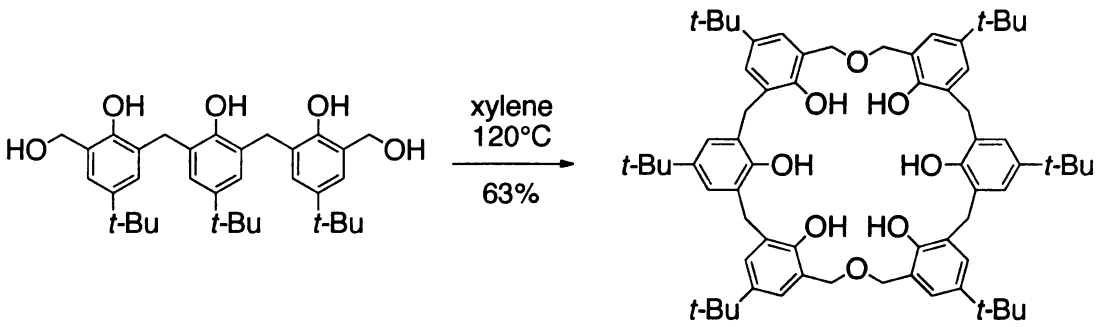
Scheme 1. 24. Dioxahomocalix[4]arene preparation.



56 **57**

Dioxacalix[6]arene **59** was prepared in 63% yield from trimeric phenol **58**; mono- and trioxacalix[6]arenes were found to be the side products with 0.4% and 0.5% yields respectively. The selective formation of **59** was attributed to the template effect of intramolecular hydrogen bonds[35].

Scheme 1. 25. Dioxahomocalix[6]arene preparation.

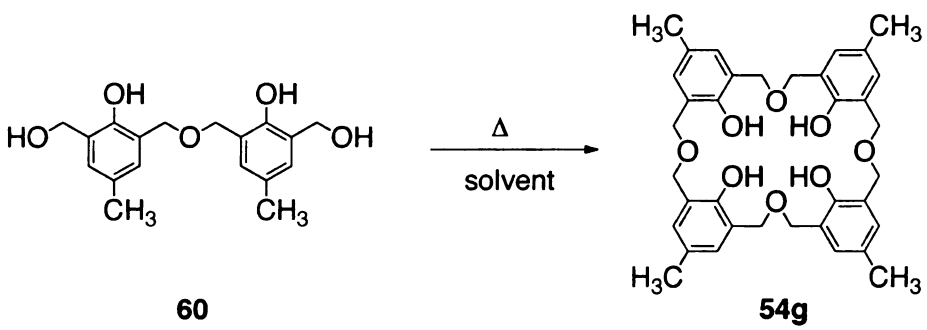


58 **59**

Precursors with phenol units bridged with other than all methylene tethers have also been used in homooxacalixarenes preparation. Linear oligomers of 2,6-

bis(hydroxymethyl)phenols have also been applied. Homooxacalix[4]arene **54g** was obtained from dimer **60**, although in low yield[25].

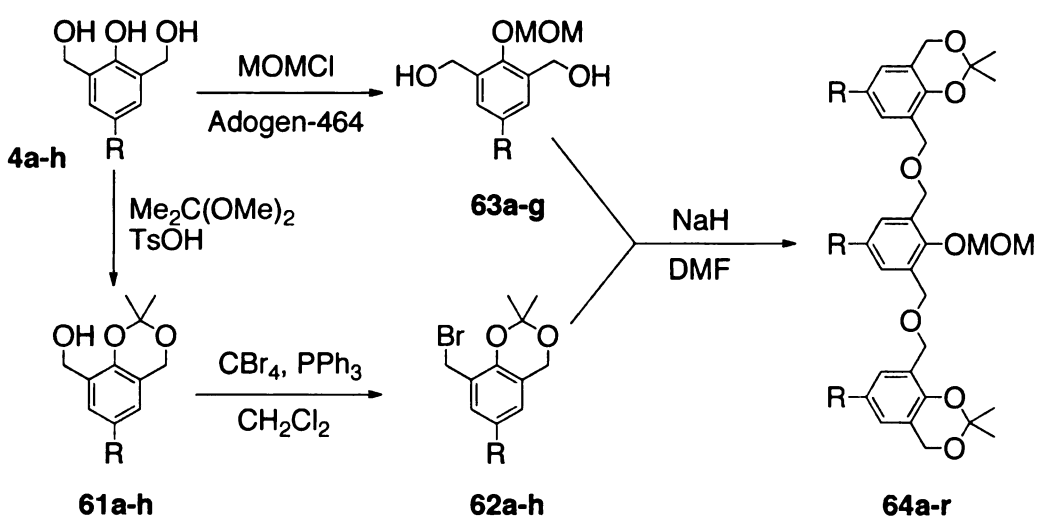
Scheme 1. 26. Tetraoxohomocalic[4]arene preparation.



60 **54g**

In 1998 a very extensive work by Tsubaki *et al.* described the cyclization of linear trimers **64** into homooxacali[3]arenes **9**[36]. The trimer itself was assembled using selective protection of phenolic and benzylic hydroxide groups:

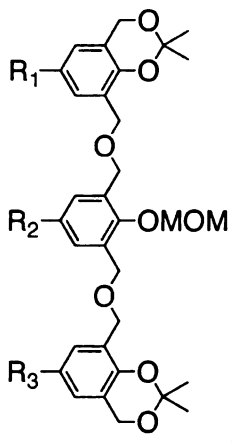
Scheme 1. 27. Preparation of acid-catalyzed cyclization precursors **64**.



Trimers **64** were then subject to $HClO_4$ catalyzed cyclization in dilute wet chloroform solution. This method not only allowed the preparation of 17 different

homooxacalix[3]arenes **9**, but also for the first time molecules with two and three different kinds of substituents in the *para*-position were prepared.

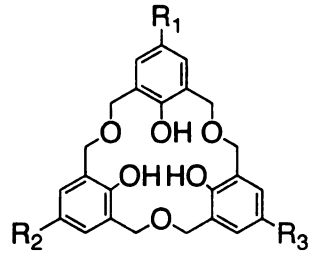
Scheme 1. 28. Acid-catalyzed homooxacalix[3]arene synthesis.



64a-r

$HClO_4$

$CHCl_3/H_2O$

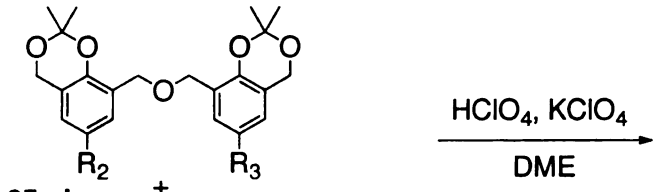


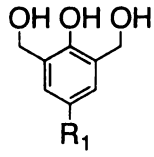
9a-w

Compound	R_1	R_2	R_3	Yield, %
9a	H	H	H	22
9j	Me	H	Me	44
9k	Et	H	Et	42
9l	*i*-Pr	H	*i*-Pr	42
9m	*t*-Bu	H	*t*-Bu	54
9n	H	*t*-Bu	H	22
9o	Me	*t*-Bu	Me	43
9p	Et	*t*-Bu	Et	50
9q	*i*-Pr	*t*-Bu	*i*-Pr	54
9b	*t*-Bu	*t*-Bu	*t*-Bu	48
9r	Me	H	Et	45
9s	Et	*t*-Bu	*i*-Pr	53
9t	OMe	OMe	OMe	20
9u	*t*-Bu	Br	*t*-Bu	51
-	Br	*t*-Bu	Bu	0
9v	Br	Br	*t*-Bu	34
9w	Br	Br	Bu	4

In 2000 the synthesis of homooxacalix[3]arenes was performed as a condensation of dimers **65** with monomers **4** (condensation of "2+1" type) in acid medium at high dilution[37].

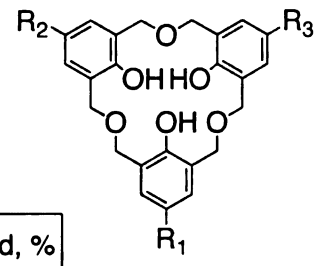
Scheme 1. 29. Acid-catalyzed "2+1" cyclization.





4a,c,d

Compound	R_1	R_2	R_3	Yield, %
9r	H	Me	Et	8
66a	H	Me	*i*-Pr	9
66b	H	Me	*t*-Bu	9
66c	H	Et	*i*-Pr	10
66d	H	Et	*t*-Bu	10
66e	H	*i*-Pr	*t*-Bu	7
66f	Me	Et	*i*-Pr	14
66g	Me	Et	*t*-Bu	16
66l	Me	*i*-Pr	*t*-Bu	13
9s	Et	*i*-Pr	*t*-Bu	20

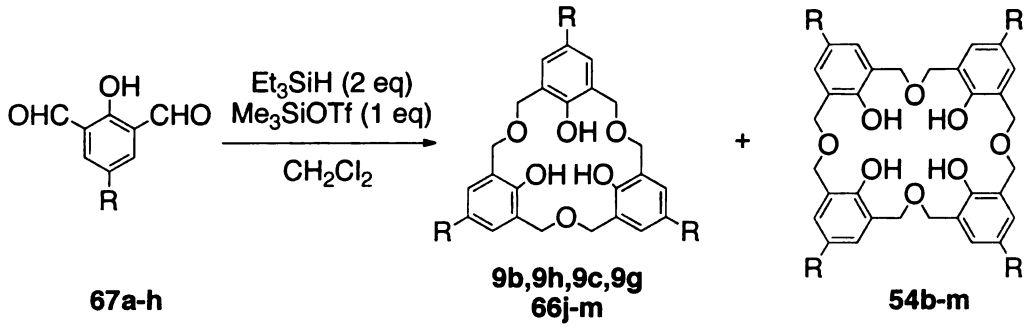


9r,9s
66a-i

This procedure was in many cases found to be more effective than linear trimer cyclization (see Scheme 1.28). Thus, compound **9s** was prepared in 6 steps and in 12.4% overall yield using "2+1" method, while a 9-step transformation including linear trimer cyclization gave target product in only 2.4% yield[36,37].

Finally, 2,6-diformylphenols were also used in the synthesis of homooxacalixarenes. In 2001 Komatsu developed a new synthetic procedure for homooxacalix[n]arenes (n = 3, 4) – reductive homo- or heterocoupling of 4-substituted-2,6-diformylphenols **67**. Treating a mixture of **67** and Me_3SiOTf in dichloromethane with triethylsilane at low temperature afforded a mixture of products **9**(**66**) and **54**[38]:

Scheme 1. 30. Reductive homocoupling of diformylphenols.



67a-h

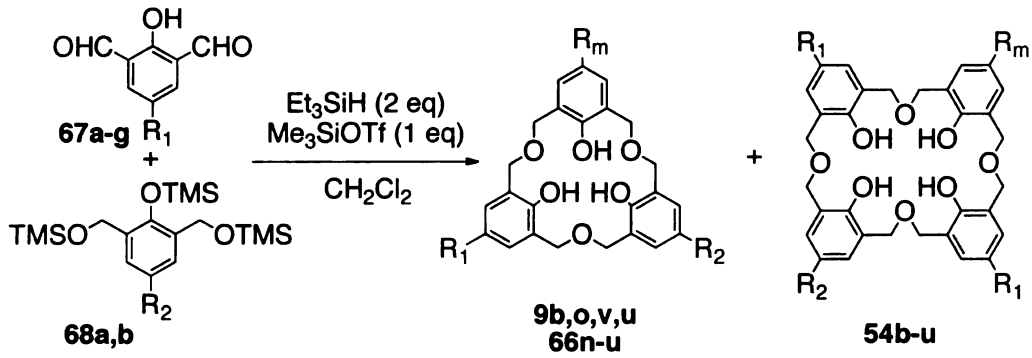
9b,9h,9c,9g
66j-m

54b-m

Compound	R	yield **9**(**66**), %	yield **54**, %
9b	*t*-Bu	38	22
9h	Me	35	12
66j	CH_2Ph	32	14
66k	Ph	11	18
66l	F	29	24
9g	Cl	29	22
9c	Br	28	26
66m	I	13	-

The reductive heterocoupling involves reaction of triethylsilane with two aromatic substrates, a substituted diformylphenol **67**, and tris(trimethylsilyl)ether of 4-substituted 2,6-bis(hydroxymethyl)phenol, **68** (Scheme 1.31).

Scheme 1. 31. Heterocoupling of diformylphenols with TMS-protected triols.

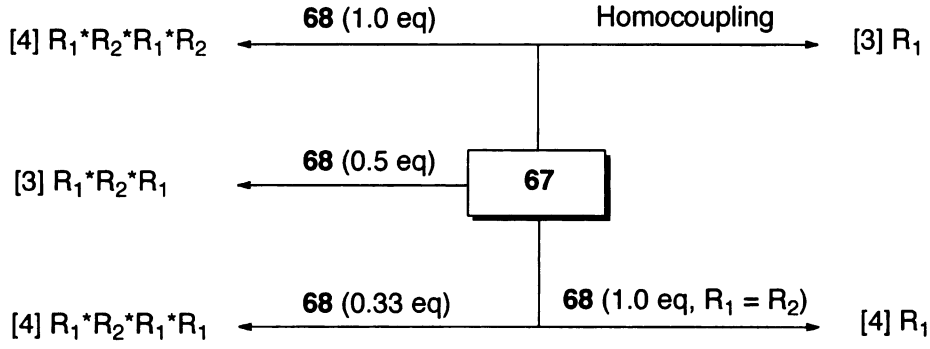


Compound	R_1	R_2	R_m	yield, %
9b	*t*-Bu	*t*-Bu	*t*-Bu	26
9o	Me	*t*-Bu	Me	19
9v	Br	*t*-Bu	Br	8
66n	CH_2Ph	*t*-Bu	CH_2Ph	15
66o	Cl	*t*-Bu	Cl	5
66p	F	*t*-Bu	F	24
9u	Br	*t*-Bu	*t*-Bu	6
66q	Me	*t*-Bu	*t*-Bu	12
66r	CH_2Ph	*t*-Bu	*t*-Bu	8
66s	Cl	*t*-Bu	*t*-Bu	7
66u	*t*-Bu	F	*t*-Bu	22

Compound	R_1	R_2	R_m	yield, %
54b	*t*-Bu	*t*-Bu	*t*-Bu	42
54n	F	*t*-Bu	F	20
54o	*t*-Bu	F	*t*-Bu	13
54p	*t*-Bu	Me	Me	28
54q	Me	*t*-Bu	*t*-Bu	32
54r	CH_2Ph	*t*-Bu	*t*-Bu	26
54s	Cl	*t*-Bu	*t*-Bu	20
54t	Br	*t*-Bu	*t*-Bu	13
54u	F	*t*-Bu	*t*-Bu	26

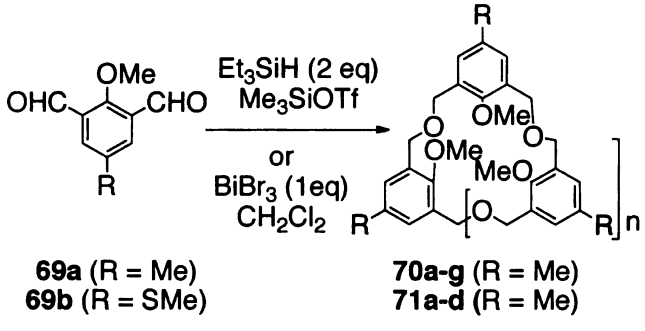
It was also shown that the ratio of initial reactants **67** and **68** significantly affected the distribution of cyclization products. The developed procedure provided a possibility, under appropriate choice of reaction conditions, initial substrates and their ratio, to prepare derivatives of homooxacalix[3]- and [4]arenes with one or two types of substituents.

Scheme 1. 32. The influence of **67/68** ratio on major product of the reaction.



Finally, the initial homocoupling conditions applied to methylated diformylphenols **69a** and **69b** afforded mixtures of homooxacalix[n]arenes having from 3 to 9 aromatic nuclei[39].

Scheme 1. 33. Synthesis of larger homooxacalixarenes.



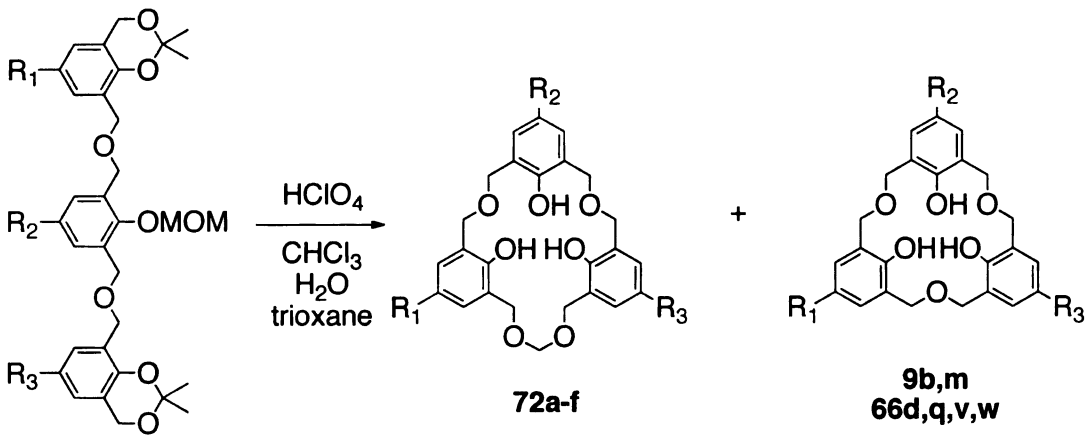
Compound	R	n	Yield, %
70a	Me	1	4
70b	Me	2	16
70c	Me	3	8
70d	Me	4	6
70e	Me	5	6
70f	Me	6	3
70g	Me	7	3
71a	SMe	2	13
71b	SMe	3	10
71c	SMe	4	8
71d	SMe	5	6

B. Larger Linkers.

The cyclization of trimers **64** in the presence of $HClO_4$ in wet $CHCl_3$ in addition to the expected products **9(66)** also afforded small amounts of derivatives of a new type of homooxacalixarenes, heptahomotetraoxacalix[3]arenes **72**. Tsubaki *et al.* studied the possibility of improving this reaction for the preparation of these compounds, and found

that addition of trioxane to the starting reagents resulted in 23-40% yield of tetraoxacalixarenes **72a-f**[40].

Scheme 1. 34. Synthesis of tetraoxahomocalix[3]arenes.



64

Compound	R_1	R_2	R_3	Yield **72**, %	Yield **9(66)**, %
72a	*t*-Bu	H	*t*-Bu	40	8
72b	*t*-Bu	Me	*t*-Bu	23	7
72c	*t*-Bu	Et	*t*-Bu	26	8
72d	*t*-Bu	*i*-Pr	*t*-Bu	29	8
72e	*t*-Bu	*t*-Bu	*t*-Bu	30	10
72f	*t*-Bu	H	Et	25	8

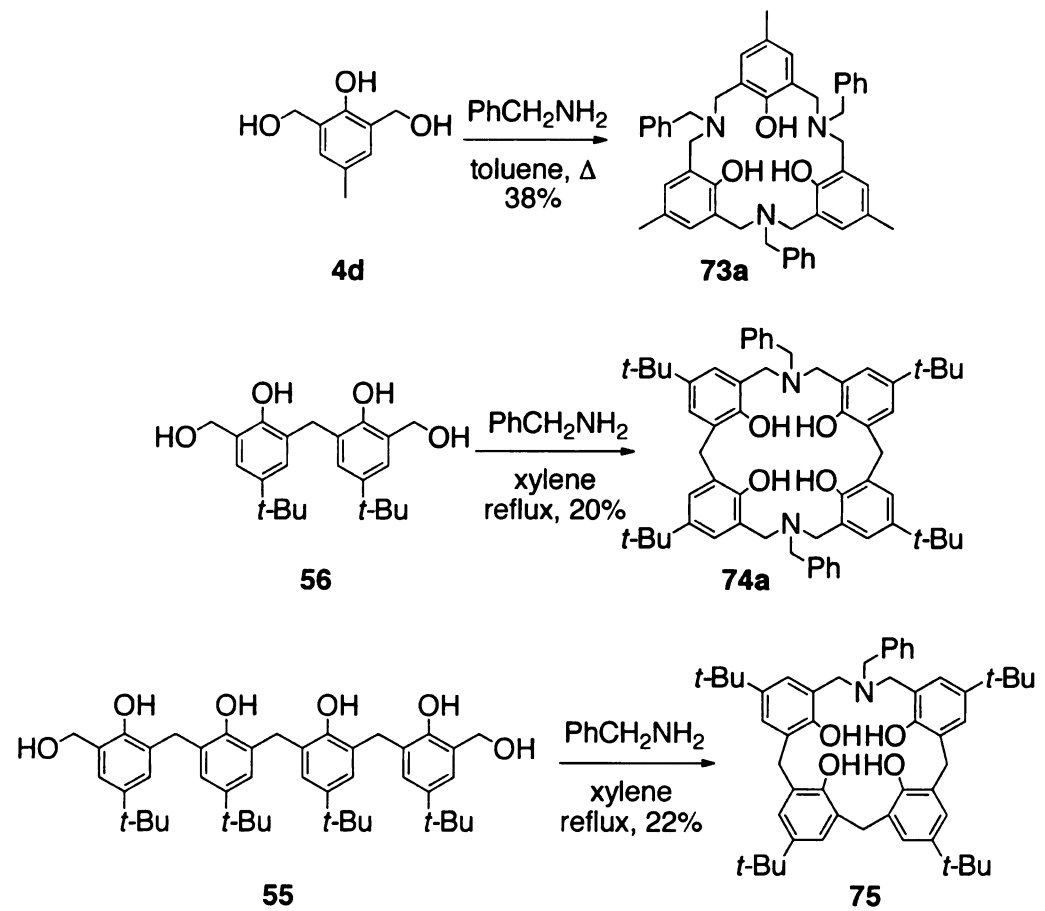
2.3. Other Heteroatoms in Homocalixarene Linkers.

A. Nitrogen.

The literature on homoazacalixarenes is more sparse than that on homooxacalixarenes, but their chemistry is in principle even richer. Both the reactivity of amino groups and the interaction of the substituents in the side arms with those on the upper and the lower rim should be considered. This can possibly increase the flexibility in designing the host molecules and ligands based on nitrogen-containing macrocycles.

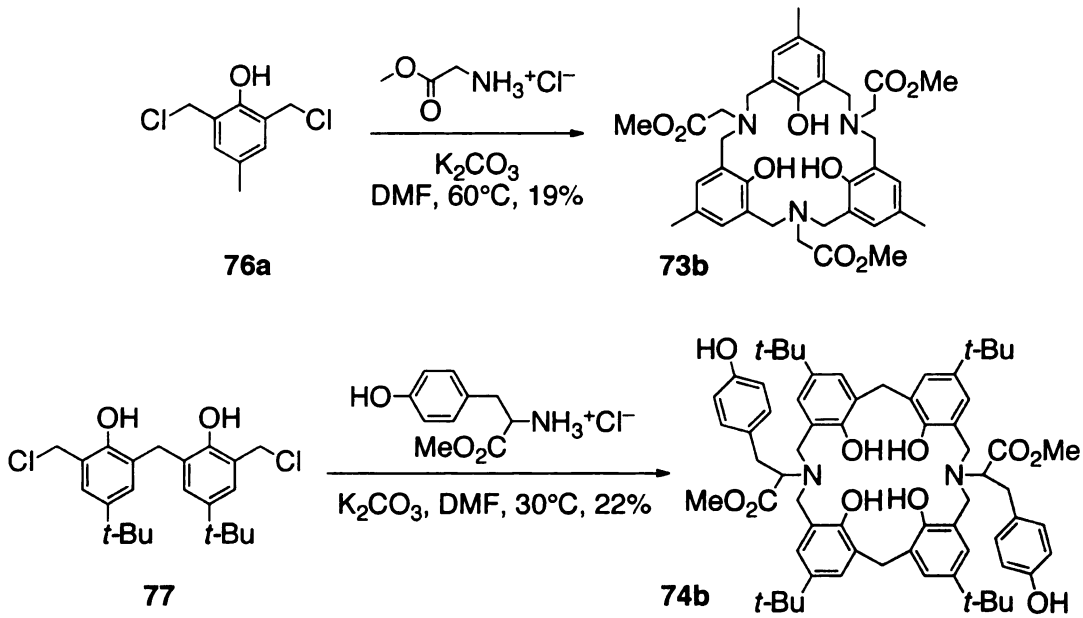
Compounds **73-75** were prepared through the thermal condensation of bis(hydroxymethyl)phenol **4d** and polyphenols **55** and **56** with alkylamines[41,42]. Water was azeotropically removed while heating relatively concentrated (~ 0.1M) solutions of the starting materials, and macrocycles **73a, 74a** and **75** were obtained in fairly good yields, apparently due to template effects from hydrogen bonding.

Scheme 1. 35. Thermal preparation of azahomocalixarenes.



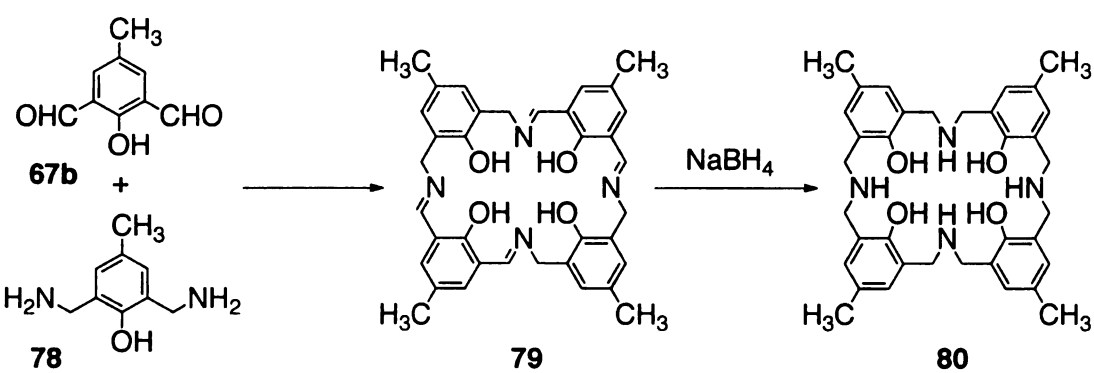
More electrophilic bis(chloromethyl)phenols **76a**[43] and **77**[44] can react with amino acid esters and their salts in presence of a base:

Scheme 1. 36. Preparation of azahomocalixarenes by nucleophilic substitution.



An N-unsubstituted azahomocalix[4]arene, **80**, was obtained through reaction of 2,6-diformyl-4-methylphenol **67b** with diamine **78** in presence of Ni(II) or Zn(II) salts, and reduction with $NaBH_4$ of the Ni_4 or Zn_4 complexes of the intermediate macrocyclic Schiff base **79**[45]:

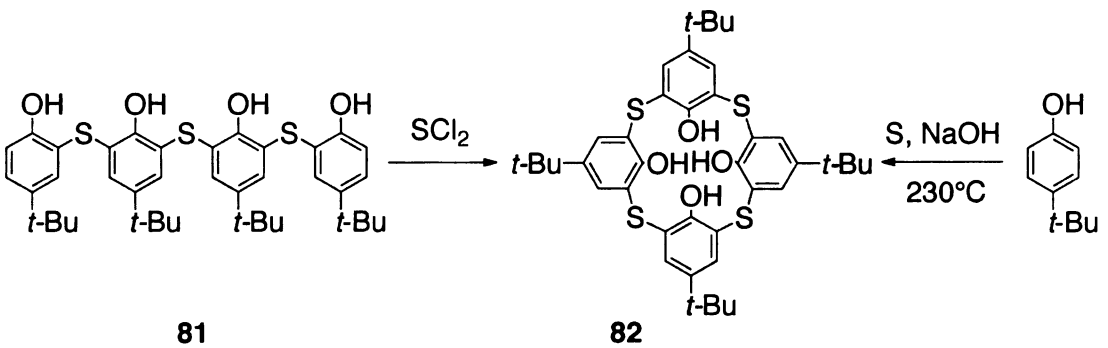
Scheme 1. 37. Unsubstituted azahomocalixarene preparation.



B. Sulfur.

Thiacalixarenes have attracted considerable recent interest as alternatives to regular calixarenes. They have been made by both stepwise and single step procedures. The tetrathiacalix[4]arene **82** was prepared in 4.1% yield by treating the linear tetramer **81** with SCl_2[46] (Scheme 1.38).

Scheme 1. 38. Thiacalix[4]arene preparation.



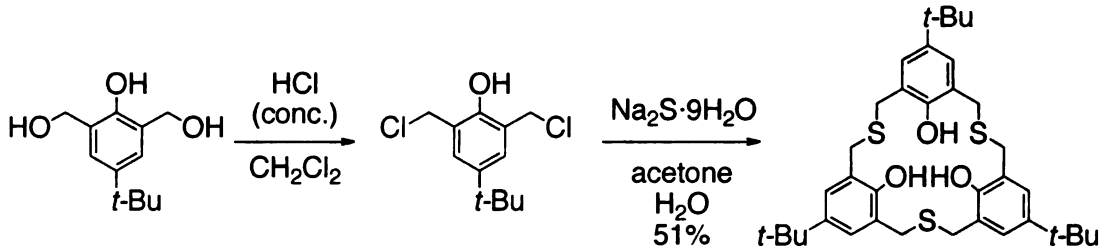
81 **82**

Much more efficient, however, is the single step synthesis in which a mixture of *p-tert*-butylphenol, elemental sulfur, and NaOH is heated to 230°C in a tetraethyleneglycol dimethyl ether solution to give **82** in yields up to 54%[47].

Homothiacalixarenes **21** and **50** already were mentioned above (Schemes 1.5, 1.16) as intermediates in the preparation of cyclophanes and homocalixarenes by the sulfur extrusion method. Their preparation is facilitated by the high nucleophilicity of sulfur atom; S_N2 reaction at high dilution provides the macrocycles in moderate yields.

More symmetrical homothiacalix[3]arenes were prepared using similar chemistry. Thus, hexahomotrithiacalix[3]arene **83a** was prepared in a simple two-stage process from 2,6-bis(hydroxymethyl)-4-*tert*-butylphenol **4a**[48]:

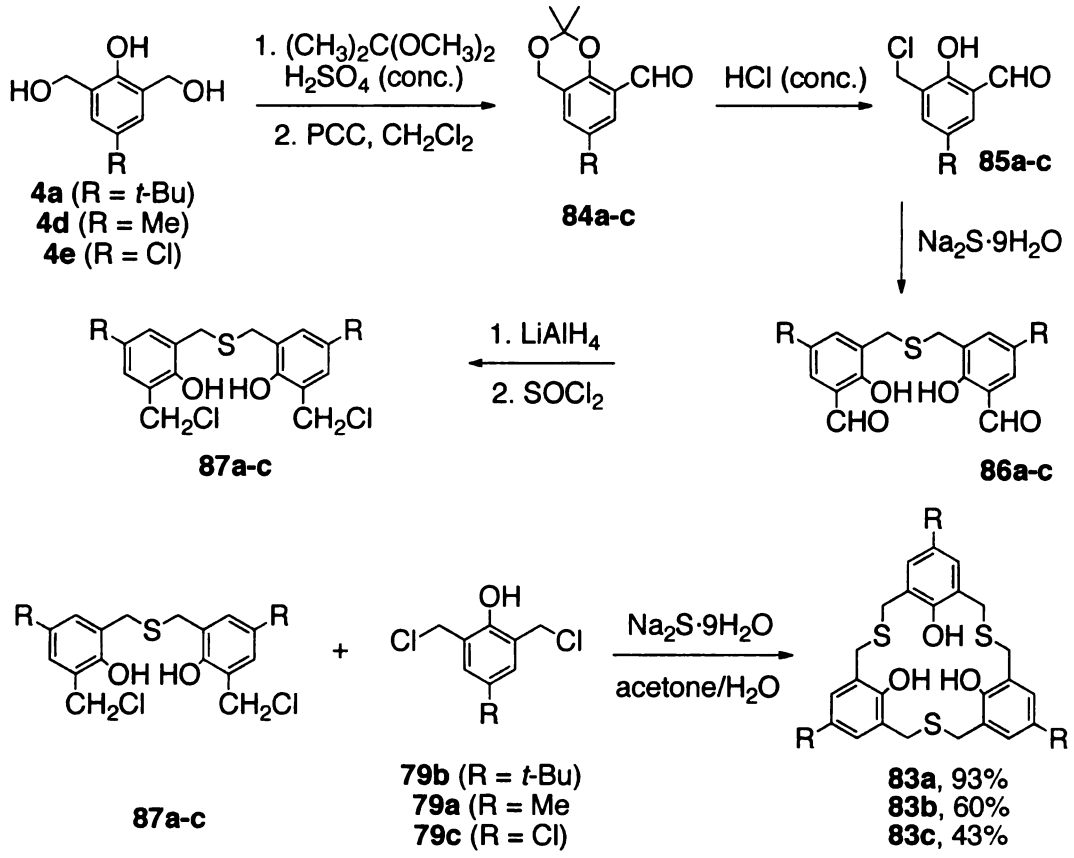
Scheme 1. 39. Thiahomocalix[3]arene preparation.



4a **76b** **83a**

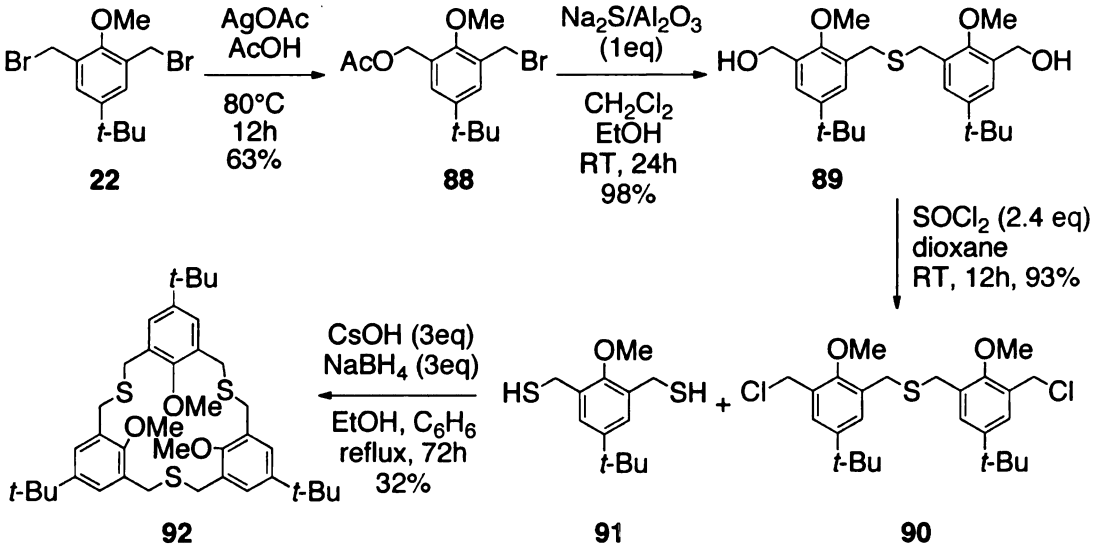
Compounds **83a-c** were also made in a "2+1" fashion using the same type of precursor – triol **4**:

Scheme 1. 40. Convergent "2+1" type synthesis of thiahomocalix[3]arenes.



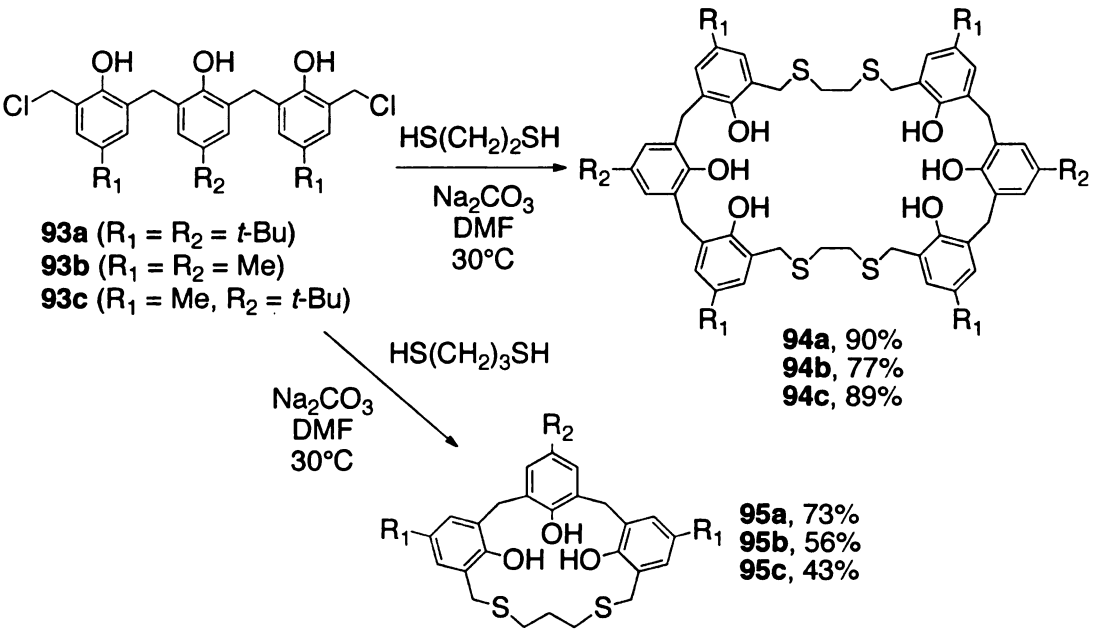
The hexahomotrithiacalix[3]arene methyl ether **92** has extremely high affinity for Ag^+ cations, and was synthesized in the following four-stage process in 18% overall yield[49]:

Scheme 1. 41. Preparation of methylated thiahomocalixarene **92**.



Other, larger homothiacalixarenes were also prepared using nucleophilic substitution reactions[50,51]:

Scheme 1. 42. Synthesis of larger sulfur-containing homocalixarenes.



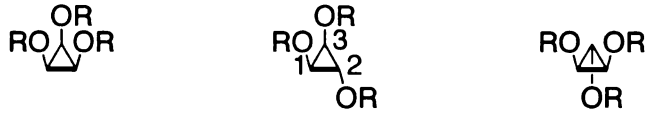
3. Homocalixarene Conformations and Receptor Properties.

Receptor (host) properties of any molecule are defined by its shape, conformational mobility, and coordination sites. Coordination sites define the forces that are responsible for binding. Often it is beneficial to have coordination sites rigidly placed at particular distances and to have symmetry that is ideal for binding; thus, shape is a very important factor in defining hosting ability. Lastly, conformational mobility often influences the *rates* of substrate coordination and release. For more dynamic coordination, more flexible hosts are preferred, while rigid systems are better for "permanent" binding.

3.1. Conformations of Homocalixarenes.

Homocalixarenes may be designated in terms of the number of benzene rings as homocalix[2]arenes, homocalix[3]arenes, homocalix[4]arenes, and higher homocalix[n]arenes. For homocalix[2]arenes ([m.n.]cyclophanes), only *syn-* and *anti-* conformers are possible. In homocalix[3]arenes, if all three benzene rings are symmetrically bridged, there are only two conformers, *cone* and *partial cone* (*paco*). However, if one of the bridges differs from the other two, two *partial cone* conformations are possible, 2-*paco* and 3-*paco*, depending on the position of substituent directed to the opposite side. Figure 1.3 illustrates the total three possible conformers, where a bold line represents the different bridge.

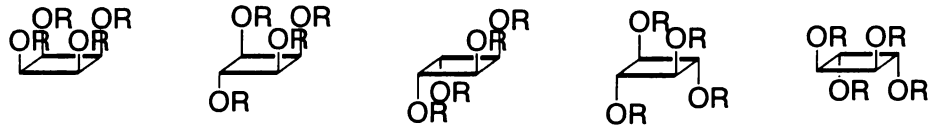
Figure 1. 3. Conformations of C_s-symmetrical homocalix[3]arene.



If all three bridges or substituents are different, there will be 3 different *partial cones*, and a total of 4 conformers.

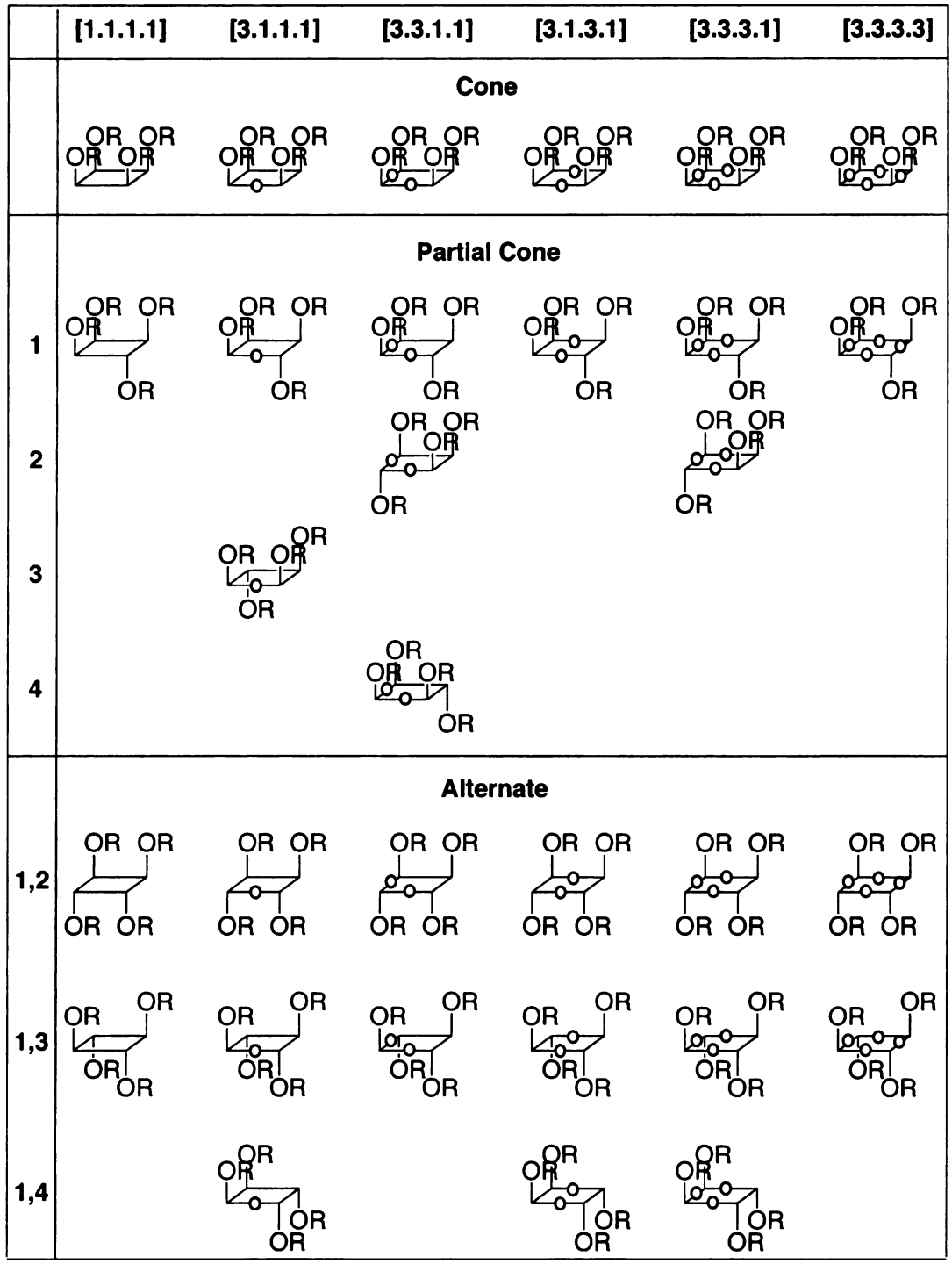
For homocalix[4]arenes with identical bridges, four conformers (*cone*, *partial cone*, *1,2-alternate,* and *1,3-alternate*) are possible, just like for normal calix[4]arene derivatives. In contrast, less symmetrical species such as [2.1.2.1]metacyclophane derivatives allow two inequivalent *1,2-alternate* conformers, differing in the location of symmetry plane. In order to distinguish them, conformers with a plane of symmetry parallel to the longer bridge and the shorter bridge can be defined as *1,2-alternate* and *1,4-alternate*, respectively. Thus, there is a total of five conformers which are illustrated in Figure 1.4, where bold lines represent the longer bridges.

Figure 1. 4. Possible conformations of [2.1.2.1]metacyclophane.



The nature of conformational isomerism for homooxacalixarenes is even more complicated than described above. The main conformations in the whole homooxacalix[4]arenes family are shown in Figure 1.5; regular calixarene is also added for comparison[52].

Figure 1. 5. Conformations of all possible oxahomocalix[4]arenes.



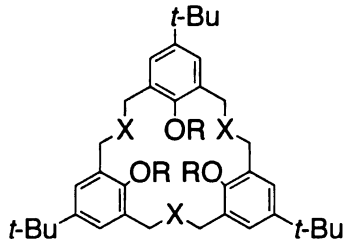
As with regular calixarenes, the conformational interconversion of homocalixarenes has been investigated by dynamic ^{1}H NMR, and the activation free energy ($\Delta G^{\neq}$) has been derived, mainly from coalescence temperatures (T_c) of suitable signals by conventional methods. The values of coalescence temperatures that can be measured with reasonable precision by this method in most of the solvents are between –90 and +150°C; thus, the calculated values of $\Delta G^{\neq}$ fall between 9 and 25 kcal/mol. Table 1.1 offers a summary of conformation properties and many different kinds of calixarenes and homocalixarenes.

Table 1. 1. Conformational and spectral properties of selected calixarenes and homocalixarenes.

Compound	IR ν(OH), cm^{-1}	^1H NMR [$CDCl_3$] δ(OH), ppm	T_c ($\Delta G^{\neq}$) °C (kcal/mol)	Reference
p-t-Bu-calix[4]arene	3160	10.19	52 (15.7) 39 (14.9) 15 (13.7)	53
p-H-calix[4]arene	-	-	36 (14.9) 18 (13.9) –22 (11.8)	–//–
p-t-Bu-calix[5]arene	3280	8.0	–2 (13.2)	–//–
p-t-Bu-calix[6]arene	3150	10.5	11 (13.3)	–//–
p-t-Bu-calix[7]arene	3155	10.3	–10 (12.3)	–//–
p-t-Bu-calix[8]arene	3230	9.6	53 (15.7)	–//–
[2.4]cyclophane	-	-	(> 25)	55
[2.6]cyclophane	-	-	(20.6)	55
[2.2.1]	-	-	60-100	56
[3.1.1]	-	-	(19.5)	22,57
Dimethoxy[3.1.1]	-	-	80 (16.7)	–//–
[3.3.3]	-	-	(< 9)	12,57
Trioxa[3.3.3]	3410	8.56	< –90 (< 9)	53
Monooxa[4]	3300	9.0, 9.7	–8 (12.9)	–//–
Dioxa[4]	3370	9.0	–24 (11.9)	–//–
Monoaza[4]	2700-3000	10.7, 11.6	(15.9) (17.8)	54
[2.1.2.1]	3418	8.8	< –40	19,20
[2.2.2.2]	3220	10.40	< –40	–//–
[3.1.3.1]	3254	9.35	0 (12.5)	–//–
[2.1.2.1.1]	3250	9.43, 9.83	85 (16.7)	–//–
[2.1.1.1.1.1]	3175, 3250, 3450	8.15, 9.76, 10.52	35 (14.5)	–//–
[2.1.2.1.2.1]	3298	8.90	–60 (~ 10)	–//–
[2.1.2.1.2.1.2.1]	3355	9.80	40 (14.4)	–//–

Through-the-annulus rotation is also strongly influenced by modifications done to the lower rim of homocalixarenes. As the substituent size increases, rotation barrier increases, and at some point the conformers become separable stereoisomers. The following table illustrates the changes of rotation barriers in homocalix[3]arene and homooxacalix[3]arene derivatives[7]:

Table 1. 2. Lower rim substituents influence on rotation barrier.



R	X = CH_2	X = O
H	flexible (T_c < –60°C)	flexible (T_c < –90°C)
Me	flexible (T_c < –50°C)	flexible (T_c < –50°C)
Et	flexible (T_c = 90°C)	flexible (T_c = 50°C)
Pr	rigid	flexible[a]
Bu	rigid	rigid

[a] The oxygen-through-the-annulus rotation is slower than the NMR timescale

Several conclusions can be drawn from the information given in Tables 1.1 and 1.2.

- The influence of upper rim substituents on rotation barrier is minimal, but lower rim substituents change the barrier a lot;
- Solvents can change rotation barrier (and conformer distribution) significantly. Basic solvents like pyridine can lower the barrier significantly by breaking the hydrogen bond network. Also, polar solvents favor polar conformers;
- Since the value of the rotation barrier is defined by both steric factors and hydrogen bonding, it does not directly correlate with intramolecular hydrogen bond strength (see values for OH groups NMR shifts and IR frequencies);
- The presence of oxygen in the linkers makes the barrier somewhat lower, despite the difference in the bond lengths between $C(sp^3)$-$C(sp^3)$, 1.54 Å and $C(sp^3)$-O, 1.43 Å. This is possibly explained by both the staggered interactions of CH_2 groups and the flexibility of ether linkages in homooxacalix[3]arene;
- Analogous homocalixarenes with nitrogen in the linkers have substantially higher rotation barrier. The reason for this is thought to lie in very strong hydrogen bonding between phenolic OH groups and nitrogen in the side chain.

The distribution of conformers becomes critically important when synthesis of receptors is attempted. If the conformers are rigid and do not inter-convert, the formation of the wrong conformers can occur which are often useless as hosts, thus, selectivity in the synthesis becomes a very important issue. For example, in the case of homocalix[3]arenes **8** or **9** (Figure 1.2), most researchers are attracted by their C_3 symmetry. Thus, only *cone* conformer is often desired.

3.2. Homocalixarenes as Ligands and Receptors.

Homocalixarenes offer great structural flexibility as receptors for neutral molecules and ions. The symmetry of the coordination centers is often an important factor; also, locking the conformation (making molecules more rigid) is used very often. Excellent hosts derived from homocalixarenes have been obtained by the introduction of functional groups similar to those found to be effective in calixarenes.

This area has been very popular recently, and a great number of publications as well as several reviews[71] on the subject are available. Thus, only several selected examples of each kind will be given.

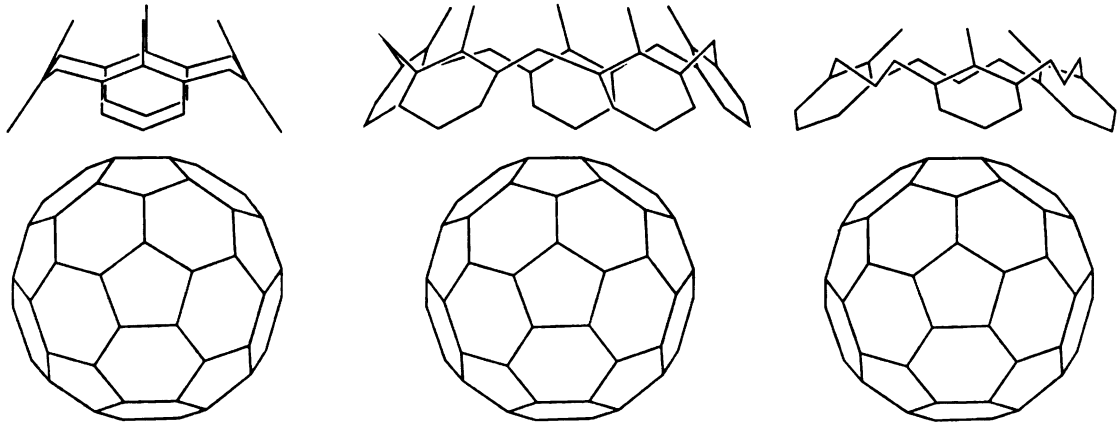
A. Neutral Molecules.

In 1994, Shinkai *et al.* and Atwood *et al.* almost simultaneously reported that *p-tert*-butylcalix[8]arene selectively includes [60]fullerene from carbon soot and forms a precipitate with 1:1 stoichiometry[58]. This was immediately used to obtain [60]fullerene in large quantities and with high purity[59]. It was believed that that the origin of selective inclusion stems from the conformity of the [60]fullerene size with the calix[8]arene

cavity. However, when this complex was solubilized (by heating or using good solvents) it dissociated into its original components, and no spectroscopic indication of complex formation could be found.

In order to find ligands that would bind fullerenes even in solution, Shinkai's group studied the problem more systematically. They screened a number of calixarenes and homooxacalix[3]arenes and studied the complex formation using UV-Vis absorption spectroscopy. It was shown that calix[5]arene, calix[6]arene, and homooxacalix[3]arene form complexes in toluene (K_{ass} are 330, 87 and 35 $dm^3\ mol^{-1}$, correspondingly)[60]. This was explained by the fact that the abovementioned calixarenes are known to exist as cone conformers in solution, and thus have a π-basic cavity of appropriate size and shape. Calix[4]arene's cavity is too small, and calix[7]- and [8]arenes adopt a *pleated loop* or a *pinched cone* conformations in solution, and thus are incapable of effective binding.

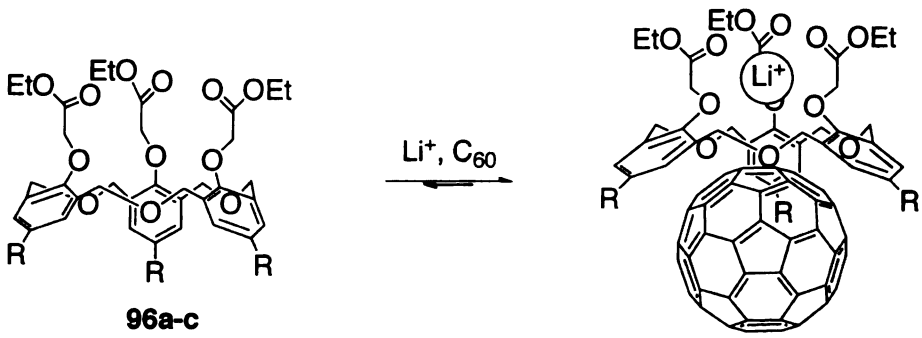
Figure 1. 6. Fullerene coordination in hydrophobic calixarene pocket.



Next, it was assumed that lower association constant for homooxacalix[3]arene can be explained by its greater conformational flexibility. Also, cooperative binding of homooxacalix[3]arene ester derivatives with [60]fullerene in presence of Li^+ cation was

studied. While esters **96** themselves don't show any binding of the fullerene, in presence of Li^+ K_{ass} between **96a** (R = *t*-Bu), **96b** (R = Br), **96c** (R = Me) and C_{60} were found to be 460, 80 and 550 dm^3 mol^{-1}, correspondingly.

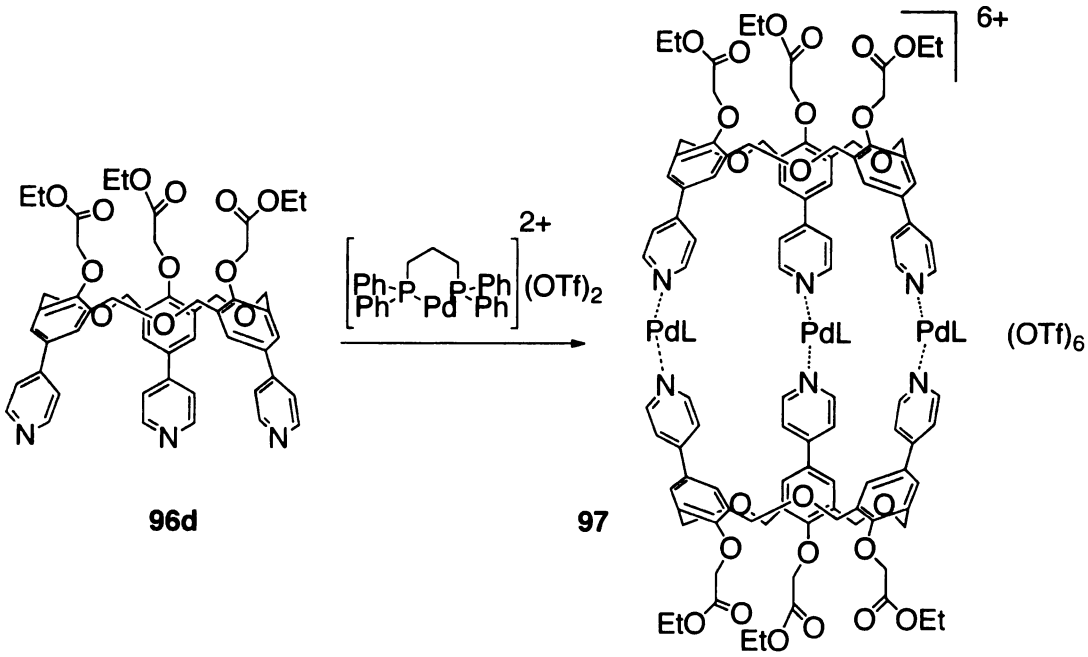
Scheme 1. 43. Fullerene coordination to esters **96** in presence of lithium ions.



96a-c

In development of these discoveries, the dimeric capsule host **97** based on homooxacalix[3]arene was prepared[61].

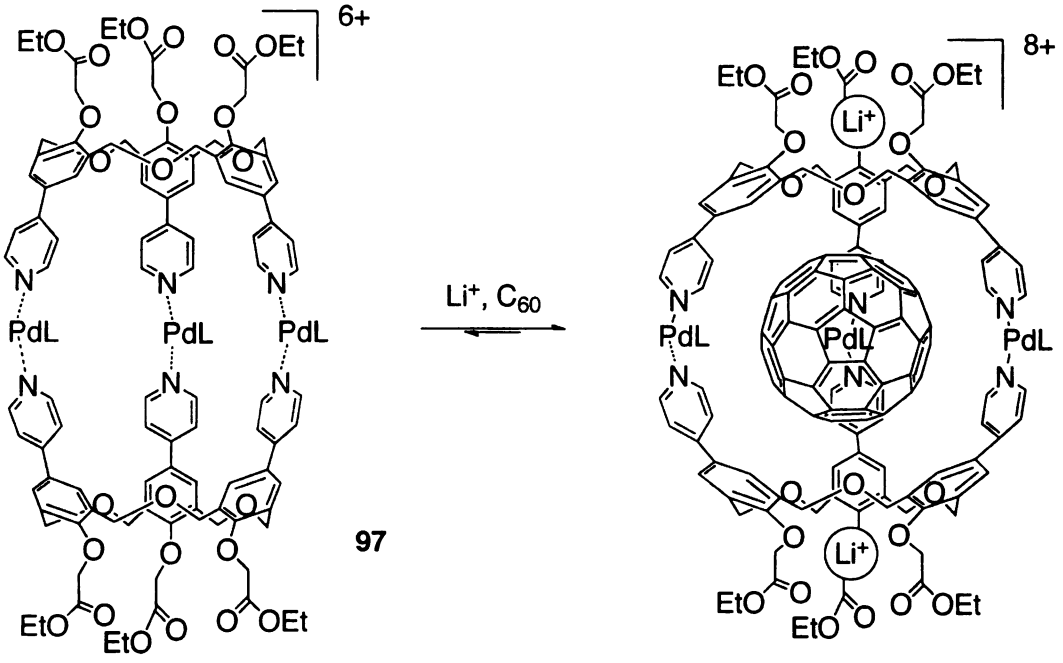
Scheme 1. 44. Dimeric palladium-based capsule preparation.



96d **97**

The association constant between **97** and [60]fullerene in toluene was found to be 39 dm^3 mol^{-1} at 30°C and 54 dm^3 mol^{-1} at 60°C. In the presence of lithium cation the binding increased dramatically, just like in case of **96a-c**. The association constant for **97**·$(Li^+)_2$ with [60]fullerene was found to be 2100 dm^3 mol^{-1}. The same constant for **97**·$(Na^+)_2$ was found to be less then 5 dm^3 mol^{-1}. Also, neither of the three – **97**, **97**·$(Li^+)_2$, or **97**·$(Na^+)_2$ – have shown any binding with [70]fullerene.

Scheme 1. 45. [60]Fullerene encapsulation by **97** in presence of lithium ions.



It was also found that the nature of interactions between the host and guest fullerene molecules changes with a change of solvent. Analyzing the changes in UV-Vis spectra of these complexes, Shinkai *et al.* came to the conclusion that in toluene most of the binding

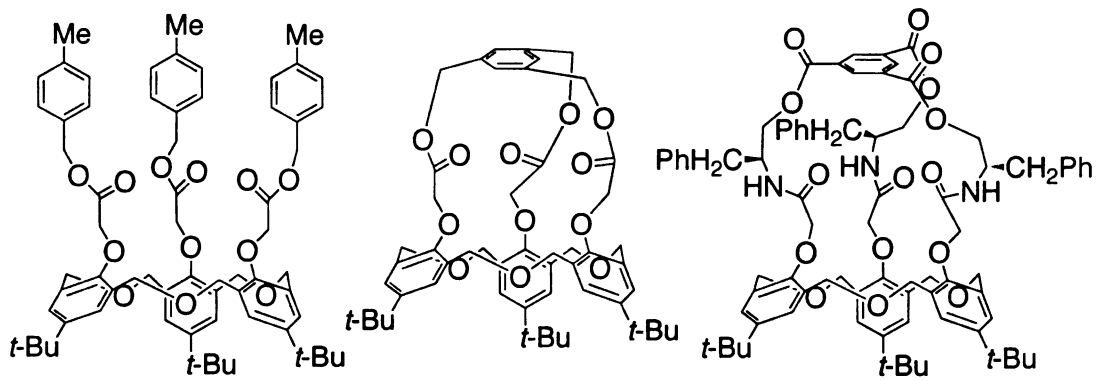
occurs due to π–π interactions, while in more polar solvent (e.g. CH_3CN) the CH(*tert*-butyl)-π interaction operates more efficiently[62].

B. Ammonium Cations.

The match in symmetry of host and guest molecule binding sites is one of the most beneficial situations for supramolecular binding. That is why homooxacalix[3]arenes that possess C_3 symmetry were often predicted to be very good receptors of primary ammonium ions, RNH_3^+.

Yamato *et al.* have studied modified homooxacalix[3]arenes for the purposes of selective primary ammonium ion binding. One of the earlier exmples includes derivative **98** and a cage-like molecule **99**[63] prepared in three steps from parent *tert*-butyl homooxacalix[3]arene (Figure 1.7).

Figure 1. 7. Receptors designed for primary ammonium ion binding.

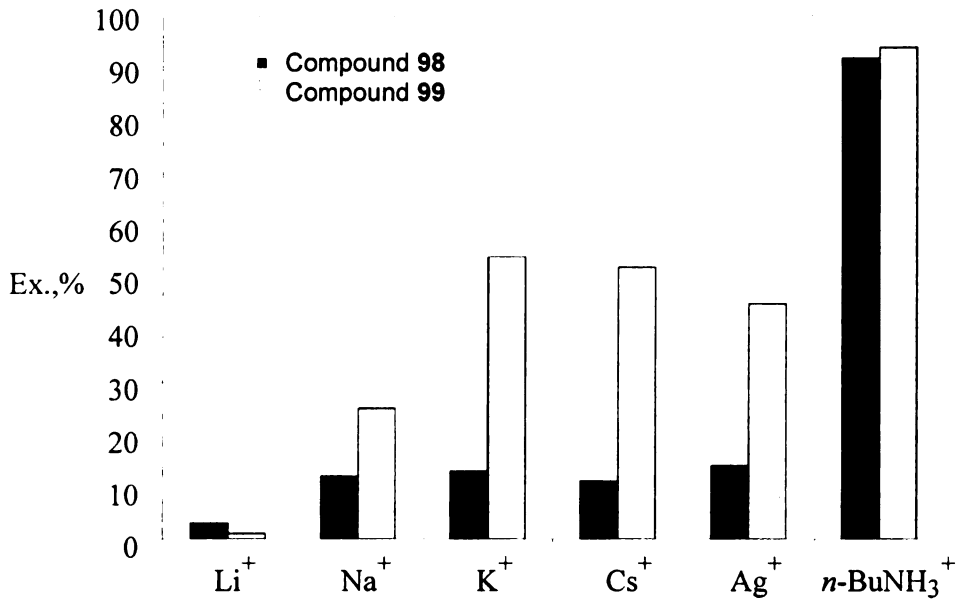


98 **99** **100**

The selectivity and effectiveness of supramolecular complexation is often accessed by extractability (Ex., %), defined as percent of cation extracted into organic phase in a

single extraction. In such expreriment, volumes of organic and aqueous phases, as well as initial concentration of ion and ionophore are equal; usually, the extracted salts are picrates. In the following Figure 1.8, molecules **98** and **99** were compared, and **98** was found to selectively extract primary ammonium ions.

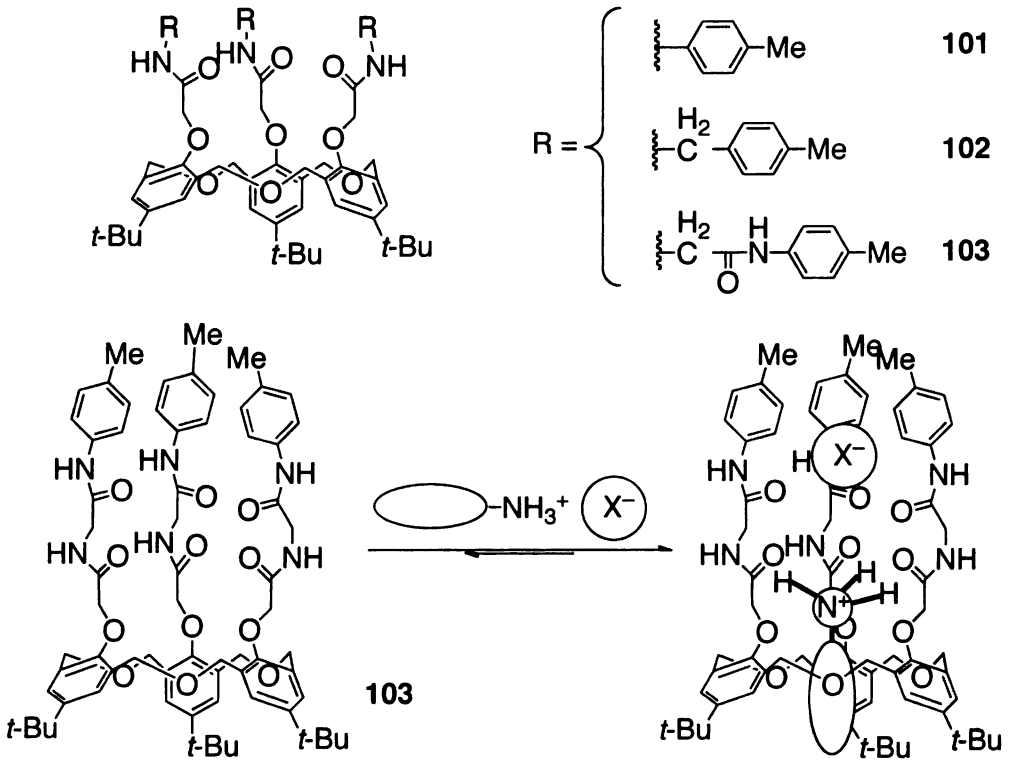
Figure 1. 8. Picrate extraction from water to organic phase.



Capped amide-based host **100** was also applied for ammonium ion binding. Compound **100** was found to bind the methyl ester of phenylalanine perchlorate 1500 times stronger then its open analog[64].

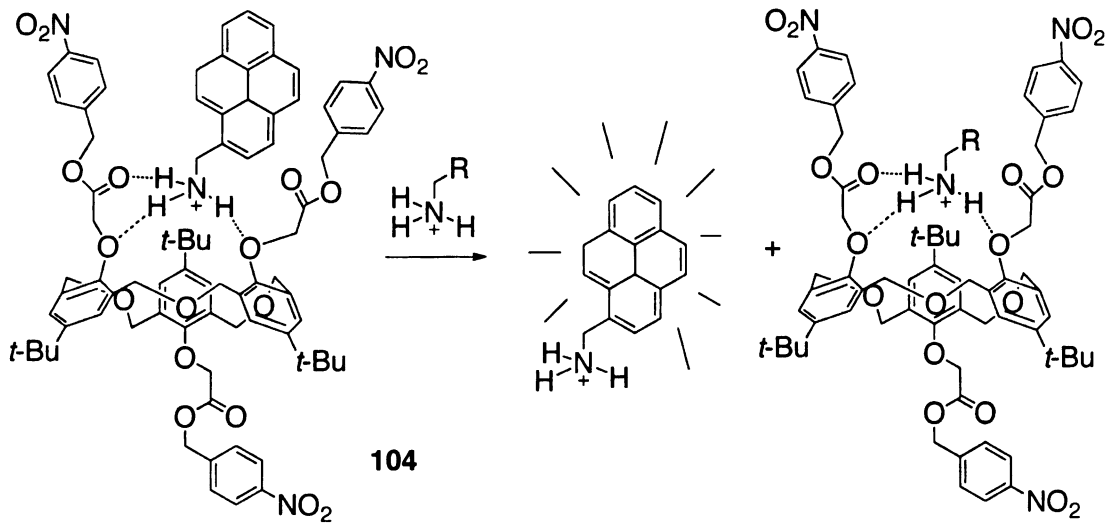
Molecular hosts **101-103** were found to be *ditopic* receptors, capable of binding both the cation and anion of primary ammonium halides (Scheme 1.46)[65] When bound, ammonium ion's aliphatic residue is situated close to hydrophobic binding pocket, the ion itself is coordinated to the amide groups, and halogen is held in the top portion of the molecule with hydrogen bonding. It is worth noticing that larger cations, such as adamantylammonium, have shown virtually no binding with the abovementioned hosts.

Scheme 1. 46. Ditopic ammonium receptors and their coordination to guest ions.



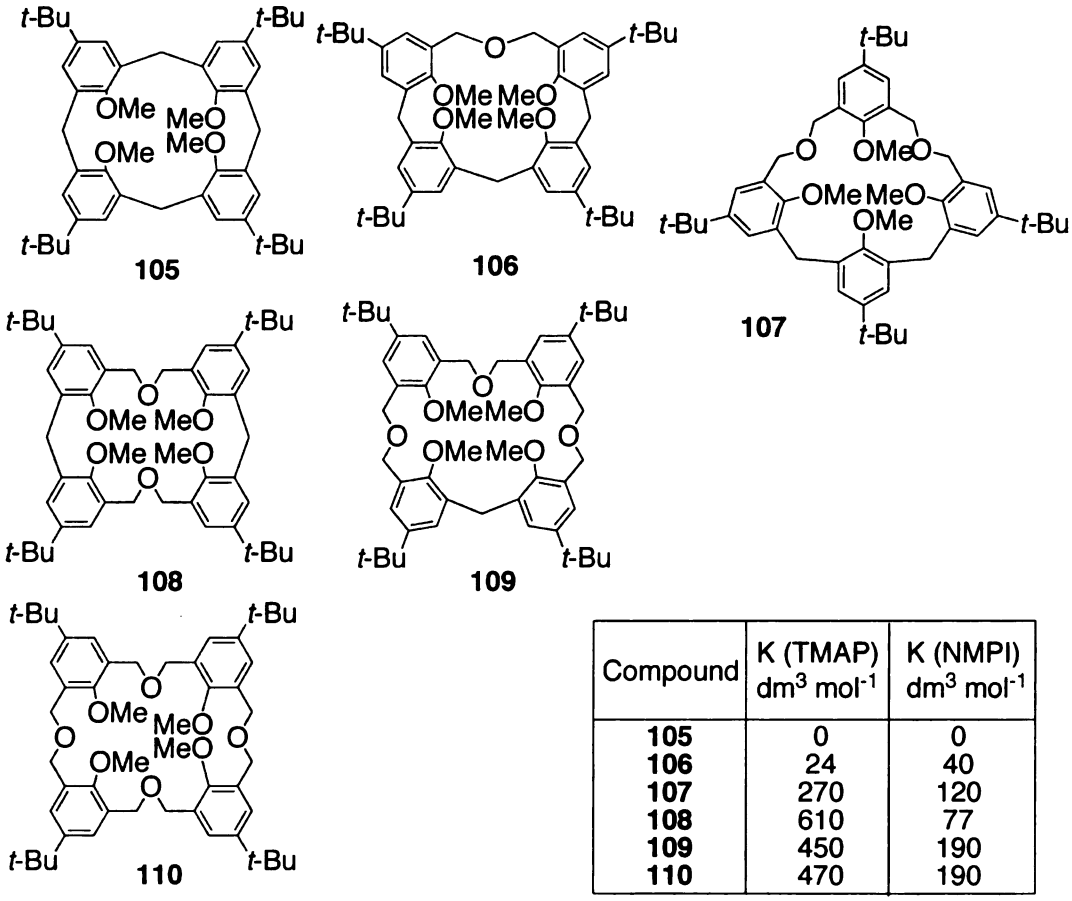
Although C_3 symmetry is of vital importance for the strongest binding, *partial cone* conformers of homooxacalix[3]arenes can also be useful in hosting ammonium cations. Ammonium ions were detected by means of fluorescence change in the pyrene functionalized amine - homotrioxacalix[3]arene **104** binary system[66]. It was shown that quantitative determination of ammonium ion microconcentrations in solution is possible due to the fact that pyrenemethylamine fluorescence is quenched by nitrogroups when it is bound to the host. When pyrenemethylamine is replaced with other cationic guests, it gives strong fluorescence.

Scheme 1. 47. The use of pyrene fluorescence for quantitative ammonium determination.



Larger homooxacalixarenes were also tested for binding of various ammonium ions. Quaternary ammonium ion binding was studied by Masci *et al.* in a number of publications, starting with unmodified macrocycles **5**, **9b** and **57** (Schemes 1.1 and 1.24, Figure 1.2), that have shown relatively weak binding to seven different quaternary ammonium ions (K_{ass} 8-90 dm^3 mol^{-1}). When phenolic OH groups were methylated, significant increase in binding was detected. A systematic study was conducted in order to determine the best cavity size; the ligands and binding measurement results are listed in Figure 1.9[68].

Figure 1. 9. Binding of tetramethylammonium picrate (TMAP) and N-methylpyridinium iodide (NMPI) by ligands **105-110**.

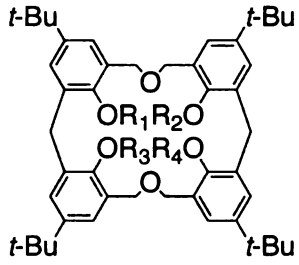


Compound	K (TMAP) $dm^3\ mol^{-1}$	K (NMPI) $dm^3\ mol^{-1}$
105	0	0
106	24	40
107	270	120
108	610	77
109	450	190
110	470	190

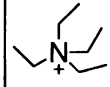
Calix[4]arene derivative **105** did not show any detectable binding.

The effect of substitution was studied in detail on derivatives of dioxahomocalix[4]arene **57** (see Scheme 1.24) such as **108**[69], which was found to have the best cavity size for quaternary ammonium ion binding:

Figure 1. 10. Quaternary ammonium ion binding by various methyl derivatives **110-111**.

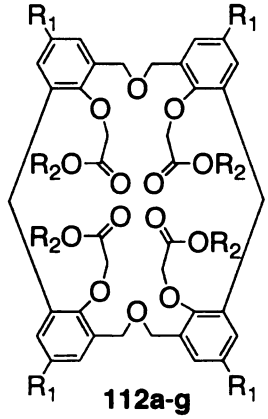


111a-f, 110

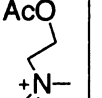
Com-pound	R_1	R_2	R_3	R_4	K_{ass}, dm^3 mol^{-1}			
								AcO 
57	H	H	H	H	15	15	30	10
111b	Me	H	H	H	110	40	120	60
111c	Me	Me	H	H	130	11	90	55
111d	Me	H	Me	H	740	15	130	190
111e	Me	H	H	Me	410	7	80	110
111f	Me	Me	H	Me	490	4	70	140
110	Me	Me	Me	Me	220	3	25	75

Still, maximum binding was found to occur when ester groups were introduced to promote additional weak binding[70]:

Figure 1. 11. Quaternary ammonium ion binding by ester derivatives **112**.



112a-g

Com-pound	R_1	R_2	Conformer	K_{ass}, dm^3 mol^{-1}		
						AcO 
112a	Ph	Et	flexible	40	-	-
112b	*t*-Bu	Me	flexible	130	25	30
112c	*t*-Bu	Et	flexible	190	45	50
112d	*t*-Bu	*i*-Pr	cone	95	20	25
112e	*t*-Bu	*i*-Pr	paco	3200	650	1000
112f	*t*-Bu	*i*-Pr	1,4-alternate	1900	200	370
112g	*t*-Bu	*t*-Bu	cone	2100	560	760

It is interesting to notice that fixed *partial cone* isomer **112e** was found to be the most effective host in the series, significantly surpassing the *cone* isomer. This was explained using X-ray diffraction data from crystals of the empty *cone* conformer; the *cone* macrocycle was found to be imperfectly preorganized for binding, with one of the *tert*-butyl groups partly occluding the cavity.

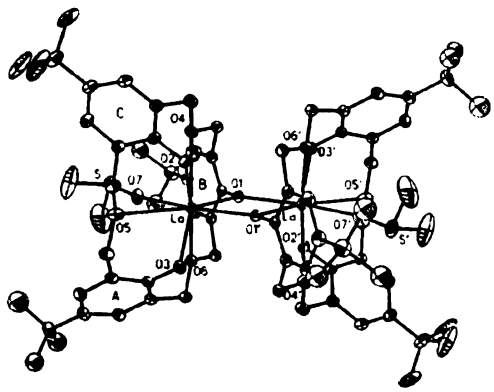
C. Metal Cations.

Numerous metal complexes with homocalixarenes were prepared in crystalline form in order to study the nature of bonding with these ligands. Homooxacalixarenes were most popular, because of both availability and additional oxygen coordination centers[71].

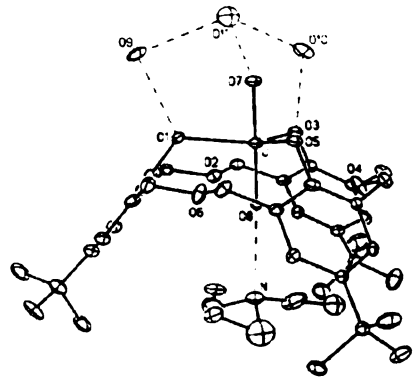
Homooxacalix[3]arenes **9b** (R = *t*-Bu), **9g** (R = Me), **9h** (R = Cl) (see Scheme 1.21) and others form complexes with a number of metal ions, including very stable compounds with trivalent metals. The constants of complex formation grow in the following sequence: Na^{+}, Li^{+}, $Ca^{2+} < Mg^{2+} < La^{3+} << Y^{3+} < Lu^{3+} << Sc^{3+}$, and the constants for ligand **9b** are smaller then those of **9h**[72]. With growing ion size the number of coordinated oxygen atoms increases. In the complex of **9b** with La^{3+} all three ether oxygen atoms are involved, and the complex is octacoordinate[73]. The macrocyclic ligand **9** assumes the cone conformation resembling that of "classic" calixarenes in their complexes with metals. The X-ray diffraction data obtained indicate that "degree of cupping" (the ring tilt angle) increased with growing metal ion size. The study of the ability of macrocycles **9b** and **9h** to transfer cations Li^{+}, Mg^{2+}, and Sc^{3+} through a liquid membrane showed that oxacalixarene **9h** selectively transferred scandium ion (44%) from solutions containing also lithium (transfer < 0.5%) and magnesium (< 0.2%).

Unmodified, large homocalixarenes and homooxacalixarenes were extensively used in preparation of complexes of uranium (IV), (V) and (VI) due to large ligand cavity sizes and uranium oxophilicity. These are probably the most studied homocalixarene metal compexes up to date.

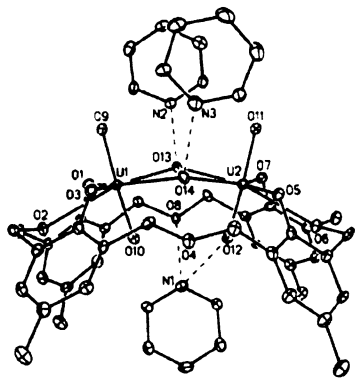
Figure 1. 12. Examples of crystal structures involving homocalixarenes as ligands ($\mathbf{L_1}$ - trianion of **9b** (see Scheme 1.21), $\mathbf{L_2}$ – tetraanion of **54g** (see Scheme 1.26), $\mathbf{L_3}$ – tetraanion of **37** (see Scheme 1.12), $\mathbf{L_4}$ – dianion of **9g** (see Scheme 1.21)).[74-79]



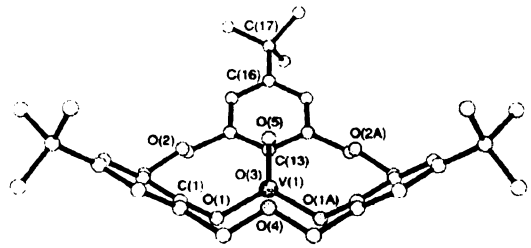
$La(\mathbf{L_1})(DMSO)]_2 \cdot (CH_3CN)_2(H_2O)$



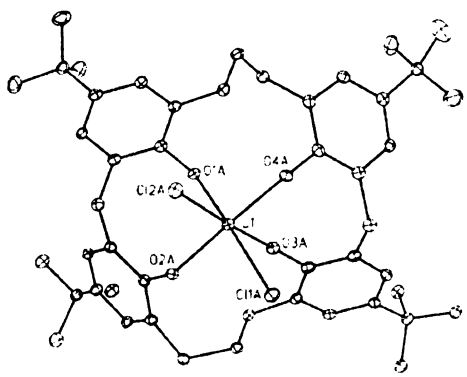
$[UO_2(\mathbf{L_1})(HNEt_3)] \cdot (H_2O)_3$



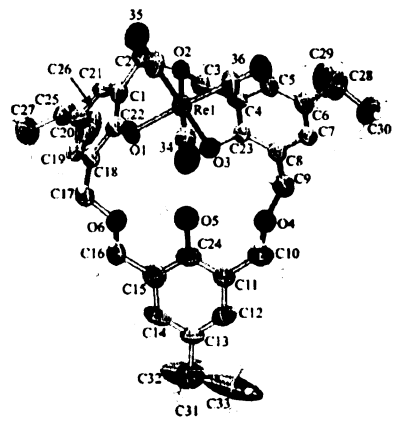
$[(UO_2)_2(\mathbf{L_2})(Hpy)(OH)(H_2O)] \cdot 2.5py$



$[VO(\mathbf{L_1})]$



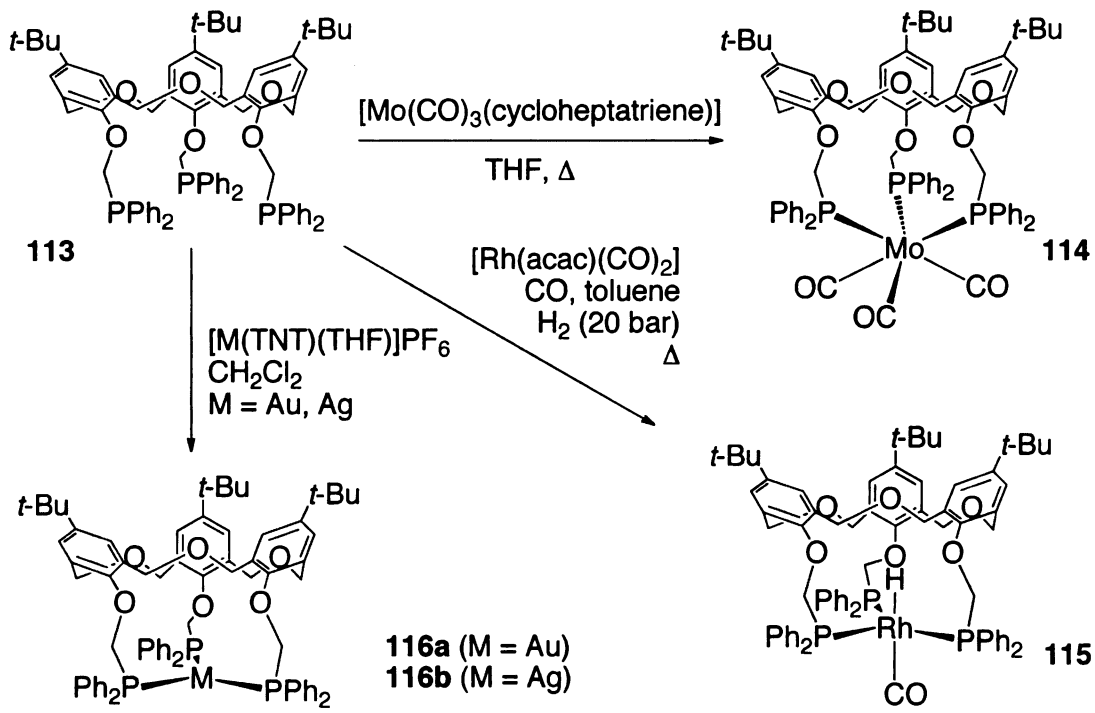
$[UCl_2(\mathbf{L_3})(Hpy)] \cdot 2.5py$



$[Re(CO)_3\mathbf{L_4}]^-$ anion

Phosphine containing macrocycle **113** was found to be an excellent ligand for "softer" metal cations (including noble metals such as silver, gold and rhodium). Complexes **114**, **115** and **116** were obtained in very high yield[80].

Scheme 1. 48. Synthesis of phosphine-based homooxacalix[3]arene **113** metal complexes.

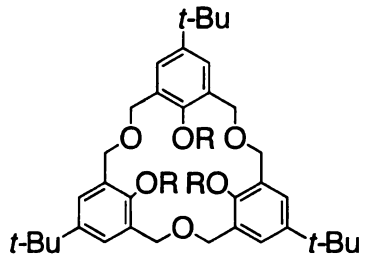


It is interesting to notice that rhodium complex **115** has it's hydride concealed inside the macrocycle cavity, and the ^{1}H NMR shift of this atom is as low as –9.6 ppm.

Metal ion selective extraction and complex formation in solution also was studied in much detail, with many modifications done to homocalixarene binding sites. As it was shown earlier, substitution of phenolic OH groups with ester and especially amide groups strongly increases ionophoric properties. Neutral ligands **117** and **118** that were among the first homooxacalix[3]arene derivatives studied as metal receptors were found

to bind alkali and alkali earth metals very well, with selectivity leaning towards the latter (Figure 1.13)[81].

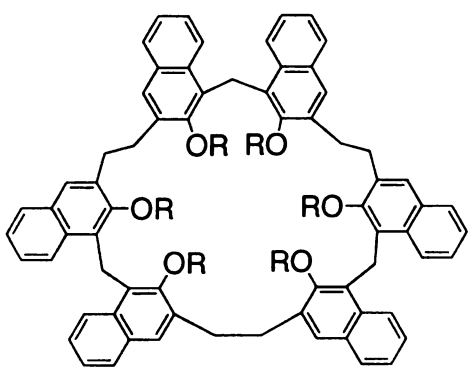
Figure 1. 13. Binding of alkaline and alkali earth metals by ester and amide homooxacalix[3]arene derivatives.



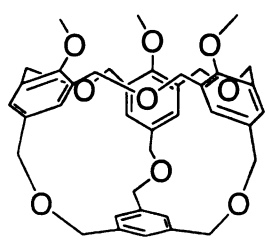
Comp.	R	Conf.	log K_{ass}						
			Na^+	K^+	Rb^+	Cs^+	Mg^{2+}	Ca^{2+}	Ba^{2+}
117a	CH_2CONEt_2	*cone*	>7	5.9	5.5	5.2	4.9	>7	>7
117b	CH_2CONEt_2	*paco*	5.1	6.2	6.0	5.5	-	-	-
118a	CH_2COOEt	*cone*	4.0	4.7	4.2	3.9	<2	<2	<2

Ligands **119**[82], **120a**[83] and **121a**[84] show very good selectivity towards potassium, cesium and silver, correspondingly.

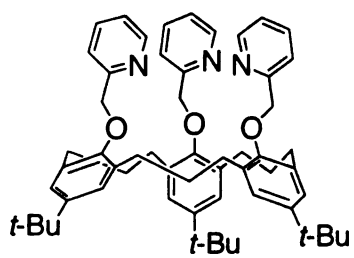
Figure 1. 14. Metal-selective ligands **119**, **120a** and **121a**.



119 (R = CH_2CO_2Et)

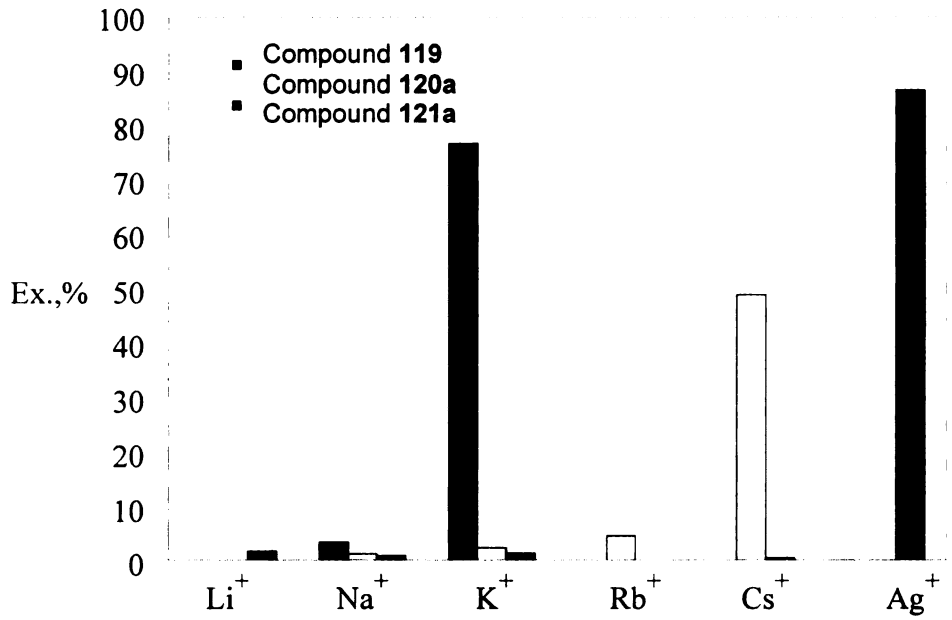


120a



121a

Figure 1. 15. Selective extraction of metal cations.



Many more extraction studies have been done, and often excellent selectivities were achieved. Even though this area is far from reaching its full potential, homocalixarenes were already called "macrorings with nearly unlimited opportunities", and are often referred to as "the third generation of hosts"[85].

4. Ring Modification of Homocalixarenes.

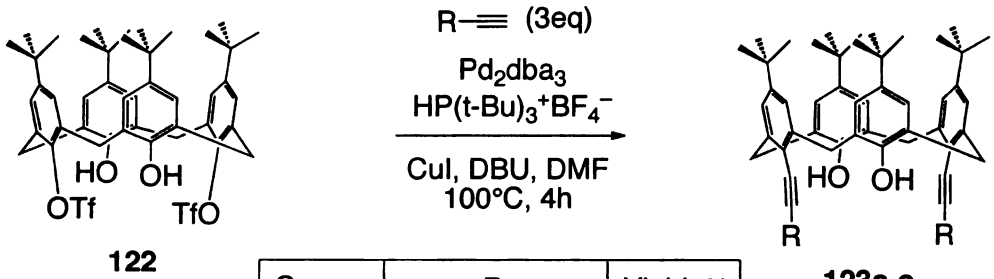
4.1. Goals and Challenges of Calixarene Ring Functionalization.

As it can be seen in the Section 3 of the current Chapter, very often effective usage of homocalixarenes requires introduction of additional functional groups. The options are limited to three choices:

- upper rim modification;
- lower rim modification;
- methylene linkers modification.

Lower rim modification requires breaking the hydrogen bond network, and any kind of substitution or coupling is complicated by significant steric hindrance. Vast majority of lower rim modifications do not replace the phenolic oxygen. The only known example of consistent and effective introduction of carbon substituent into calix[4]arenes is described in Scheme 1.49. Sonogashira reaction using a bulky tri(*tert*-butyl)phosphine as palladium ligand was used, and harsh conditions (DMF, 100°C) were also required[86].

Scheme 1. 49. Sonogashira reaction use for calix[4]arene modification.



122

123a-e

Comp.	R	Yield, %
123a	C_6H_5	89
123b	4-$MeOC_6H_4$	75
123c	4-MeC_6H_4	65
123d	4-$CF_3C_6H_4$	70
123e	3,5-$(CF_3)_2C_6H_3$	75

As can be seen from Table 1.2, introduction of large enough substituents in the lower rim makes conformer interconversion impossible. Thus, the problem of selective preparation of the necessary stereoisomer is also often present.

Upper rim modification is much more common, and has almost no limitations. Numerous couplings, selective and total substitutions have been reported. Upper rim substituents generally do not change "through the annulus" rotation barrier to any significant extent, which also reduces possible complications.

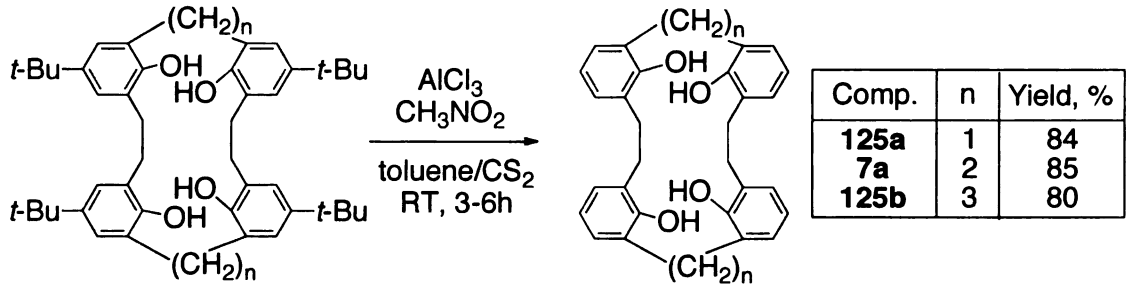
Modification of methylene linkers is very rare, and mostly occurs as a result of particular synthetic method used for preparation of the homocalixarene. Some examples can be seen in Schemes 1.7 and 1.9. This kind of homocalixarene derivatization will not be discussed here in detail.

4.2. Upper Rim Modification.

A. Homocalixarenes.

Since *tert*-butyl substituted calixarenes are by far the easiest to obtain, one of the first known upper rim transformations in calixarene chemistry was a *tert*-butyl group removal by *ipso*-substitution. The same transformations can be performed with homocalixarenes. For example, unsubstituted homocalix[4]arenes **125a-b** and **7a** were prepared in good yields from their tert-butylated derivatives (Scheme 1.50)[11].

Scheme 1. 50. *Tert*-butyl group electrophilic removal from homocalixarenes.

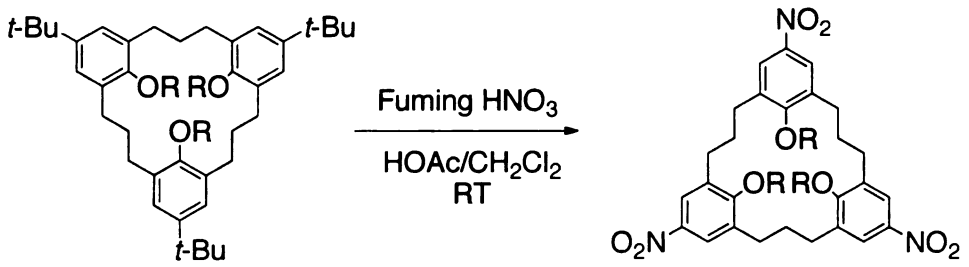


Comp.	n	Yield, %
125a	1	84
7a	2	85
125b	3	80

124a, 7b, 124b **125a, 7a, 125b**

Electrophilic *ipso*-substitution was found to be an effective way of nitro group introduction. The protection of phenolic hydroxy groups was required, and while ester and ether groups were stable under nitration conditions, amide derivatives **121e** and **121f** gave no identifiable products:

Scheme 1. 51. *Ipso*-substitution of *tert*-butyl by nitration.

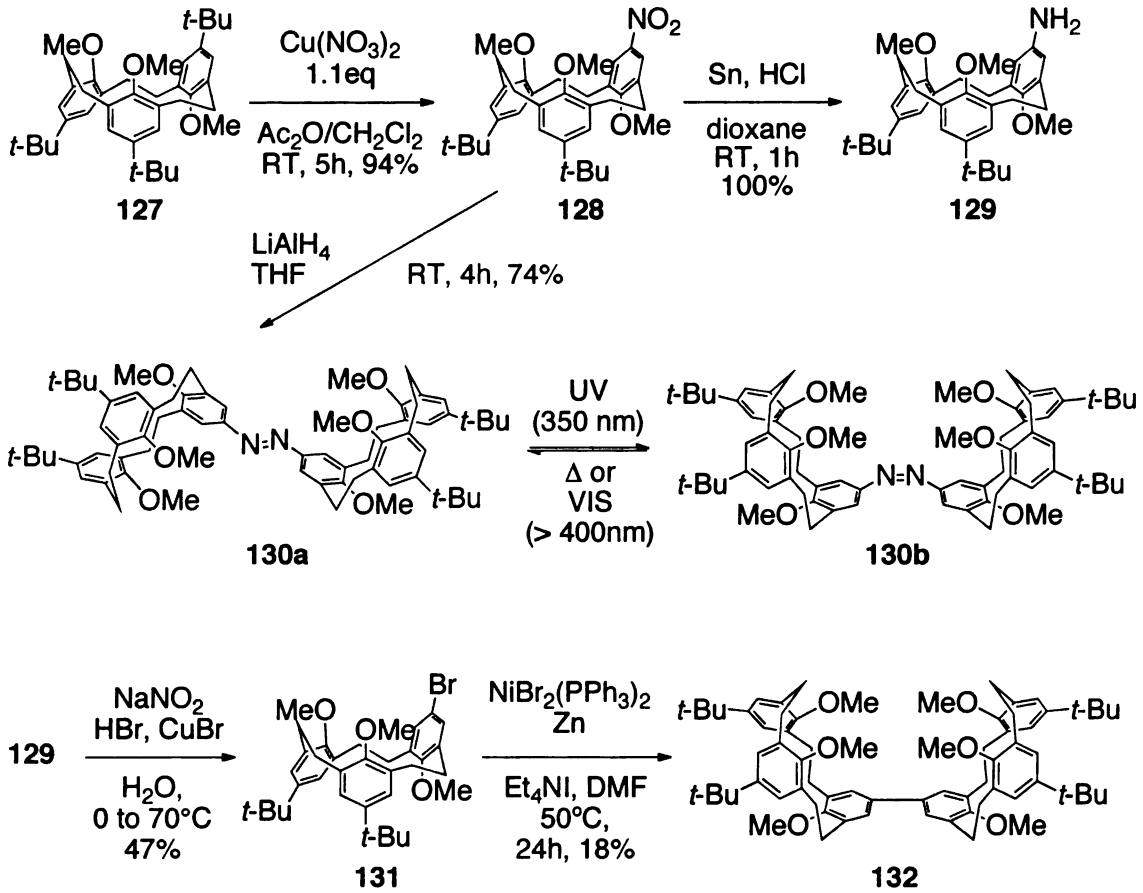


121c-f **126a-f**

Compound	R	Conformation	Reaction time (h)	Yield of **126**, %
126a	Me	flexible	0.5	95
126b	Bu	*paco*	0.5	90
126c	CH_2COOEt	*cone*	2.0	90
126d	CH_2COOEt	*paco*	0.5	89
126e	CH_2CONEt_2	*cone*	0.5	0
126f	CH_2CONEt_2	*paco*	0.5	0

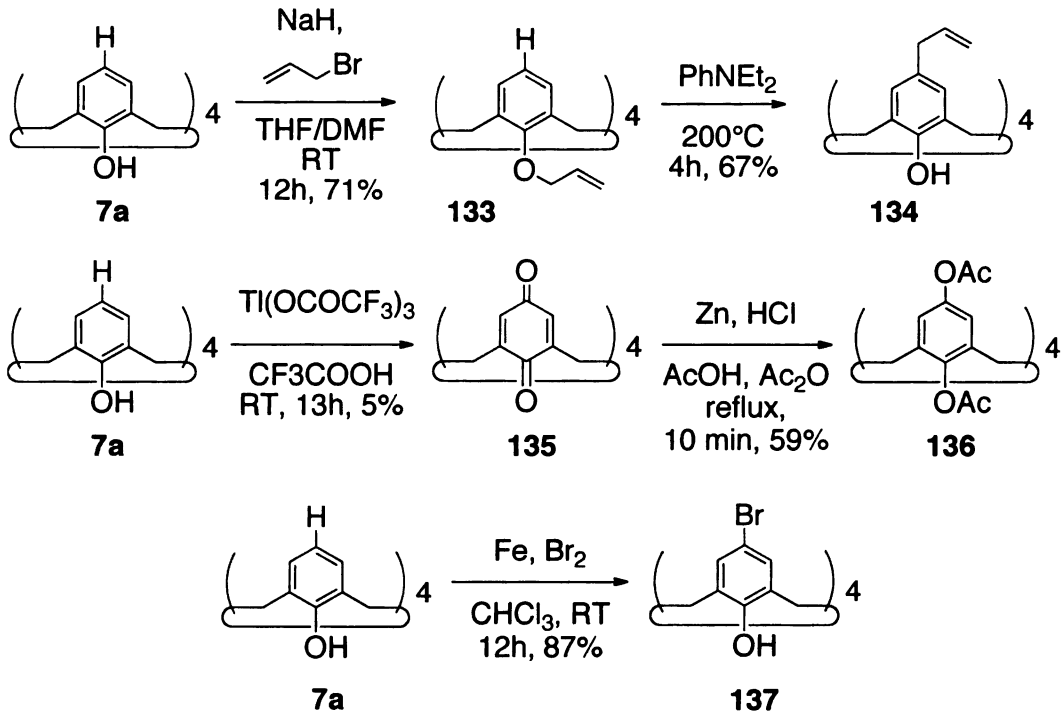
Another *ipso*-nitration, selective monosubstitution with copper (II) nitrate, was used for a fairly complex derivatization of homo[3]calixarene **127**, leading to the preparation of *molecular tweezers* **130** and **132** (Scheme 1.52)[88]:

Scheme 1. 52. Preparation of molecular tweezers from [2.2.2]cyclophane **127**.



In case of unsubstituted homocalixarenes, typical phenol transformations can be used effectively to introduce substituents in *para*-position. Bromination, oxidation and Claisen rearrangement gave products **134**, **136** and **137** (Scheme 1.53)[11].

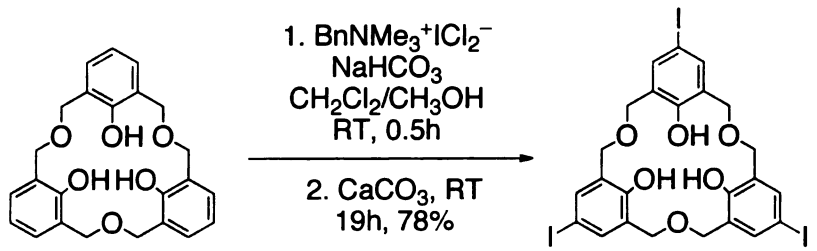
Scheme 1. 53. All-homocalix[4]arene derivatization.



B. Homooxacalixarenes.

Homooxacalixarenes cannot be ridden of *para-tert*-butyl group in the abovementioned way (Scheme 1.49) due to competing Lewis acid catalyzed ring opening reactions. This partly explains the necessity of synthetic methods described in Schemes 1.27, 1.28 and 1.30. Similar reasons make electrophilic substitution in presence of Lewis acid difficult. Still, if the reaction can proceed without such catalyst – for example, iodination with $BnNMe_3^+ICl_2^-$, it can be used effectively for substituent(s) introduction[89]:

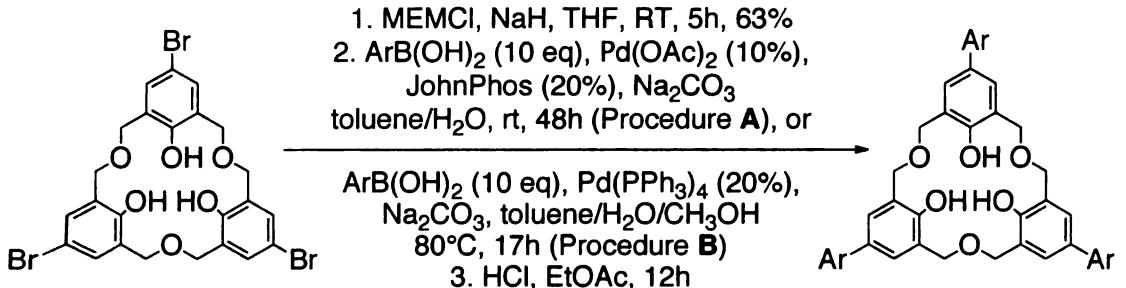
Scheme 1. 54. Mild iodination of homooxacalix[3]arene **9a**.



9a **66m**

Suzuki-Miyaura coupling was also effectively used on halogenated homooxacalixarenes; numerous aromatic substituents were introduced (Scheme 1.55)[90].

Scheme 1. 55. Suzuki-Miyaura coupling applied to upper rim modification of **9**.



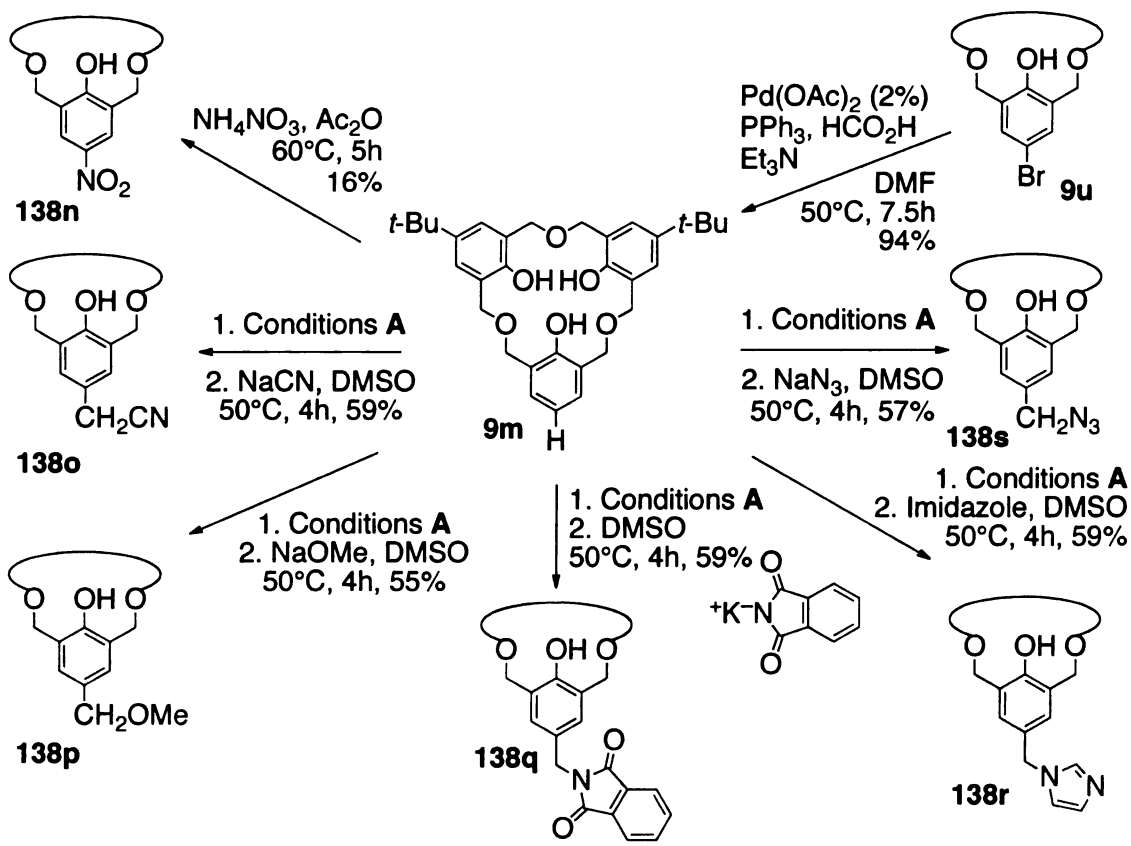
9c **138a-m**

Compound	Ar	Procedure	Yield of **138**, %
138a	Ph	**A**	77
138b	*p*-Me-C_6H_4	**A**	90
138c	*p*-MeO-C_6H_4	**A**	89
138d	*p*-F-C_6H_4	**A**	74
138e	*o*-NC-C_6H_4	**B**	36
138f	*p*-CHO-C_6H_4	**B**	59
138g	*p*-O_2N-C_6H_4	**B**	62
138h	*o*-MeO-C_6H_4	**B**	78
138i	*o*-HO-C_6H_4	**B**	67
138j	*o*-EtO_2C-C_6H_4	**B**	63
138k	*o*-MeCONH-C_6H_4	**B**	43
138l	3-Pyridinyl	**B**	50
138m	4-Pyridinyl	**B**	60

The Mannich reaction was applied for homooxacalix[3]arene monofunctionalization. Mono-unsubstituted homooxacalix[3]arene **9m** can be prepared by either acid-catalyzed

"2+1" condensation (see Scheme 1.28), or by palladium-catalyzed reduction of bromohomooxacalix[3]arene **9u**. The latter is also obtained by "2+1" condensation[91].

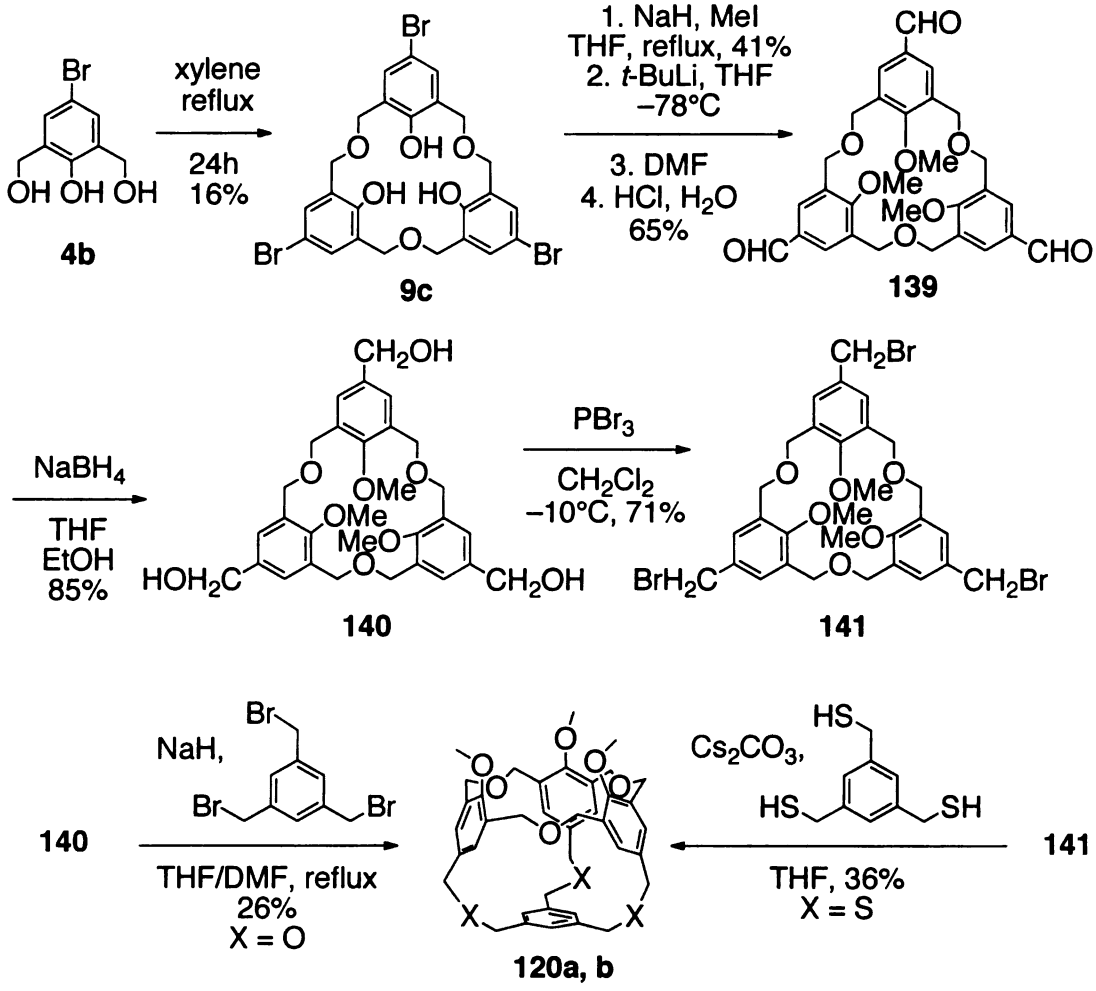
Scheme 1. 56. The use of Mannich reaction for selective derivatization of **9m**.



Conditions **A**: 1.Me_2NH, HCHO, AcOH, 80°C, 17h; 2. MeI, DMSO, RT, 40 min

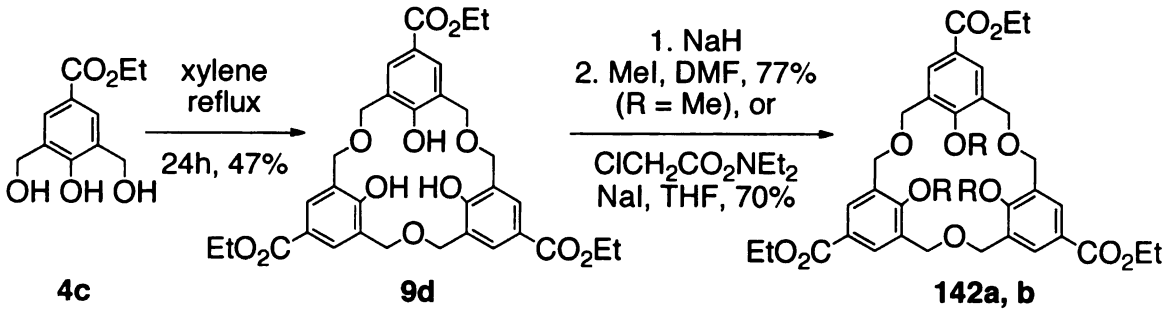
The abovementioned capped ligand **120a** and its sulfur analog **120b** was prepared from bromocalixarene **9c** in the following way[83]:

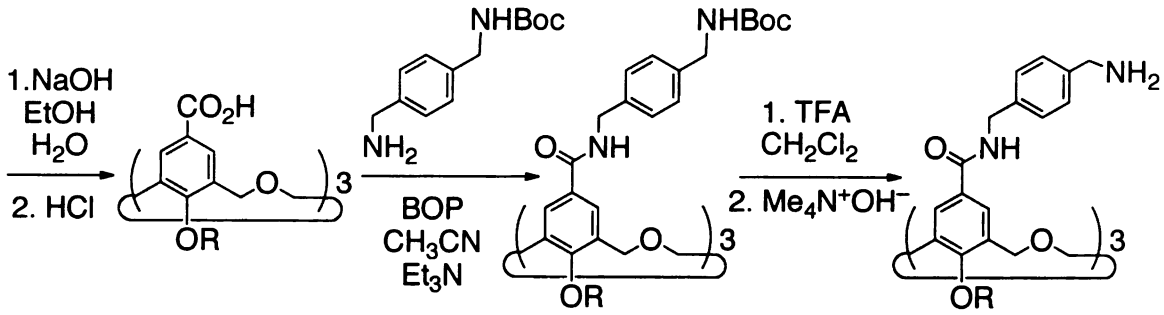
Scheme 1. 57. Preparation of capped ligands **120**.

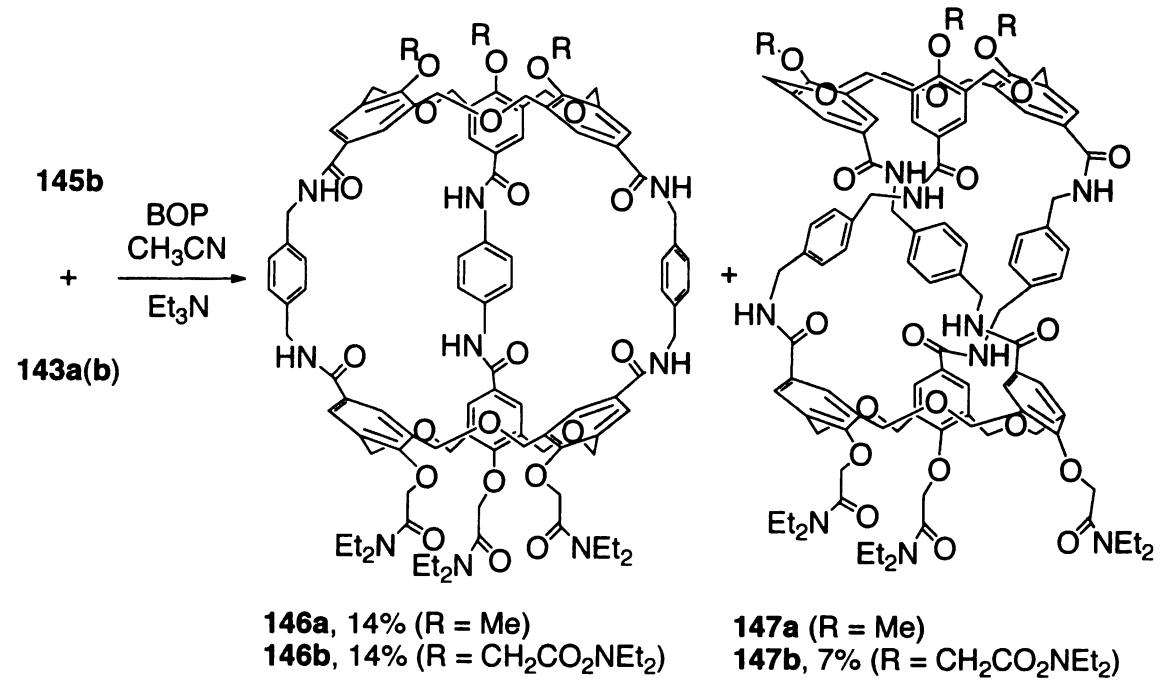


Sometimes, the initial functional group present in a homooxacalix[3]arene defines its modification potential. Shinkai *et al.* reported a self-threaded rotaxane **147** based on homooxacalix[3]arene, modified in both upper and lower rims. In order to prepare the target molecules, they started with macrocycle **9d** having ester functional group that later was hydrolyzed and used in formation of amide bonds (Scheme 1.58). Interestingly, compounds **146b** and **147b** are separable isomers, while **146a** and **147a** exist in equilibrium at room temperature[33].

Scheme 1. 58. Self-threaded rotaxane **147** and molecular capsule **146**.







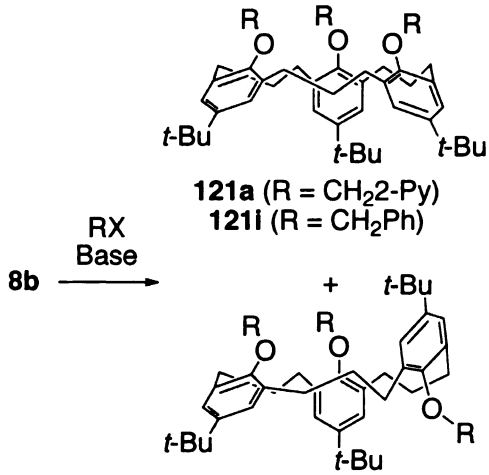
4.3. Lower Rim Modification.

A. Homocalixarenes.

The most common substituents on the lower rim of homocalixarenes are alkyl groups. Often the macrocycle formation is made with protected phenolic hydroxide groups, and in order to obtain the free homocalixarene one needs to perform demethylation, e.g. with BBr_3 (see Schemes 1.4 – 1.6). Large enough alkyl groups hinder the "through the annulus" rotation to the extent that conformers become separable isomers.

Benzyl and (2-pyridylmethyl) substituents were introduced into homocalix[3]arene **8b** with only limited stereoselectivity (Scheme 1.59).[84]

Scheme 1. 59. Ester group introduction into homooxacalix[3]arene **8b**.

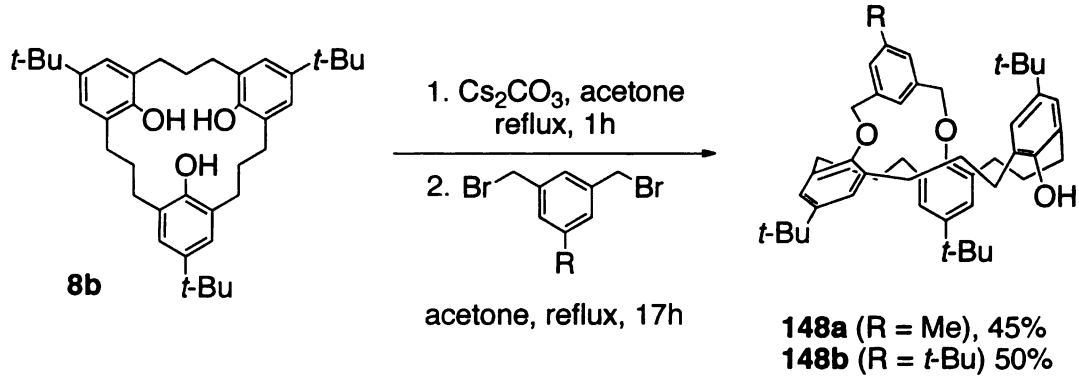


RX	Base	Solvent	Yield of **121**, %	
			cone	*paco*
BnBr	NaH	THF/DMF	10	70
BnBr	Na_2CO_3	acetone	0	0
BnBr	K_2CO_3	acetone	0	96
BnBr	Cs_2CO_3	acetone	0	95
PicCl	NaH	THF/DMF	80	0
PicCl	Cs_2CO_3	acetone	50	17

While some conditions allow selective preparation of *paco*-isomers **121b** and **121j**, no reaction afforded *cone* **121i** selectively. Compound **121a**, as it was mentioned before (Figures 1.14-1.15), shows excellent selectivity for silver in extraction experiments.

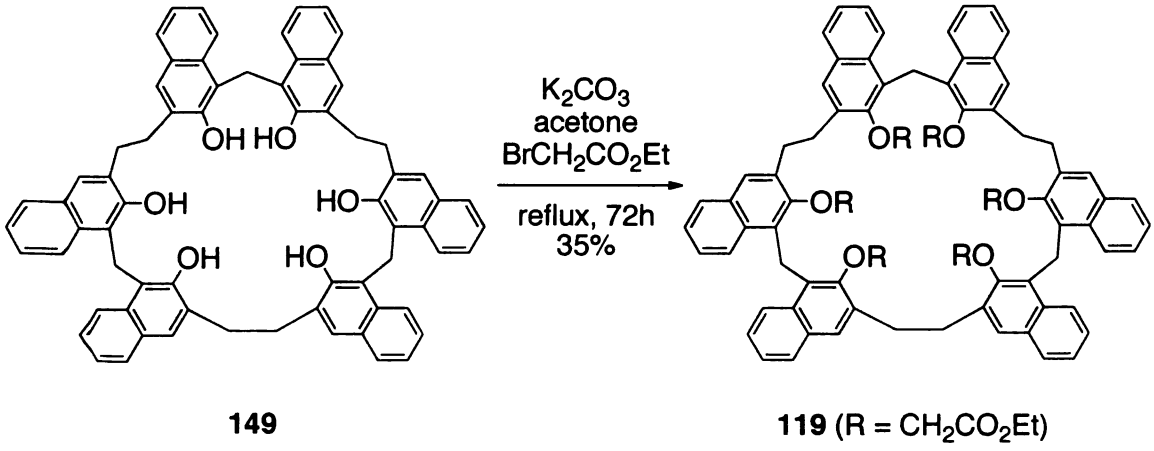
The same homocalix[3]arene **8b** was partially capped with 3,5-bromomethyltoluene and 3,5-bromomethyl-1-*tert*-butylbenzene to give derivatives **148**. These compounds were shown by NMR to have *paco* conformations[92].

Scheme 1. 60. Preparation of partially capped derivatives **148**.



The introduction of ester and amide groups is very popular in preparation of metal receptors in calixarene chemistry. In homocalixarenes these moieties were found to be very useful as well. Above-mentioned potassium-selective host **119** (Figure 1.14) was prepared from the parent homocalixarene **149** in a standard way[82]:

Scheme 1. 61. Preparation of potassium-selective homocalixnaphtalene **119**.

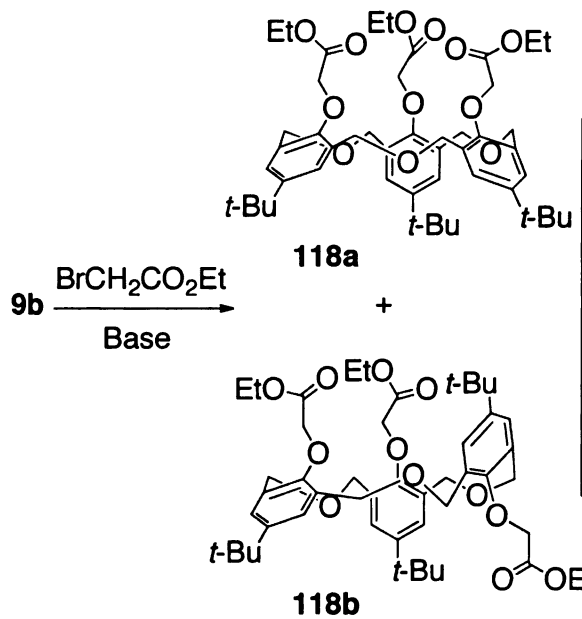


B. Homooxacalixarenes.

Due to significantly easier large scale preparation, modification of homooxacalix[3]arenes (and some bigger members of this family) was studied in much detail. Two groups that turned out to be the most useful for metal complexation as well as further derivatization were ester and amide functionalities.

Ester groups can be introduced easily, but only with limited selectivity (Scheme 1.62). As it was stated earlier, the *cone* conformer is most often the target, and no method afforded the *cone* conformer **118a** in more than 22% yield[93].

Scheme 1. 62. Ester group introduction into homooxocalix[3]arene **9b**.

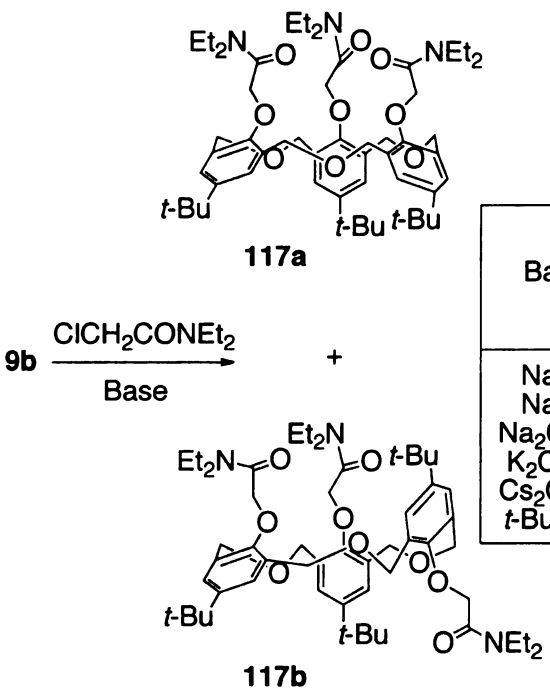


Base (eq)	Solvent	Yield **118**, %	
		cone	*paco*
NaH (2.2)	THF	9	14
NaH (3.3)	THF	20	52
NaH (9.0)	THF	20	75
NaH (3.6)	DMF	8	89
NaH (3.6)	DMF	6	90
Na_2CO_3 (9.0)	acetone	2	4
K_2CO_3 (9.0)	acetone	0	100
Cs_2CO_3 (9.0)	acetone	0	100
t-BuOK	THF	22	78

A good solution to the selective derivatization problem came with the use of N,N-diethylchloroacetamide for the phenolate alkylation. Reaction of **9b** with sodium hydride and amide electrophile in THF at reflux afforded *cone* isomer **117a** quantitatively; the use of cesium and potassium carbonates in acetone gave only *paco* compound **117b**. The

reasons for such selectivity are attributed to cation coordination to the macrocycle during the nucleophilic substitution[81].

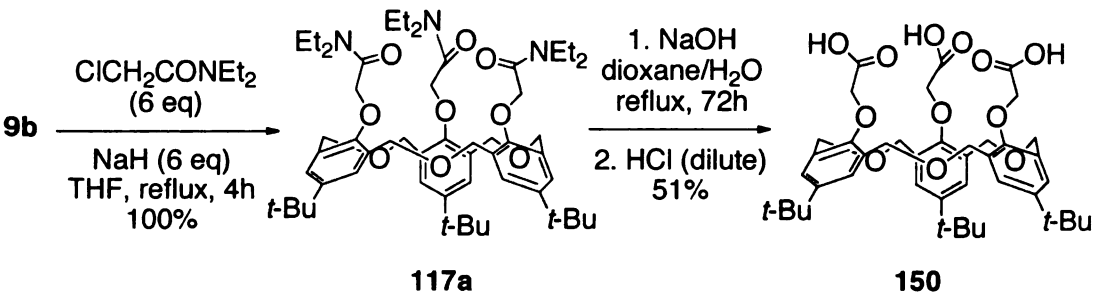
Scheme 1. 63. Selective addition of amide functionality to macrocycle **9b**.



Base (eq)	Solvent	Yield of **117**, %	
		cone	*paco*
NaH (6.0)	THF	96	0
NaH (6.0)	DMF	29	26
Na_2CO_3 (6.0)	acetone	0	30
K_2CO_3 (6.0)	acetone	0	99
Cs_2CO_3 (6.0)	acetone	0	99
t-BuOK (6.0)	THF	60	38

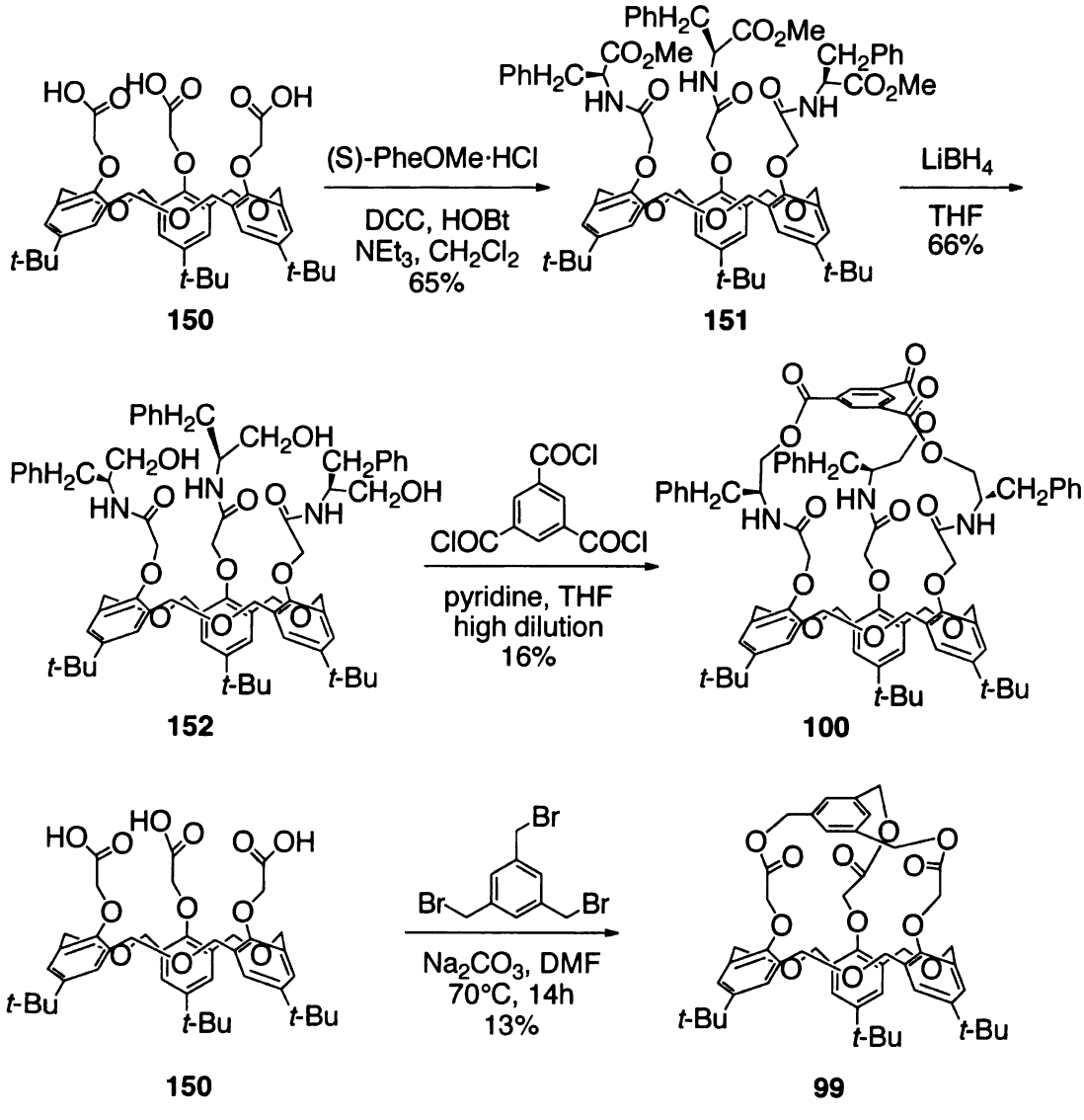
This was immediately used to prepare a very popular intermediate, triacid **150**.

Scheme 1. 64. Synthesis of triacid **150**.



Most of the cone derivatives of homooxacalix[3]arenes from this point in time were based on **150** or its analogues. For example, the abovementioned capped ligands **99**[63] and **100**[64] were prepared from **150** in the following way

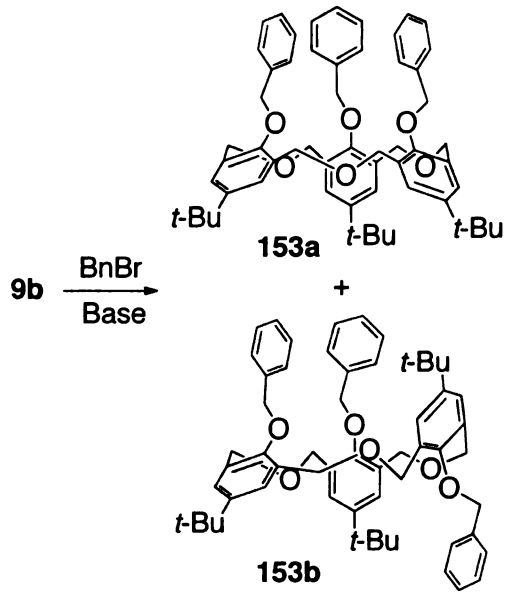
Scheme 1. 65. Synthesis of capped ligands **99** and **100**.



Even though from the previous examples it seems like the coordination between amide groups and sodium ion is essential for selective cone isomer formation, cone-selective

benzyl group introduction was also achieved in the conditions very similar to ones in Scheme 1.63[94]:

Scheme 1. 66. Benzylation of homooxacalix[3]arene **9b**.

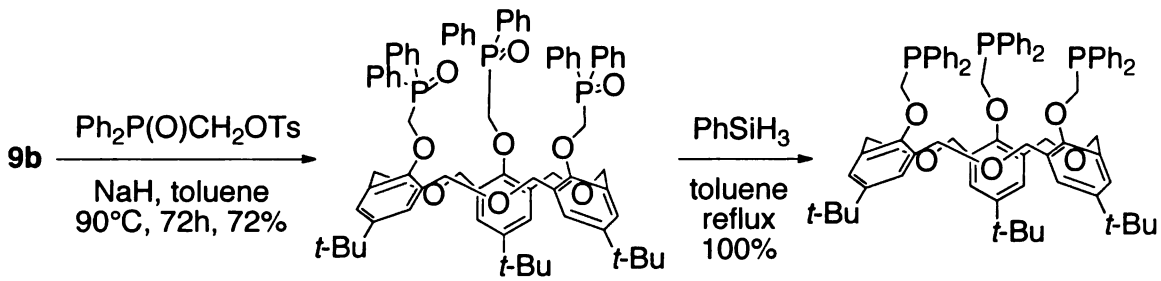


Base	Solvent	Yield of **153**, %	
		cone	*paco*
NaH	THF	45	16
Na_2CO_3	acetone	0	0
K_2CO_3	acetone	4	82
Cs_2CO_3	acetone	0	86

It seems like coordination of sodium ions to phenolic oxygen atoms can affect the stereoselectivity as well.

Similarly, treatment of **9b** with $Ph_2P(O)CH_2OTs$ in presence of sodium hydride in THF afforded 4:1 mixture of *cone* and *paco* isomers, that can be separated by chromatography. The following reduction with phenylsilane afforded ligand **113** in quantitative yield[80].

Scheme 1. 67. Preparation of phosphine ligand **113**.



154 **113**

Many other similar homocalix[3]arene derivatives were prepared[71], but the selection above is representative of the methods used.

5. Concluding Remarks.

Homocalixarenes have proven themselves as useful and selective ligands, supramolecular hosts, models for enzyme active centers, and so on. While they often have a higher degree of conformational mobility in comparison with the regular calixarenes, which can limit their binding abilities, homocalixarenes also offer a lot more flexibility in chemical modification, positioning of binding sites, and cavity size and shape adjustability.

As it can be seen from the illustrative selection in this chapter, the use of homocalixarenes is mostly limited by their availability. Homooxacalix[3]arenes have been very popular ever since an easy method for their large scale preparation by thermal trimerization of triols (e.g. Scheme 1.19) was discovered. Unfortunately, there are no comparably effective methods of homocalixarene preparation. Our first goal thus was to develop a synthetic method that can allow homocalixarene to be made on relatively large scale and with greater amount of functional group control and selectivity.

Secondly, the review of ring modification methods shows that there is virtually no known way of phenolic oxygen substitution in homocalixarenes. Thus, our second goal was to

investigate the possibilities for lower rim modification with the intent of carbon substituents introductions, and to create new ligands based on homocalixarene macrocycles.

CHAPTER TWO

BENZANNULATION REACTION IN MACROCYCLIZATIONS

Cycle tracks will abound in Utopia.

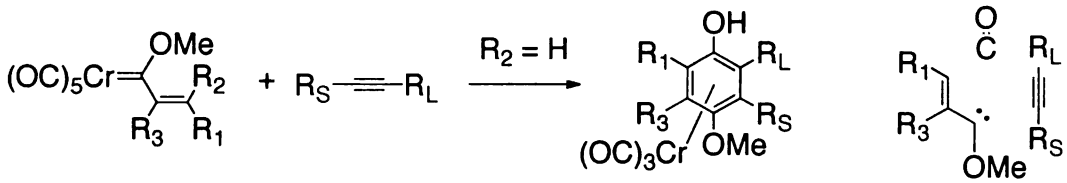
H. G. Wells

1. Benzannulation Reaction of Fischer Carbene Complexes, its Mechanism and Selectivity.

1.1. Benzannulation Reaction and its Mechanism.

The benzannulation reaction of Fischer carbene complexes with alkynes to give *p*-alkoxy phenols was first reported by Dötz[95] and has become one of the most synthetically valuable methods for the synthesis of phenols and quinones[96]. The reaction requires the carbene complex to be α,β-unsaturated; aryl carbene complexes can be used as well. Most popular are benzannulation reactions with Group VI metals, especially chromium (Scheme 2.1).

Scheme 2. 1. The benzannulation reaction of Fischer carbene complexes.

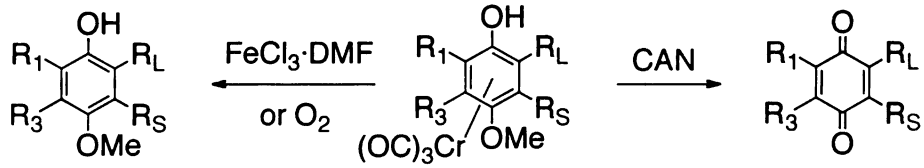


155 **156**

As it can be seen from Scheme 2.1, the resulting aromatic ring is composed of three carbons originating from the carbene complex, two acetylenic carbons, and one CO. The

resulting phenol is formed (at least partially) as chromium tricarbonyl η^6-complex **156**, which is usually very sensitive to oxidation, and can be converted into free phenol by exposure of the reaction mixture to air, or by $FeCl_3$-DMF complex. If stronger oxidants like CAN are applied, quinones are formed as main products[97].

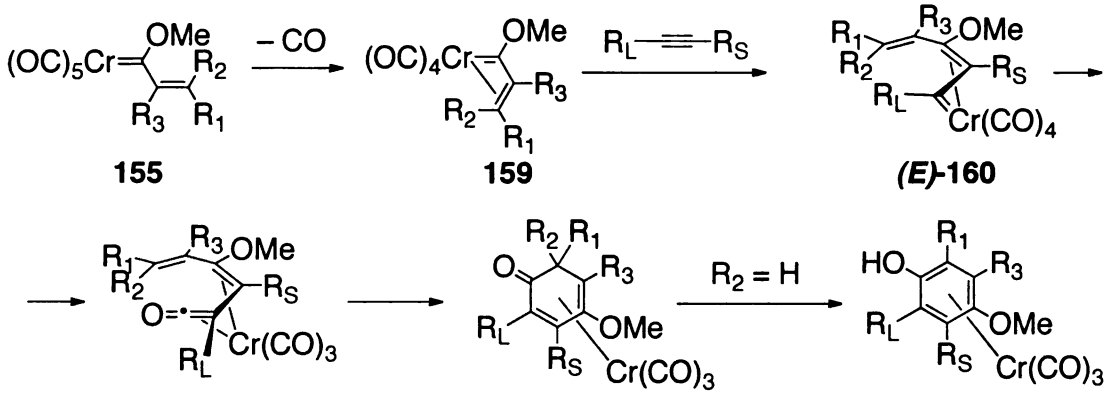
Scheme 2. 2. Possible work-up options for benzannulation products.



157 **156** **158**

The mechanism of the benzannulation reaction is very complex, and certain details of it are yet to be determined. Still, most of the researchers have agreed upon the main steps. These steps are also confirmed by extensive experimental data (Scheme 2.3)[98].

Scheme 2. 3. Mechanistic outline of the benzannulation reaction.



155 **159** ***(E)*-160**

***(E)*-161** **162** **156**

As it can be seen from Scheme 2.3, there are six main steps that determine the outcome of the reaction: 1) CO dissociation; 2) alkyne coordination; 3) alkyne insertion; 4) CO

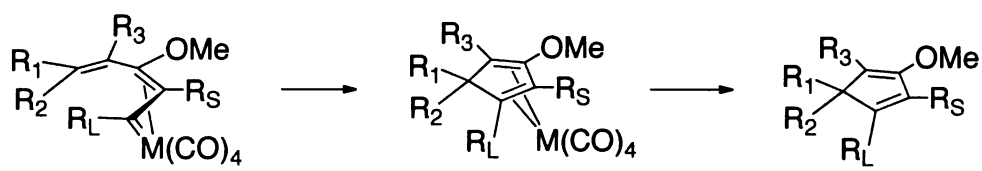
insertion; 5) ring closure; 6) tautometization. Each step is crucial, and changes in their relative rates can influence the outcome of the reaction dramatically.

1.2. The Selectivity of the Benzannulation Reaction.

The benzannulation reaction can produce a staggering number of various products[96]. While making its application sometimes challenging, this fact can also provide numerous synthetic opportunitites. The appearance of virtually all the side products can be explained by inclusion of branchpoints in the mechanism depicted in Scheme 2.3.

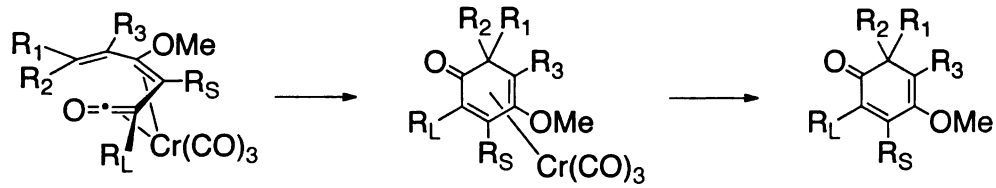
In one of the most common side-products, CO insertion is interrupted. It is especially slow for molybdenum and tungsten complexes, which leads to the formation of cyclopentadiene **164** instead of the phenol (Scheme 2.4). For this reason, chromium carbene complexes are most popular in reactions where phenol formation is desired. Still, even for chromium complexes cyclopentadiene (or indene) formation can be a major side reaction under certain conditions[99].

Scheme 2. 4. Cyclopentadiene (indene) formation.



If neither substituent on the β-carbon of carbene complex is a hydrogen, the final aromatization can not occur, and the non-enolizable dienone **165** is obtained instead[100]:

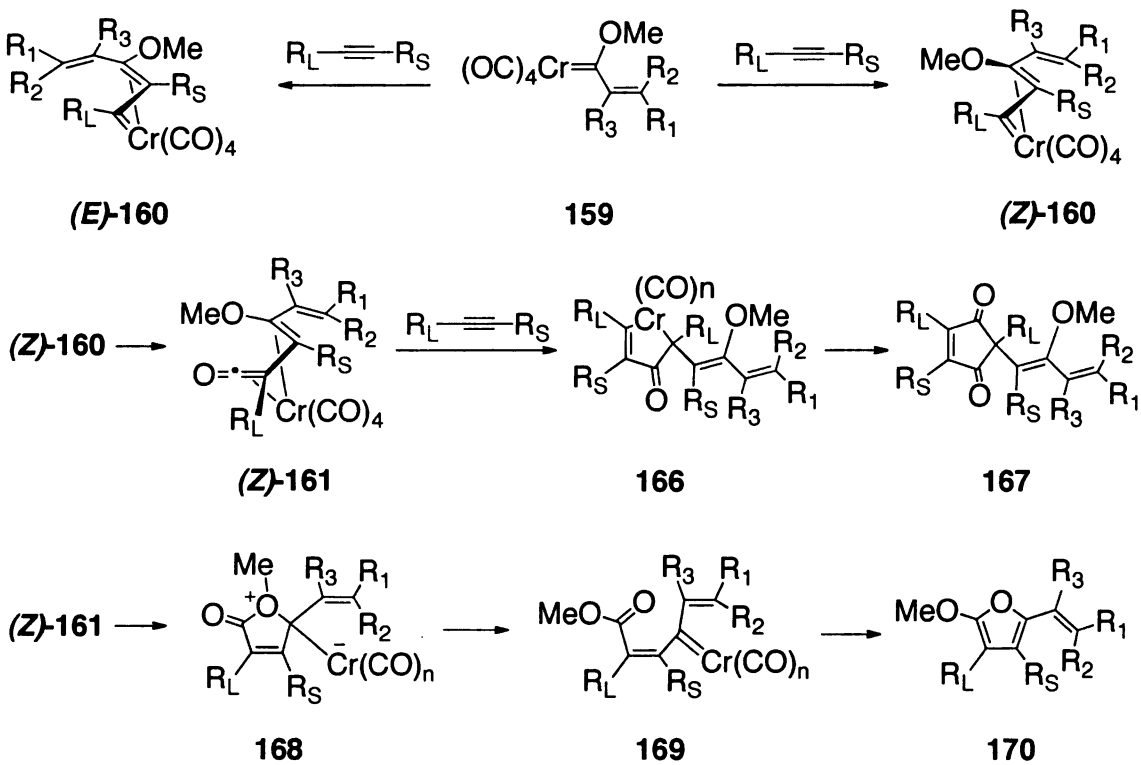
Scheme 2. 5. Benzannulation resulting in cyclohexadienone formation.



***(E)*-161** **162** **165**

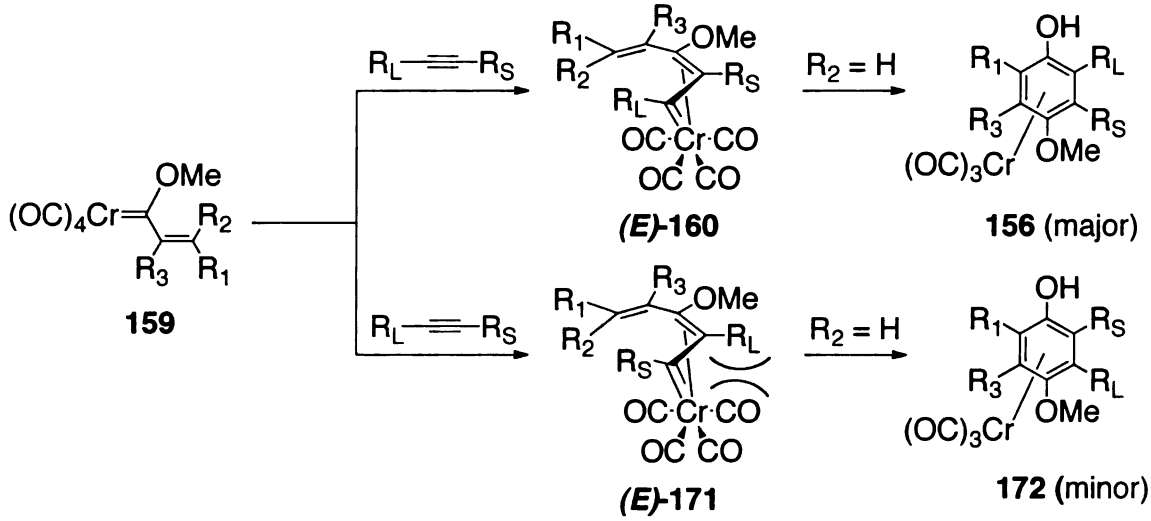
Furans, indanones, and other products can also be obtained. These products result from the insertion of the alkyne to give the *(Z)*-isomer of the η^1,η^3-vinyl carbene complexed intermediate **160**. Normally alkyne inserts to selectively give the *(E)*-isomer, which has been attributed to the eletronic influence of alkoxy group[101]. Combined yield of products **167** and **170** thus does not normally exceed 20%, but under certain conditions they do become major products[102].

Scheme 2. 6. Formation of furan and cyclopentendione side products.



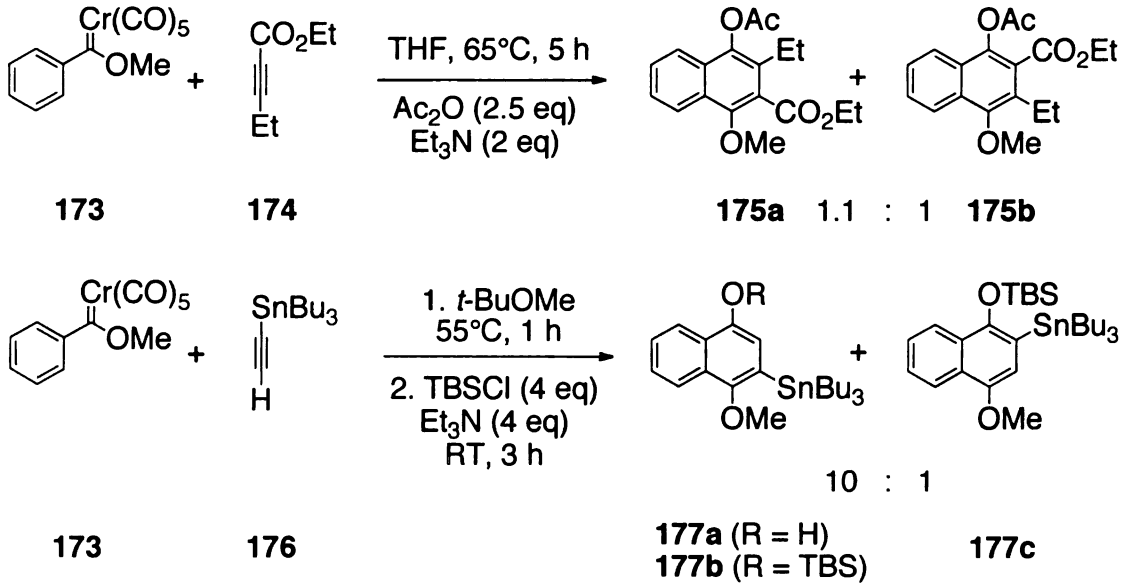
Phenol preparation from the reaction of chromium carbene complexes and terminal alkynes is usually very regioselective. The selectivity is such that the large substituent of the alkyne ends up *ortho* to phenol OH group (see Scheme 2.1), and thus has been explained with the help of theoretical calculations. According to Hofmann[103a], unfavourable interaction between the larger substituent and one of the CO ligands on chromium is present in the alkyne insertion product *(E)*-**171** but not in the regioisomeric insertion complex *(E)*-**160**. Thus, the equilibrium between these intermediates is shifted towards more stable *(E)*-**160**. Computational studies by modern methods provide somewhat different explanation, holding steric repulsion in *transition state* of *irreversible* alkyne insertion responsible[103b].

Scheme 2. 7. Regioselectivity of the benzannulation reaction.



In case of internal alkynes, the selectivity is significantly diminished. Electronic factors are rarely of significant influence; only ketone and tributylstannyl substituents have been reported to reverse the regioselectivity from the one imposed by steric factors[104].

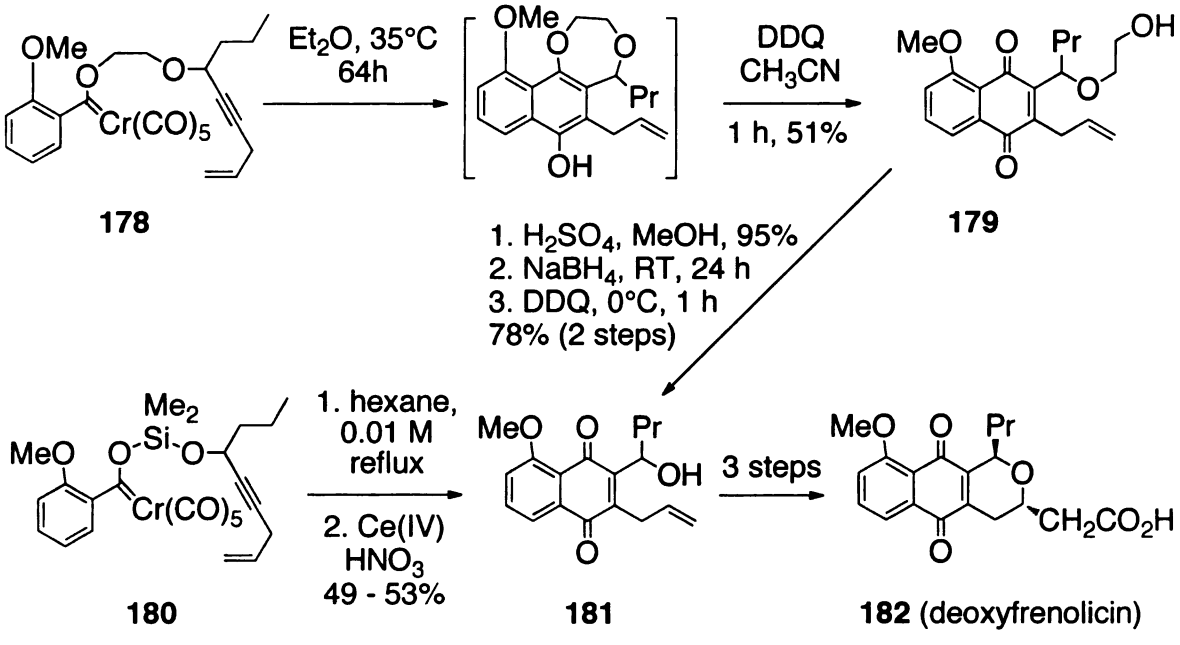
Scheme 2. 8. Some examples of benzannulation regioselectivity.



In order to solve the regioselectivity problem with internal alkynes, intramolecular cyclizations have been employed. The forming ring size was a limiting factor in isomer

distribution, preventing the formation of less stable intermediates (the tether usually was selected to be too short to allow the second isomer to be formed). For example, in an effort to synthesise deoxyfrenolicin **182**, an advanced synthetic intermediate **181** was prepared by the groups of Semmelhack[105] and Finn[106] in two different ways, both involving intramolecular cyclizations of chromium carbene complexes:

Scheme 2. 9. Intermolecular benzannulation reactions in syntheses of deoxyfrenolicin.



To sum up, in order to prepare phenols, vinyl carbene complexes of chromium should be used. Terminal alkynes are the most reliable partners in terms of regioselectivity prediction. This reaction was studied in much detail, and was found to work consistently in many different solvents; the choice of the latter usually depends on the nature of the starting materials and can be made with the help of solvent screening studies.

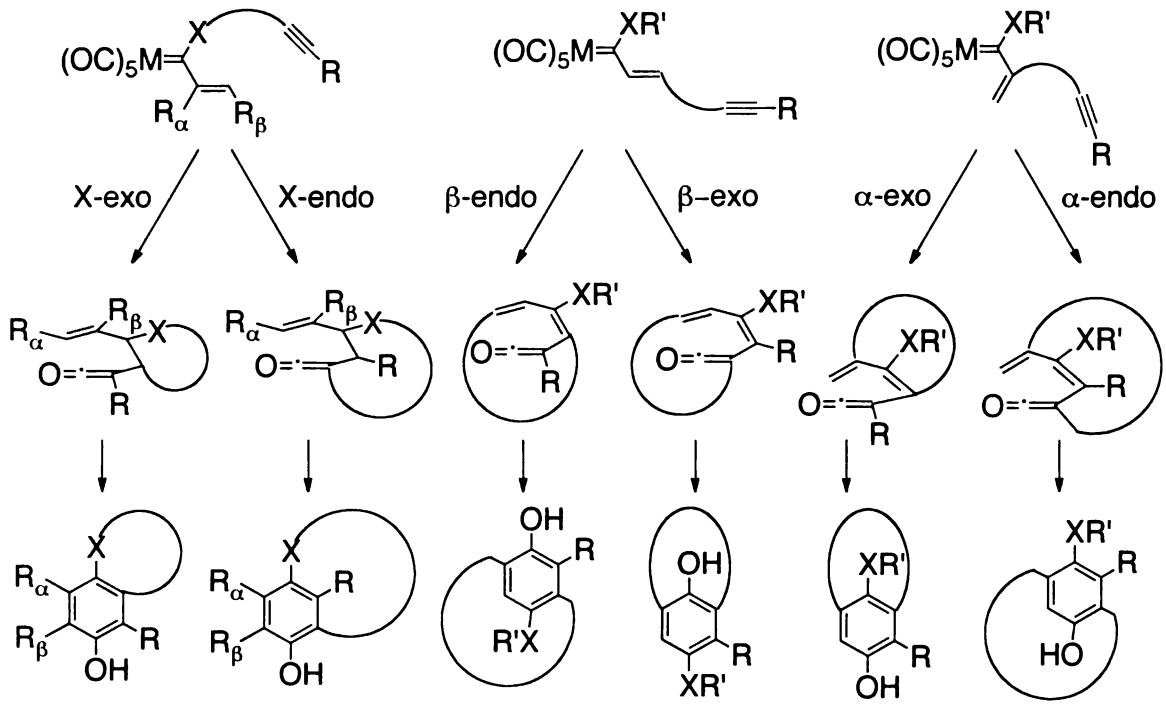
2. Benzannulation Reaction Used to Prepare Macrocycles.

The intramolecular benzannulation producing medium-sized rings has been relatively well studied (most commonly 5, 6 and 7-membered rings were made). For a comprehensive review of the intramolecular benzannulation see reference 96, Table 21, pp. 524 – 557. At the same time, no reports of all-carbon macrocycle preparation with alkynes tethered to the vinyl group of the carbene complex can be found in the literature prior to the work of Dr. Huan Wang[113]. Most of the contributions in this area were made by Wulff laboratory[111–116,118], with the exception of several papers published by Dötz *et al.*[107,108] (see Schemes 13 and 14 for examples).

2.1. Systematic Intramolecular Benzannulation Investigation by Dr. Wang.

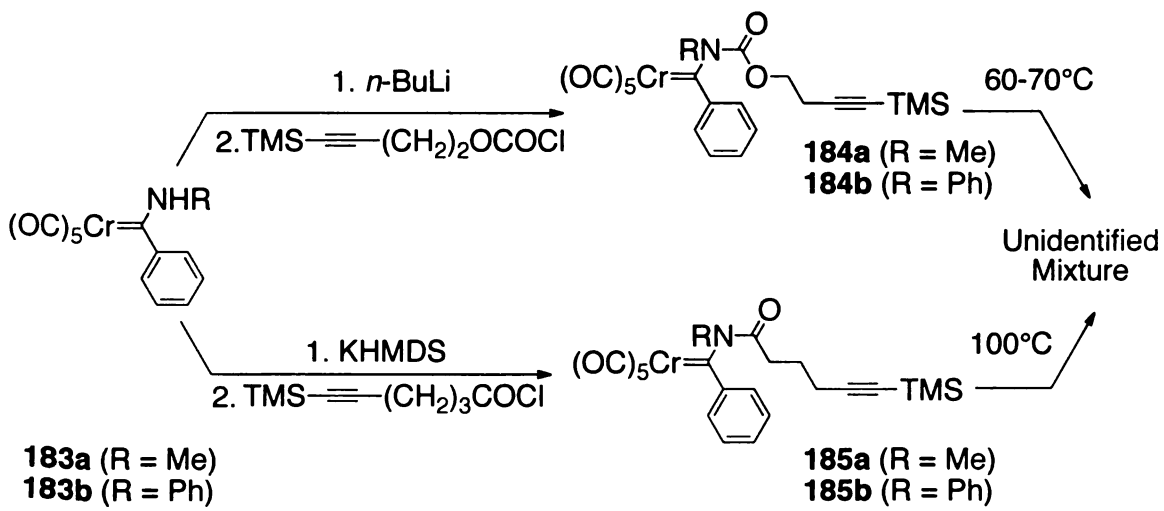
During what seems to be the first systematic study of the intramolecular benzannulation reaction, Dr. Wang logically classified all of the possible intermolecular cyclizations into 6 different types: *X-exo*, *X-endo*, *β-exo*, *β-endo*, *α-exo*, and *α-endo* (Scheme 2.10). Prior to his work only the reactions of *X-exo* type had been reported (see Scheme 2.9 for an example).

Scheme 2. 10. Classification of intermolecular benzannulation reactions.



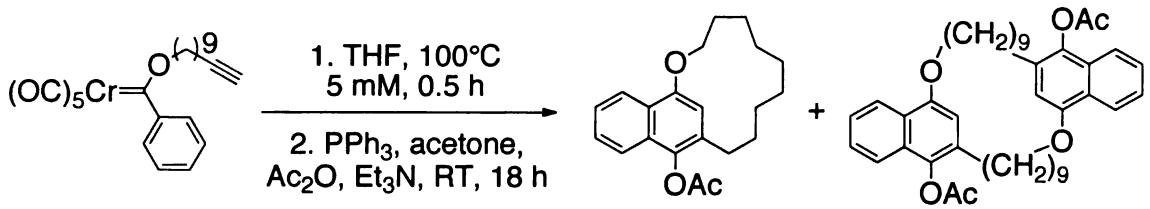
In order to develop more synthetically useful intramolecular *X-exo* processes, complexes **184** and **185** were prepared. Unfortunately, the acylation step proved to be very sluggish and gave low yield of impure products, and cyclization only afforded complex unindentified mixtures of products[113a].

Scheme 2. 11. Attempts at cyclizations of amidocarbene complexes.



It was also suggested that with tethers that are long enough, the *O-endo* process should be achieved selectively with terminal alkynes. Indeed, the cyclization of complex **186** was found to give products **187** and **188** in 15 and 8% yields, correspondingly[113b]:

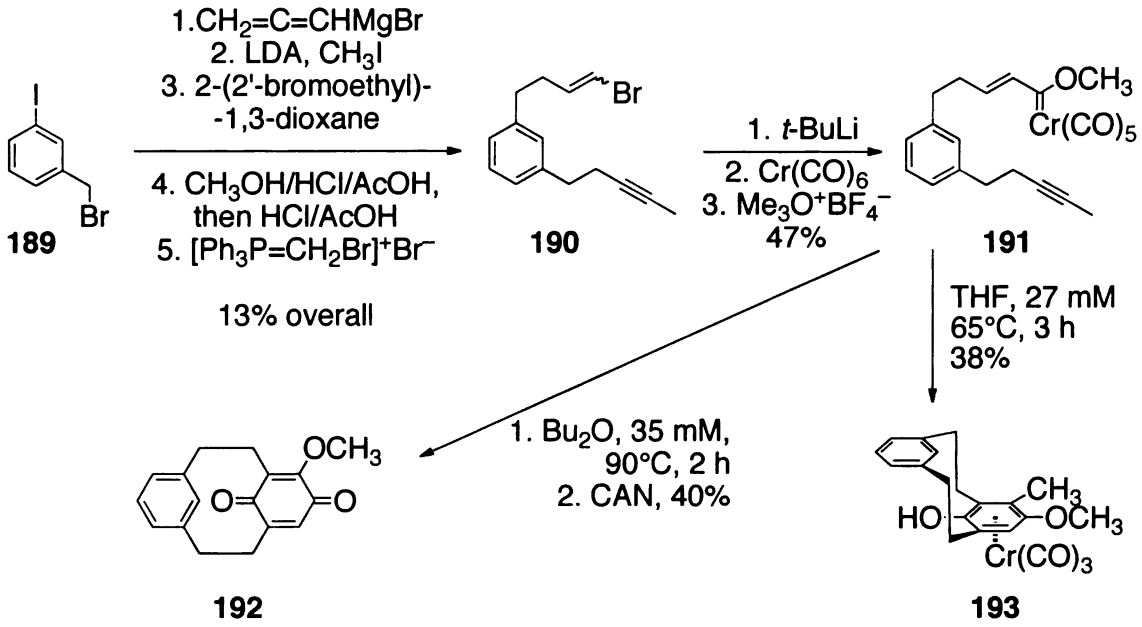
Scheme 2. 12. Regioselective *O-endo* macrocyclization.



186 **187**, 15% **188**, 8%

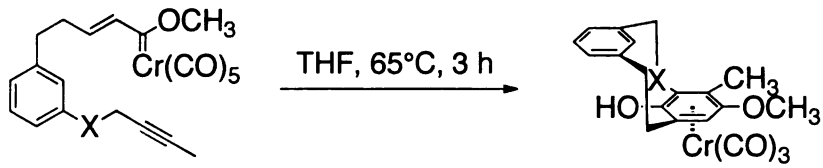
In the course of further investigations, *β-endo* processes were studied. Interestingly, about the same time (1999) the Dötz group reported[107] an example of [2,2]metacyclophane formation from carbene complex **191** containing internal alkyne. According to the abovementioned classification, this is a *β-endo* process as well. It is worth mentioning that product **193** was formed as a single diastereomer.

Scheme 2. 13. Meta[2.2]cyclophane formation by benzannulation reaction.



In later work, the same laboratory published the synthesis of hetero-analogs of the abovementioned cyclophane[108] (Scheme 2.14).

Scheme 2. 14. Preparation of hetero-analogs of meta[2.2]cyclophane **193**.



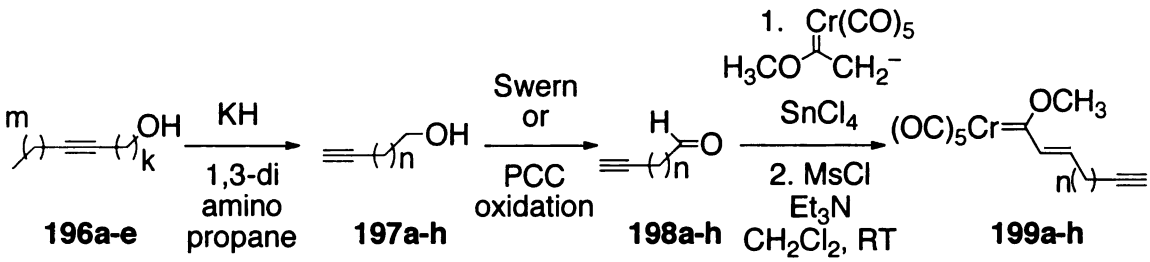
194a (X = O)
194b (X = NMe)

195a (X = O), 25%
195b (X = NMe), 20%

A series of carbene complexes **199** were prepared using the aldol reaction of Fischer carbene complexes, first described by C. P. Casey[109] (Scheme 2.15). The procedure was later improved by Wulff and Gilbertson, allowing the use of enolizable aldehydes by virtue of Lewis acid catalysis[110]. Unfortunately, this method also gave unsatisfactory

results with aldehydes **198**, and further improvements were introduced and published separately[111].

Scheme 2. 15. Preparation of linear carbene complexes **199**.



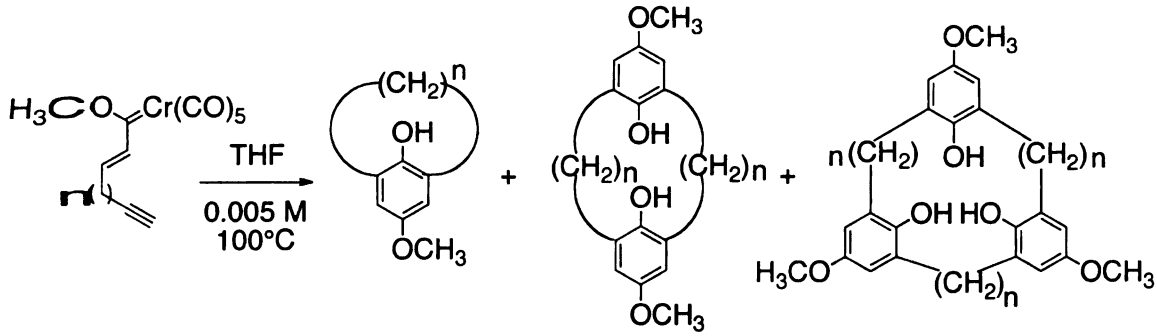
196a-e **197a-h** **198a-h** **199a-h**

Carbene	n	Yield of **197**, %	Oxidation	Yield **198**, %	Yield **199**, %
199a	2	- [a]	Swern	84	42
199b	3	- [a]	PCC	47	29
199c	4	- [b]	PCC	57[b]	37
199d	6	95	Swern	95	57
199e	8	- [a]	Swern	95	48
199f	10	91	Swern or PCC[c]	90	60
199g	13	90	Swern	84	33
199h	17	82	PCC	73	8

[a] Commercially available [b] Combined yield over two steps
[c] The two methods gave identical yield of the product

Cyclization of complexes **199a-h** afforded a range of metacyclophane products, including homocalix[3]arenes **202** in three cases (though only in the case of n = 6 can the method be synthetically useful). The thermolysis was carried out at 5 mM concentration in THF at 100°C, since higher concentrations and non-polar solvents (e.g. hexane or benzene) were found to decrease the combined yield of products very significantly[112]. While the concentration effect is expected because of the intramolecular nature of the cyclization, the solvent trend was the opposite from what it is known for the intermolecular benzannulation reaction. High reaction temperatures were also found to be beneficial. Cyclizations of carbenes **199a** and **199b** (n = 2 and 3) failed to give any identifiable products.

Scheme 2. 16. Cyclization of carbene complexes **199** with various tether lengths.

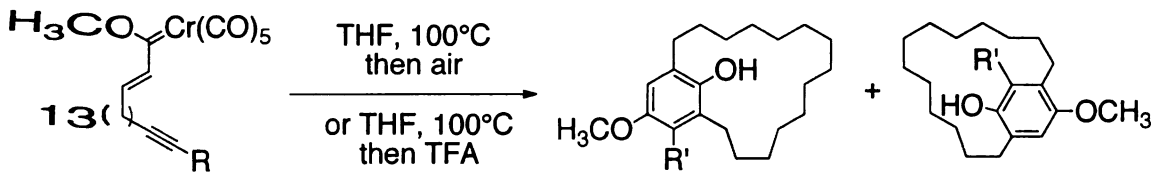


199c-h **200c-h** **201c-h** **202c-h**

Carbene	n	Yield **200**, %	Yield **201**, %	Yield **202**, %
199c	4	-	29	6
199d	6	-	39	18
199e	8	43	25	2
199f	10	58	5	-
199g	13	65	-	-
199h	17	60	-	-

Regiochemistry reversal was achieved with the help of internal alkynes. While complex **199g** (R = H), as was mentioned before, gave product **200g** selectively, introduction of substituents on the alkyne (Ph, TMS) lead to significant amounts of paracyclophanes *via* the *β-exo* cyclization process. Also, in case of R = TIPS (triisopropylsilyl) group, the cyclization failed utterly (Scheme 2.17).

Scheme 2. 17. Regioselectivity of cyclization in case of internal alkyne tether.

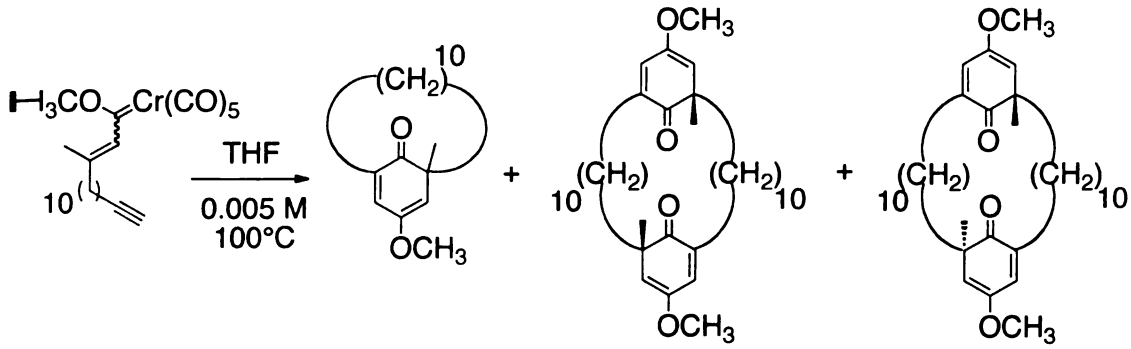


203a, b **199g** **204a** **200g** **205a** **205b**

Precursor	R	R'	Total yield, %	Ratio *meta/para*
203a	Ph	Ph	66	20 : 80
203b	TMS	H	31	61 : 39
199g	H	H	>65	> 30: 1

Cyclohexadienones were also obtained in a similar process, in which the carbene complex precursor **206c** had a methyl group in β-position[113c].

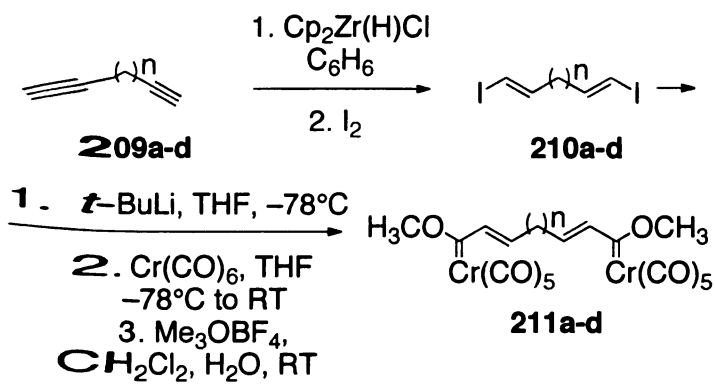
Scheme 2. 18. Cyclohexadienone formation in intramolecular benzannulation.



206c **207c**, 37% *syn*-**208c**, 7% *anti*-**208c**, 7%

The double benzannulation of bis-carbene complexes and dialkynes (which still constitutes the *β-endo* process) was found to be an effective and selective way of metacyclophane preparation. The series of bis-carbene complexes **211a-d** was prepared according to the following scheme[113d]:

Scheme 2. 19. Preparation of bis-carbene complexes **211**.

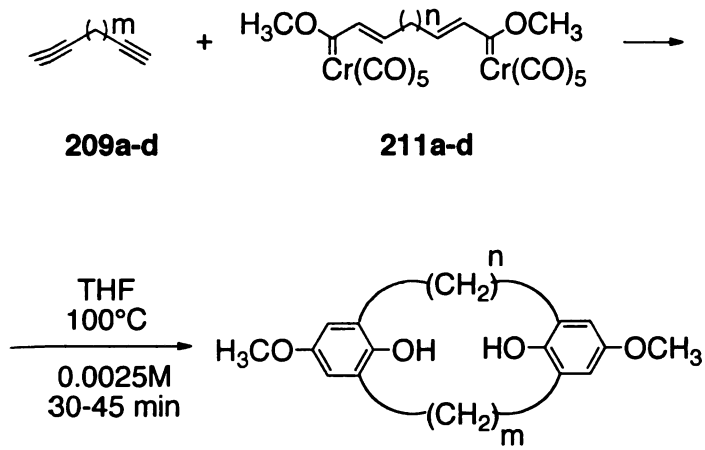


n	Yield of **210**, %	Yield of **211**, %
2	61	33
4	68[a]	61
6	74	46
10	72	42

[a] THF used as a solvent

Cyclizations were performed at 2.5 mM concentration in THF at 100°C, and took 30 to 45 minutes except for the smallest members of metacyclophane family (Scheme 2.20). Cyclophanes with the tethers of different length (n ≠ m) can also be prepared.

Scheme 2. 20. Synthesis of meta[m.n]cyclophanes.

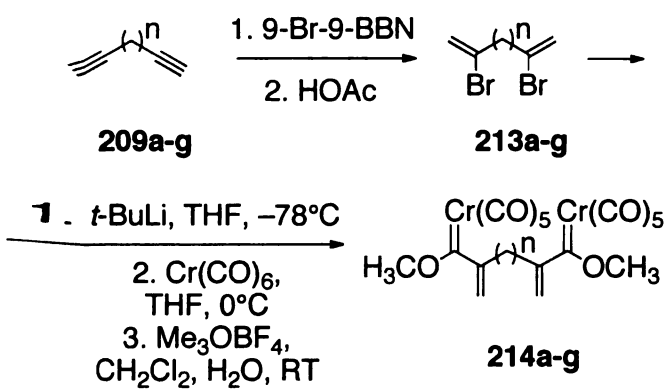


n	m	Product	Yield, %
2	2	**212a**	21[a]
4	4	**201c**	28
4	4	**201c**	30[b]
6	6	**201d**	31
6	6	**201d**	7[b]
10	10	**201f**	31
4	2	**212b**	44
4	6	**212c**	27
4	6	**212c**	27[c]
4	6	**212c**	33[d]
4	6	**212c**	30[d,e]

[a] Reaction completed in 12 h
[b] Syringe pump addition
[c] Reaction in presence of 10 eq of phenylacetylene
[d] Reaction run at 1mM
[e] THF was degassed by Ar bubbling rather than freeze-thaw method

In the course of further studies, another series of Fischer carbene complexes, **214a-g**, was prepared in the following way:

Scheme 2. 21. Synthesis of bis-carbene complexes **214**.

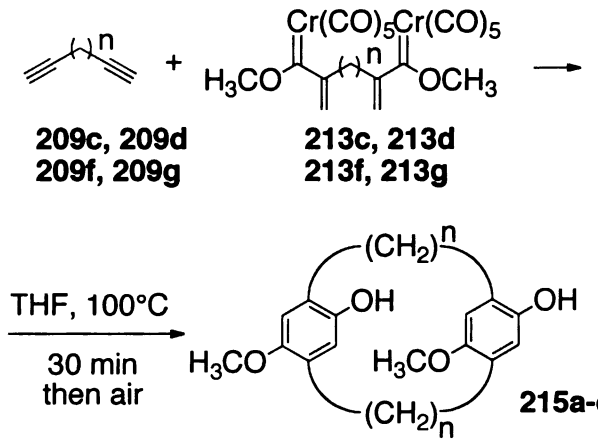


Starting Material	n	Yield of **213**, %	Yield of **214**, %
209a	2	88	< 2
209e	3	-	25[a]
209c	4	-	35[a]
209c	6	80	60
209d	10	25[b]	36
209f	13	19[b]	38
209g	16	19[b]	47

[a] Combined yield over two steps;
[b] Side product from monobromide preparation.

Reactions of these complexes with alkynes **209a-g** afforded paracyclophanes **215a-g**. As one could expect, this reaction proved to be more sterically demanding: In case of n = 3, the cyclophane failed to form. Also, a lower concentration (0.001M) than in previous examples (0.0025 M) was found to be beneficial for this cyclization.

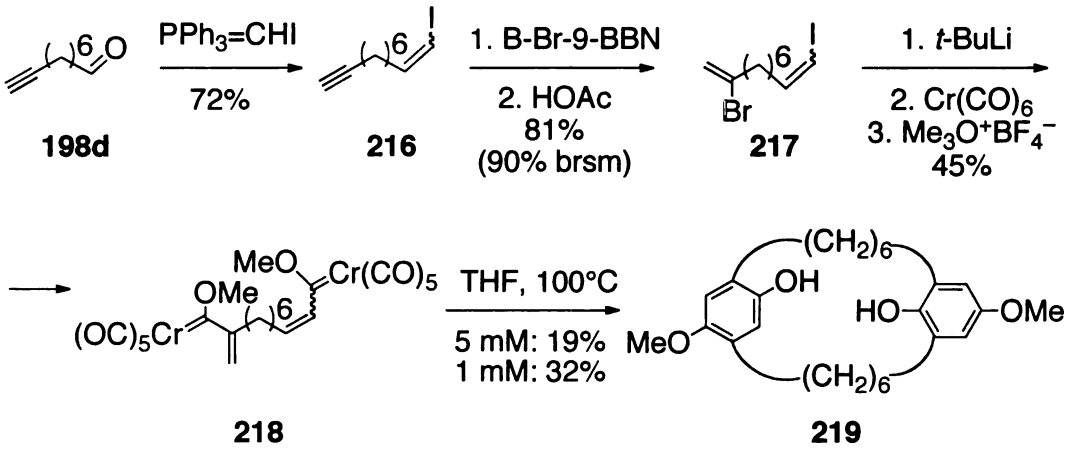
Scheme 2. 22. Synthesis of para[m.n]cyclophanes.



n	C, M	Product	Yield, %
6	0.005	**215a**	19
6	0.0025	**215a**	30
6	0.001	**215a**	42
10	0.001	**215b**	35
13	0.001	**215c**	28
16	0.001	**215d**	31

In the final demonstration of method's versatility, a mixed structure, metaparacyclophane **219**, was prepared in the following synthetic sequence:

Scheme 2. 23. Synthesis of metapara[6.6]cyclophane.

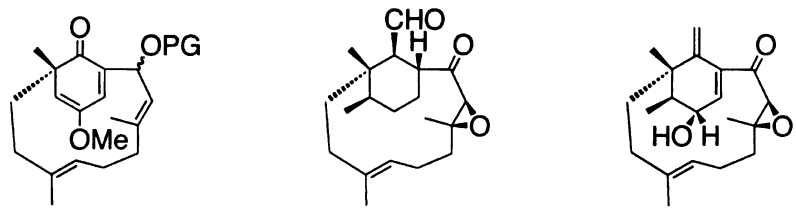


Thus, the work of Dr. Wang contained several very important findings. First, it was shown that various cyclophanes can be effectively prepared using the intramolecular benzannulation reaction. Second, the ring size was found to be of virtualy no significance with respect to the yield, except for very short tether lengths. Third, high temperatures, low concentrations, and polar ethereal solvents (namely THF) were found to be beneficial to the intermolecular cyclization.

2.2 Synthetic Studies Towards Phomactin Family.

Phomactins are a family of macrocyclic marine natural products sharing a common bicyclo[9.3.1]pentadecane ring system (Figure 2.1). Having in mind the result depicted in Scheme 2.18, it was suggested that a common intermediate with the structure presented in Figure 2.1 would be useful in the synthesis of several phomactins, and in principle could be prepared by an intramolecular benzannulation reaction.

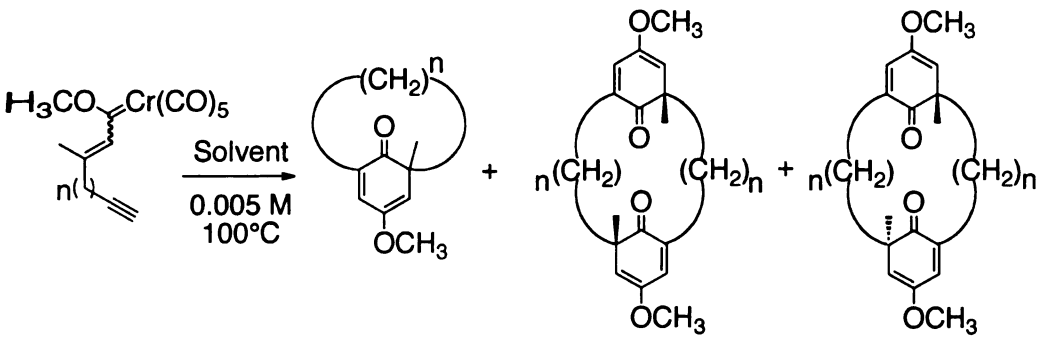
Figure 2. 1. Two members of the phomactin family and a suggested intermediate for their synthesis.



Intermediate Phomactin D Phomactin B2

A series of model studies was undertaken for the intramolecular cyclohexadienone annulation[114], and the results reveal a reactivity pattern very similar to those found by Dr. Wang for the intramolecular benzannulation. As it can be seen from Scheme 2.24, larger rings produce only the products of the type **207**. It is interesting to notice that the pure *(E)*-isomer of carbene complex **206c** gives only **207c** as the product, which suggests that it is the presence of the *(Z)*-isomer that is responsible for the formation of **208c** in the example described earlier by Dr. Wang. This deduction appears reasonable considering that β,β-disubstituted Fischer carbene complexes are configurationally stable under the conditions described.

Scheme 2. 24. Extended study on cyclohexadienone preparation by intramolecular benzannulation reaction.



206a-d **207a-d** ***syn*-208a-d** ***anti*-208a-d**

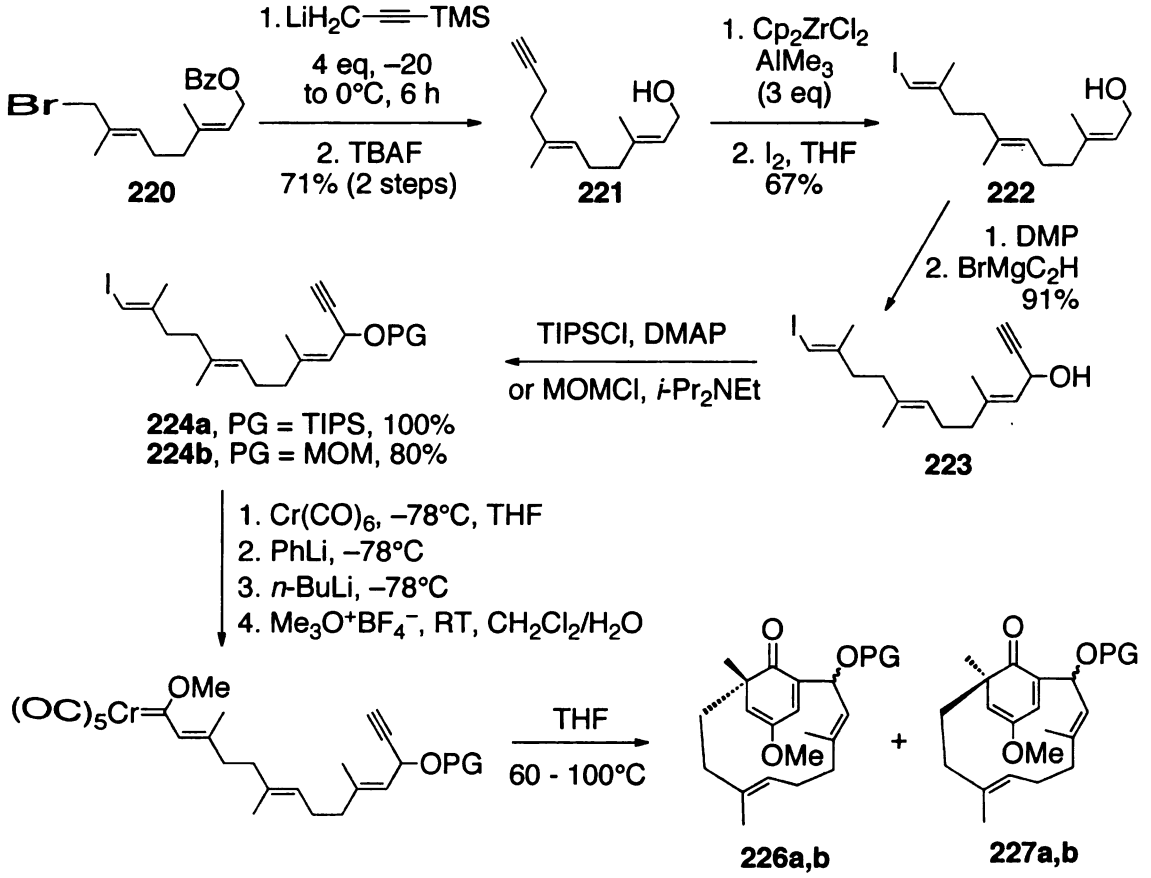
Carbene	n	Solvent	Yield **207**, %	Yield **208**, %	Ratio *anti/syn*
(E)-**206a**	6	THF[a]		18	1.3 : 1
(E)-**206a**	6	MeCN[b]		22	1.8 : 1
(E)-**206a**	6	benzene[c]		46	1.1 : 1
(E)-**206b**	8	THF	45		
(E)-**206b**	8	MeCN	45		
(E)-**206b**	8	benzene	10		
(Z)-**206c**	10	THF	15	[d]	
(Z)+(E)-**206c**[e]	10	THF	37	14	1 : 1
(E)-**206c**	10	THF	43		
(E)-**206c**	10	MeCN	64		
(E)-**206c**	10	benzene	36		
(E)-**206d**	13	THF	64		
(E)-**206d**	13	MeCN	51		
(E)-**206d**	13	benzene	32		

[a] 6% of the trimer isolated [b] 4% of the trimer isolated
[c] 13% of the trimer, ratio assessed by HPLC
[d] five other unidentified compounds were detected in the mixture
[e] 71:29 ratio of *E:Z* isomers

Later in the course of this project, the intermediates **226a** and **226b** were prepared in a multistep synthesis (Scheme 2.25). The synthesis started with the known bromide **220**, which can be prepared from geraniol in three steps, and which ultimately leads to carbene complexes **225a** and **225b** (Scheme 2.25). The results of benzannulation were found to be dependent on both the cyclization conditions and on the substituents present in the

carbene complex **225**; the best yield and diastereoselectivity were achieved in the case of the triisopropylsilyl-protected carbene complex **225a**, when cyclization was performed at 60°C for 40 hours. Intermediate **226a** was converted into (±)-phomactin B2 in 12 steps[115].

Scheme 2. 25. Preparation of advanced synthetic intermediates **226a** and **226b**.

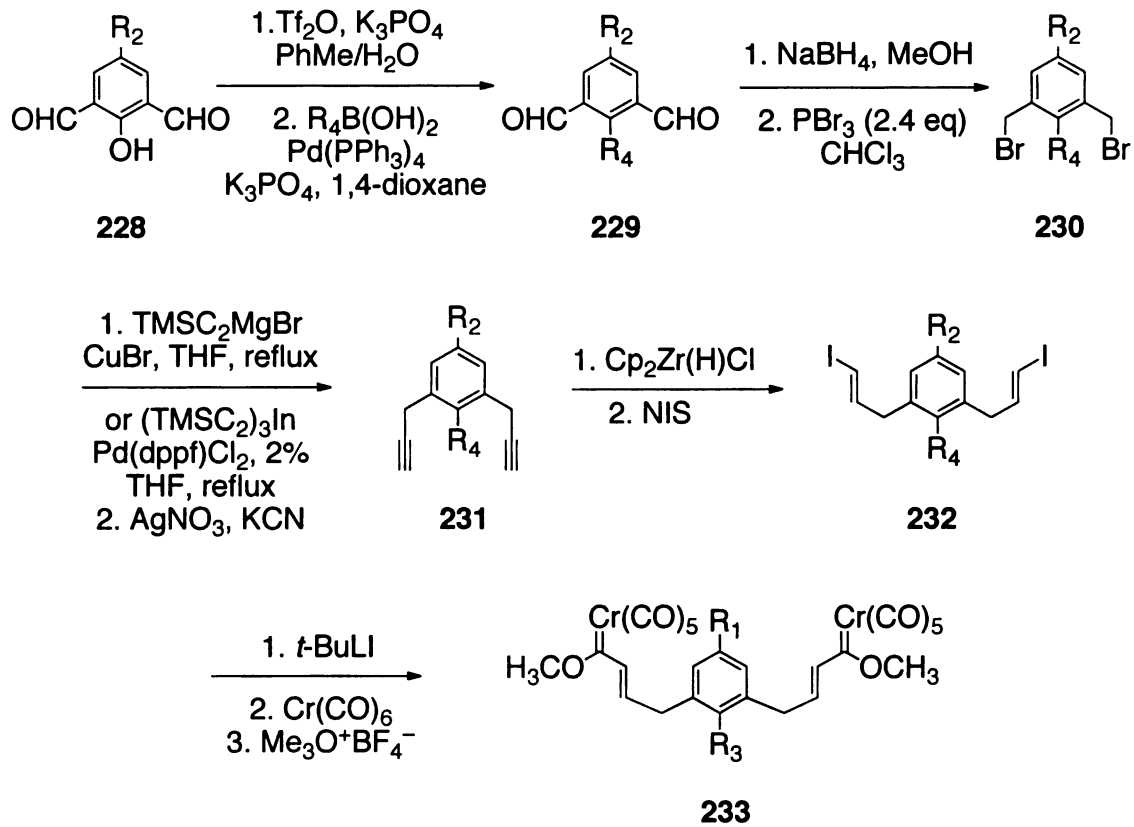


The studies on the synthesis of phomactins are still an ongoing project in our laboratory, and a number of other approaches are currently under development.

2.3. The Synthesis of Substituted Calix[4]arenes by a "Triple Annulation" Approach.

In another logical course of Dr. Wang's project development, it was envisaged that calix[4]arenes bearing various useful functionalities can be selectively prepared using a similar strategy. Carbene complexes **233** were prepared according to the following sequence[116]:

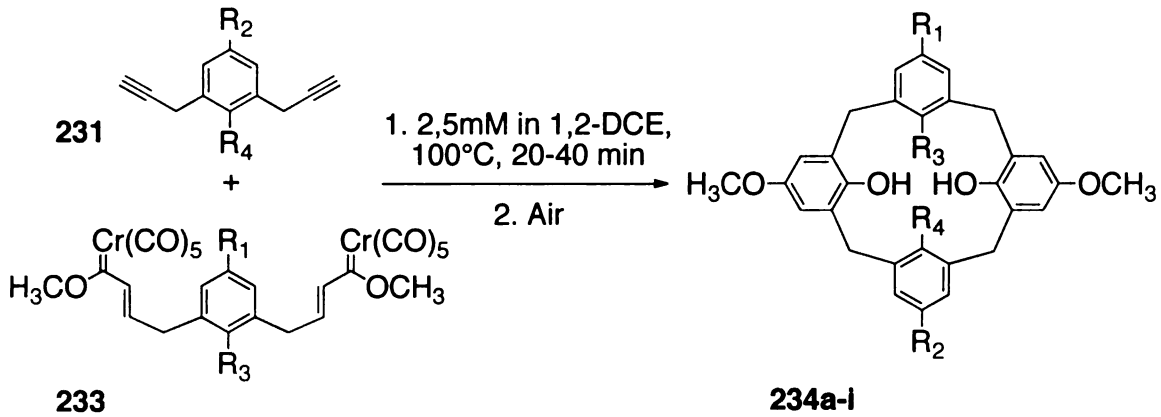
Scheme 2. 26. Preparation of aromatic bis-carbene complexes **233**.



Even though the presence of benzylic hydrogens in the propargyl benzene units in compounds **231**, **232** and **233** makes them relatively unstable and potentially vulnerable to temperature, acidic/basic reagents, and light, they were found to be stable enough to give reproducible moderate yields in a process dubbed the "triple annulation", a

cyclization involving one intermolecular and one intramolecular benzannulation reaction, forming three rings in one synthetic step:

Scheme 2. 27. Preparation of substituted calix[4]arenes.



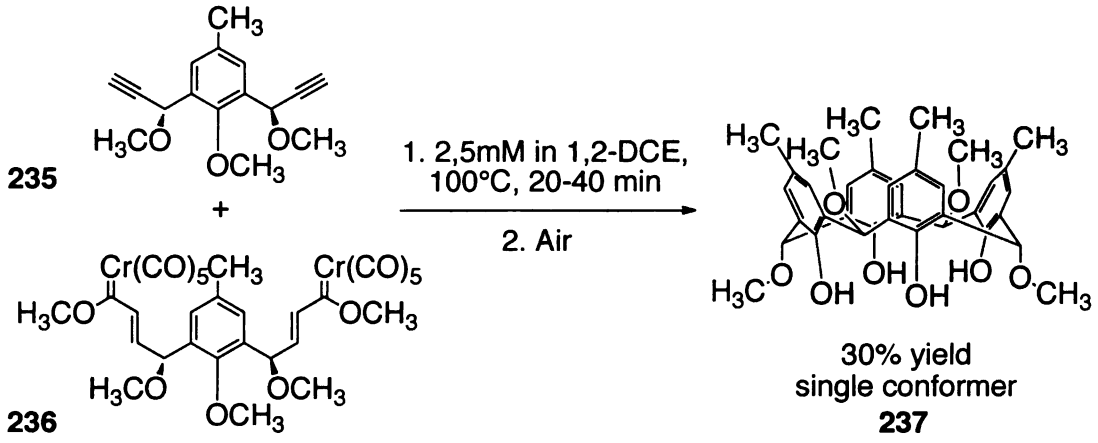
Compound	R_1	R_2	R_3	R_4	Yield **234**, %
234a	Me	OMe	Me	OMe	36
234b	Me	*n*-Hex	Me	*n*-Hex	22
234c	Me	Ph	Me	Ph	35
234d	Ph	OMe	Ph	OMe	41
234e	Me	OMe	Me	Ph	31
234f	Ph	OMe	Me	Ph	35
234g	Me	OMe	Me	*n*-Hex	22
234h	Me	*n*-Hex	Ph	OMe	35
234i	Me	OMe	Ph	OMe	40

Even though this reaction is very closely related to Dr. Wang's cyclization shown in Scheme 2.20, the ideal conditions were found to be somewhat different: heating 2.5 mM solutions of carbene complex and diyne in 1,2-dichloroethane for 20 to 40 minutes gave the best yields of the target molecules. There is a report in the literature[117] describing 1,2-DCE as a solvent providing increased benzannulation reaction rates, but the reasons for such behaviour are not yet fully understood.

Preparation of calixarenes with chiral centers in the methylene bridges was also considered an opportunity for this reaction, since these types of calix[4]arenes have not

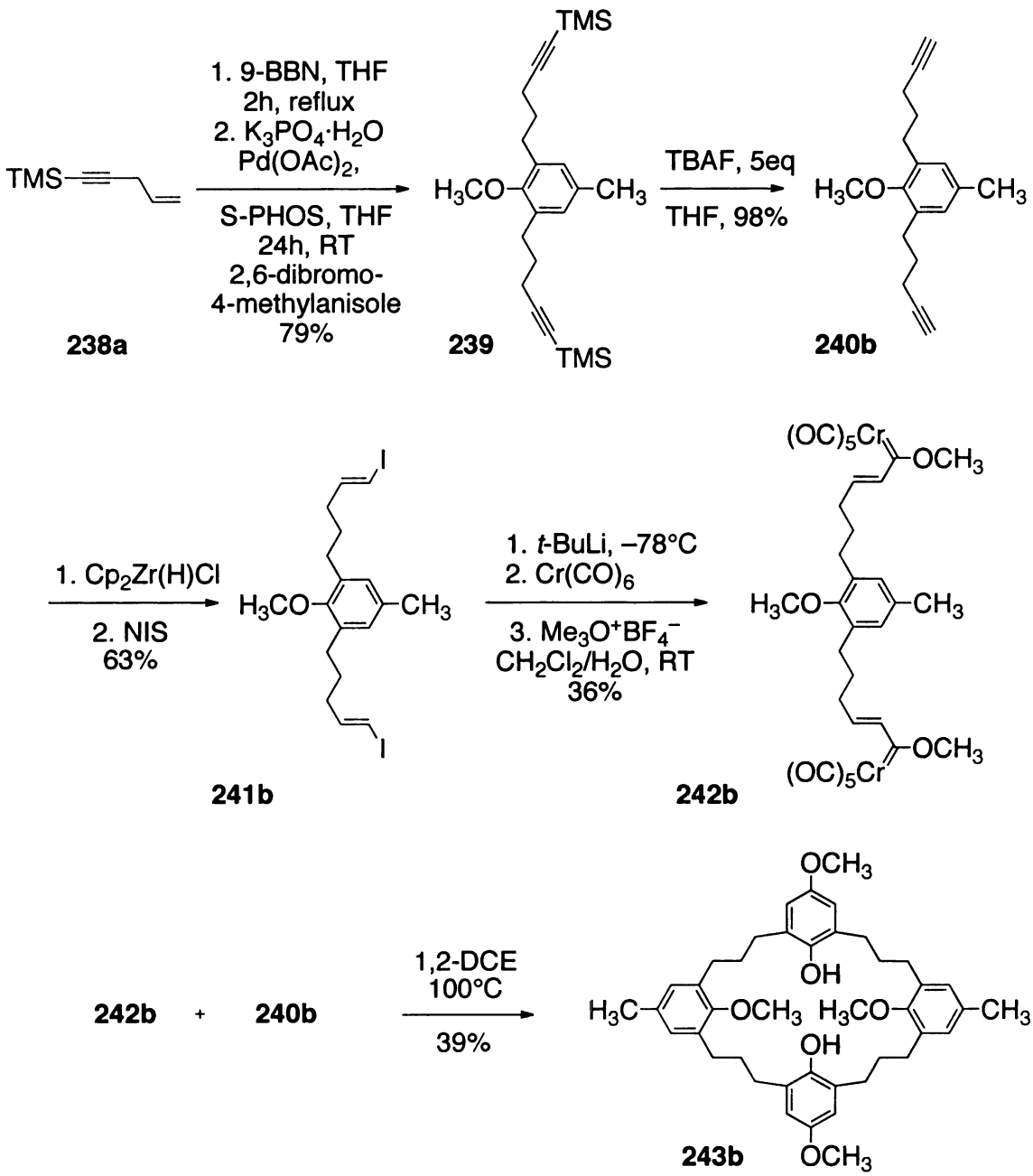
been made before in optically active form and certainly envisioned to have applications in chiral supramolecular recognition processes. Several diynes with methoxy groups in benzylic positions were prepared in optically pure form and used to make carbene complexes and ultimately chiral calixarenes. One such example is given in Scheme 2.28[118].

Scheme 2. 28. Preparation of chiral calix[4]arene **237**.



Finally, Dr. Gopalsamuthiram also described a single example of the synthesis of a homocalix[4]arene:

Scheme 2. 29. First example of homocalix[4]arene synthesis using benzannulation reaction.



Overall, the work of Dr. Gopalsamuthiram showed that the "triple annulation" is an efficient and highly convergent approach to the construction of various calix[4]arenes in a highly controllable way. This method does not have comparable analogs among known

calixarene synthesis methodologies, for it allows unprecedented generality and predictablility of substituent placement in the target molecules.

3. Concluding Remarks.

The benzannulation reaction of α,β-unsaturated chromium carbene complexes has proven to be a very useful method for macrocycle preparation. It was shown that the reaction remains effective even in the case of very large ring sizes. It was also demonstrated that this reaction can be used as a synthetic method for calixarene and homocalixarene preparation.

From Chapter 1, one can see that there is a lack of general methods for homocalixarene synthesis, and that availibility of these molecules often seems to be the limiting factor in their application. The benzannulation reaction appears to be a very good candidate to provide for such a general method. The following chapters will be dedicated to the application of chromium carbene complex macrocyclizations in homocalixarene synthesis, to the preparation of homocalixarenes on a practically useful scale, and to the chemical modification of homocalixarenes.

CHAPTER THREE

PREPARATION OF HOMOCALIXARENES BY TRIPLE ANNULATION APPROACH

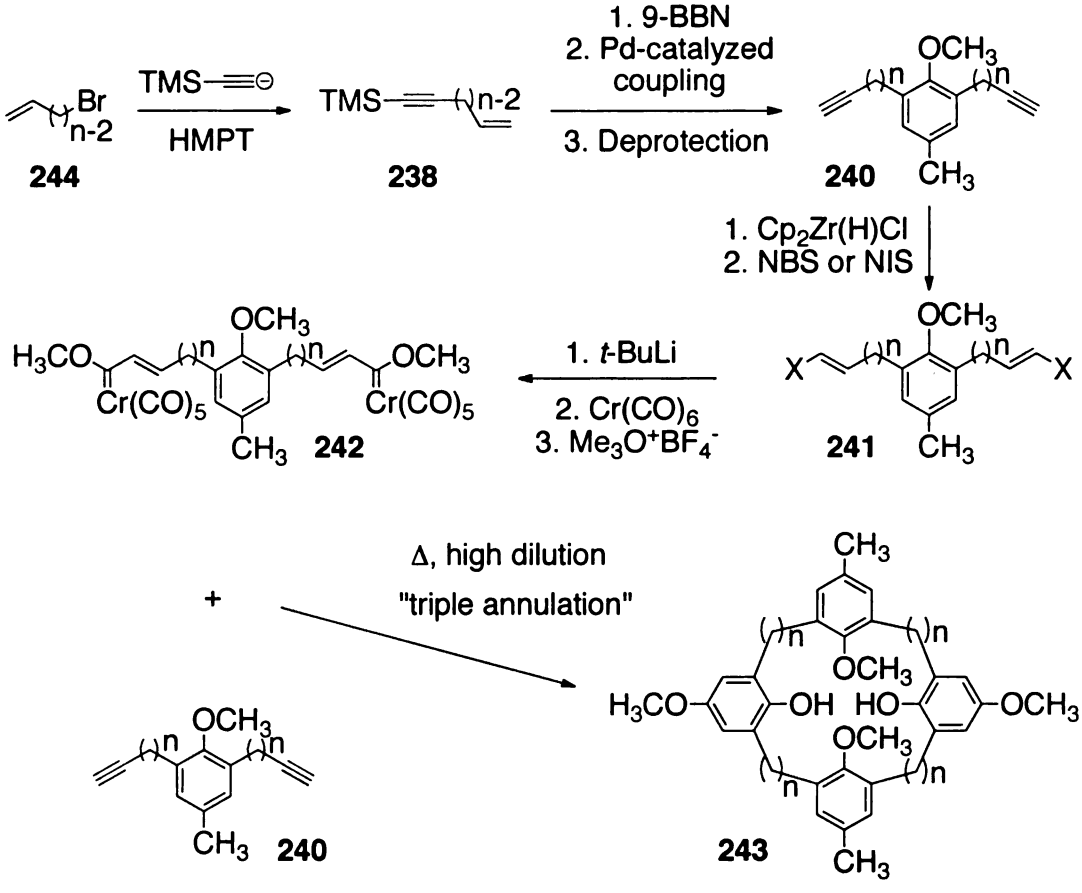
A science is any discipline in which the fool of this generation can go beyond the point reached by the genius of the last generation.

Max Gluckman

1. Initial Project.

As can be seen from Chapter 1, while homocalixarenes are very attractive synthetic targets altogether, there seems to be a significant lack of general and selective methods for their preparation. In order to bring about such a method, the "triple annulation" was envisaged to potentially be a very useful and general approach. The planned synthetic route is presented in Scheme 3.1:

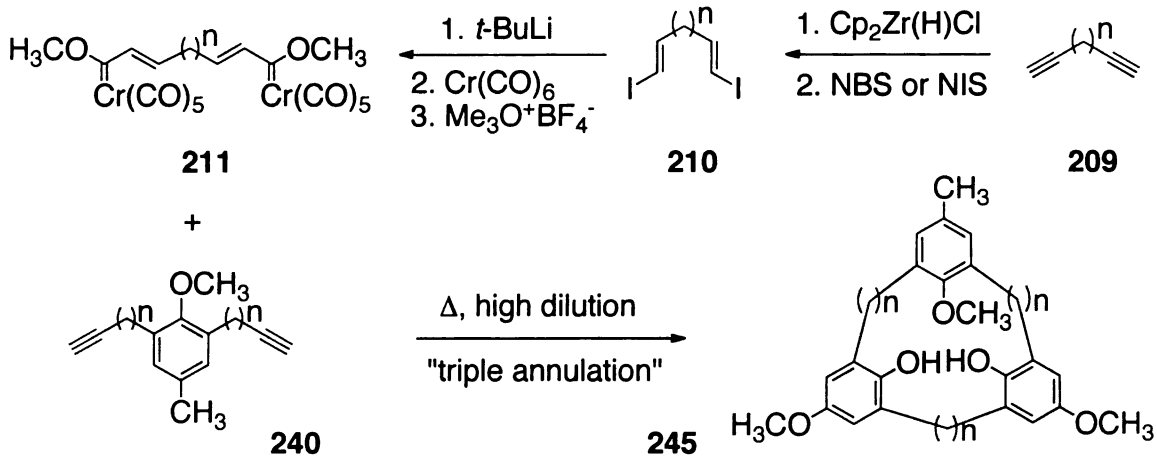
Scheme 3. 1. Planned synthesis of homocalix[4]arenes.



Key steps of this approach include: 1) preparation of aromatic diynes **240**, 2) their conversion into appropriate vinyl halides **241**, 3) making Fischer carbene complexes **242** *via* vinyl lithium derivatives, and 4) "triple annulation" by reacting carbene complexes **242** with the above-mentioned diynes **240**.

Somewhat later it was understood that homocalix[3]arenes **245** can also be prepared using aromatic diynes **240** and carbene complexes **211**, that can be made starting from relatively cheap, commercially available alkynes **209**:

Scheme 3. 2. Planned synthetic route to homocalix[3]arenes.

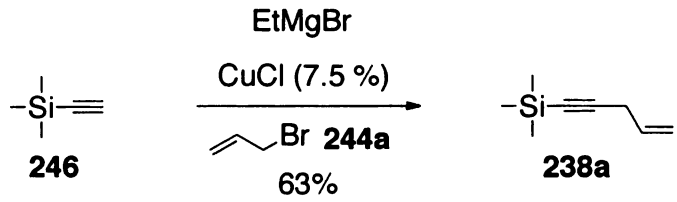


From what was known about similar reactions, it was not obvious what kind of solvent should be used for such cyclizations. Dr. Gopalsamuthiram found 1,2-dichloroethane to be the best solvent for making calix[4]arenes[118], while Dr. Wang's solvent of choice was THF[113]. Also, the effectiveness of the "triple annulation" had to be tested on large rings (e.g. for n = 11, **243** contains a 56-membered ring!) and on larger scale; due to high dilution, often significant amounts of solvents have to be used, which in turn limits the possbility of freeze-thaw degassing, etc.

2. Preparation of Aromatic Alkynes.

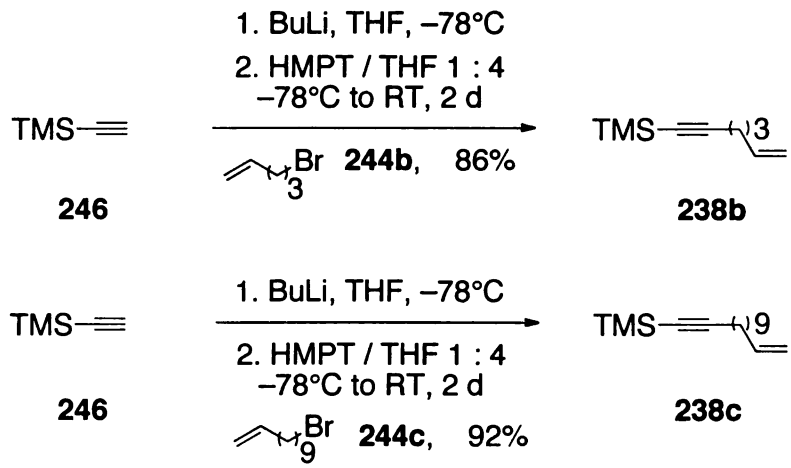
In order to prepare diynes **240**, we first had to find a (preferably general) method of making various enynes of type **238**. Enyne **238a** was prepared using facile copper-catalyzed coupling of Grignard reagent with 3-bromopropene (Scheme 3.3)[119]. Albeit being simple and efficient on ~ 25 g scale, this method is only effective for this particular (allylic) bromide.

Scheme 3. 3. Preparation of enyne **238a**.



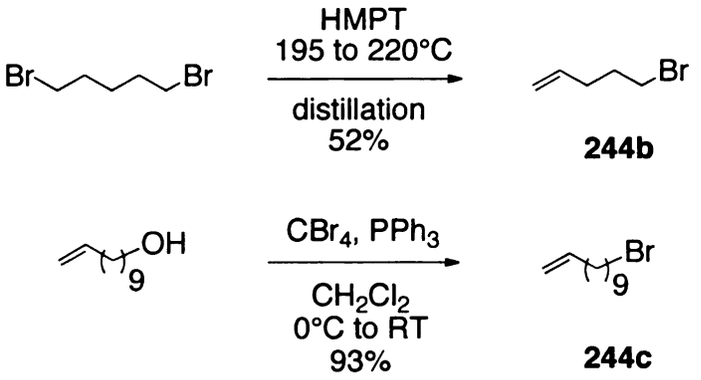
In order to prepare larger enynes, one can take advantage of the many methods that have been developed for acetylene alkylation. Reactions in liquid ammonia are not applicable in the case of trimethylsilylacetylene **246**, since alkali metal amides are known to break the C-Si bond of alkynes[120]. Thus, deprotonation of TMS-acetylene with *n*-butyllithium with subsequent addition of the corresponding bromide **244** in HMPT-THF mixture was used[121]. Reactions turned out to be somewhat slow, but very efficient and clean (Scheme 3.4). No column purification or distillation are necessary.

Scheme 3. 4. Preparation of enynes **238b** and **238c**.



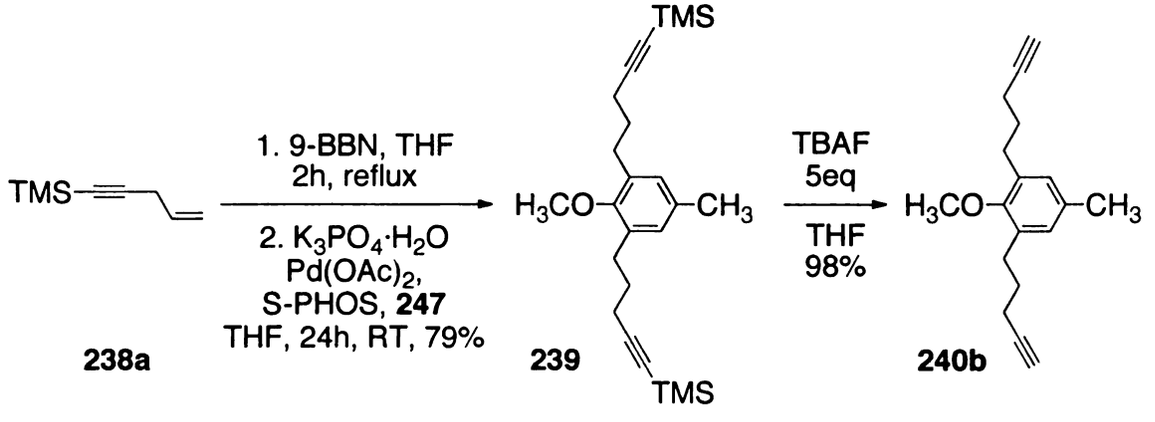
Bromides **244b** and **244c** were prepared according to the literature procedures employing cheap starting materials – 1,5-dibromopentane[122] and 10-undecen-1-ol[123].

Scheme 3. 5. Preparation of bromides **244b** and **244c**.



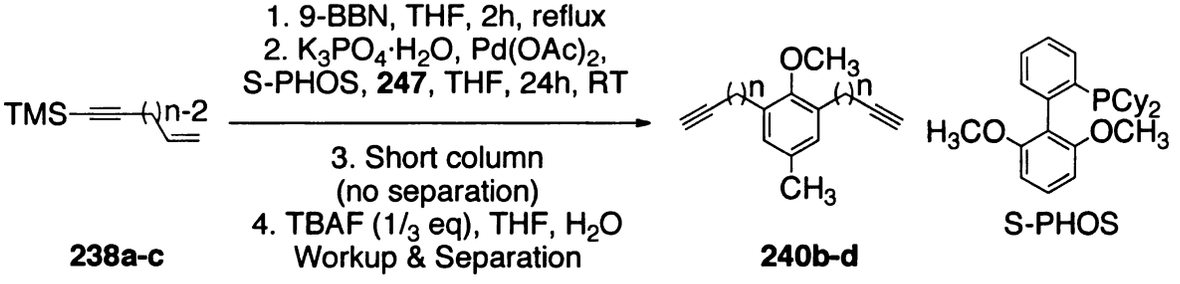
The next step was a palladium-catalyzed double coupling of alkynyl 9-BBN derivatives with 1,3-dibromo-2-methoxy-5-methylbenzene **247**. Dr. Gopalsamuthiram has described the coupling of enyne **238a** with aromatic dibromide **247** to proceed smoothly at room temperature in 24 h (1% palladium acetate, 2% S-PHOS ligand), as well as at 70°C in 8h (2% palladium acetate, 4% S-PHOS ligand) with almost no difference in the yield (~70%)[124]. He has also discovered that column purification of the resulting silylated product is usually quite tedious. Deprotection with 5 equivalents of TBAF was found to give a more chromatographically polar product **240b**.

Scheme 3. 6. Synthesis of **240b** reported by Dr. Gopalsamuthiram.



Thus, it was decided to run the two steps without purification of the TMS-protected diynes. After simple work-up, the intermediate TMS-diynes were treated with TBAF. It was also found that 1/3 equivalent of TBAF in wet THF[125] gives good yields of deprotected diynes **240**. Final purification of the product was smooth and unproblematic; yields over two steps were around 70% (Scheme 3.7).

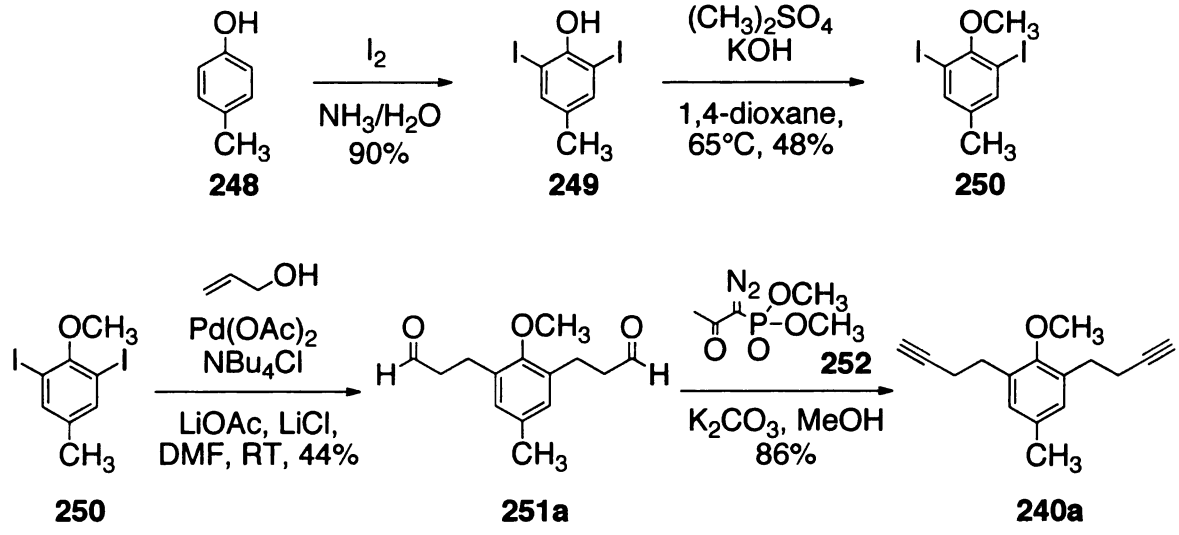
Scheme 3. 7. Improved synthesis of aromatic diynes **240**.



n = 3, 68%; n = 5, 72%; n = 11, 66%

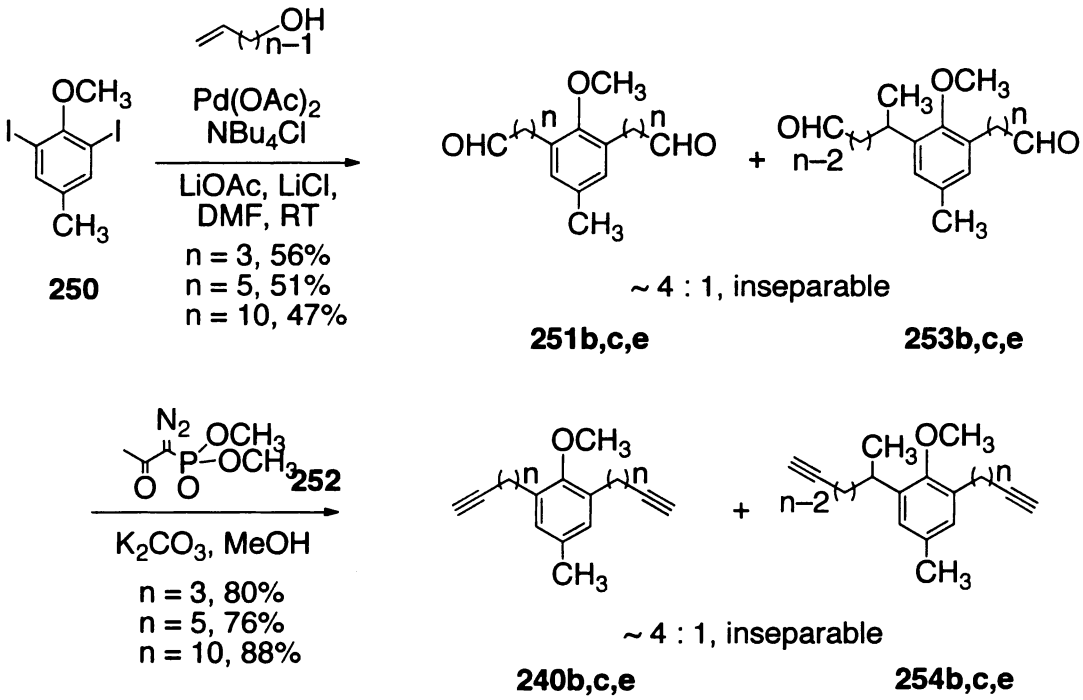
The preparation of diyne **240a** (n = 2) was accomplished in a different fashion (Scheme 3.8). Iodination[126] and methylation[127] of *para*-cresol afforded 2,6-diiodo-4-methylanisole **250**, which was converted into dialdehyde **251a** by Heck reaction under Jeffery conditions (in presence of a quaternary ammonium salt and lithium acetate as a base). In the course of this reaction the double bond of the allylic alcohol is shifted to the end of the chain, giving the unbranched aldehyde as major product[128]. Finally, diyne **240a** was prepared in 86% yield by treatment of **251a** with Bestmann-Ohira reagent, dimethyl-1-diazo-2-oxopropylphosphonate **252**[129].

Scheme 3. 8. Preparation of diyne **240a**.



It also should be noted that an approach analogous to the one in Scheme 3.8 could be envisaged for higher homologues of acetylene **240a** due to the fact that under the conditions described, the double bond usually migrates down the carbon chain for a very significant distance[128]. Indeed, such a migration was found to take place. Unfortunately, the resulting aldehydes were also found to be contaminated by an inseparable impurity, most probably a branched isomer of the target dialdehyde. Even when the mixture was treated with Bestmann-Ohira reagent, the resulting diyne still had about 20% of an isomeric impurity that could not be separated.

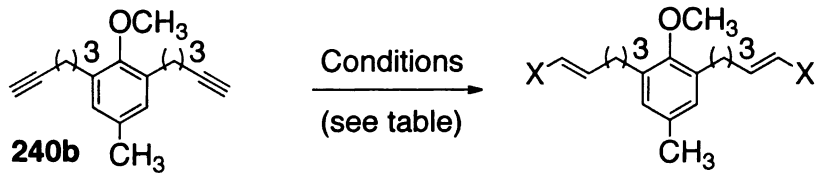
Scheme 3. 9. Attempted alternative preparation of diynes **240**.



3. Preparation of Vinyl Halides.

Initially, both vinyl bromides and iodides were considered equally usable in Fischer bis-carbene complex preparation. Vinyl bromides have an advantage of being significantly more stable, while vinyl iodides provide significantly faster halide-lithium exchange in most solvents. The results of different methods tested on preparation of the diiodide **241b** or the analogous bromides are shown in Scheme 3.10:

Scheme 3. 10. The search for the best vinyl halide preparation method.



X	Method	Yield, %
I	$Cp_2Zr(H)Cl$, 1 h, THF, then NIS, 4 h, THF	25 - 55
I	Cp_2ZrCl_2 + SuperHydride, 1 h, then NIS, 4 h, THF	44
I	**$HBBr_2{\cdot}SMe_2$, 4 h, then NaOH, I_2, Et_2O/H_2O, 0°C, 30 min**	**40-48**
I	**$Cp_2Zr(H)Cl$, CH_2Cl_2, 15 min, then I_2, 0°C to RT, 15 min**	**77**
I	Catecholborane, H_2O, then NaOH, I_2, Et_2O/H_2O, 0°C, 30 min	0
Br	$Cp_2Zr(H)Cl$, 1 h, THF, then NBS, 4 h, THF	44
Br	Catecholborane, then H_2O, then NBS, CH_3CN	0
Br	DIBAL-H, then NBS	0
Br	Catecholborane, then H_2O, then $Hg(OAc)_2$, then Br_2	0
Br (cis)	Catecholborane, then Br_2, then CH_3ONa	62

Later from various experiments it came to be understood that the corresponding bis-vinyl lithium derivatives have a fairly poor stability in THF even at –78°C, and it was crucial to be able to exchange the halide for lithium rapidly. Also, vinyl iodides of type **241** that have more than 1 methylene group between the aromatic ring and the double bond were surprisingly found to possess significant thermal and photolytic stability. These observations have focused the scope of usable vinyl halides to only iodides.

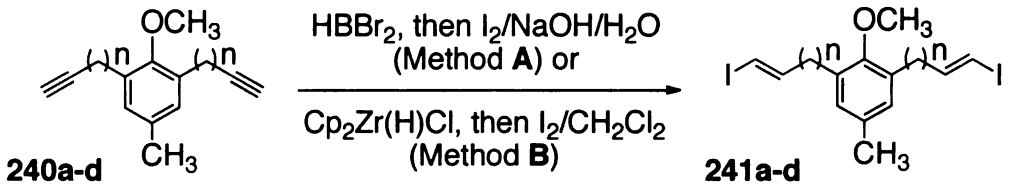
The drawbacks of using Schwartz reagent are its instability and cost. The use of dichloromethane as solvent, first reported in similar reaction by Jacobsen[130], allows the reaction to proceed very fast and with minimal excess of the zirconium reagent, and also employs iodine instead of light-sensitive and relatively expensive N-iodosuccinimide.

As an alternative to zirconium-based methods of vinyl iodide preparation, dibromoborane addition[131] was employed for the same purpose with moderate effectiveness (~ 40 - 50% yield). While dibromoborane does provide a cheaper alternative to zirconium reagents, it

should be noted that in an attempt to run several reactions on larger scale (~ 20 mmol), even lower yields (~ 20%) were observed, while Schwartz reagent addition still provided excellent yields on the same scale.

Thus, two methods were found generally usable to prepare vinyl iodides; the summary of those methods applied to aromatic diynes is presented in Scheme 3.11:

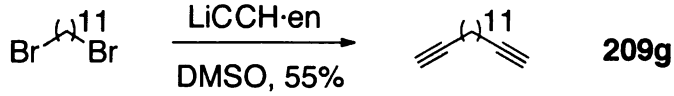
Scheme 3. 11. Preparation of vinyl iodides **241**.



Product	n	Method	Yield, %
241a	2	**A**	37
241a	2	**B**	89
241b	3	**A**	48
241b	3	**B**	77
241c	5	**A**	45
241c	5	**B**	80
241d	11	**A**	43
241d	11	**B**	93

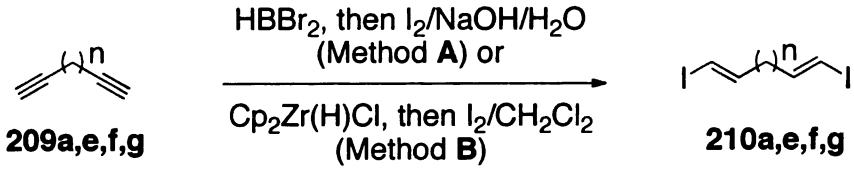
In the case of aromatic alkynes **240** that have to be prepared in a multistep synthesis, the method involving Schwartz's reagent actually becomes *cheaper* per gram of the target product due to the significantly higher yield. The situation is somewhat different with the cheap commercial alkynes **209a**, **209e** and **209f** (Scheme 3.13). Diyne **209g** was prepared using the procedure described below from 1,11-dibromoundecane[132].

Scheme 3. 12. Preparation of diyne **209g**.



209g

Scheme 3. 13. Preparation of linear diiodides **210**.



209a,e,f,g **210a,e,f,g**

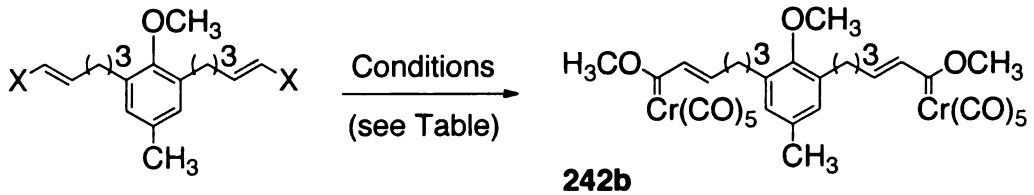
Product	n	Method	Yield, %
210a	2	**A**	40
210a	2	**B**	90
210e	3	**A**	46
210e	3	**B**	75
210f	5	**A**	63
210f	5	**B**	79
210g	11	**A**	-
210g	11	**B**	90

All of the resulting diiodides are stable compounds that can be stored at –20°C under argon in the dark for several months without any significant decomposition.

4. Preparation of Carbene Complexes.

The most popular (and usually most effective) method for chromium carbene complex preparation remains the original method of Fischer[133], with some modifications in solvents, reaction temperatures, times, equivalents of reagents, *etc.* As described in Dr. Gopalsamuthiram's dissertation, the yields for the bis-carbene complexes he prepared usually ranged from 20 to 40%, significantly decreasing the effectiveness of the method. Thus it was reasonable to try and improve the preparation of bis-carbene complexes by tweaking the above mentioned conditions. The results are summed up in the Scheme 3.14; just like with the diiodides, carbene complex **242b** (n = 3) was chosen for model studies.

Scheme 3. 14. Model studies on preparation of Fischer bis-carbene complexes.



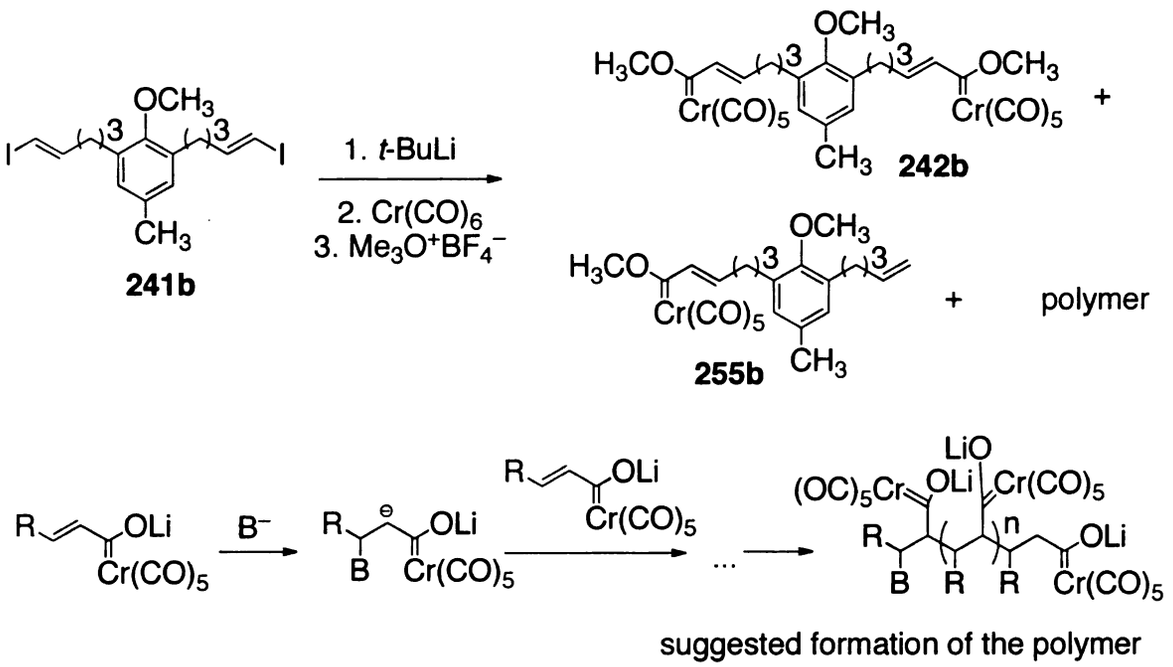
242b

X	Method	Yield, %
I	*t*-BuLi, –78°C, THF, 30 min; <-- $Cr(CO)_6$, THF, –78°C to RT, 3 h[a]	36
Br	*t*-BuLi, –100°C, THF, 30 min; --> $Cr(CO)_6$, THF, –100°C to RT, 3 h	10
Br	*t*-BuLi, –78°C, Et_2O, 30 min; --> $Cr(CO)_6$, Et_2O, –78°C to RT, 3 h	5
I	*t*-BuLi, –95°C, THF, 10 min; --> $Cr(CO)_6$, THF, RT (40°C bath), 15 min	48
I	**t-BuLi, –95°C, THF; --> $Cr(CO)_6$, THF, RT (40°C bath), 15 min**	**79**

[a] Arrows "<--" and "-->" indicate which solution is being added *via* cannula into the other solution

With these data in hand, several conclusions were made. First, it was understood that bis-vinyllithiums are not stable enough at –78°C, and lower temperatures should be employed. Second, the main byproducts whose formation results in the lowering of the yield of the target carbene complex were identified to be the partially reduced complex **255b** and in addition red polymeric material of unknown nature, the latter being the predominant by-product. Even though the mechanism of the polymer formation is unknown, one can hypothesize that the α,β-unsaturated nature of the carbene complex allows the base catalyzed polymerization consisting of a series of Michael additions, catalyzed by the presence of excess organolithium species (Scheme 3.15):

Scheme 3. 15. Byproducts of bis-carbene complex preparation.



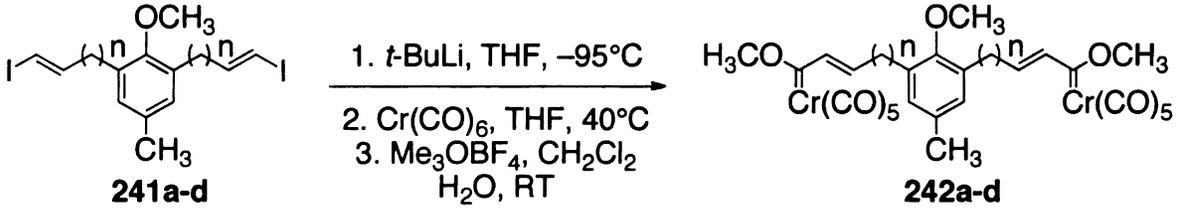
Third, despite the poor solubility of $Cr(CO)_6$ in THF at low temperatures, whenever the vinyllithium is added to chromium carbonyl even at –78°C in THF, the reaction mixture turns yellow immediately. This suggests that reaction has very low activation barrier, and should be nearly diffusion controlled at room temperature.

Altogether, from the abovementioned facts about the side reactions one can suggest the following changes: 1) *tert*-butyllithium excess should be avoided, since strong bases can initiate carbene salt polymerization; 2) low reaction temperature should be maintained for bis-vinyllithium preparation; 3) fast addition of the bis-vinyllithium into warm chromium carbonyl solution might be beneficial for the overall yield of the process. When all these factors were taken into consideration, the best conditions (shown in Scheme 3.14 in bold) were achieved: bis-vinyllithium is generated in THF at –95°C, and immediately transferred into stirred chromium carbonyl solution, placed into a ~ 40°C water bath to

maintain constant positive reaction temperature. The sequence is very quick, and allows the formation of the target carbene complex in very high 79% yield.

For carbene complexes with an aromatic nucleus, this protocol worked well for all tether lengths from n = 2 to 11. The yields are given in Scheme 3.16.

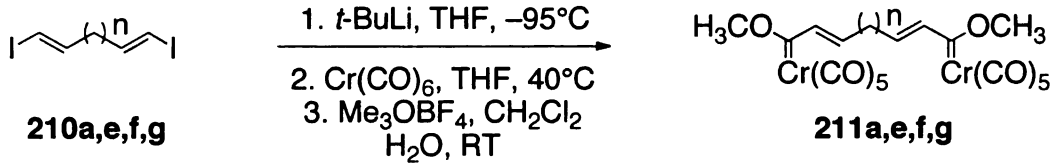
Scheme 3. 16. Preparation of aromatic bis-carbene complexes **242**.



Product	n	Yield, %
242a	2	67
242b	3	79
242c	5	68
242d	11	49

For non-aromatic bis-carbene complexes **211**, this procedure was equally effective (Scheme 3.17). It is interesting to notice that, while for aromatic carbene complexes **242** the beneficial effect of immediate bis-vinyllithium transfer was very significant, the yield of non-aromatic complexes **211** remained virtually the same if the reaction mixture was allowed to stir for 15 min at –95°C after *tert*-butyllithium addition.

Scheme 3. 17. Preparation of non-aromatic carbene complexes **211**.



210a,e,f,g **211a,e,f,g**

Product	n	Yield, %
211a	2	65
211e	3	71
211f	5	75
211g	11	67

Altogether, a very significant increase in the yield of bis-carbene complexes was achieved. Also, this procedure has proven to be quite clean, producing only trace amounts of abovementioned polymeric material and mono-carbene **255** (Scheme 3.15). Thus, preparation of multigram amounts of bis-carbene complexes in one loading was made possible.

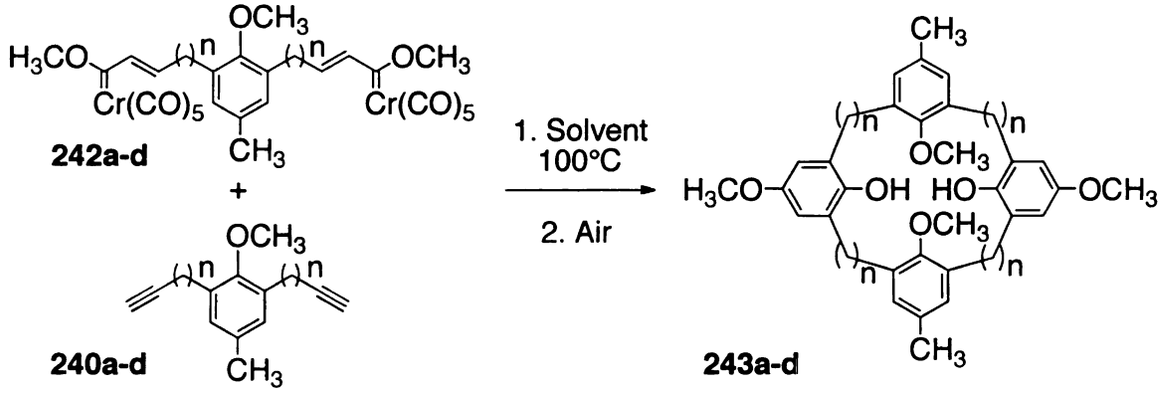
5. Cyclization Reactions Giving Homocalixarenes and their Properties.

Cyclization reactions were studied with two purposes: 1) finding the conditions giving the highest yield, and 2) finding the conditions that allow relatively large-scale preparations. The conditions for macrocyclizations were described by Dr. Wang and Dr. Gopalsamuthiram in their Ph.D. dissertations. For such cyclizations, three solvents (THF, 1,2-dichloroethane, and 1,4-dioxane) were tested. 1,2-Dichloroethane gave the highest yields in the preparation of substituted calix[4]arenes[118]. Tetrahydrofuran was a solvent of choice in Dr. Wang's work[113]. 1,4-Dioxane was expected to be similar to THF and would be expected to have an advantage of allowing the benzannulation reaction to be conducted at atmospheric pressure due to its high boiling point (101.1°C). This, together

with nitrogen bubbling instead of freeze-thaw degassing, could help increase the loads significantly.

For homocalix[4]arenes, the results that were obtained are summarized in the Scheme 3.18.

Scheme 3. 18. Preparation of homocalix[4]arenes by the "triple annulation" method.



Product	n	Solvent[a]	Yield, %
243a	2	THF 1,2-DCE 1,4-dioxane	25 35 22
243b	3	THF 1,2-DCE 1,4-dioxane	25 39 25
243c	5	THF 1,2-DCE 1,4-dioxane	27 10 17
243d	11	THF 1,2-DCE 1,4-dioxane	13 0 18[b]

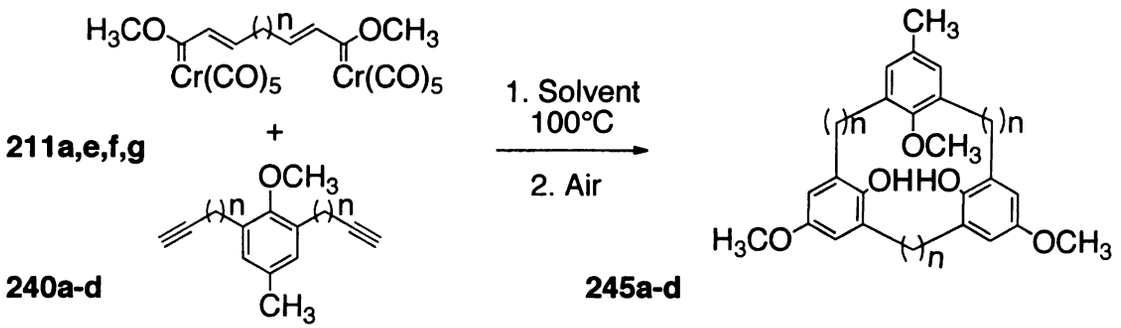
[a] Reactions in THF and 1,2-DCE were degassed by freeze-thaw method, while reactions in 1,4-dioxane were degassed by bubbling nitrogen through the solution for several hours;
[b] Reaction was conducted at 115°C.

Overall, 1,2-dichloromethane was found to give the highest yields for short tether lengths, but the yields dramatically fell with longer tether lengths. Only the 99.8% anhydrous 1,2-dichloroethane from Sigma - Aldrich can be used for this reaction; the

yields are drastically diminished with lower quality solvent, even if it is freshly distilled from calcium hydride. The ethereal solvents - THF and 1,4-dioxane - gave similar results, but reactions were a lot more reproducible and the yields did not fluctuate depending on the solvent quality. It is interesting to notice that the biggest macrocycle **243d** that was prepared by this method gave a higher yield at 115°C (18%) than at 100°C (13%).

Based on the results in Scheme 3.18, only THF and 1,4-dioxane were tested for homocalix[3]arene preparation (Scheme 3.19).

Scheme 3. 19. Preparation of homocalix[3]arenes by the "triple annulation" method.



Product	n	Solvent[a]	Yield, %
245a	2	THF 1,4-dioxane	9 17
245b	3	THF 1,4-dioxane	30 31
245c	5	THF 1,4-dioxane	28 25
245d	11	THF 1,4-dioxane	10 11[b]

[a] Reactions in THF were degassed by freeze-thaw method, while reactions in 1,4-dioxane were degassed by bubbling nitrogen through the solution for several hours;
[b] Reaction was conducted at 115°C.

The yield of **245d** does not improve significantly at elevated temperature; reaction in 1,4-dioxane at 115°C gave a result practically identical to THF at 100°C (11 and 10%, respectively). Macrocycle **245a** possesses significant ring strain and gives low yield in

THF (9%), but this improves to 17% in 1,4-dioxane at 100°C. If this cyclization is conducted at 115°C, the yield actually is slightly decreased (15%).

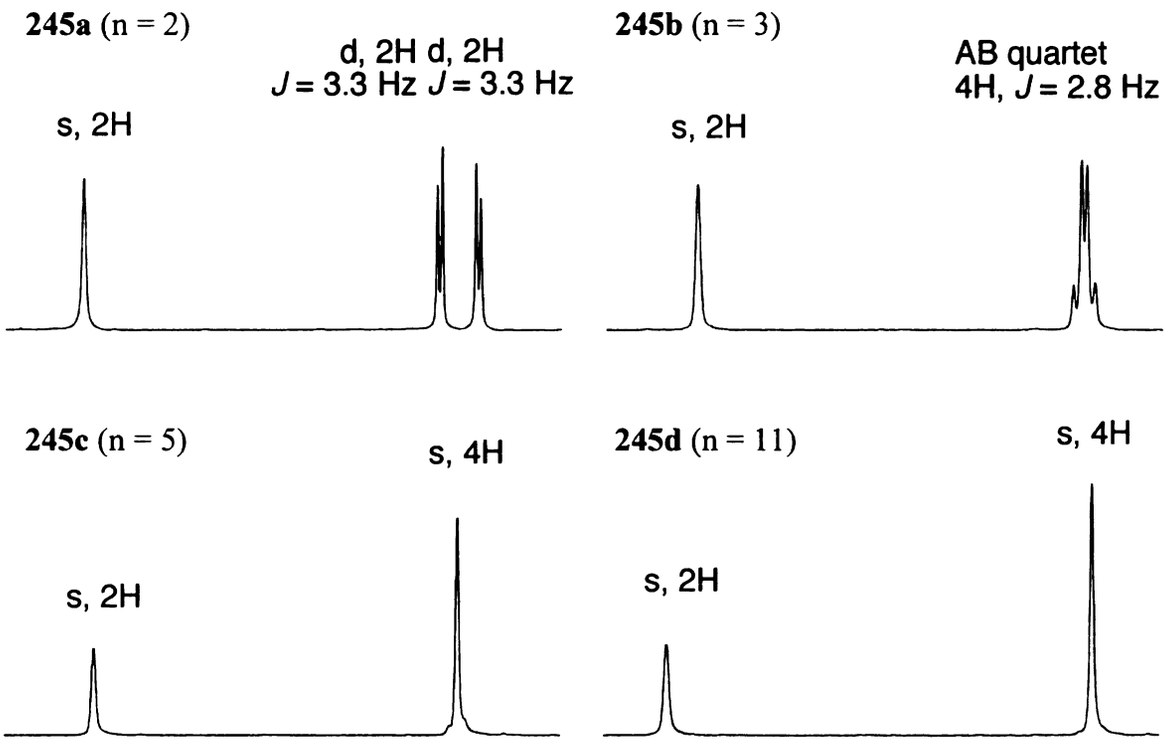
All of the eight macrocycles described above have never been prepared before. Table 3.1 summarizes some of their physical and spectroscopic properties.

Table 3. 1. Selected physical properties of homocalixarenes **243** and **245**.

Compound	**243a**	**243b**	**243c**	**243d**	**245a**	**245b**	**245c**	**245d**
mp, °C	180	155	153	44	181	159	142	58
δ(OH), ppm	5.48	5.67	4.58	4.29	4.01	5.74	4.77	4.29
ν(OH), cm^{-1}	3490	3390	3453	3480 3613	3499	3414	3455	3486 3613

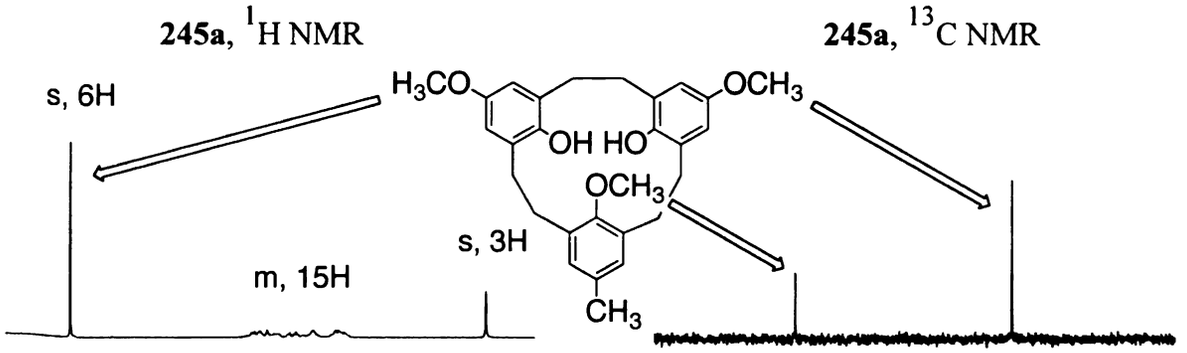
Interestingly, the series of homocalix[3]arenes **245** (n = 2, 3, 5, and 11) shows a very illustrative change in aromatic region of the ^{1}H-NMR spectrum (Figure 3.1). While the aromatic hydrogens in the phenolic rings of larger cycles (n = 5, 11) give singlets around 6.5 ppm, in case of n = 3 they present themselves as a classic AB quartet (J = 2.8 Hz, C = 2.6 Hz), shifting even more apart, to an almost perfect AX case, for n = 2 (2 doublets with J = 3.3 Hz).

Figure 3. 1. Changes in ^{1}H-NMR spectrum in homocalix[3]arenes **245**.



It is also worth noticing that the ^{1}H-NMR spectrum of compound **245a** lacks the signal from one of the $-OCH_3$ groups, usually found in the region between 3.5 and 3.7 ppm. The corresponding signal in ^{13}C-NMR spectrum is still present (Figure 3.2).

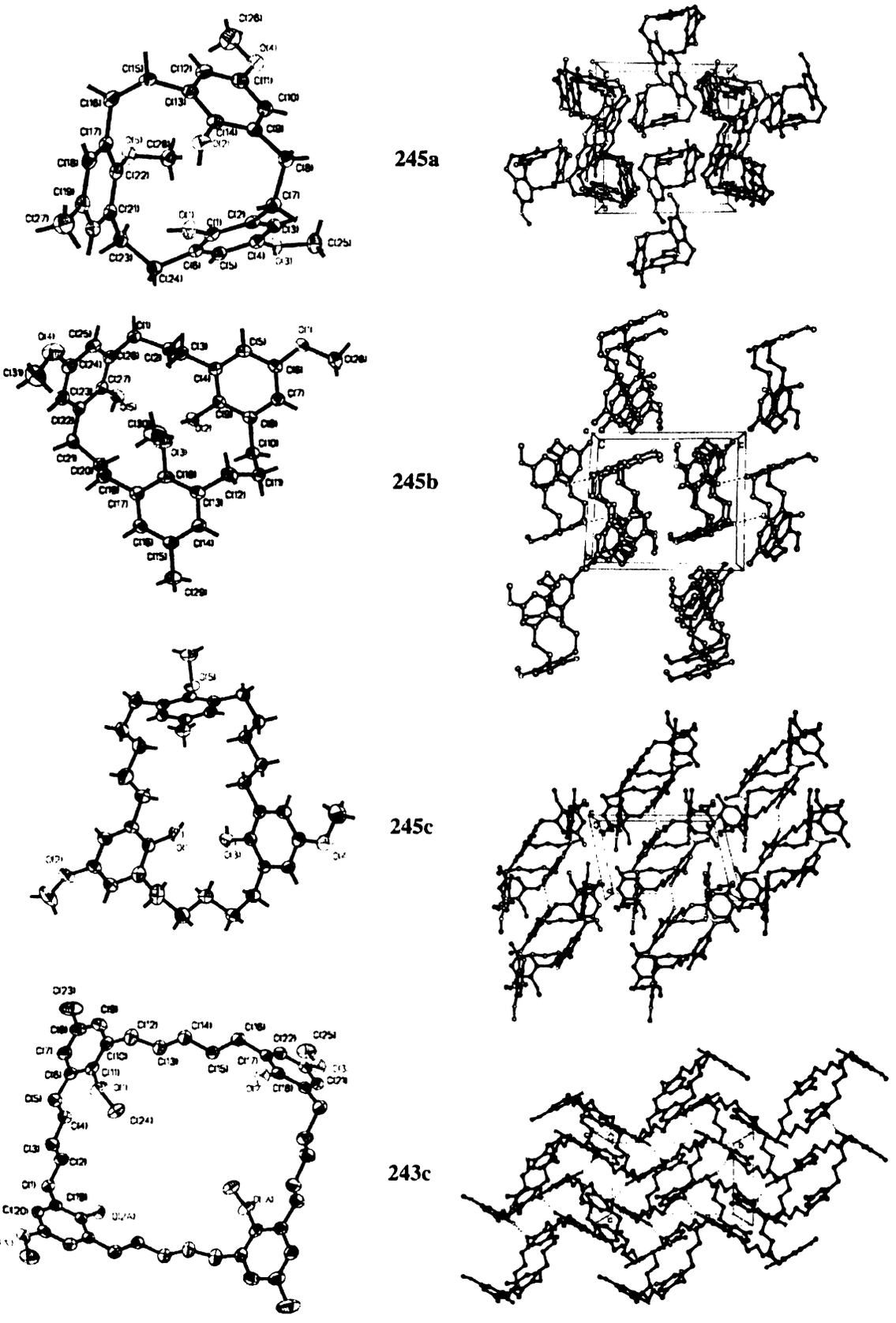
Figure 3. 2. "Missing" methoxy group in the ^{1}H-NMR spectrum of **245a**.



This can be explained by the possibility of shielding effect by one of the neighboring aromatic rings due to conformational rigidity of **245a**. The hypothesis is confirmed by the integral intensity of multiplet at 2.78 – 3.12 ppm (15 hydrogens instead of expected 12) As can be seen from the 3D-diagram of the macrocyclic molecule in the crystal form (Figure 3.3), this suggestion seems legitimate, because the lower rim methoxy group is positioned close to one of the benzene rings.

For 4 out of the 8 target products, X-ray single crystal analysis was performed in order to confirm the structure, and to see the patterns in hydrogen bonding and crystal packing. In Figure 3.3, on the left the single molecule conformation is presented, while on the right the elementary cell structure is given.

Figure 3. 3. Crystal structures of macrocycles **245a-c** and **243c**.



For homocalix[3]arene **245a** (n = 2), the structure was solved in the space group $P2_1/n$. The unit cell was found to belong to a monoclinic crystal system ($\alpha = \gamma = 90°$, $\beta = 100.8°$), with 4 molecules per cell. No intermolecular hydrogen bonding was discovered; the only hydrogen bond found was between two phenolic OH groups of the same molecule, with d(H···O) = 2.160 Å.

For homocalix[3]arene **245b** (n = 3), the structure was solved in the space group P_1. The unit cell was found to belong to a triclinic crystal system ($\alpha = 88.9°$, $\beta = 82.3°$, $\gamma = 70.6°$), with 2 molecules per cell. Both inter- and intramolecular hydrogen bonding was discovered. The intramolecular hydrogen bond between one of the phenolic OH groups and the lower rim OCH_3 was found to have d(H···O) = 1.805 Å, and the intermolecular hydrogen bond between two phenolic OH groups was found to have d(H···O) = 2.066 Å.

For homocalix[3]arene **245c** (n = 5), the structure was solved in the space group P_1. The unit cell was found to belong to a triclinic crystal system ($\alpha = 88.3°$, $\beta = 71.8°$, $\gamma = 77.6°$), with 2 molecules per cell. Only intermolecular hydrogen bonding was discovered for this molecule. The intermolecular hydrogen bond between two phenolic OH groups was found to have d(H···O) = 1.993 Å, and the intermolecular hydrogen bond between the phenolic OH group and the upper rim OCH_3 was found to have d(H···O) = 2.178 Å.

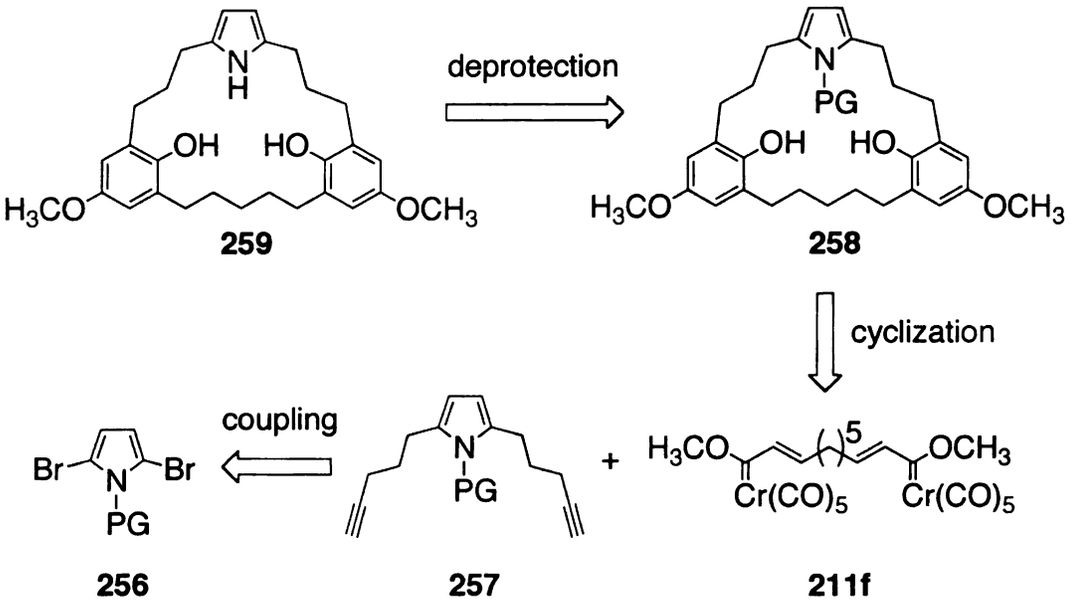
Finally, homocalix[4]arene **243c** (n = 5) had the structure solved in the P_{bca} space group. The unit cell was found to belong to an orthorhombic crystal system ($\alpha = \beta = \gamma = 90°$), with 4 molecules per cell. Due to the symmetry of the crystal, only one kind on hydrogen bond was present: an intermolecular bond between a phenolic OH group and the lower rim OCH_3 group that was 2.044 Å long.

It is interesting to notice that the series minimum for the O–H stretching in the IR spectra in the solid state and the maximum of the chemical shift (δ, ppm) for the hydroxyl proton in the ^{1}H NMR spectrum in chloroform solutions both fall on macrocycles **243b** and **245b**, having three-carbon tethers between aromatic rings (Table 3.1). Macrocycle **245b** was also found to have the shortest H···O distance in the crystal among all determined structures. It seems reasonable to assume that the conformational strain is minimal in the case of n = 3, which facilitates intramolecular hydrogen bonding both in solution and in solid state.

6. Testing the New Method: Synthesis and Structure of a Pyrrole-Containing Macrocycle.

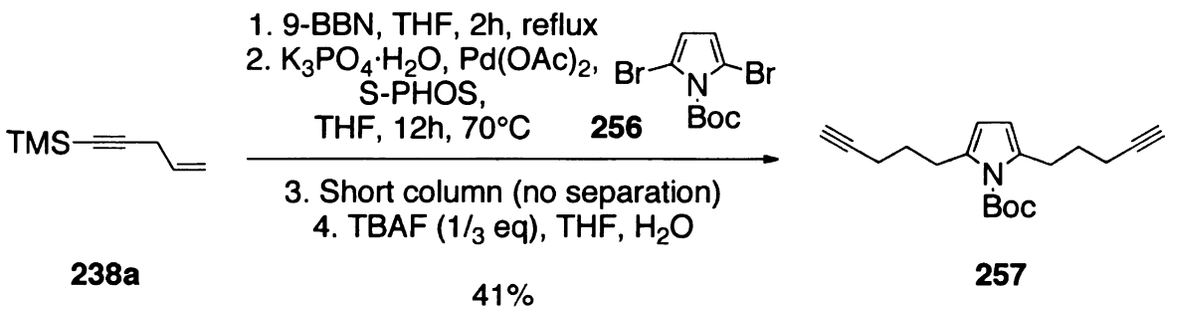
In an attempt to demonstrate the usability of the new method in advanced homocalixarene preparation, a synthetic target containing a heterocyclic nucleus was chosen. It is known that homocalixarenes containing unprotected pyrroles interest supramolecular chemists for their potential as anionic receptors[134]. The synthesis of macrocycle **259** was envisaged to follow the basic strategy outlined in Scheme 3.20:

Scheme 3. 20. The strategy for the synthesis of macrocycle **259**.



Diyne **257** (PG = Boc) was prepared as described in Scheme 3.21. Protected 2,5-dibromopyrrole **256** was prepared by NBS bromination of commercially available *tert*-butyl 1*H*-pyrrole-1-carboxylate as has been described before[135]. The coupling of heterocyclic substrates is often problematic, so a higher-temperature, higher-catalyst load version of the Suzuki-Miyaura coupling procedure was employed. The resulting product was desilylated to afford **257** in 41% combined yield over two steps.

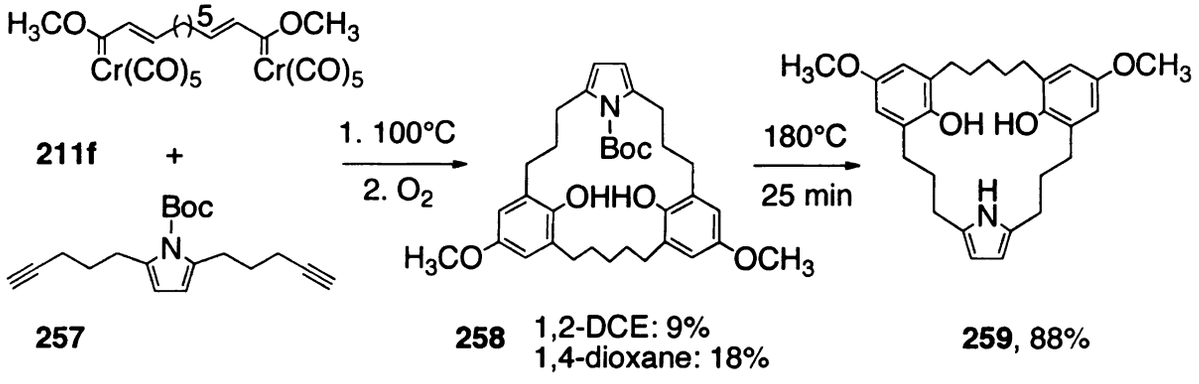
Scheme 3. 21. Preparation of heterocyclic diyne **257**.



The cyclization was attempted in two solvents, 1,2-dichloromethane and 1,4-dioxane. Reaction in 1,2-DCE proved to be less effective in this case, giving only a 9% yield of

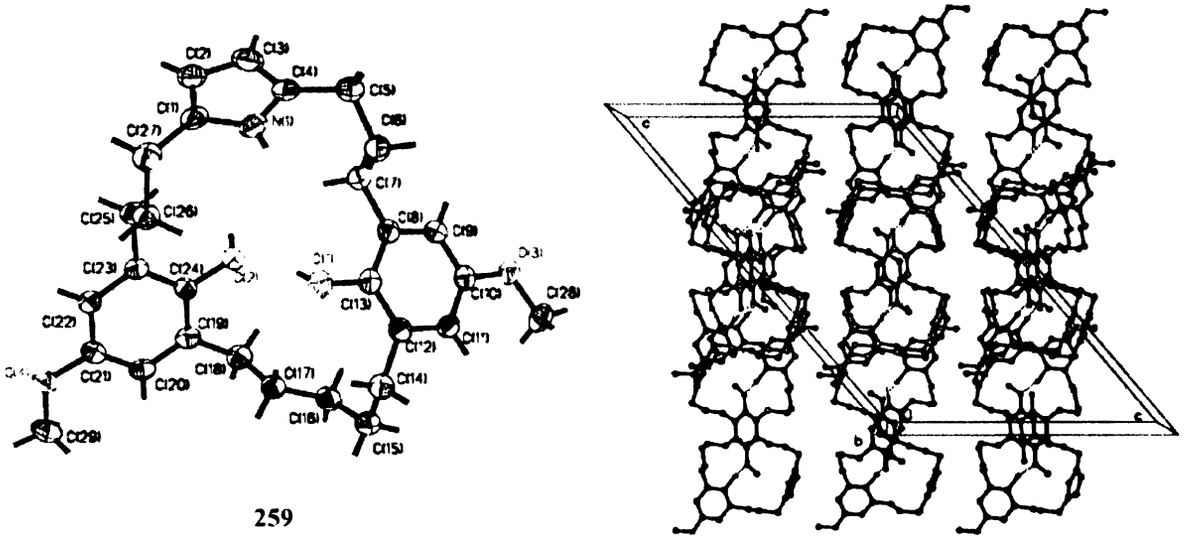
the target product. The latter solvent provided 18% yield of the protected product **258** in pure form as well as 5% yield of a fraction that consisted mainly of the deprotected product **259**. This deprotected material contained unidentified impurities that could not be removed by column purification, and was not used further. Thermal deprotection of **258** smoothly gave chemically pure **259** in 88% yield (Scheme 3.22).

Scheme 3. 22. Preparation of unprotected pyrrole-containing macrocycle **259**.



Compound **259** is moderately sensitive to oxygen, and dark-red polymeric material precipitates over time from its nearly colorless solutions when open to air. Despite that, it was only by slow crystallization in an open vial that a crystal good enough for an X-ray single crystal analysis could be obtained. The structures of the single molecule conformation and the elementary cell can be seen in Figure 3.4.

Figure 3. 4. Crystal structure of pyrrole-containing macrocycle **259**.



259

The structure of macrocycle **259** was solved in the space group C2/c. The unit cell was found to belong to the triclinic crystal system ($\alpha = \gamma = 90°$, $\beta = 130.3°$), with 8 molecules per cell. Intramolecular hydrogen bond was found between the two phenolic OH groups; d(H···O) = 1.993 Å. The intermolecular hydrogen bond between a phenolic OH group and upper rim OCH_3 group was found to have d(H···O) = 1.964 Å, and the intermolecular hydrogen bond between pyrrole NH and the upper rim OCH_3 was found to have d(H···O) = 2.264 Å.

7. Concluding Remarks.

Overall, the "triple annulation" method has proven successful in the preparation of a wide variety of homocalixarenes, with ring size spanning from 15 to 56 members. The yields of the final cyclization are low to moderate, but the reaction did not fail in a single case, and all of the previous steps are high yielding, opening the way for gram-scale preparation of homocalixarenes. The sequence is also relatively insensitive to the presence of various functional groups (the benzannulation reaction of Fischer carbene

complexes tolerate all but the most acidic and basic functionalities). Previously unknown pyrrole-containing macrocycle **259** was prepared in 3 steps from the known pyrrole **256**.

CHAPTER FOUR

HOMOCALIXARENE MODIFICATION: INTRODUCTION OF CARBON SUBSTITUENTS INTO THE LOWER RIM

Without change something sleeps inside us and seldom awakens.

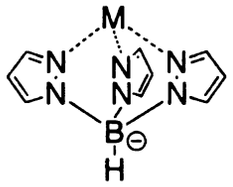
The sleeper must awaken.

Duke Leto Artreides, "Dune"

1. Pyrazole-Based Ligands and Homocalixarene Modification.

As can be seen from Chapter 1, homocalixarenes can have an enormous number of applications in supramolecular chemistry, as they can display an array of functionality and maintain a variety of rigid shapes at the same time. The method of homocalixarene preparation described in Chapter 3 *via* the "triple annulation" of carbene complexes is very general in terms of both ring size and tolerated functional groups. Logically, in order to make practical use of these homocalixarenes (as ligands, etc.) one would need to be able to modify these molecules in a systematic way. The search for efficient methods of such modification is the central theme of the current Chapter.

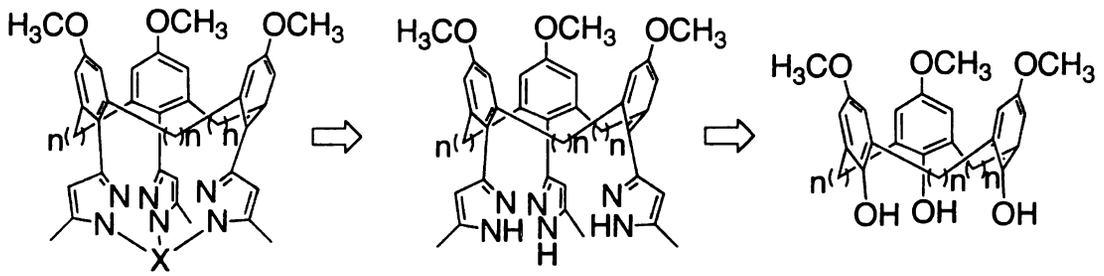
Scorpionates are a class of ligands widely applied in organometallic catalysis[136]. While not being very popular for quite a long time since their discovery in 1966, they have seen a lot of applications during last 25 years. One of the most typical ligands of this type, tris(pyrazolyl)borate (*Tp*), is isoelectronic to cyclopentadienyl (*Cp*), and makes stable complexes with metals from every group of the periodic table.



Tp

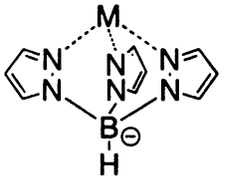
During our collaboration project with Prof. Figueroa (University of California at San Diego), it was suggested to us that ligands of the type **262** could be very useful in stabilizing unusual geometries in noble metals. Thus, the target of our part of the project was to make direct precursors of such ligands, namely **261**, based on homocalix[3]arenes **260**, possessing a C_3 axis of symmetry (Scheme 4.1):

Scheme 4. 1. Retrosynthetic analysis for calixarene-based scorpionate ligands.



262 (X = BH^-, CH) **261** (n = 3, 5) **260** (n = 3, 5)

In order to achieve this, the following tentative pathway was suggested (Scheme 4.2): 1) preparation of protected 2,6-dibromo-4-methoxyphenol **263**; 2) Suzuki-Miyaura coupling of the protected phenol to obtain diynes **264**; 3) "triple annulation" cyclization followed by deprotection; 4) preparation of triflate derivative; 5) coupling-based transformation (possibly multistep) to obtain the pyrazole substituents.



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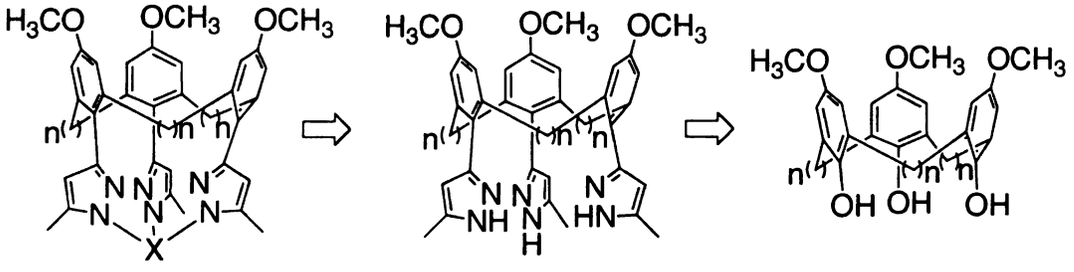
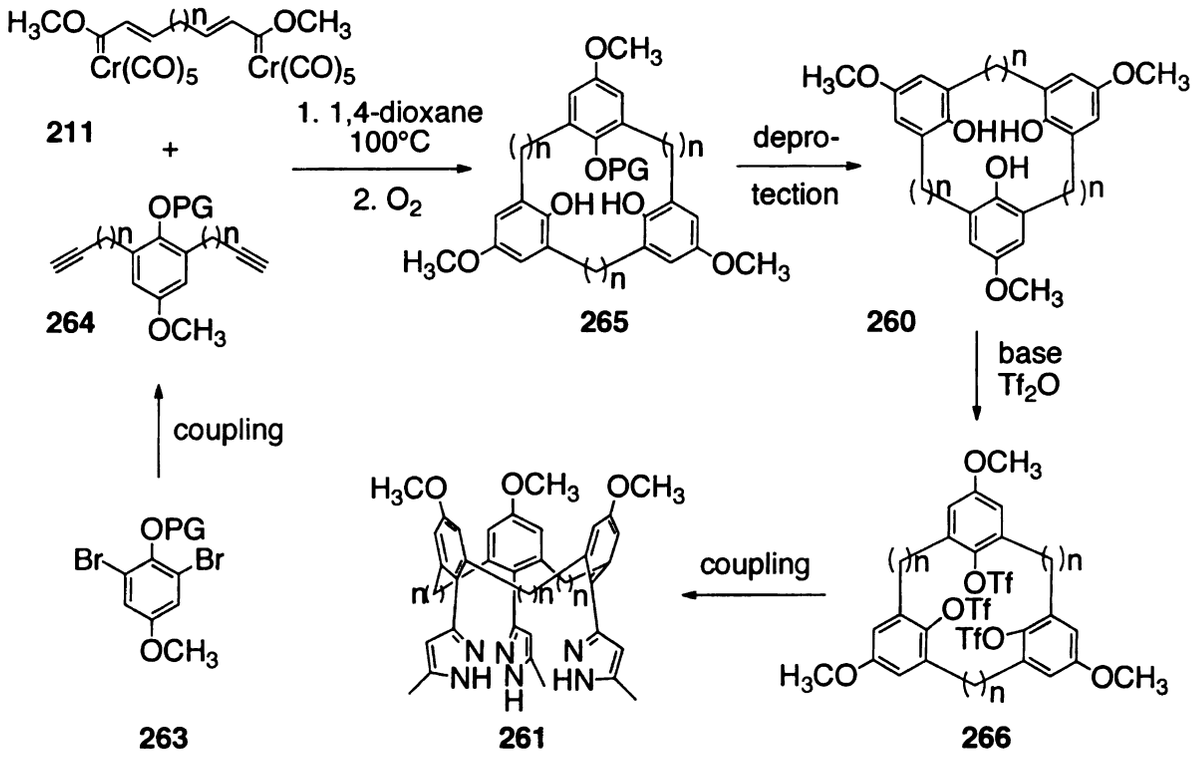


262 (X = BH^-, CH) **261** (n = 3, 5) **260** (n = 3, 5)

In order to achieve this, the following tentative pathway was suggested (Scheme 4.2): 1) preparation of protected 2,6-dibromo-4-methoxyphenol **263**; 2) Suzuki-Miyaura coupling of the protected phenol to obtain diynes **264**; 3) "triple annulation" cyclization followed by deprotection; 4) preparation of triflate derivative; 5) coupling-based transformation (possibly multistep) to obtain the pyrazole substituents.

Scheme 4. 2. Tentative pathway of preparation of substituted homocalixarenes.

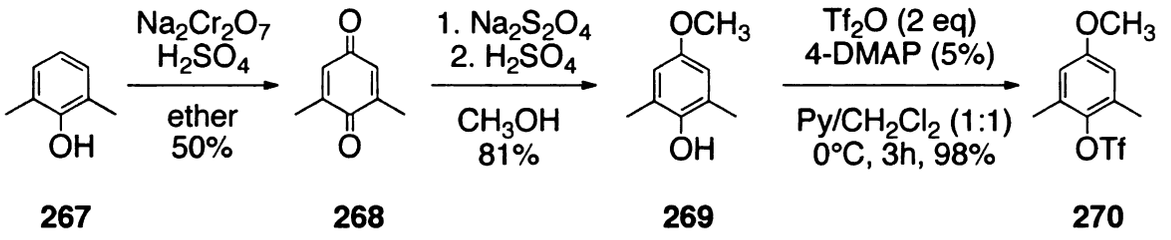


The studies have begun with the choice of appropriate model reactions allowing the preparation of target pyrazoles in the crowded environment of aromatic triflate **266**.

2. Model Studies For Homocalixarene Lower Rim Substitution.

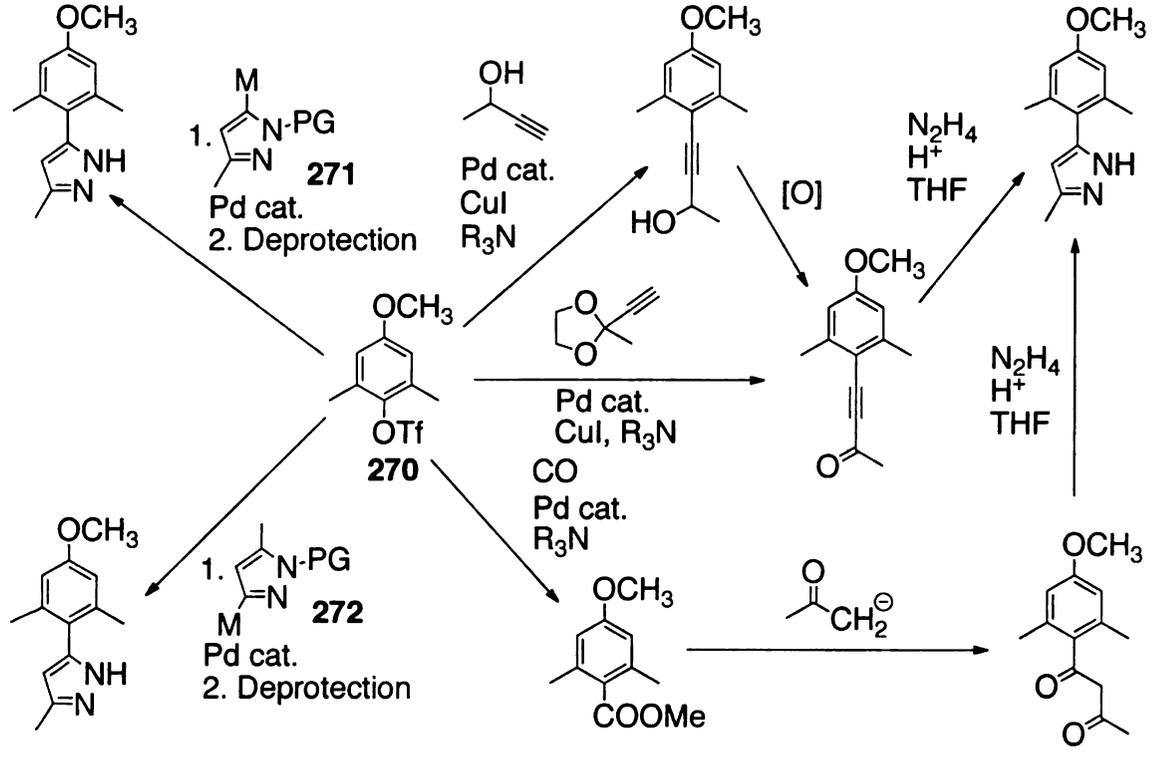
In order to achieve the substitution shown in the last transformation of Scheme 4.2, several methods can be employed. Since we are inevitably starting with the phenol and are attempting to introduce carbon substituents (creating a C–C bond) into a crowded environment, our choices are limited to transition metal couplings with an aromatic triflate as an electrophile. Such aromatic triflates are undoubtedly a poor coupling partner, for both steric (*ortho*,*ortho*-disubstituted) and electronic (*para*-methoxy substituent) reasons. In order to allow easier and more broad experimetation, the easily available model triflate **270** was prepared according to Scheme 4.3.

Scheme 4. 3. Preparation of model triflate **270**.



The overview of coupling methods that were considered useful is given in Scheme 4.4. These are certainly not all *possible* methods, but the reactions given have been broadly studied, and numerous advanced ligands and conditions are known, thus increasing the possibility of a successful outcome.

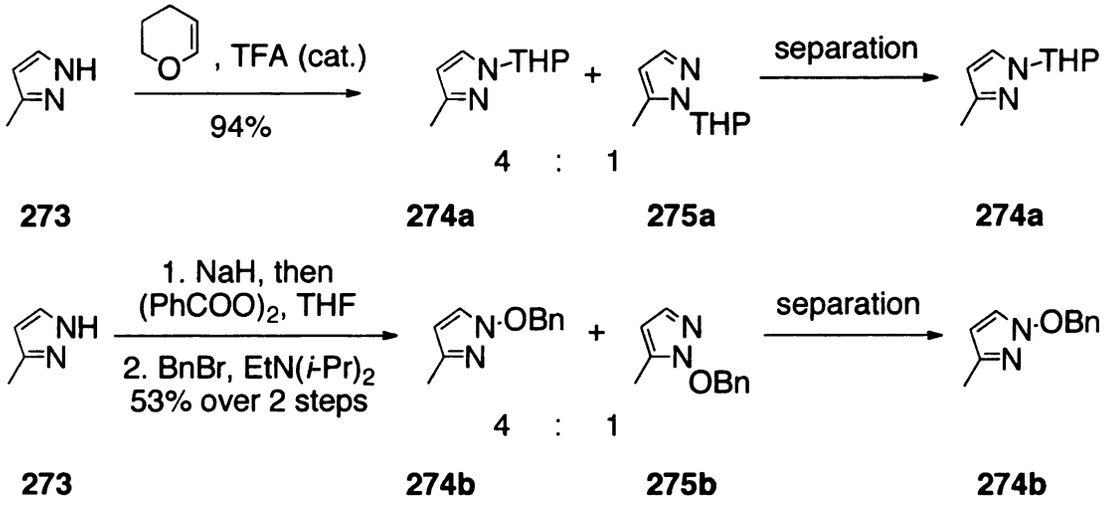
Scheme 4. 4. Suggested pathways for substitution of a hindered triflate group.



Among the methods described, routes that involve coupling with pre-made pyrazole nucleophiles are the most convergent. Pyrazoles of type **271** can be most easily prepared if the protecting group on a nitrogen is a group capable of directing a metallation reaction

(metal-directing group, or MDG). Two of the most convenient MDGs that are used on pyrazoles and that are compatible with most coupling conditions are tetrahydropyran (THP) and benzyloxy (OBn). The preparation of corresponding pyrazoles is shown in Scheme 4.5:

Scheme 4. 5. Preparation of MDG-protected pyrazoles.



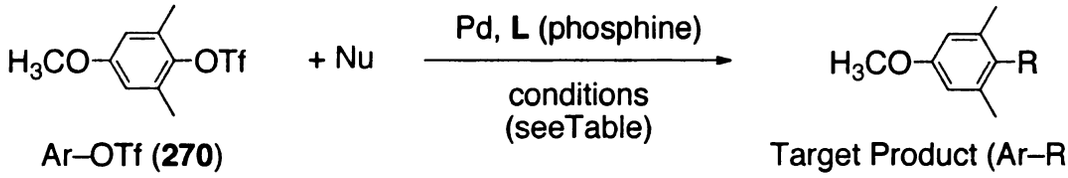
Neither oxidation nor acid-catalyzed reaction with DHP turned out to be completely selective, both providing ~ 4 : 1 mixtures of isomers, that can be separated later. It should be noticed that the minor isomer in both cases is not capable of metallation (pyrazoles **275** do not have hydrogens in *ortho* position to their protecting groups), and thus the separation of individual compounds **274a** and **274b** is not crucial for the preparation of the final product.

2.1. Model Reactions With Triflate 270.

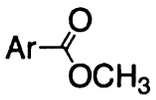
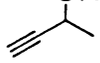
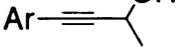
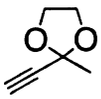
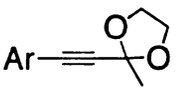
The reactions that were attempted are summarized in Tables 4.1 – 4.3. It should be noted that in order to be successful in triple substitution, reaction on a single-site model (like triflate **270**) must be very clean and efficient, because statistically a 50% yield in a single substitution would only afford around 12.5% yield in a triple substitution. Alternatively

put, in order to obtain a minimum 50% yield in a triple substitution consisting of a series of three independent reactions, each individual reaction must have a yield of at least 79%.

Table 4. 1. Attempts at carbonylation and Sonogashira coupling of **270**.



Ar–OTf (**270**) Target Product (Ar–R)

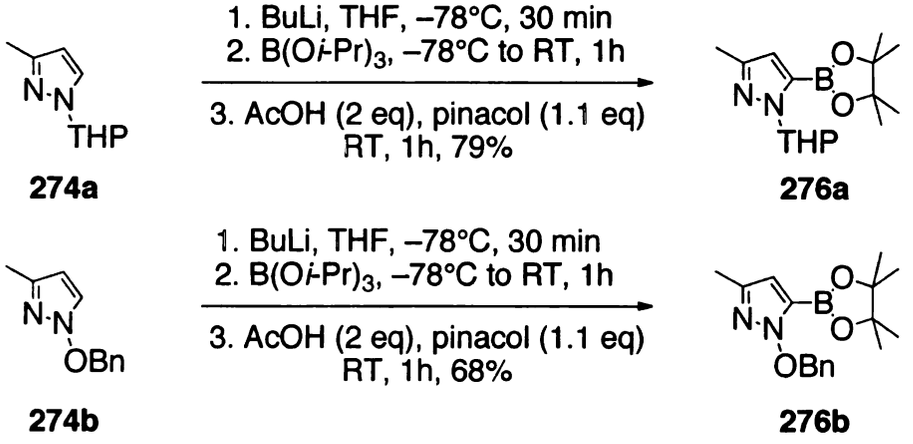
#	Nu	Conditions	TP (Ar–R)	Outcome
1	CO + CH_3OH	3% $Pd(OAc)_2$, 3% dppp, NEt_3, (1.1 eq), DMSO/CH_3OH 3:2, CO (1 atm), 70°C, 48 h [137]		~ 20% conversion
2		10% $Pd(OAc)_2$, 10% dppp, NEt_3 (1.1 eq), DMSO/CH_3OH 3:2, CO (1 atm), 85°C, 12 h [137]		~ 80% conversion ~ 40% red. elimination
3		2 eq Nu, 5% $Pd(PPh_3)Cl_2$, Bu_4NI, CuI (50%), Et_2NH, 70°C, 48 h [138]		no conversion
4		3 eq Nu, 10% P(*t*-Bu)$_3$H$^+$BF$_4^-$ 2.5% $Pd_2(dba)_3$, DBU (4 eq), CuI (2.4 eq), DMF, 100°C, 18 h [86]		~ 10% conversion no TP
5		2 eq Nu, 3% $Pd(PhCN)_2Cl_2$, 6% P(*t*-Bu)$_3$H$^+$BF$_4^-$ $HN(i\text{-}Pr)_2$ (1.2 eq), CuI (2 %), 1,4-dioxane,100°C, 18 h [139]		~ 10% conversion no TP
6		3 eq Nu, 2.5% $Pd_2(dba)_3$, 10% P(*t*-Bu)$_3$H$^+$BF$_4^-$, DBU (4 eq), CuI (2.4 eq), DMF, 100°C, 18 h [86]		~ 10% conversion no TP

The palladium-catalyzed carbonylation[137] of triflate **270** generated a mixture of compounds, but the GC yield of the target ester ($ArCOOCH_3$) did not exceed 40%. The

main side reaction observed was reduction of the triflate insertion intermediate, which leads to 3,5-dimethylanisole as byproduct.

Sonogashira coupling[86,138,139] was also a reaction of choice for reasons similar to that for palladium-catalyzed carbonylation: the incoming nucleophile has a very small angular size (sp-hybridized nucleophile) and should be able to couple with more crowded substrates easier. It is also the only known method of successful lower rim modification in classical calix[4]arenes[86] (see Chapter 1, Scheme 1.49). Unfortunately, the conditions that were appropriate for triflate **122** (Chapter 1, Scheme 1.49) were not successful at effecting reaction of the much more electron rich triflate **270**. In all cases studied, less than 10% conversion was observed, and most of the starting triflate was recovered unchanged (Table 4.1).

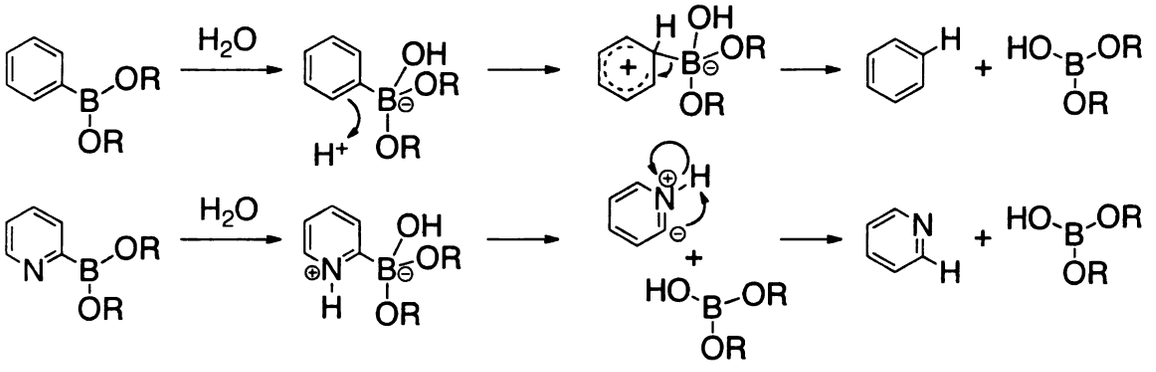
Scheme 4. 6. Preparation of pinacolboronates **276**.



In order to attempt Suzuki-Miyaura coupling, boronates **276a** and **276b** were prepared (Scheme 4.6). The preparation followed the standard procedure described for similar substrates[140].

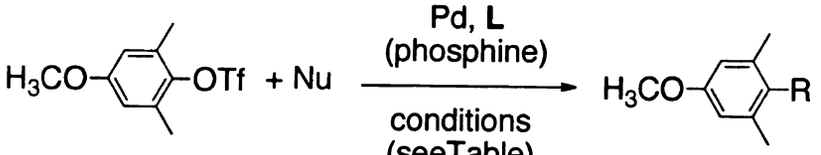
Protodeboronation is a known problem in Suzuki-Miyaura couplings. The mechanism in Scheme 4.7 is formulated here based on discussions in the literature[141]. The coupling of heterocyclic boronates containing electron-donating heteroatoms is affected especially strongly. Higher temperatures and the presence of protic solvents, such as water or alcohols, further increase the rate of this process.

Scheme 4. 7. Tentative mechanism of protodeboronation.



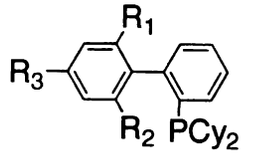
Due to the mechanism described in Scheme 4.7, compounds with boron groups in positions analogous to the 2-positions in pyridines are particularly susceptible; successful Suzuki-Miyaura coupling of 2-pyridine boronic derivatives has been the subject of much targeted research effort[141b]. For pyrazole, the 3-position would be similar to the 2-position in pyridine, and thus pyrazole partners of type **272** (Scheme 4.4) are anticipated to be problematic. Indeed, protodeboronation was found to be a problem for boronates **276**, and complete conversion of the triflate **270** was never achieved in the Suzuki-Miyaura approach. In order to suppress this side reaction, anhydrous conditions were attempted. Also, higher catalyst and pyrazole loadings were used in attempt to make the couplings go faster than protodeboronation. Unfortunately, complete conversion was still not achieved (Table 4.2).

Table 4. 2. Attempted Suzuki-Miyaura couplings of the triflate **270**.

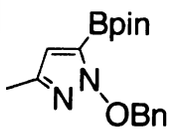
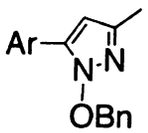


Ar–OTf (**270**)

Target Product (Ar–R)

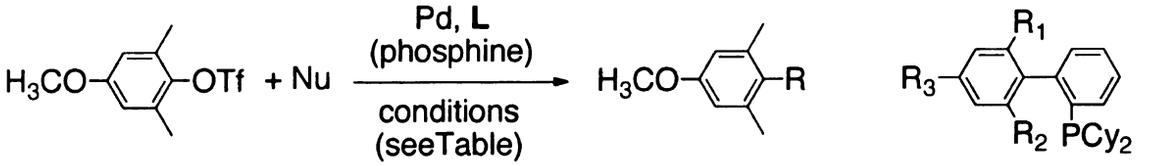


L_1: R_1,R_2 = OMe, R_3 = H
L_3: R_1 = R_2 = R_3 = *i*-Pr
L_4: R_1 = R_2 = R_3 = H

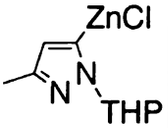
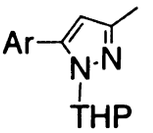
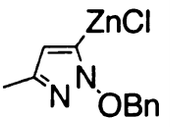
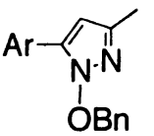
#	Nu	Conditions	TP (Ar–R)	Outcome
1	 **276b**	1.5 eq Nu, 2% $Pd(OAc)_2$, 4% **L_1** K_3PO_4 (2 eq), BuOH/H_2O 10:1, 100°C, 18 h [142]	 **277b**	~ 50% conv. phenol (ArOH) deboronation
2		1.5 eq Nu, 1% $Pd_2(dba)_3$, 4% **L_3** K_3PO_4 (2 eq), BuOH/H_2O 10:1, 100°C, 18 h [142]		~ 60% conv. phenol (ArOH) deboronation
3		1.1 eq Nu, 1% $Pd_2(dba)_3$, 2.4% $PCy_3K_3PO_4$ (1.7 eq), dioxane/H_2O 2:1, 100°C, 18 h [143]		numerous byproducts, no TP
4		1.5 eq Nu, 5% $Pd(OAc)_2$, 10% **L_1** K_3PO_4 (2 eq), dioxane/H_2O 10:1, 100°C, 48 h [142]		~ 60% conv. clean TP deboronation
5		1.5 eq Nu, 5% $Pd(OAc)_2$, 10% **L_1** K_2CO_3 (2 eq), CH_3CN/H_2O 10:1, 100°C, 48 h [142]		~ 60% conv. clean TP deboronation
6		1.5 eq Nu, 5% $Pd(OAc)_2$, 10% **L_3** K_3PO_4 (2 eq), dioxane/H_2O 10:1, 100°C, 48 h [142]		~ 75% conv. clean TP deboronation
7		1.5 eq Nu, 5% $Pd(OAc)_2$, 10% **L_4**, K_3PO_4 (2 eq), dioxane/H_2O 10:1, 100°C, 48 h [142]		~ 10% conversion
8		3 eq Nu, 5% $Pd(OAc)_2$, 10% **L_1** K_3PO_4 (3 eq), dioxane, 100°C, 48 h [140]		~ 80% conv. clean TP deboronation
9		3 eq Nu, 5% $Pd(OAc)_2$, 10% **L_3** K_3PO_4 (3 eq), dioxane, 100°C, 48 h [140]		~ 60% conv. clean TP deboronation
10		3 eq Nu, 5% $Pd(OAc)_2$, 10% **L_1** $K_3PO_4 \cdot H_2O$ (2 eq), dioxane, 100°C, 48 h [140]		~ 60% conv. clean TP deboronation

The Negishi coupling is known to be less tolerant towards functional groups due to the higher reactivity of organozinc species, but is not usually affected by the demetallation problem[144]. Thus, using advanced Buchwald ligands and conditions designed specifically for Negishi coupling[145], we were able to obtain the model coupling product **277a** in 79% yield in the case of the THP-protected pyrazole. The conversion of the triflate conversion was found to be complete. An increase of the pyrazole to triflate ratio from 1.5 : 1 to 3 : 1 afforded an additional rise in yield to an excellent 90%. Surprisingly, the benzyloxy protecting group, which is expected to be more stable under high temperature conditions, gave a lower yield of the coupling product **277b**. The best result was 73% yield obtained with a 3 : 1 ratio of pyrazole to triflate (Table 4.3).

Table 4. 3. Negishi coupling of the triflate **270**.



Ar–OTf (**270**) Target Product (Ar–R) **L2**: $R_1 = R_2 = O$*i*-Pr, $R_3 = H$

#	Nu	Conditions	TP (Ar–R)	Outcome
1	 **278a**	1.5 eq Nu, 1% $Pd_2(dba)_3$, 4% **L2** THF/NMP 2:1, 100°C, 24 h [145]	 **277a**	~ 70% conversion clean TP
2		1.5 eq Nu, 2.5% $Pd_2(dba)_3$, 10% **L2**, THF/NMP 2:1 100°C, 24 h [145]		~ 90% conversion clean TP
3		1.5 eq Nu, 5% $Pd_2(dba)_3$, 20% **L2** THF/NMP 2:1, 100°C, 24 h [145]		100% conversion 79% yield TP
4		3 eq Nu, 5% $Pd_2(dba)_3$, 20% **L2** THF/NMP 2:1, 100°C, 24 h [145]		100% conversion 90% yield TP
5	 **278b**	1.5 eq Nu, 5% $Pd_2(dba)_3$, 20% **L2** THF/NMP 2:1, 100°C, 24 h [145]	 **277b**	100% conversion 48% yield TP[a]
6		3 eq Nu, 5% $Pd_2(dba)_3$, 20% **L2** THF/NMP 2:1, 100°C, 24 h [145]		100% conversion 73% yield TP[a]

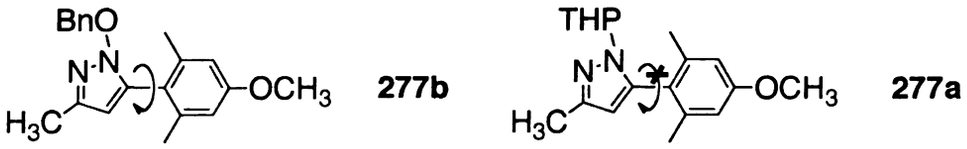
[a] Isolated as mixture of **277b** and **274b**, yield of **277b** calculated using NMR ratio

Overall, Negishi coupling was found to be the most promising method based on the model studies with the triflate **270**.

2.2. Deprotection of the Model Compounds.

Despite the fact that THP group gave significantly better results than OBn in Negishi coupling with the triflate **270**, it may not be wise abandon the latter at this stage of the model studies. The reason for that is that THP group hinders the rotation around the newly formed C–C bond, and in the ^{1}H-NMR spectrum of **277a** methyl groups of the benzene ring show up as two separate singlets. Molecular modeling suggests that **277b** should have significantly lower rotation barrier around this C–C bond.

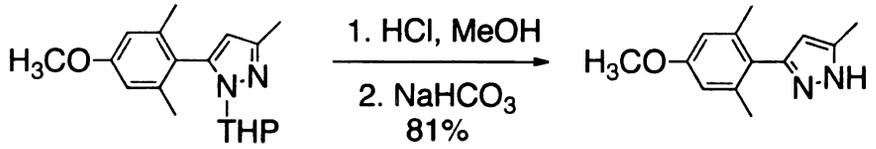
Figure 4. 1. Changes in rotation barriers of model pyrazoles depending on protecting group.



If the steric environment in an actual calixarene gets too crowded after the first coupling, such rotation might provide the steric relief necessary for the next substitution. Thus, both pyrazoles **277a** and **277b** should be considered for coupling to homocalixarenes.

Deprotection of **277a** was achieved easily by an earlier reported method[140]:

Scheme 4. 8. Deprotection of compound **277a**.

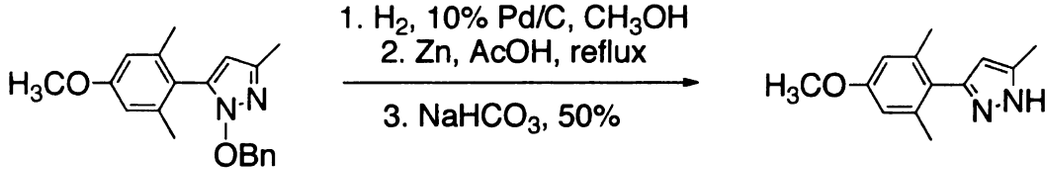


277a **279**

Deprotection of **277b** proved to be significantly harder to accomplish. There are no described methods for the cleavage of N–O bond in N-benzyloxy protected pyrazoles. However, the conversion of N–OBn unit into a N-OH group in pyrazoles using palladium

on activated carbon is a well established process[146]. In addition, examples of reduction of a N–OH group on a pyrazole to a NH pyrazole are scarce[188]. Thus, a two-step procedure was developed:

Scheme 4. 9. Two-step deprotection of benzyloxy group.

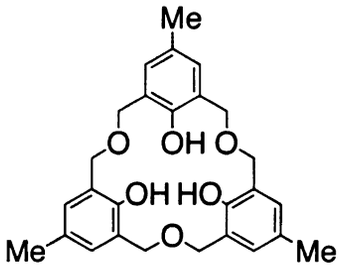


277b **279**

To sum up, both pyrazoles **274a** and **274b** can be useful in the Negishi coupling reaction, but the THP protecting group gives higher yields in coupling with the model triflate **270** and is easier to introduce and remove.

3. Homooxacalix[3]arene as an Advanced Model for Substitution Reactions.

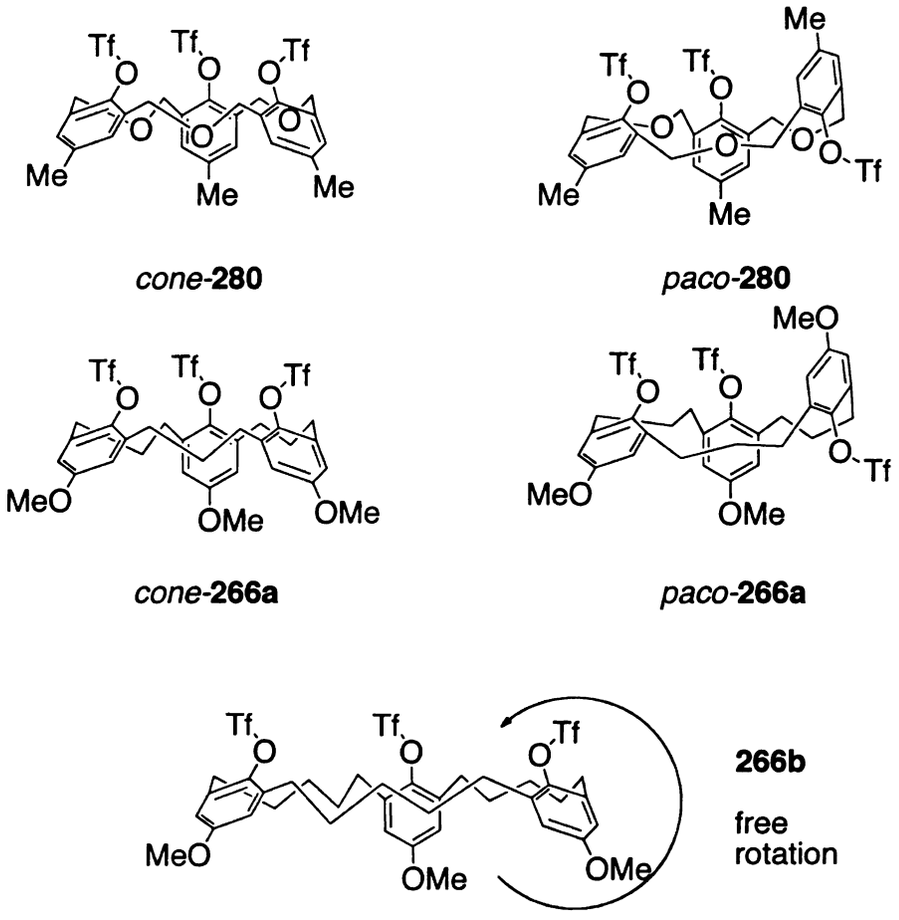
The original projected route for the preparation of ligands of type **262** (Scheme 4.1) allowed some flexibility in terms of their structure; only the overall shape and pyrazole binding sites were considered to be of importance (at least before any of the experiments on metal binding are done). Thus, homooxacalix[3]arene **9h**, that can be prepared relatively easy[34,38] (see Chapter 1, Schemes 1.21 and 1.30), can be used as a secondary model system to test the preparation of the corresponding triflates and their coupling reactions to give target ligands.



9h

As it was shown before in oxahomocalix[3]arene system (Chapter 1, Table 1.2), any three lower rim substituents attached to the phenol function that are bigger than a propoxy group will make the rotation barrier too high for conformer interconversion. Thus, the conformers (*paco*, for partial cone, and *cone*) become separable isomers. Simple theoretical studies[189] show that in case of triflate **280**, the rotation barrier is too high to be crossed even at high temperatures; also, barriers are very similar for homooxacalix[3]arene and homocalix[3]arene triflates **280** and **266a** (Figure 4.2).

Figure 4. 2. Conformations of triflates **280**, **266a** and **266b**.

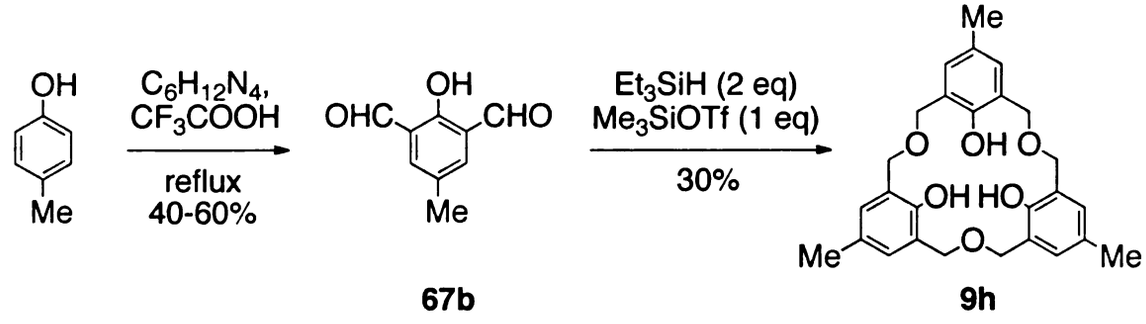


In contrast to that, the cavity of homocalix[3]arene **266b** (n = 5) is large enough for rotation of triflate to be free at room temperature. In fact, molecular modeling suggests that target (deprotected) pyrazole derivative **261b** (n = 5, Scheme 4.2) should also be able to rotate through the annulus at room temperature.

3.1. Preparation of Triflate Derivatives of Homooxacalix[3]arene 9h.

For reasons of convenience, the method of aldehyde reductive coupling was used for preparation of homooxacalix[3]arene **9h**[38]. The aldehyde in turn was prepared by a modified Duff reaction, involving the use of hexamethylenetetramine in TFA as both solvent and catalyst[147].

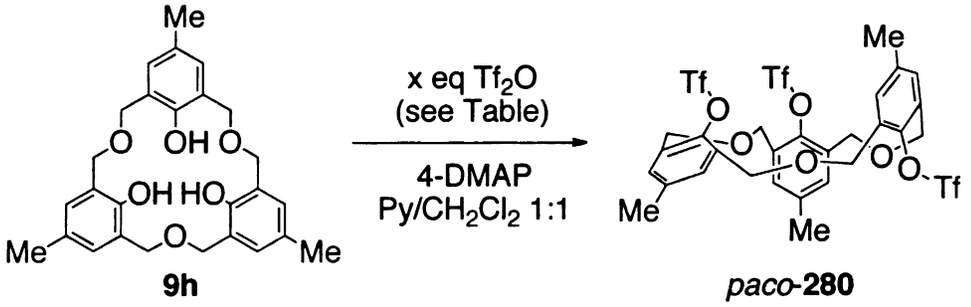
Scheme 4. 10. Preparation of homooxacalix[3]arene **9h**.



67b **9h**

The method used to introduce the trifluoromethanesulfonate moiety to the model compound **270** (see Scheme 4.3) was particularly targeted for sterically crowded phenols. Thus, it was considered a good candidate for the preparation of triflate **280**. Surprisingly, the original conditions afforded only disubstituted triflate in 80% yield. In order to obtain the trisubstituted triflate **280**, overnight reaction at room temperature with 6 eq of triflic anhydride had to be used. An increased excess of triflic anhydride afforded significantly higher yields of the target compound (Scheme 4.11). All reactions gave *paco* isomer of triflate **280** selectively.

Scheme 4. 11. Preparation of *paco*-**280**.

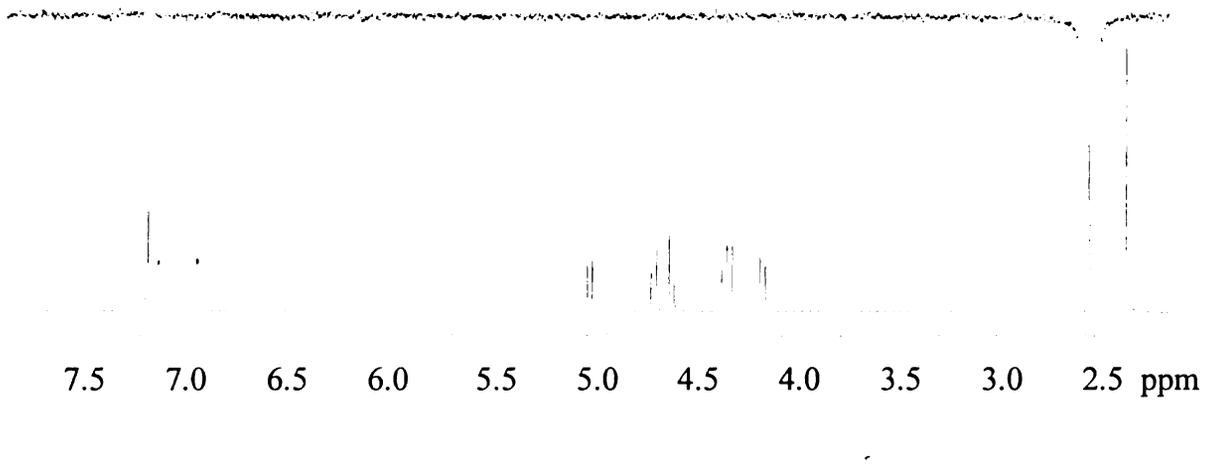


Method	Yield, %
6 eq Tf_2O, 15% 4-DMAP, 0°C, 3 h	80[a]
6 eq Tf_2O, 15% 4-DMAP, 0°C to RT, 12 h	52
9 eq Tf_2O, 15% 4-DMAP, 0°C to RT, 12h	79
9 eq Tf_2O, 45% 4-DMAP, 0°C to RT, 12h	79
9 eq Tf_2O, 15% 4-DMAP, 0°C to RT, 12h, then again 9 eq Tf_2O, 0°C to RT, 6h	80

[a] *Paco* isomer of di-triflate obtained instead of trisubstituted compound **280**

In order to prove that *paco*-triflate **280** does not rotate "through the annulus" at room temperature on the NMR timescale, an NOESY-1D experiment was undertaken. During the experiment, the signal of methyl group that is sterically opposite to the two others in *paco*-triflate was saturated, and NOE effect was observed. No polarization transfer was observed between methyl groups; the only signal that had NOE enhancement was a singlet due to the adjacent aromatic protons, as would be expected in the case when no "through the annulus" rotation is observed (Figure 4.3).

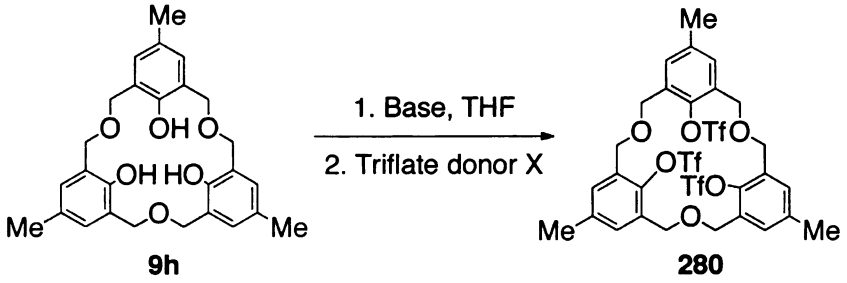
Figure 4. 3. NOESY-1D experiment saturating the unique methyl group (δ = 2.39 ppm) in *paco*-trilfate **280**, showing no exchange with the other methyl groups (δ = 2.20 ppm).



Since it is more stable thermodynamically, the *paco* isomer of **280** is expected to be the main product in almost every case, unless chelation is involved. We have already seen similar behaviour in the preparation of homooxacalix[3]arene derivatives (see Chapter 1, Schemes 1.59, 1.62). Thus, in order to have a chance of preparing *cone* pyrazole derivatives, we must first try and solve the problem of the preparation of *cone* triflate **280**.

From Scheme 1.62 (Chapter 1) one can notice that the outcome of attempts to functionalize the lower rim phenols with electrophiles is influenced not only by the nature of the chelating metal, but also by the nature of the electrophile used. Among the metals, only sodium was found to be able to give necessary chelation, and thus only sodium-containing bases were used. There are several reagents that are available for triflate preparation, and most of them have been tested during our effort (Scheme 4.12).

Scheme 4. 12. Attempts at preparation of *cone*-**280**.



9h **280**

Base	X	Method	Result
NaH	Tf_2O	NaH at RT, then X, –78°C to RT, 18 h	– [a]
NaHMDS	Tf_2O	NaHMDS at RT, then X, –78°C to RT, 18 h	– [a]
NaHMDS	$PhNTf_2$	NaHMDS at RT, then X, –78°C to RT, 18 h	*paco* **280**
NaHMDS	(5-Cl-2-Py)NTf_2	NaHMDS at RT, then X, –78°C to RT, 18 h	– [a]

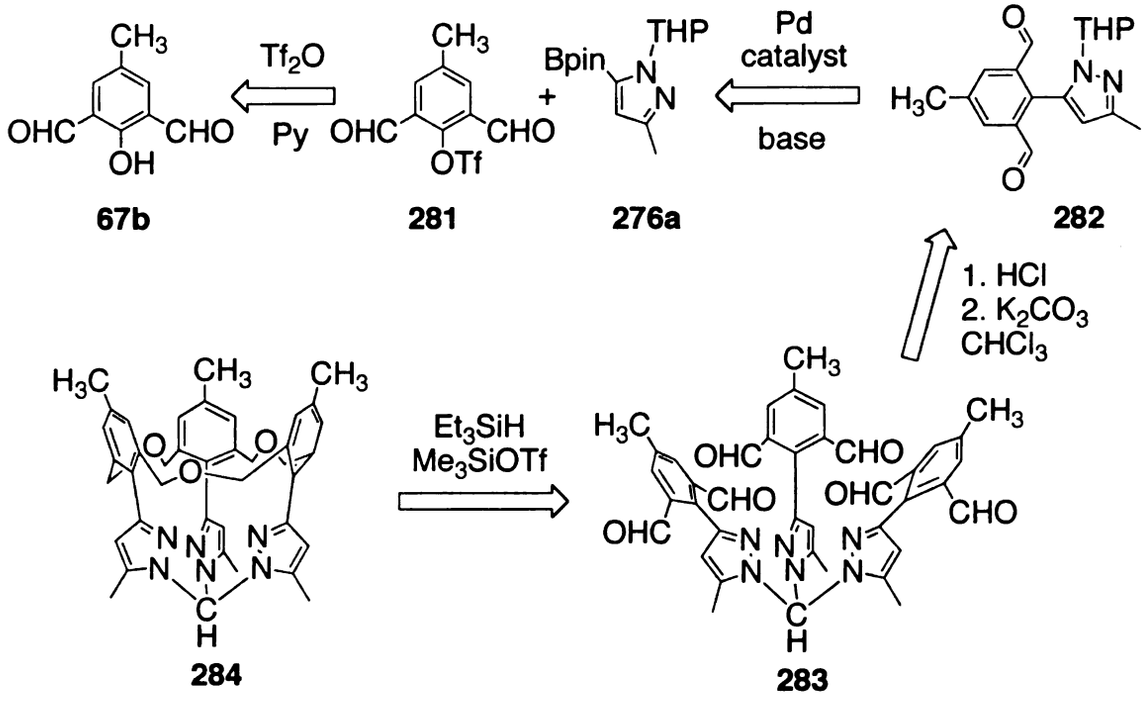
[a] Complex mixture of products was obtained

Unfortunately, the preparation of the *cone* triflate was never achieved. The reasons for this failure are not clear, but high electrophilicity of triflate donors might be responsible.

3.2. An Attempt at Templated Assembly of Homooxacalix[3]arene Core.

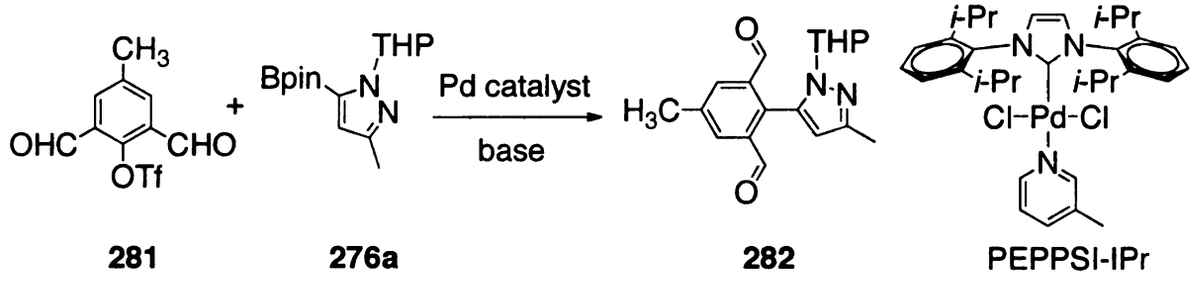
Since the preparation of the *cone* isomer of the tris-triflate **280** has proven to be evasive, and since it is anticipated the coupling reactions of the triflates in such a crowded environment may also be very hard to achieve, an alternative route based on reductive aldehyde coupling (see Scheme 4.13) was appealing. Many scorpionate ligands contain a boron atom bound by pyrazole moieties, but this in fact is not necessary. Carbon atoms can be in the bridgehead position as well, and such (neutral) ligands can also be used for similar purposes[136]. The outline of the proposed synthesis is given below:

Scheme 4. 13. Suggested synthesis of ligand **284**.



Triflate **281** is known[116] and was prepared the using standard procedure[148]. Unfortunately, the successful coupling between triflate **281** and pyrazole **276a** was found to be very hard to achieve, and numerous attempts failed utterly (Scheme 4.14).

Scheme 4. 14. Attempted coupling of triflate **281** and pyrazole **276a**.



Pd salt	Ligand	Conditions	Result
$Pd_2(dba)_3$	PCy_3	3 eq K_3PO_4, 1,4-dioxane, 80°C	0% TM, 100% conv.
$Pd(OAc)_2$	S-PHOS	2 eq K_3PO_4, *n*-BuOH, 80°C	0% TM, deboronation
PEPPSI-IPr		2 eq K_2CO_3, 1,4-dioxane, RT	0% TM, 100% conv.
$Pd(OAc)_2$	PCy_3	2.4 eq KF, THF, RT	0% TM, 100% conv.
$Pd_2(dba)_3$	$P(t\text{-}Bu)_3H^+BF_4^-$	2.4 eq KF, THF, RT	0% TM, 100% conv.

It was discovered that in all cases triflate **281** was consumed completely, but only insoluble material (and no target product) were obtained. The reason for these failures remains unclear, but the large gap in reactivities of the electrophile (active dialdehyde triflate) and the nucleophile (hard-to-activate heterocyclic boronate) could possibly be responsible.

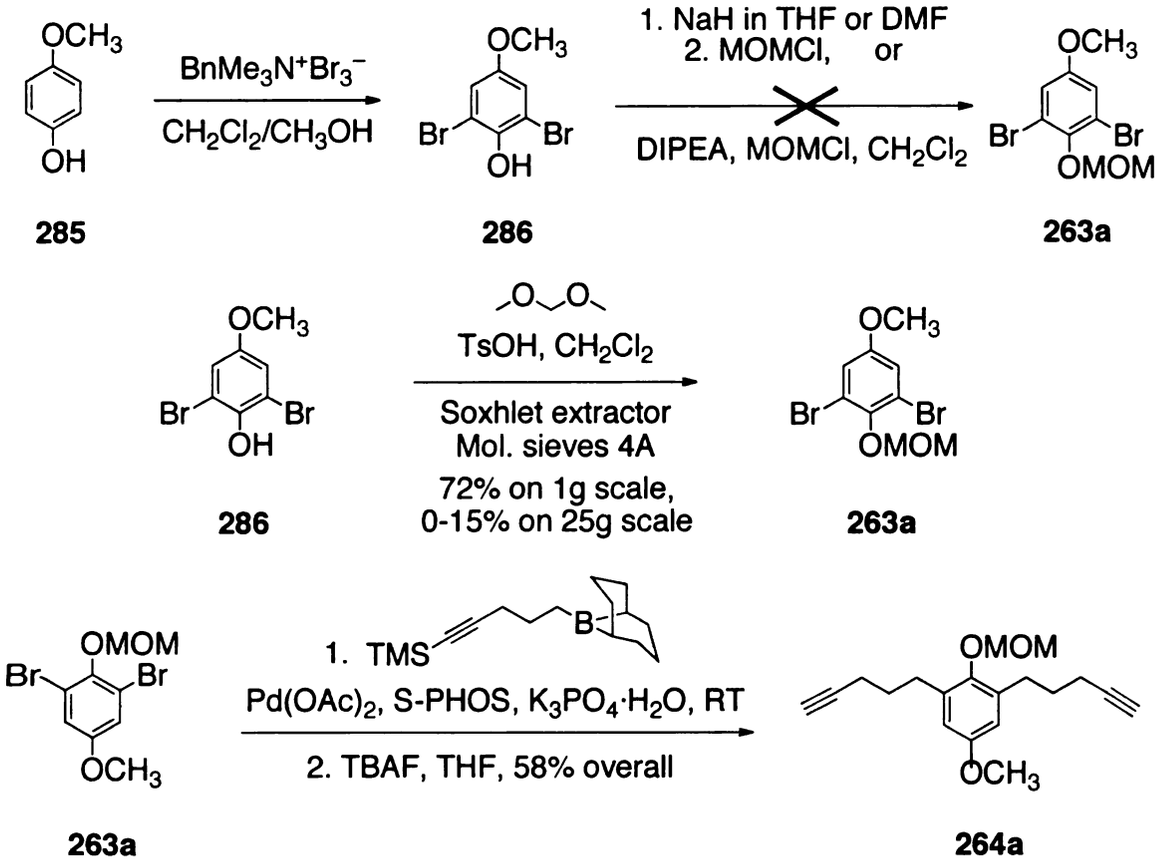
4. Large Scale Preparation of C_3-Symmetrical Homocalix[3]arenes.

In order to prepare our initial target molecules of the type **262** (Scheme 4.1), the C_3-symmetrical homocalix[3]arenes **260** (Scheme 4.2) had to be prepared using appropriate protecting groups and preferrably on a large scale. Homocalix[3]arenes **260** are also of interest in many other respects because of their symmetry. The synthesis commenced with the preparation of appropriate protected diynes **264**.

4.1. Preparation of Diynes 264 and the Choice of Protecting Group.

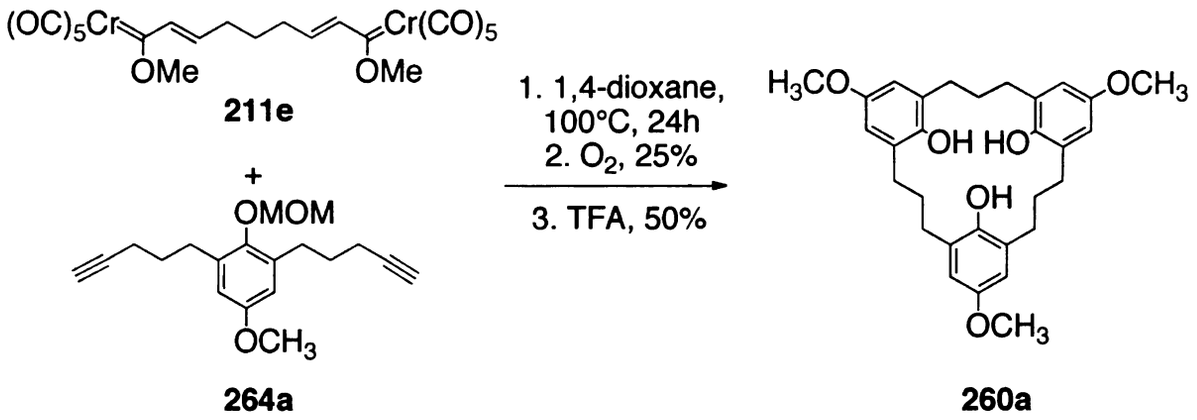
Initial studies on the protection of phenol **286**[180] have shown that any method involving the use of base (and thus preparation of the phenolate) fails to produce any identifiable individual products, generating a mass of a deep colored, soluble polymer instead. The reason for such behaviour is unclear, but this certainly narrows the usable protecting groups very significantly. With this forced shift to acid-catalyzed methods, it was discovered that the only reported method of MOM protection that uses acidic catalysis[149] works inconsistently on scales larger than 1 g:

Scheme 4. 15. Preparation of MOM-protected diyne **264a**.



The coupling of the MOM-protected dibromide **263a** went smoothly at room temperature, and after the desilylation afforded 58% yield of the diyne **264a**. The benzannulation with complex **211e** gave only one product, the protected macrocycle **260a** in 25% yield. The removal of MOM group with trifluoroacetic acid afforded 50% yield of **260a** (Scheme 4.16).

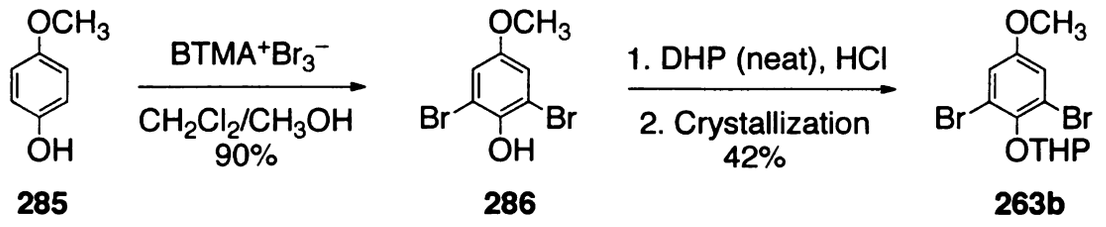
Scheme 4. 16. Preparation of homocalix[3]arene **260a** using MOM-protected diyne **264a**.



While the protection-deprotection approach to C_3-symmetrical homocalix[3]arenes was shown to be generally effective, the inability to produce the intermediate **263a** reliably on a large scale made it impossible to produce **260a** in quantities sufficient for further studies. Thus, a different approach was tested.

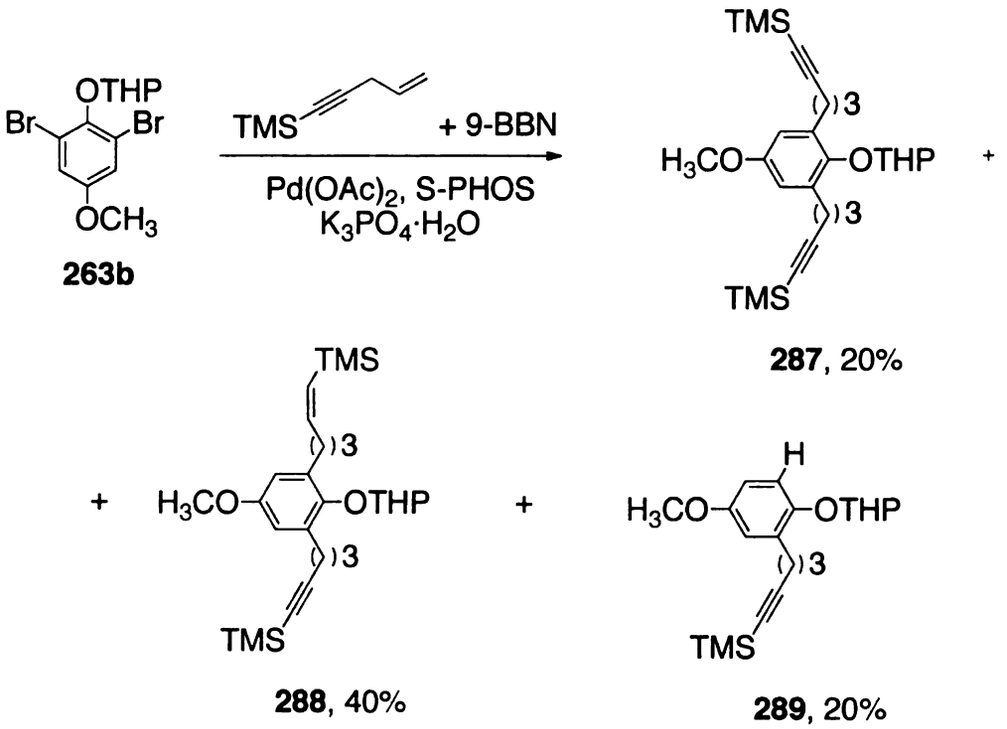
In contrast to the difficulties associated with the preparation of the MOM-protected dibromide **263a**, a THP protecting group was introduced easily[150] and afforded the target intermediate **263b** in ca. 20 g by simple crystallization (Scheme 4.17). The protected phenol **263b** is unstable at room temperature, and in a few days of storage it completely turns into the original phenol **286** even under nitrogen. However, it can be stored virtually indefinitely under a nitrogen atmosphere at –20°C.

Scheme 4. 17. Preparation of protected intermediate **263b**.



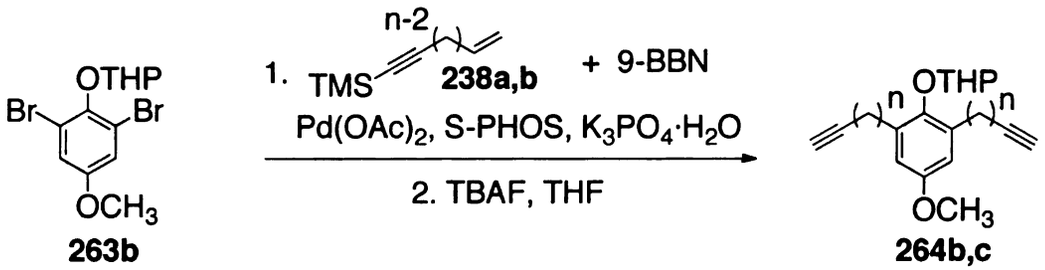
The coupling reaction of **263b** turned out to be somewhat more troublesome. Due to the increased bulk of the O–THP group in comparison with O–CH_3 or O–MOM groups, the coupling did not proceed at room temperature at all. At elevated temperatures (50 – 70°C) the same coupling reaction produced significant amounts of the alkyne reduction product **288** and the bromide reduction product **289** (Scheme 4.18).

Scheme 4. 18. The byproducts of alkyl-aryl coupling with intermediate **263b**.



The side reactions indicated in Scheme 4.18 have decreased the yield of **287** dramatically, and the separation was also much more tedious then for analogous couplings described earlier. Thus, some reaction condition tuning was undertaken, and a much more practical result was achieved (Scheme 4.19).

Scheme 4. 19. Preparation of dyines **264b** and **264c**.



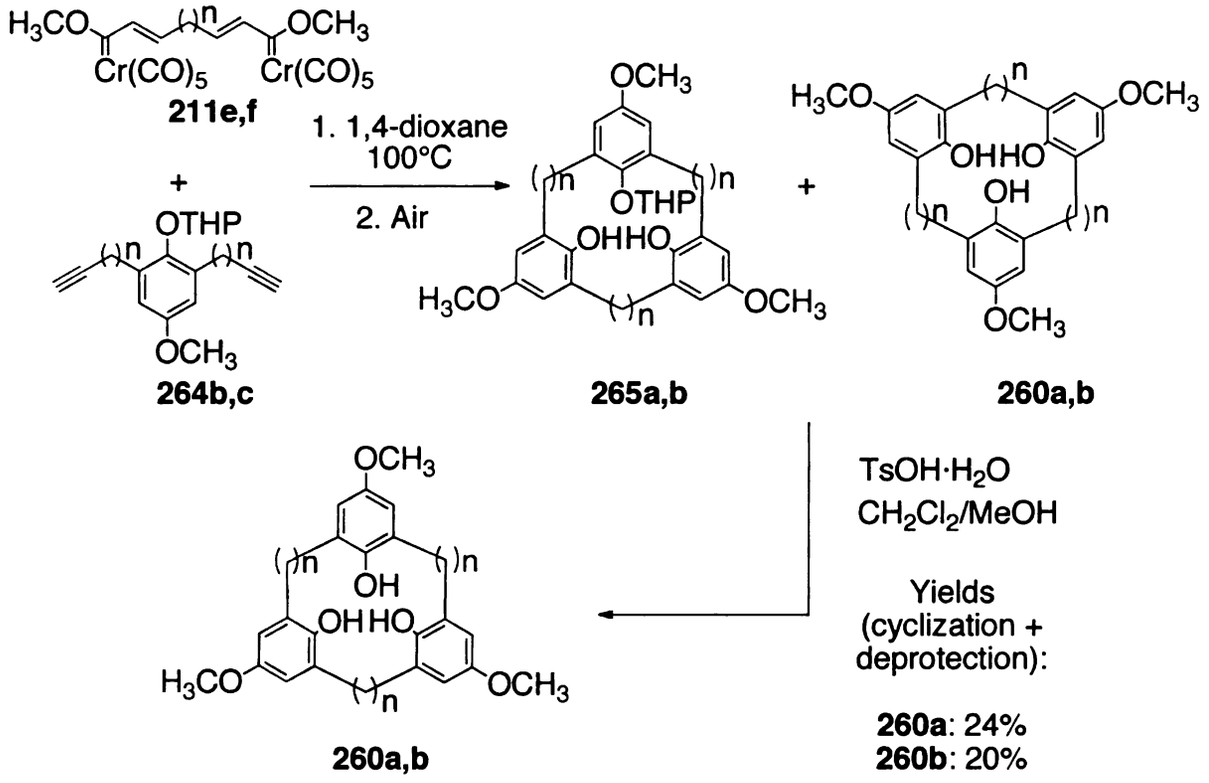
n	Conditions	Yield,%	Notes
3	RT, 1% Pd, 9-BBN : **238** : **263b** = 2.75 : 2.5 : 1, 12 h	0	no reaction
3	70°C, 2% Pd, 9-BBN : **238** : **263b** = 2.75 : 2.5 : 1, 12 h	22	lots of **289**
3	60°C, 2% Pd, 9-BBN : **238** : **263b** = 2.75 : 2.5 : 1, 12 h	35	– // –
3	50°C, 2% Pd, 9-BBN : **238** : **263b** = 2.75 : 2.5 : 1, 12 h	34	– // –
5	70°C, 2% Pd, 9-BBN : **238** : **263b** = 2 : 2 : 1, 12 h	39	some **289**
3	70°C, 4% Pd, 9-BBN : **238** : **263b** = 2 : 2 : 1, 4 h	50	clean reaction
5	70°C, 4% Pd, 9-BBN : **238** : **263b** = 2 : 2 : 1, 4 h	52	clean reaction

The key to the successful and clean coupling was in having no excess 9-BBN and enyne reagents relatively to **263b**, higher catalyst loading (4% Pd, 8% S-PHOS ligand), and a shorter reaction time of 4 hours. The resulting diynes **264b** and **264c** were isolated as transparent yellowish oils, completely stable in open air. Preparations were exercised on a scale giving about 4 g of final product in one loading.

4.2. Cyclization Reactions and Deprotection.

The cyclization reaction of dyines **264b** and **264c** with their respective carbene complexes **211e** and **211f** also gave somewhat unexpected results. Analysis of the reaction mixture by TLC showed two spots, that were identified as the protected and unprotected target phenols **265** and **260** (Scheme 4.20):

Scheme 4. 20. Triple annulation with diynes **264b** and **264c**.

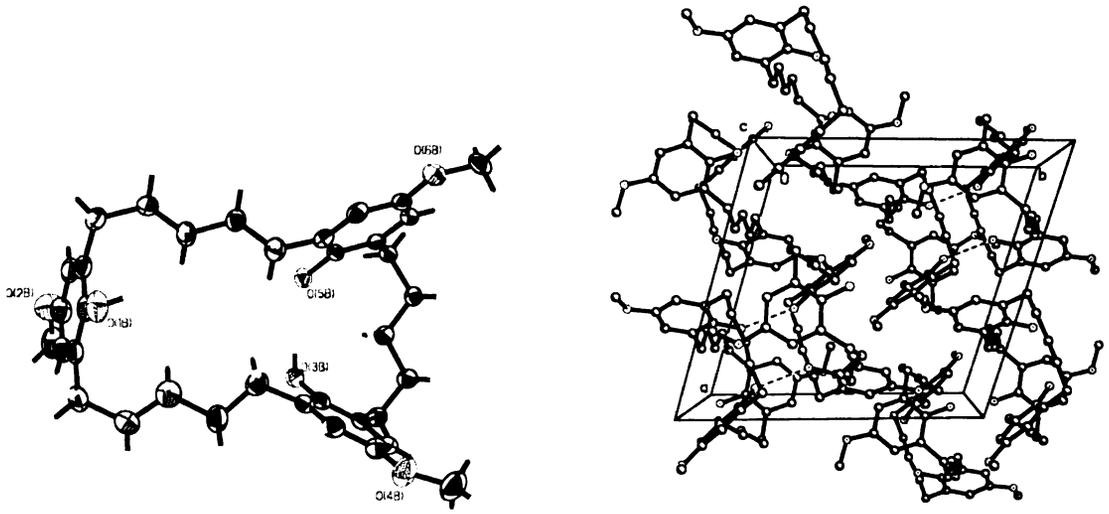


The reason for the instability of the THP group in these macrocycles is unknown; one can suggest both thermal and acid-catalyzed (from the newly formed phenolic OH groups) pathways. At any rate, such deprotection is not problematic to the preparation of the final target molecule. Deprotection of the mixture of phenols with *p*-toluenesulfonic acid monohydrate in methanol – dichloromethane (1:1)[151] afforded **260a** and **260b** cleanly.

Macrocycle **260a** (n = 3) was found to be very poorly soluble in most organic solvents (e.g., its NMR spectra had to be taken in pyridine-d5!). Crystallization from hot benzene gave very small staticky yellow crystals; crystallization from ethyl acetate – dichloromethane afforded white crystalline powder. In contrast to that, homocalix[3]arene **260b** (n = 5) was crystallized from a mixture of hexane and

dichloromethane (~ 5:1) affording crystals good enough for X-Ray single crystal study (see Figure 4.4).

Figure 4. 4. The C_3-symmetrical macrocycle **260b** in a crystal: conformation of a single molecule (left) and packing in the elementary cell along c-axis (right).



Similarly to the preparation of Boc-protected pyrrole macrocyle **258** (Chapter 3, Scheme 3.22), the yields are somewhat lower than 30% expected for this ring size (Scheme 3.19), and this is probably due to the loss of the protecting group and subsequent related side reactions. At any rate, the reaction is efficient on a large scale, affording more than 1 g of the final material in a single preparation that is carried out in a 5L flask, with 4L of solvent (2.5 mM concentration of the reagents) degassed by bubbling nitrogen through the reaction mixture for several hours.

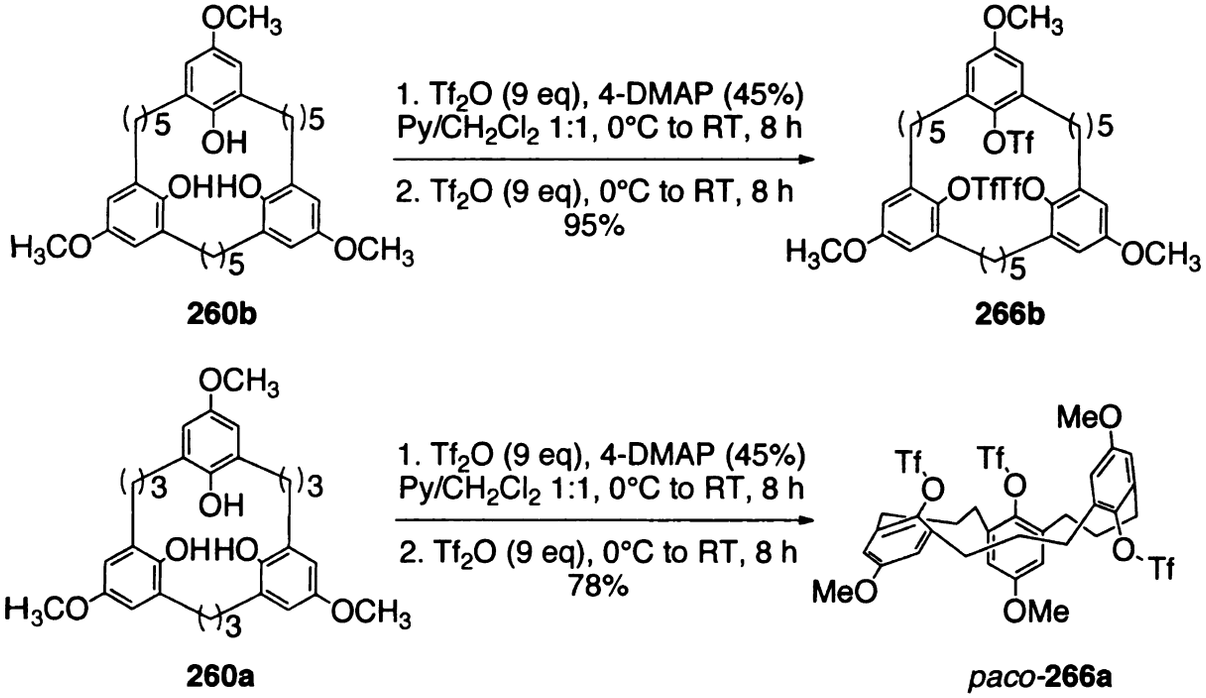
On a separate note, different protecting groups may be useful in this preparation, and a broader study could be beneficial in the future. Most of the appropriate silicon groups are too bulky and cannot be installed on phenol **286** (Scheme 4.18) using acid-catalyzed methods. However, ester protecting group, such as acetate, should be more stable to the

benzannulation reaction, and also make the alkyl-aryl Suzuki-Miyaura couplings go smoother.

5. Introduction of Pyrazole Functional Groups into Symmetrical Homocalix[3]arenes.

As expected, homocalix[3]arenes **260a** and **260b** can be converted to their corresponding tris-triflates in good to excellent yields, using the method employed for preparation of *paco*-**280** (Scheme 4.11). Triflate **266b** was shown to have free rotation through the annulus at room temperature by ^{1}H NMR spectrum. Triflate **266a** was prepared exclusively as the *paco* isomer.

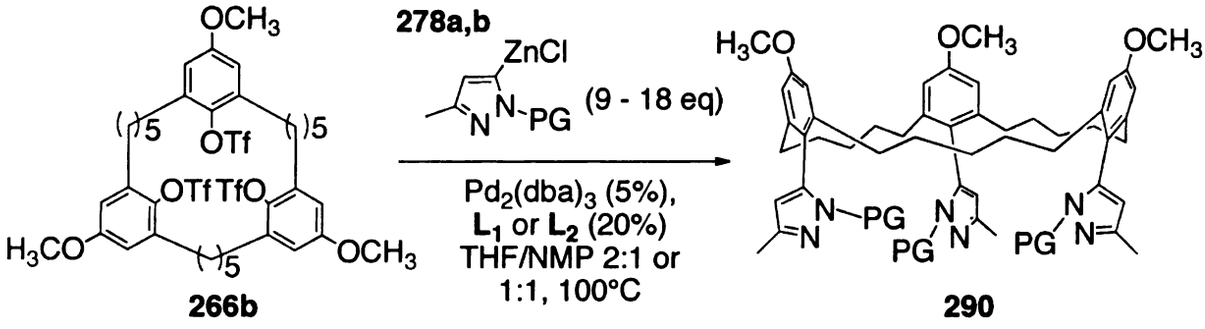
Scheme 4. 21. Preparation of macrocyclic triflates **266b** and *paco*-**266a**.

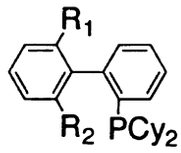


The coupling reactions of **266b** reflect that the original concerns about bulkiness of the THP protectiong group were in fact legitimate. The reaction with the THP-protected organozinc nucleophile **278a** gave no identifiable products, even when larger excess of

nucleophile (6 eq per triflate group) and more polar solvent (THF/NMP 1:1) were used (see Scheme 4.22).

Scheme 4. 22. Attempted couplings of macrocyclic triflate **266b**.





L1: $R_1 = R_2 = OMe$,
L2: $R_1 = R_2 = O\textit{i}\text{-Pr}$

Ligand	Nu	PG	Equiv. Nu	THF:NMP	Yield **290**, %
L2	**278a**	THP	9	2:1	0
L2	**278a**	THP	18	1:1	0
L2	**278b**	OBn	18	1:1	0
L1	**278b**	OBn	18	1:1	0

Unfortunately, use of the pyrazole zinc species **278b** with a benzyloxy protecting group did not result in successful substitution either. Used in combination with the diisopropoxy ligand $\mathbf{L_2}$, nucleophile **278b** failed to produce macrocycle **290**, giving a complex mixture of products instead. The use of S-PHOS ($\mathbf{L_1}$) as a ligand (which could have possibly been beneficial in this very crowded environment, being structurally similar to $\mathbf{L_2}$ yet less bulky) proved even less efficient, leaving the original triflate **266b** unchanged.

The complex product mixtures obtained in the Negishi coupling of **266b** can be explained as follows. After the first (or the second) coupling happens, the steric environment in the molecule becomes too crowded for the third coupling to happen effectively, but still allows palladium to insert into the remaining triflate. The resulting active palladium

complex, being unable to react with the pyrazole nucleophile, decomposes, giving a complex mixture of products rather then a single product of partial substitution.

6. Concluding Remarks.

The method of "triple annulation" that have proven effective in the synthesis of homocalixarenes, was successfully applied to the gram-scale synthesis of C_3-symmetrical homocalix[3]arenes. Unfortunately, the task of lower rim modification of these homocalix[3]arenes was discovered to be quite challenging, and successful substitution conditions were not found.

CHAPTER FIVE

APPLICATION OF CHROMIUM TRIMETHYLENEMETHANE COMPLEXES IN INTRAMOLECULAR CYCLIZATION REACTIONS

TMM: Too Much Maintenance (relationship slang)

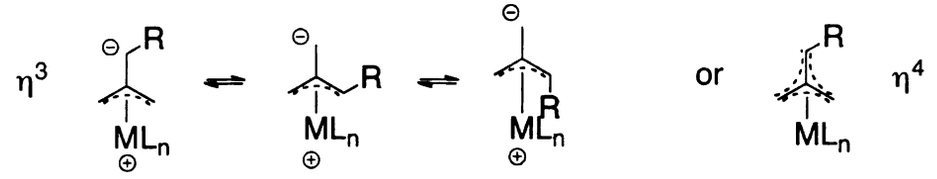
http://acronyms.thefreedictionary.com/

1. Introduction.

Trimethylenemethane, or TMM, complexes have become well known because of series of studies by Barry Trost, starting in early 80's[152]. In his papers, Trost used palladium TMM complexes, generated from bipolar precursors (Scheme 5.1). Using these complexes he successfully developed methods for various cycloadditions, including [3+2][153], [4+3][154], [6+3][155], regiocontrolled cycloadditions to α,β-unsaturated carbonyl compounds[156], and related reactions.

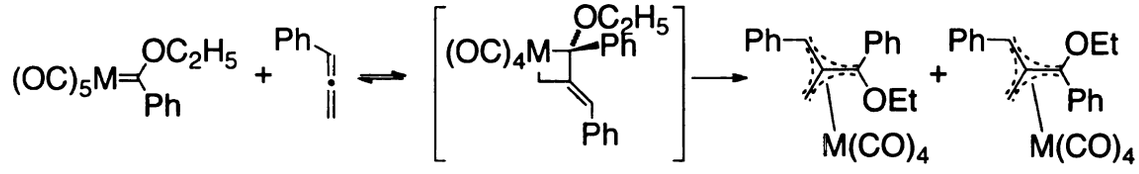
TMM complexes of the following metals are known: iron, molybdenum, ruthenium, osmium, iridium, palladium, tantalum, chromium, tungsten, zirconium, and platinum. For a long period of time, their structure was subject to discussion. Two coordination patterns, which are possible for TMM ligand, are η^3 and η^4 coordination (Scheme 5.1). Currently most of the known TMM complexes, except for palladium and platinum[157], are thought to be η^4.

Scheme 5. 1. TMM binding modes and typical palladium TMM preparation.



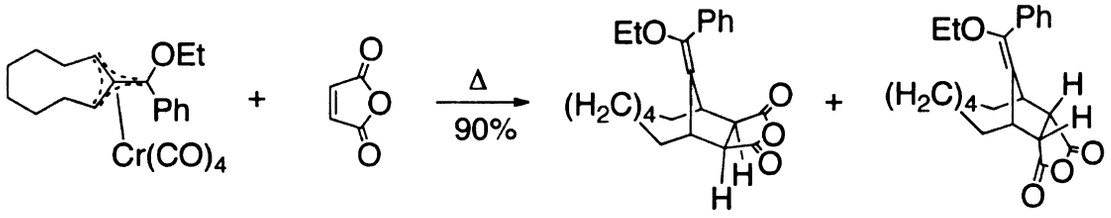
In 1987 Rudolph Aumann reported a novel method for synthesis of TMM complexes, applicable to Group 6 metals (Cr, Mo, W)[158]. This method included heating a mixture of an allene and a Fischer carbene complex. This reaction is thought to proceed through a metallacyclobutane intermediate (Scheme 5.2).

Scheme 5. 2. Preparation of TMM complexes by reaction of Fischer carbene complexes with allenes.



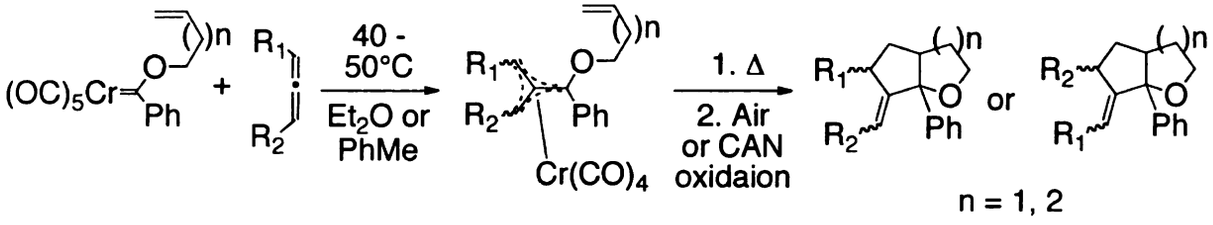
Trost's palladium TMM chemistry was already well known at that time, so one of the most obvious possible uses of the complexes obtained was [3+2] addition. The Aumann research group studied cycloaddition reactions only on intermolecular examples[159]. He examined both alkenes with electron-withdrawing substituents and alkynes. Most of the results obtained were less than satisfactory. While the yields of of the cycloaddition products were consistently high, most of the reactions exhibited poor selectivity. An example of such a cycloaddition is given in Scheme 5.3.

Scheme 5. 3. An example of [3+2] cycloaddition reaction involving chromium TMM complex[159].



In general, intramolecular cycloaddition reactions are known to proceed smoother and more selectively than their intermolecular counterparts[160]. Our goal was to explore the intramolecular [3+2] cycloadditions of chromium TMM complexes with both activated and non-activated substrates. In this particular project, we tried to introduce the double bond in the carbene complex side chain (Scheme 5.4, n = 1 or 2). The allenes of interest varied in substitution pattern, as well as the nature of the substituents.

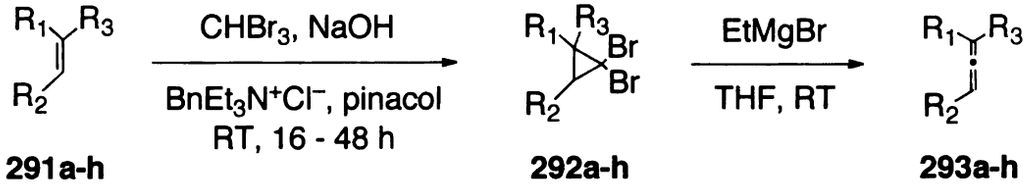
Scheme 5. 4. Proposed intramolecular cyclization reaction.



2. Prepration of Allenes.

Most of the allenes were synthesized using the Doring-Skatteböl method[161], which includes formation of substituted dibromo- (sometimes dichloro) cyclopropane followed by ring opening, using methyllithium or some other organometallic reagent (Scheme 5.5).

Scheme 5. 5. Preparation of allenes **293a-h**.



291a-h **292a-h** **293a-h**

Allene	R_1, R_2, R_3	Yield of **292**, %	Yield of **293**, %
293a	$R_1 + R_2 = (CH_2)_6$, $R_3 = H$	93	68
293b	$R_2 = R_3 = Pr$, $R_1 = H$	91	81
293c	$R_2 = R_3 = Ph$, $R_1 = H$	49	90
293d	$R_1 = Ph$, $R_2 = H$, $R_3 = H$	60	85
293e	$R_1 = R_3 = Ph$, $R_2 = H$	89	96
293f	$R_1 + R_2 = (CH_2)_{10}$, $R_3 = H$	93	42
293g	$R_1 = n\text{-}C_6H_{13}$, $R_2 = H$, $R_3 = H$	89	81
293h	$R_1 = Cy$, $R_2 = H$, $R_3 = H$	69	58

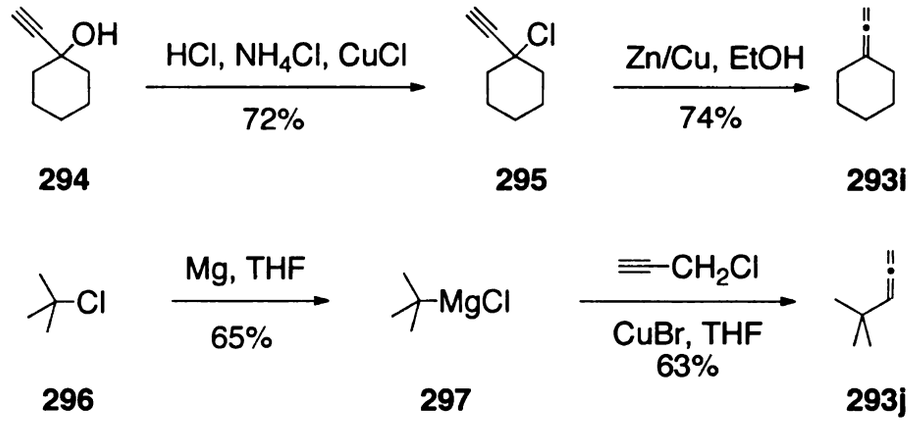
Several experimental details are to be noted. The best procedure for making dibromocyclopropanes was published in 1988[162]. In this procedure, reagents (bromoform, substrate, and NaOH) and catalysts (TEBA and pinacol) are stirred at room temperature for 16 - 48h. This procedure was found to be superior to any other method tried in both experimental simplicity and in yield. For example, 9,9-dibromobicyclo[6.1.0]nonane **292a** was prepared in 93% yield (after distillation), while the best result reported under common phase-transfer conditions was 47%[161].

The ring opening of dibromocyclopropanes can be performed using various organometallic reagents, most popular being BuLi and MeLi. Recently it was reported[163] that treatment of the dibromocyclopropanes with 1.3 - 2 equivalents of ethylmagnesium bromide in THF at room temperature gives allenes in excellent yields. This procedure was found to give best yields, while also being practically very simple.

Commercially available methylenecyclohexane is expensive, so vinylidenecyclohexane **293i** was synthesized as shown in Scheme 5.6. Cheap 1-ethynylcyclohexanol **294** was first converted to the corresponding propargylic chloride **295**, followed by reduction with Zn/Cu couple, which afforded the required allene **293i** in 58% overall yield[164] (Scheme 5.6).

Tert-butylallene **293j** cannot be prepared via dibromocyclopropane opening. Dibromocarbene addition to 3,3-dimethyl-1-butene under usual phase-transfer conditions is known to proceed abnormally, giving a complex mixture of products[165]. Thus, an easy two-step method[166] using the reaction of a Grignard reagent with propargyl chloride in presence of a copper (I) salt was used (Scheme 5.6).

Scheme 5. 6. Preparation of allenes **293i** and **293j**.

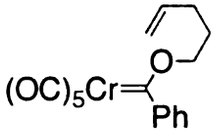


3. Preparation of TMM Complexes and Cyclization Reactions.

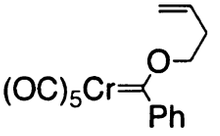
3.1 Preparation of Carbene Complexes.

Two Fischer carbene complexes originally picked for cyclizations were **298a** and **298b** (Scheme 5.7).

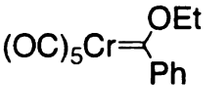
Scheme 5. 7. Carbene complexes used for TMM preparation.



298a



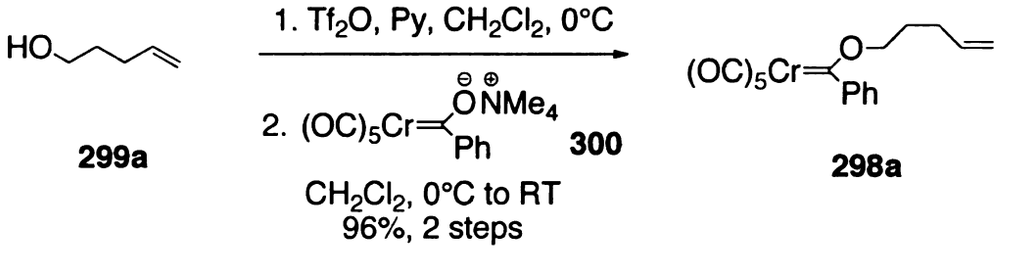
298b



298c

Both of these complexes are known compounds[167]. Their reactivity towards allenes is expected to be very close to complex **298c,** which was used by the Aumann group in most of their TMM preparations[158,159]. This gives us the advantage of anticipating approximate reaction times and solvents. Complexes **298a** and **298b** were prepared *via* the corresponding triflates, using crystalline tetramethylammonium salt **300** as a nucleophile (Scheme 5.8):

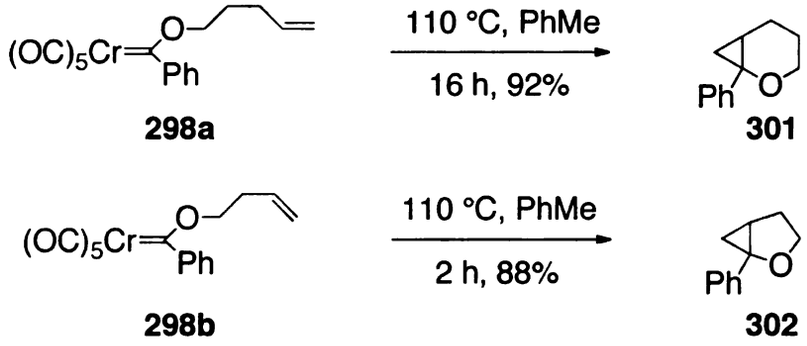
Scheme 5. 8. Preparation of carbene complexes **298a** and **298b**.



It's worth noticing that both **298a** and **298b** are known to be unstable. Hegedus[167] included these complexes among the substrates examined for intramolecular cyclopropanation reactions. Complex **298b** is especially labile, decomposing even at –

20°C in several weeks. Their cyclopropanation reactions were carried out at 110°C in toluene (Scheme 5.9).

Scheme 5. 9. Preparative decomposition of complexes **298a** and **298b**.



298a **301**

298b **302**

3.2. Preparation of TMM Complexes.

The trimethylenemethane complexes of chromium (**303**) were synthesized using the standard procedures reported by Aumann[158]. In the case of allenes with aromatic substituents, 3.0 equivalents of the allene in toluene and a temperature of 40°C were used. Alkylallenes were taken in twofold excess and were allowed to react in ether at 50°C. The results are summarized in Table 5.1.

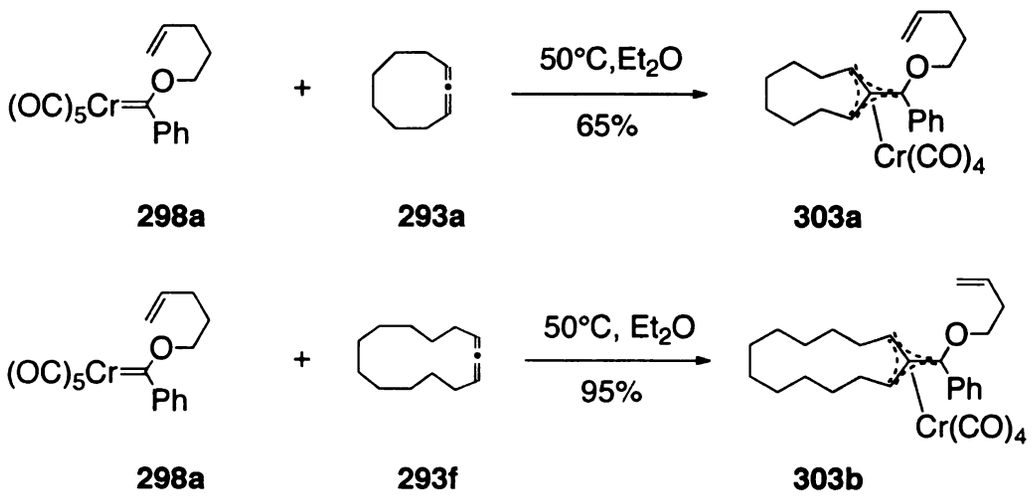
Table 5. 1. Summary of attempted TMM complex syntheses.

Allene	Carb.	Conditions	TMM	Yield of TMM	Observations
293a	**298a**	ether, 50°C	**303a**	65%, 1 isomer	clear yellow solution
293f	**298a**	ether, 50°C	**303b**	95%, 1 isomer	clear yellow solution
293g	**298a**	ether, 50°C	**303c**	43%, 1 isomer	clear yellow solution
293h	**298a**	ether, 50°C	**303d**	54%, 1 isomer	clear yellow solution
293j	**298a**	ether, 50°C	**303e**	58%, 1 isomer	clear yellow solution
293a	**298b**	ether, 50°C	**303f**	29%, 1 isomer	clear yellow solution
293b	**298a**	ether, 50°C	**303g,h**	60%, 2 isomers (5:1)	clear yellow solution
293b	**298b**	ether, 50°C	**303i,j**	22%, 2 isomers (5:1)	clear yellow solution
293d	**298a**	toluene, 40°C	**303k,l**	60%, 2 isomers (3:1)	dark solution
293d	**298b**	toluene, 40°C	-	0%	dark viscous solution
293c	**298a**	toluene, 40°C	-	12%, 2 isomers (?)	orange soln. + precipitate
293c	**298b**	toluene, 40°C	-	0%	dark solution
293e	**298a**	toluene, 40°C	-	0%	totally solidified
293e	**298b**	toluene, 40°C	-	0%	totally solidified
293i	**298a**	ether, 50°C	-	0%	dark solution + precipitate
293i	**298b**	ether, 50°C	-	0%	dark solution + precipitate

Overall, only monosubstituted or 1,3-disubstituted allenes were able to produce TMM complexes in reactions with Fischer carbene complexes. Alkylallenes reacted more smoothly and gave higher yields. Complex **298b** repeatedly gave poor yields of TMM complexes, probably due to its thermal instability.

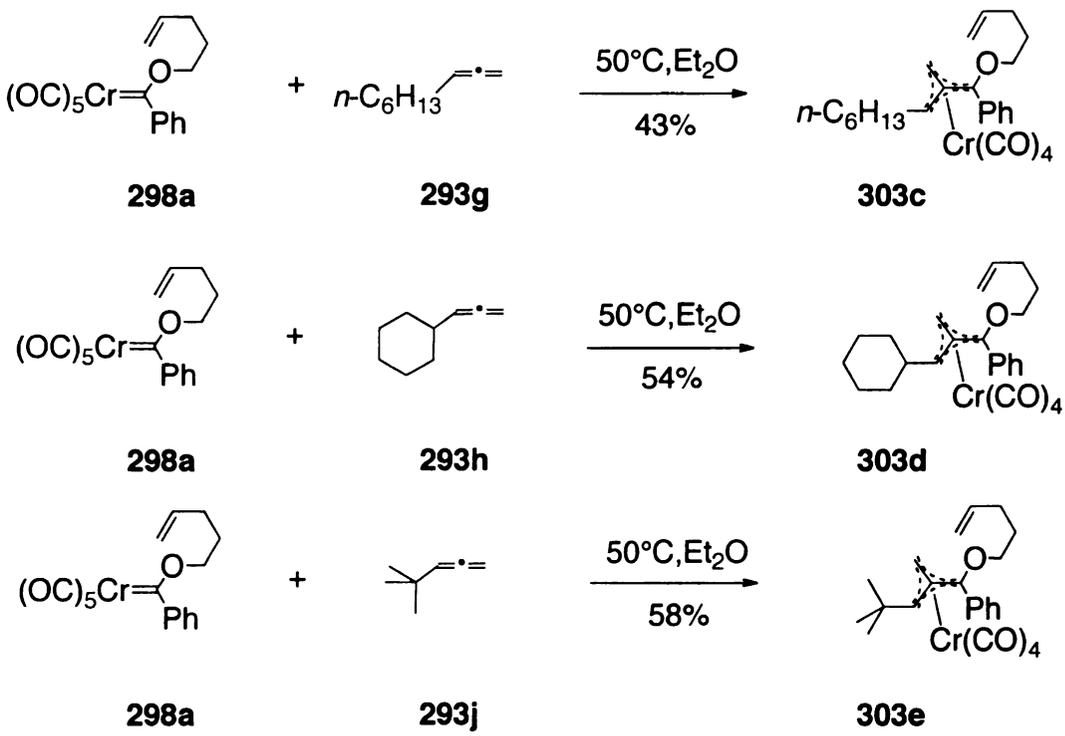
Cyclic allenes **293a** and **293f** gave single isomers of TMM complexes which was attributed to the influence of steric strain in medium-size rings.

Scheme 5. 10. Preparation of TMM complexes **303a** and **303b**.



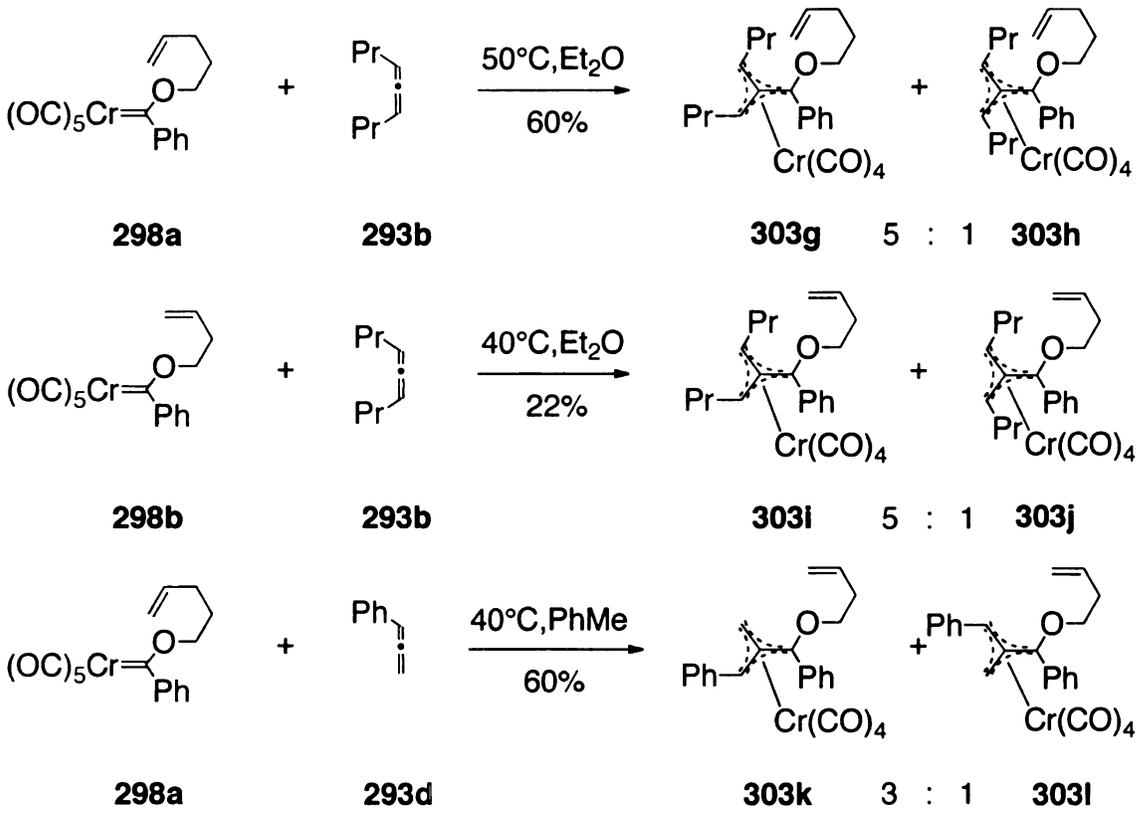
Monosubstituted alkylallenes gave single isomer of TMM complex as product.

Scheme 5. 11. Preparation of TMM complexes **303c-e**.



Phenylallene and 4,5-nonadiene afforded mixtures of isomers. Due to instability of the TMM complexes (and thus paramagnetic chromium impurities) NOESY analysis targeted to the determination of the stereochemistry was not successful for complexes **303g-l**. Instead, tentative assignment was done by comparison with the ^{1}H NMR spectra of related complexes reported by Aumann[158,159] (Scheme 5.12):

Scheme 5. 12. Preparation of TMM complexes **303g-l**.

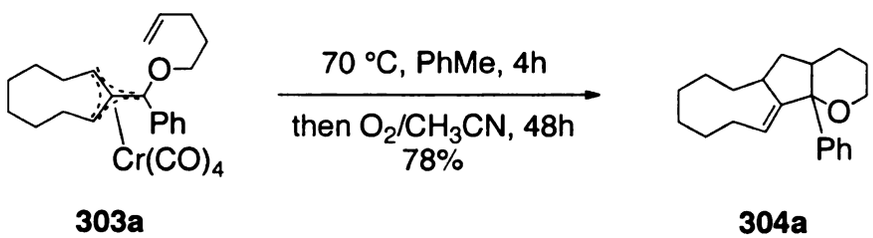


Following these preparations, cyclization reactions were studied.

3.3. Cyclization Reactions.

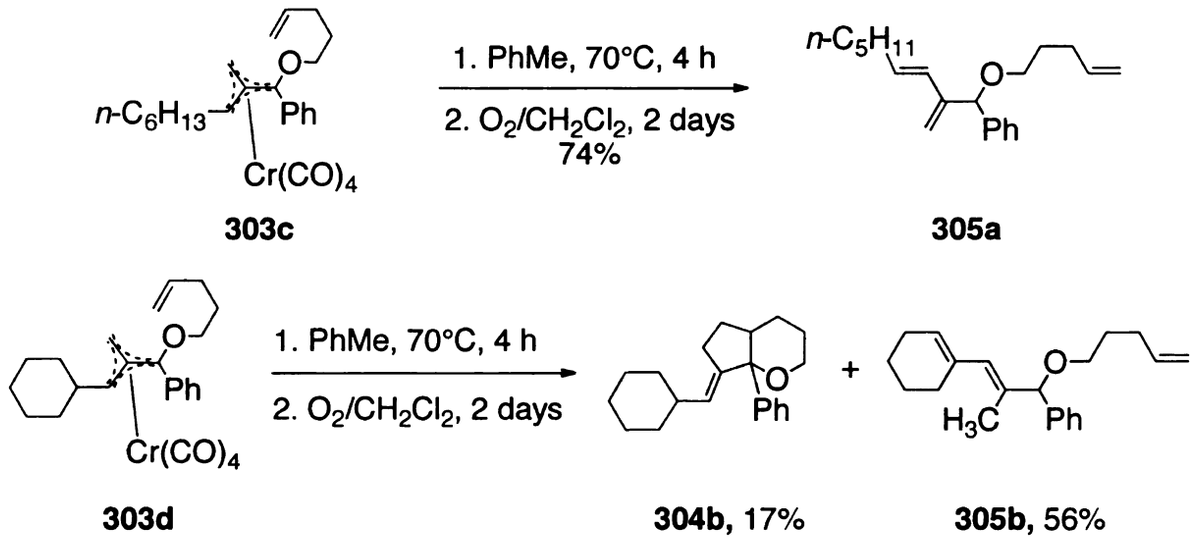
The original very promising result was obtained with TMM complex **303g** obtained from 1,2-cyclononadiene **293a**. Cyclization at 70°C in toluene under oxygen-free conditions with subsequent air oxidation to remove any chromium species coordinated to the product afforded a single diastereomer of the cycloadduct **304a**:

Scheme 5. 13. Cyclization of TMM complex **303a**.



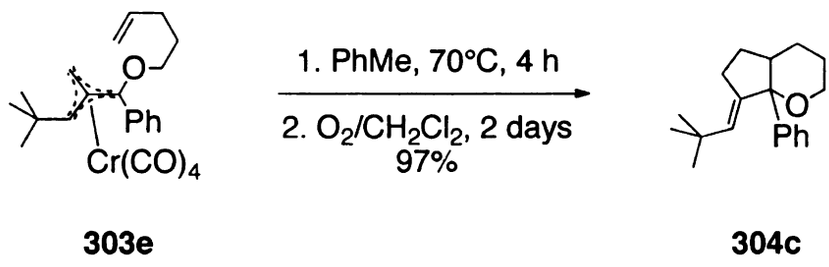
In the next example studied, a side reaction involving β-hydride elimination and readdition was discovered. The product of attempted cyclization of complex **303c** was identified as the 1,3-diene **305a**. The reaction of complex **303d**, containing cyclohexyl group, afforded a mixture of non-cyclized product **305b** and cyclization product **304b** (Scheme 5.14):

Scheme 5. 14. The competition between hydrogen elimination and cyclization.



While the reasons for such behaviour were unclear, it was obvious that some kind of β-hydride elimination is happening instead of cycloaddition. Quite logically, it was found that TMM complex **303e**, not having any hydrogens in the β-position that could possibly be eliminated, gave an amazing 97% yield of the cycloaddition product **304c** as a single diastereomer.

Scheme 5. 15. Cyclization of TMM complex **303e**.



With this knowledge in hand, it seemed that in order for the cyclization reaction to have broad enough scope to have significant applications, a way to suppress the β-hydride elimination had to be found. It was hypothesised that the presence of a coordinating solvent or ligating additive could suppress this elimination, if the mechanism involves CO dissociation from the chromium center. Unfortunately, neither change of solvents (THF, CH_2Cl_2, CH_3CN) nor use of phosphines (1-5 equivalents of PPh_3, PBu_3) as additives have improved the situation to any detectable degree, and the project was stopped at that time.

4. Concluding Remarks.

While TMM complexes generated from 1,2-cyclononadiene, as well as *tert*-butylallene, afford excellent yields of intramolecular [3+2] cycloadditions, TMM complexes from other allenes have not proven to be as synthetically useful. At the same time, the very high degree of diastereoselectivity, as well as high yields of cyclization products for tertiary alkyl substituent on the allene, suggest that for certain substitution patterns this could be a useful reaction.

CHAPTER SIX

EXPERIMENTAL SECTION

Life is a hideous thing, and from the background behind what we know of it peer daemoniacal hints of truth which make it sometimes a thousandfold more hideous. Science, already oppressive with its shocking revelations, will perhaps be the ultimate exterminator of our human species -- if separate species we be -- for its reserve of unguessed horrors could never be borne by mortal brains if loosed upon the world.

H.P. Lovecraft,

"Facts Concerning the Late Arthur Jermyn and His Family"

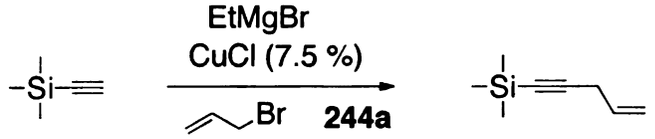
1. General Considerations.

All reactions were performed using either oven-dried or flame-dried glassware under an inert atmosphere of nitrogen. Chemicals used were of commercial quality and used as supplied unless otherwise noted. Whenever the following solvents had to be dry and oxygen-free, they were distilled from the listed drying agents: Tetrahydrofuran (Na, benzophenone), ether (Na, benzophenone), toluene (Na), dichloromethane (CaH_2). Anhydrous 1,2-dichloroethane (99.8%) was purchased from Aldrich and used under nitrogen. Chromatographic purification was performed using Sorbent Technologies 230x400 mesh Standard Grade silica gel, and TLC analyses were performed on Merck Silica Gel 60 coated aluminum TLC plates. Compounds were visualized by dipping into $KMnO_4$ stain solution (prepared by mixing 3 g $KMnO_4$, 20 g of K_2CO_3, 5 mL of 5% NaOH, and 300 mL of water) followed by heating with heat gun. Hydrogen ^1H NMR

data were obtained either on a Varian 300 MHz or 500 MHz instrument. Chemical shifts are reported in parts per million (δ, ppm) relative to tetramethylsilane (δ = 0.00 ppm) or chloroform (δ = 7.24 ppm) for spectra run in $CDCl_3$, and multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sext (sextet), dd (doublet of doublets), dt (doublet of triplets) and br (broad). Carbon ^{13}C NMR data were obtained on a Varian 300 MHz or 500 MHz instrument (working frequencies for ^{13}C NMR are 75 MHz and 125 MHz, correspondingly), and chemical shifts are reported in parts per million (δ, ppm) relative to the middle peak of $CDCl_3$ triplet (δ = 77.00 ppm). Infrared spectra were recorded on a Perkin Elmer FT IR instrument and the peaks are reported in cm^{-1}. Mass spectral data and high-resolution mass spectra were obtained from the Michigan State University Biochemistry Mass Spectrometry Facility. The mass spectra were obtained using one of the following methods: 1) Direct probe EI (electron impact); 2) FAB (fast atom bombardment), using various matrices; 3) ESI (electrospray ionization). Data are reported in the form of *m/z* (intensity relative to base peak = 100). Organolithium and Grignard reagents were purchased from Aldrich and used as is. The indicated reaction temperatures are of the oil bath temperature monitored by digital temperature controller. Melting points (uncorrected) were recorded on a Thomas Hoover capillary melting point apparatus using 1.5-1.8x90 mm capillary tubes. Compounds that used in preparations that are not commercially available were prepared according to the referenced published procedures.

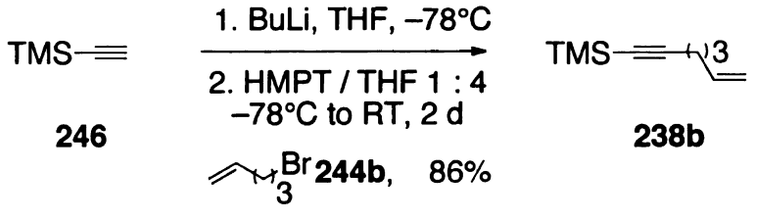
2. Procedures for Chapter 3.

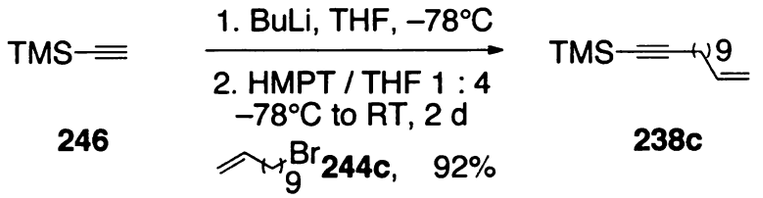
Preparation of TMS-protected enynes.



246 **238a**

Trimethyl(pent-4-en-1-ynyl)silane (238a). A dry 500 mL round-bottom flask was charged with trimethylsilylacetylene (178 mmol, 25.0 mL, 17.4 g) and dry THF (170 mL). The mixture was cooled to –78°C and ethylmagnesium bromide (210 mmol, 70.0 mL, 3.0 M solution in THF) was added dropwise. After stirring for 0.5 h at –78°C, copper (I) chloride (13.3 mmol, 1.32 g) was added and stirring continued for 0.5 h at room temperature. The slurry was then cooled down to 0°C and allyl bromide (350 mmol, 30.0 mL, 42.0 g) was added. The reaction mixture was stirred at 0°C for an additional 2 h and quenched by the addition of saturated ammonium chloride solution (100 mL). The organic layer was separated, and the water layer was extracted with 2x100 mL of ether; combined organic extracts were dried over $MgSO_4$, concentrated, and distilled *in vacuo,* collecting the fraction boiling at 44°C/1 mm Hg (receiver was cooled in ice - NaCl - H_2O mixture, –10 to –20°C) which afforded 15.5 g (112 mmol, 63%) of trimethyl(pent-4-en-1-ynyl)silane **238a** as a colorless liquid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.17 (s, 9H), 3.01 (m, 2H), 5.10 - 5.14 (m, 1H), 5.30 - 5.36 (m, 1H), 5.74 - 5.87 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 0.04, 24.11, 87.00, 103.38, 116.19, 132.11. These spectral data match those reported for this compound[119].





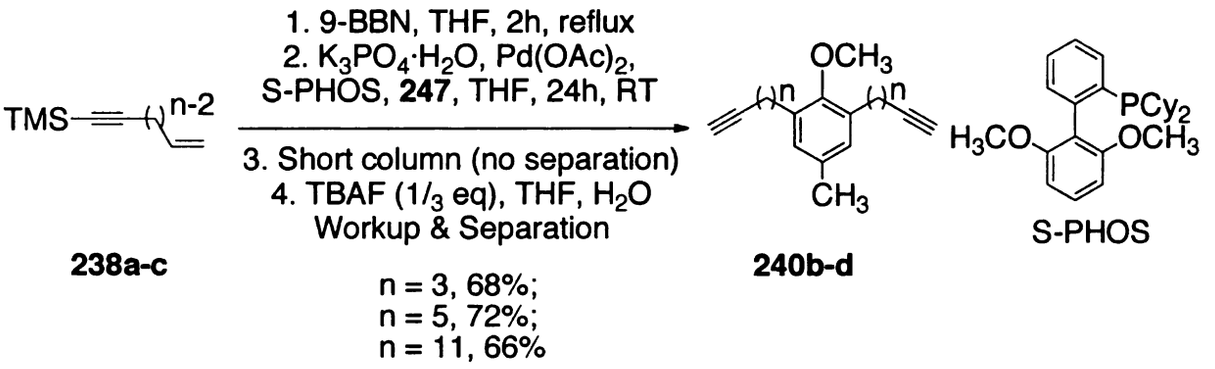
General procedure for (trimethylsilyl)acetylene alkylation. A dry 250 mL round-bottom flask was charged with trimethylsilylacetylene (60 mmol, 5.9 g, 8.5 mL) and dry THF (120 mL). The mixture was stirred and cooled to –78°C, and butyllithium (64 mmol, 25.6 mL, 2.5 M solution in hexane) was added dropwise. The mixture was allowed to stir for 30 min at –78°C, after which dry HMPA (30 mL) was added, reaction mixture was stirred for 15 min at –78°C, and then the appropriate bromide (**244b**[122] or **244c**[123], 40 mmol) was added dropwise. The reaction mixture was allowed to warm up to room temperature and stir for 36 h. The mixture was poured into 200 mL of water and 200 mL of ether. The layers were separated and the water layer was extracted with 100 mL of ether. The combined organic extracts were washed with 4x200 mL of water and 200 mL of brine, dried over $MgSO_4$, and the solvents removed on a rotovap. The residue was dissolved in pentane and filtered through silica gel and concentrated on a rotovap again. In the case of (hept-6-en-1-ynyl)trimethylsilane **238b** (n = 3), distillation at reduced pressure can be used to obtain the product free of solvent and trimethylsilylacetylene

impurities. In case of trimethyl(tridec-12-en-1-ynyl)silane **238c** (n = 9), the product can just be dried *in vacuo* and used without further purification.

(Hept-6-en-1-ynyl)trimethylsilane (238b) was obtained as a colorless liquid (86% yield); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.16 (s, 9H), 1.62 (m, 2H), 2.11 - 2.26 (m, 4H), 4.95 - 5.07 (m, 2H), 5.75 - 5.84 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 0.17, 19.24, 27.84, 32.74, 84.68, 107.18, 115.15, 137.84. These spectral data match those reported for this compound[168].

Trimethyl(tridec-12-en-1-ynyl)silane (238c) was obtained as a colorless liquid (92% yield); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.14 (s, 9H), 1.26 - 1.42 (m, 12H), 1.51 (quint, 2H, J = 7.3 Hz), 2.04 (q, 2H, J = 7.3 Hz), 2.21 (t, 2H, J = 7.3 Hz), 4.91 - 5.01 (m, 2H), 5.78 - 5.83 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 0.17, 19.85, 28.63, 28.78, 28.95, 29.06, 29.12, 29.42, 29.43, 33.81, 84.21, 107.72, 114.11, 139.16; IR (neat) 3079, 2928, 2856, 2176, 1641, 1464, 1250 cm^{-1}; MS (EI), *m/z* (% rel. intensity) 235 (M^{+}–CH_3, 0.5), 179 (12), 176 (15), 154 (28), 139 (57), 125 (47), 109 (30), 99 (36), 85 (25), 73 (100), 59 (80); HRMS (EI) calcd for M^{+}–CH_3 ($C_{15}H_{27}Si$) *m/z* 235.1882, found 235.1884.

General procedure for aromatic diynes preparation.[124]



The appropriate TMS-protected enyne (20 mmol) was put in a dry 100 mL Schlenk flask and 9-BBN (22 mmol, 44.0 mL, 0.5 M in THF) was added. The resulting solution was heated at 70°C for 2 h, cooled down to room temperature and transferred *via* cannula to a 250 mL Schlenk flask containing 2,6-dibromo-4-methylanisole **247**[169] (8 mmol, 2.24 g), potassium phosphate monohydrate (16 mmol, 3.68 g), palladium acetate (0.08 mmol, 18 mg), S-PHOS ligand (0.16 mmol, 66 mg), and 40 mL of dry THF under nitrogen atmosphere. The Schlenk flask solution was degassed using freeze-thaw method (3 cycles), warmed up to room temperature, and stirred at RT for 24 h. The reaction mixture was poured over a Celite pad, which was then rinsed with 4x25 mL of ether. The solvent was removed, the residue dissolved in 5% ethyl acetate in hexane and passed through a thick pad of silica gel (100 g) placed on a large Schott filter. The resulting solution was concentrated *in vacuo*, diluted with 100 mL of THF, and then water (0.2 mL) and TBAF (4 mmol, 4 mL, 1.0 M solution in THF) were added, and the mixture was stirred for 1 h (monitored by TLC)[125]. The reaction mixture was extracted with 100 mL of water, the organic layer was separated, and water layer was extracted with 50 mL of ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, concentrated on a

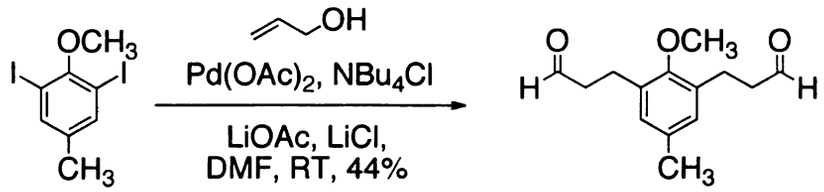
rotovap, and subjected to column chromatography (silica gel, 3% ethyl acetate in pentane for n = 3 and 5, 2% for n = 11).

2-Methoxy-5-methyl-1,3-di(pent-4-ynyl)benzene (240b, n = 3) was obtained as a yellowish oil in 68% yield, R_f 0.54 (5% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.80 - 1.86 (m, 4H), 1.98 (t, 2H, *J* = 2.7 Hz), 2.24 (td, 4H, *J* = 7.0 Hz, 2.7 Hz), 2.25 (s, 3H), 2.70 (t, 4H, *J* = 7.8 Hz), 3.71 (s, 3H), 6.85 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.33, 20.77, 28.91, 29.42, 61.22, 68.45, 84.32, 128.69, 133.25, 134.20, 154.42; IR (neat) 3299, 2940, 2850, 2116, 1477, 1458, 1431, 1223, 1134, 1014 cm^{-1}; MS (EI), *m/z* (% rel. intensity) 254 (M^+, 100), 239 (20), 223 (30), 211 (25), 195 (13), 187 (53), 171 (25), 155 (20), 141 (16), 115 (19), 105 (15), 91 (21), 77 (11), 65 (5); HRMS (EI) calcd for M^+ ($C_{18}H_{22}O$) *m/z* 254.1671, found 254.1662.

1,3-Di(hept-6-ynyl)-2-methoxy-5-methylbenzene (240c, n = 5) was obtained as a yellowish oil in 72% yield, R_f 0.31 (20% CH_2Cl_2 in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.47 - 1.53 (m, 4H), 1.54 – 1.64 (m, 8H), 1.93 (t, 2H, *J* = 2.5 Hz), 2.19 (td, 4H, *J* = 7.0 Hz, 2.5 Hz), 2.25 (s, 3H), 2.59 (t, 4H, *J* = 7.8 Hz), 3.69 (s, 3H), 6.83 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.33, 20.85, 28.35, 28.87, 29.68, 30.35, 61.21, 68.11, 84.63, 128.28, 133.13, 135.09, 154.17; IR (neat) 3299, 2938, 2860, 2110, 1478, 1464, 1431, 1219, 1016 cm^{-1}; MS (FAB+, NBA matrix), *m/z* (% rel. intensity) 310 (M^+, 28), 229 (8),

187 (12), 173 (18), 161 (19), 149 (15), 135 (26), 119 (18), 105 (14), 73 (100); HRMS (FAB+, NBA matrix) calcd for M^+ ($C_{22}H_{30}O$) *m/z* 310.2297, found 310.2296.

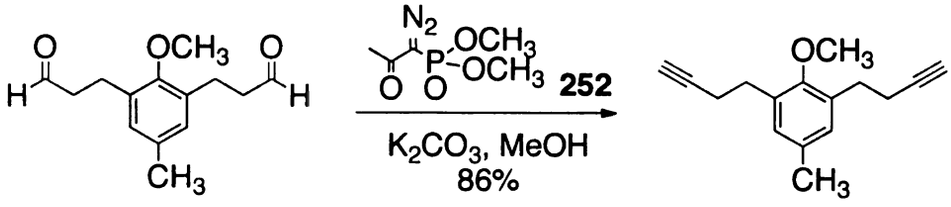
1,3-Di(dodec-11-ynyl)-2-methoxy-5-methylbenzene (240d, n = 11) was obtained as a yellowish oil in 66% yield, R_f 0.45 (20% CH_2Cl_2 in hexane); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.24 - 1.43 (m, 28H), 1.49 - 1.56 (m, 4H), 1.57 - 1.62 (m, 4H), 1.92 (t, 2H, J = 2.7 Hz), 2.17 (td, 4H, J = 7.3 Hz, 2.7 Hz), 2.26 (s, 3H), 2.57 (t, 4H, J = 8.0 Hz), 3.70 (s, 3H), 6.82 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.35, 20.84, 28.46, 28.72, 29.07, 29.46, 29.49, 29.53, 29.56, 29.81 (integrates to 2 carbons), 30.92, 61.16, 68.00, 84.70, 128.15, 132.98, 135.34, 154.13; IR (neat) 3312, 2928, 2855, 2150, 1477, 1468, 1219, 1142, 1018 cm^{-1}; MS (FAB+, NBA matrix), *m/z* (% rel. intensity) 478 (M^+, 65), 339 (2), 313 (9), 187 (12), 175 (32), 161 (52), 149 (66), 135 (100), 119 (44), 105 (22), 81 (31), 67 (25), 55 (35); HRMS (FAB+, NBA matrix) calcd for M^+ ($C_{34}H_{54}O$) *m/z* 478.4175, found 478.4171.



250 **251a**

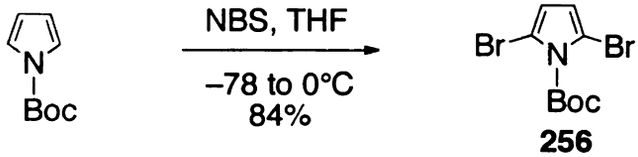
1,3-Di(3-oxopropyl)-2-methoxy-5-methylbenzene (251a).[128] Palladium acetate (0.3 mmol, 67.2 mg), tetrabutylammonium chloride (20 mmol, 5.55 g), lithium acetate (25 mmol, 1.65 g), lithium chloride (10 mmol, 425 mg), 1,3-diiodo-2-methoxy-5-

methylbenzene **250**[126,127] (5 mmol, 1.87 g), allyl alcohol (10 mmol, 0.58 g, 0.68 mL) and 20 mL of dry DMF were stirred in a 50 mL Schlenk flask under N_2 atmosphere for 4 days at room temperature. The resulting mixture was diluted with 50 mL of water and extracted with 2x50 mL ether; the combined organic layers were washed with 7x50 mL of water, 50 mL of brine, and dried over $MgSO_4$. The solvents were removed, and the residue was subjected to column chromatography (silica gel, 20% ethyl acetate in pentane). Dialdehyde **251a** was obtained as a yellowish oil (514 mg, 2.20 mmol, 44%), R_f 0.18 (20% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.25 (s, 3H), 2.76 (m, 4H), 2.92 (t, 4H, J = 7.8 Hz), 3.72 (s, 3H), 6.85 (s, 2H), 9.82 (t, 2H, J = 1.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.57, 22.46, 44.30, 60.86, 128.77, 133.11, 133.64, 154.15, 201.58; IR (neat) 3430, 2936, 2828, 2715, 1725, 1480, 1448, 1438, 1223, 1140, 1010 cm^{-1}; MS (FAB+, TEGDME matrix), *m/z* (% rel. intensity) 234 (M^+, 28), 223 (100), 221 (76), 191 (12), 177 (10), 147 (46), 133 (14), 103 (91), 89 (12), 87 (10), 73 (5), 59 (86); HRMS (FAB+, TEGDME matrix) calcd for M^+ ($C_{14}H_{18}O_3$) *m/z* 234.1256, found 234.1255.



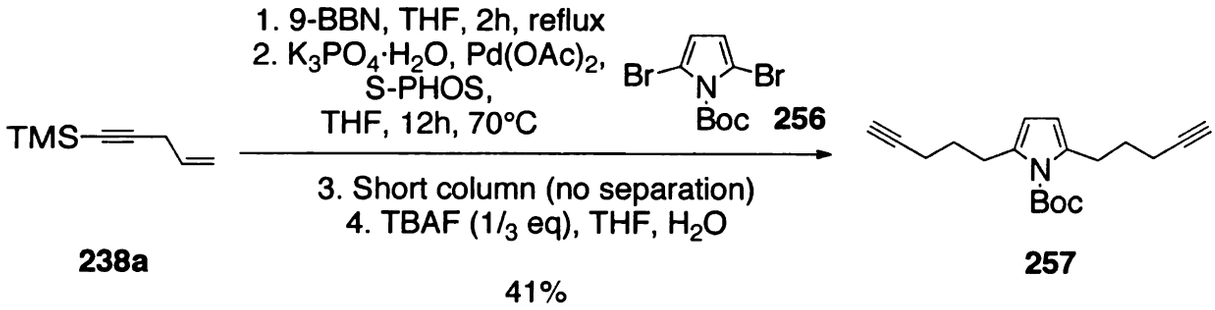
251a **240a**

1,3-Di(but-3-ynyl)-2-methoxy-5-methylbenzene (240a).[129] In a dry 250 mL round bottom flask, dialdehyde **251a** (1.59 g, 6.78 mmol) was dissolved in 180 mL of anhydrous methanol under nitrogen, and potassium carbonate (3.74 g, 27.1 mmol) and dimethyl 1-diazo-2-oxopropylphosphonate **252**[129] (3.12 g, 16.3 mmol) were added to the solution. The reaction mixture was stirred at RT for 5 h (TLC completion control), after which the mixture was diluted with ether (250 mL), washed with 150 mL of 5% $NaHCO_3$ (sat.), 150 mL of NaCl (sat.), dried over $MgSO_4$, concentrated on a rotovap, and subjected to column chromatography (silica gel, 3% ethyl acetate in pentane). Diyne **240a** was obtained as a yellowish oil (1.32 g, 5.84 mmol, 86%), R_f 0.52 (5% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.98 (t, 2H, J = 2.7 Hz), 2.26 (s, 3H), 2.47 (td, 4H, J = 8.0, 2.7 Hz), 2.84 (t, 4H, J = 7.7 Hz), 3.72 (s, 3H), 6.91 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.47, 20.76, 29.12, 61.31, 68.62, 84.09, 128.96, 133.04, 133.30, 154.28; IR (neat) 3292, 2937, 2838, 2805, 2115, 1480, 1451, 1435, 1223, 1136, 1013 cm^{-1}; MS (EI), *m/z* (% rel. intensity) 226 (M^+, 56), 211 (12), 195 (15), 187 (100), 172 (23), 159 (17), 141 (30), 135 (23), 128 (20), 115 (26), 105 (21), 91 (18), 77 (18), 65 (5); HRMS (EI) calcd for M^+ ($C_{14}H_{18}O_3$) *m/z* 226.1358, found 226.1351.



256

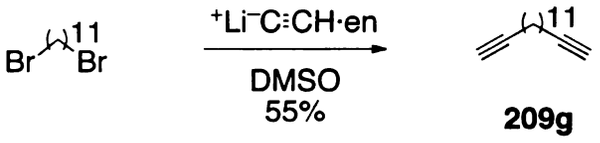
***tert*-Butyl 2,5-dibromo-1*H*-pyrrole-1-carboxylate (256).**[135] To a stirred solution of *tert*-butyl 1*H*-pyrrole-1-carboxylate (29.9 mmol, 5.00 g) in 200 mL of anhydrous THF at –78°C, freshly recrystallized N-bromosuccinimide (60.0 mmol, 10.60 g) was added in portions. The reaction mixture was stirred at –78°C for 1 h, after which it was warmed up to 0°C and stirred at this temperature for 18 h. Sodium sulfite (3.9 g) was added to the mixture, the solvent evaporated on a rotovap, and carbon tetrachloride (170 mL) added. The resulting precipitate was filtered off, and the solution was concentrated on a rotovap again, and subjected to column chromatography (silica gel, 2.5% ethyl acetate in hexane). *tert*-Butyl 2,5-dibromo-1*H*-pyrrole-1-carboxylate **256** was obtained as a colorless oil (8.18 g, 25.2 mmol, 84%), R_f 0.66 (5% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.64 (s, 9H), 6.24 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.75, 86.27, 100.23, 116.08, 147.12. These spectral data match those reported for this compound[135].



***tert*-Butyl 2,5-di(pent-4-ynyl)-1*H*-pyrrole-1-carboxylate (257).** Trimethyl(pent-4-en-1-ynyl)silane **238a** (16.3 mmol, 2.25 g) was put in a dry 100 mL Schlenk flask and 9-BBN (17.9 mmol, 35.9 mL, 0.5 M in THF) was added. The resulting solution was heated at 70°C for 2 h, cooled down to room temperature and transferred *via* cannula to a 250 mL Schlenk flask containing *tert*-butyl 2,5-dibromo-1*H*-pyrrole-1-carboxylate **256** (6.52

mmol, 2.12 g), potassium phosphate monohydrate (13.0 mmol, 3.00 g), palladium acetate (0.13 mmol, 29 mg), S-PHOS ligand (0.26 mmol, 107 mg), and 40 mL of dry THF under a nitrogen atmosphere. The Schlenk flask solution was then degassed using the freeze-thaw method (3 cycles), warmed up to room temperature and back-filled with nitrogen, after which the flask was sealed and heated at 70°C for 12 h. Reaction mixture was poured over a Celite pad which was rinsed with 4x25 mL of ether. The solvent was removed, the residue dissolved in 5% ethyl acetate in hexane and passed through a thick pad of silica gel (100 g) and placed on a large Schott filter. The resulting filtrate was concentrated *in vacuo*, diluted with 50 mL of THF, and then TBAF (4.9 mmol, 1.8 mL, 75% solution in water) was added, and mixture was stirred for 1 h (monitored by TLC). The reaction mixture was extracted with 100 mL of water, the organic layer was separated, and the water layer was extracted with 50 mL of ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, concentrated on a rotovap, and subjected to column chromatography (silica gel, 3% ethyl acetate in hexane). *tert*-Butyl-2,5-di(pent-4-ynyl)-1*H*-pyrrole-1-carboxylate **257** was obtained as a colorless oil (0.80 g, 2.68 mmol, 41%) that darkens over time and should be stored under an inert atmosphere, R_f 0.53 (5% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.60 (s, 9H), 1.82 (quint, 4H, J = 7.3 Hz), 1.96 (t, 2H, J = 2.8 Hz), 2.23 (td, 4H, J = 7.0 Hz, 2.5 Hz), 2.89 (t, 4H, J = 7.5 Hz), 5.86 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.98, 27.86, 28.01, 28.60, 68.51, 83.56, 84.23, 109.65, 134.80, 150.23; IR (neat) 3297, 2978, 2936, 2869, 2118, 1736, 1534, 1480, 1456, 1435, 1389, 1323, 1256, 1172, 1115, 1022 cm^{-1}; MS (ES+), *m/z*

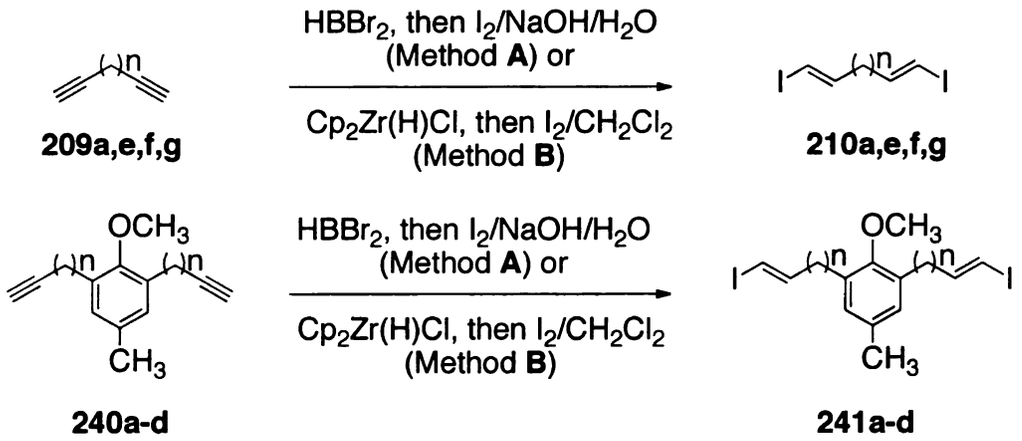
(% rel. intensity) 300 ($M+H^+$, 20), 298 (6), 244 (100), 216 (14), 200 (50), 198 (5); HRMS (ES+) calcd for $(M+H)^+$ ($C_{19}H_{26}NO_2$) *m/z* 300.1964, found 300.1968.



209g

Pentadeca-1,14-diyne (209g).[132] To a dry 250 mL round bottom flask, lithium acetylide – ethylenediamine complex (34 mmol, 3.13 g) was added and then the flask was flushed with nitrogen, and 50 mL of dry DMSO was added. The solution was stirred, cooled down to 8°C, and 1,11-dibromoundecane (16 mmol, 5.00 g) was added dropwise over a period of 1 h, after which the solution was allowed to warm up to room temperature and stirred for an additional 2 h. Water (50 mL) was added, the mixture poured into 100 mL of water, and extracted with 3x50 mL of pentane. The combined organic layers were dried over $MgSO_4$, evaporated to dryness, and the residue subjected to column chromatography (silica gel, gradient: pure pentane → 1% ethyl acetate in pentane) to afford pentadeca-1,14-diyne (1.80 g, 8.82 mmol, 55%) as a colorless liquid, R_f 0.42 (pentane); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.24 – 1.32 (m, 10H), 1.38 – 1.43 (m, 4H), 1.49 – 1.55 (m, 4H), 1.93 (t, 2H, J = 2.8 Hz), 2.17 (td, 4H, J = 7.1 Hz, 2.8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.38, 28.49, 28.74, 29.08, 29.45, 29.51, 68.01, 84.70. These spectral data match those reported for this compound[132].

General procedures for *bis*-vinyliodides preparation



Method A (using dibromoborane).[131] At room temperature, the appropriate diyne (4 mmol) was dissolved in 10 mL of dry CH_2Cl_2, and dibromoborane-dimethyl sulfide complex (8 mmol, 8.0 mL of 1M solution in CH_2Cl_2) was added dropwise. The solution was stirred for 4h, after which it was cooled down to 0°C and transferred *via* cannula to a vigorously stirring mixture of 100 mL ether and 50 mL of water, which were also precooled to 0°C in an ice bath. After 15 min of stirring, an ice-cold solution of sodium hydroxide (40 mmol, 1.60 g NaOH in 10 mL of water) was added in one portion, and then an ice-cold ether solution of iodine (9.6 mmol, 2.46 g I_2 in 40 mL of ether) was added dropwise with a pipette. The resulting mixture was allowed to stir for 30 min at 0°C, then the layers were separated, and the water layer was extracted with 2x30 mL of ether. The combined organic layers were washed with 25 mL saturated sodium thiosulfate and 25 mL saturated brine. After drying and evaporating on a rotovap (room temperature bath), the residue was subjected to column chromatography (silica gel, 2%

ethyl acetate in pentane for **241a-c**, 1% ethyl acetate in pentane for **241d**, and pure pentane for **210a, e, f, g**).

Method B (using Schwartz's reagent).[130] The appropriate diyne (4 mmol) was dissolved in 10 mL of dry CH_2Cl_2 was added in one portion to Schwartz's reagent[187] (2.50 g, 9.69 mmol) dispersed in 20 mL of dry CH_2Cl_2 in 100 mL round bottom flask, shielded from light with foil. After stirring at RT for 15 min, the resulting transparent yellow solution was cooled to 0°C, part of the foil shield was removed for observation purposes, and iodine (2.54 g, 10 mmol) dissolved in 50 mL of dry CH_2Cl_2 was slowly added dropwise until the color of the solution abruptly changed from yellow to orange. The solution was allowed to stir for an additional 30 min, after which the reaction mixture was poured out into the beaker containing 300 mL of pentane and 100 mL of saturated sodium hydrosulfite, and stirred for 30 min. The water layer was removed, and the organic layer was washed consecutively with 100 mL of saturated sodium bicarbonate, water, saturated sodium bicarbonate, and brine. The resulting organic solution was dried with $MgSO_4$ and filtered through a pad of silica gel. The filtrate was evaporated to dryness on a rotovap (room temperature bath) and subjected to column chromatography (silica gel, 2% ethyl acetate in pentane for **241a-c**, 1% ethyl acetate in pentane for **241d**, and pure pentane for **210a, e, f, g**).

(1*E*,5*E*)-1,6-diiodohexa-1,5-diene (210a, n = 2) was obtained as a light-pink solid (Method B: 90% yield, Method A: 40% yield), mp 43 – 46°C, R_f 0.49 (pentane); ^1H

NMR ($CDCl_3$, 500 MHz) δ 2.14 – 2.17 (m, 4H), 6.06 (dd, 2H, *J* = 15.5 Hz, 1.0 Hz), 6.45 – 6.51 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 34.70, 75.78, 144.60; IR (neat) 3048, 3009, 2930, 2909, 2841, 1609, 1442, 1294, 1213, 1182, 1130, 943 cm^{-1}; MS (EI), *m/z* (% rel. intensity) 334 (M^+, 55), 207 (10), 167 (100), 153 (5), 127 (23), 80 (55), 79 (53), 77 (7); HRMS (EI) calcd for M^+ ($C_6H_8I_2$) *m/z* 333.8716, found 333.8720.

(1*E*,6*E*)-1,7-diiodohepta-1,6-diene (210e, n = 3) was obtained as a light-pink oil (Method B: 86% yield, Method A: 46% yield), R_f 0.59 (pentane); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.48 (quint, 2H, *J* = 7.5 Hz), 2.04 (qd, 4H, *J* = 7.5 Hz, 1.5 Hz), 5.99 (dt, 2H, *J* = 14.3 Hz, 1.5 Hz), 6.47 (dt, 2H, *J* = 14.3 Hz, 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.81, 35.05, 75.17, 145.60; IR (neat) 3046, 3005, 2932, 2855, 1604, 1452, 1435, 1277, 1205, 1184, 1132, 943 cm^{-1}; MS (EI), *m/z* (% rel. intensity) 348 (M^+, 18), 221 (16), 180 (28), 167 (100), 155 (8), 127 (17), 94 (63), 93 (84), 79 (31), 77 (13); HRMS (EI) calcd for M^+ ($C_7H_{10}I_2$) *m/z* 347.8872, found 347.8876.

(1E,8E)-1,9-diiodonona-1,8-diene (210f, n = 5) was obtained as a light-pink oil (Method A: 63% yield), R_f 0.63 (pentane); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.23 – 1.30 (m, 2H), 1.32 – 1.39 (m, 4H), 2.02 (qd, 4H, *J* = 7.3 Hz, 1.5 Hz), 5.96 (dt, 2H, *J* = 14.3 Hz, 1.5 Hz), 6.47 (dt, 2H, *J* = 14.3 Hz, 7.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.99, 28.09, 35.81, 74.57, 146.31; IR (neat) 3048, 3005, 2928, 2855, 1605, 1460, 1435, 1282, 1205,

1194, 943 cm^{-1}; MS (FAB+, NBA matrix), *m/z* (% rel. intensity) 376 (M^+, 30), 307 (6), 249 (26), 195 (8), 167 (100), 121 (51), 81 (40); HRMS (FAB+, NBA matrix) calcd for M^+ ($C_9H_{14}I_2$) *m/z* 375.9186, found 375.9183.

(1*E*,14*E*)-1,15-diiodopentadeca-1,14-diene (210g, n = 11) was obtained as a light-pink solid (Method B: 90% yield), mp 33 – 35°C, R_f 0.65 (pentane); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.24 – 1.30 (m, 14H), 1.38 (quint, 4H, *J* = 7.3 Hz), 2.02 (qd, 4H, *J* = 7.3 Hz, 1.5 Hz), 5.96 (dt, 2H, *J* = 14.5 Hz, 1.5 Hz), 6.50 (dt, 2H, *J* = 14.5 Hz, 7.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.31, 28.87, 29.29, 29.45, 29.51, 36.00, 74.27, 146.69; IR (neat) 3048, 2926, 2851, 1605, 1476, 1456, 1281, 1219, 1142, 1019, 945 cm^{-1}; MS (EI), *m/z* (% rel. intensity) 460 (M^+, 65), 333 (96), 180 (17), 167 (100), 123 (13), 109 (24), 97 (14), 95 (31), 83 (23), 81 (34), 69 (19), 67 (24), 55 (15); HRMS (EI) calcd for M^+ ($C_{15}H_{26}I_2$) *m/z* 460.0124, found 460.0118.

Aromatic vinyl iodide 241a (n = 2) was obtained as a light-pink solid (Method B: 89% yield, Method A: 37% yield), mp 47 – 48°C, R_f 0.69 (5% EtOAc in hexane); ^1H NMR ($CDCl_3$, 500 MHz) δ 2.26 (s, 3H), 2.32 – 2.37 (m, 4H), 2.65 – 2.69 (m, 4H), 3.68 (s, 3H), 6.02 (dt, 2H, *J* = 14.6 Hz, 1.5 Hz), 6.57 (dt, 2H, *J* = 14.6 Hz, 7.2 Hz), 6.81 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.80, 28.81, 36.94, 61.27, 75.18, 128.70, 133.36, 133.52,

145.81, 154.22; IR (neat) 3046, 2930, 2857, 2826, 1605, 1477, 1448, 1431, 1289, 1221, 1149, 1012, 939 cm^{-1}; MS (EI), *m/z* (% rel. intensity) 482 (M^+, 53), 315 (60), 228 (32), 188 (30), 187 (70), 173 (100), 159 (25), 128 (22), 115 (17), 105 (6), 91 (10), 77 (6); HRMS (EI) calcd for M^+ ($C_{16}H_{20}OI_2$) *m/z* 481.9604, found 481.9601.

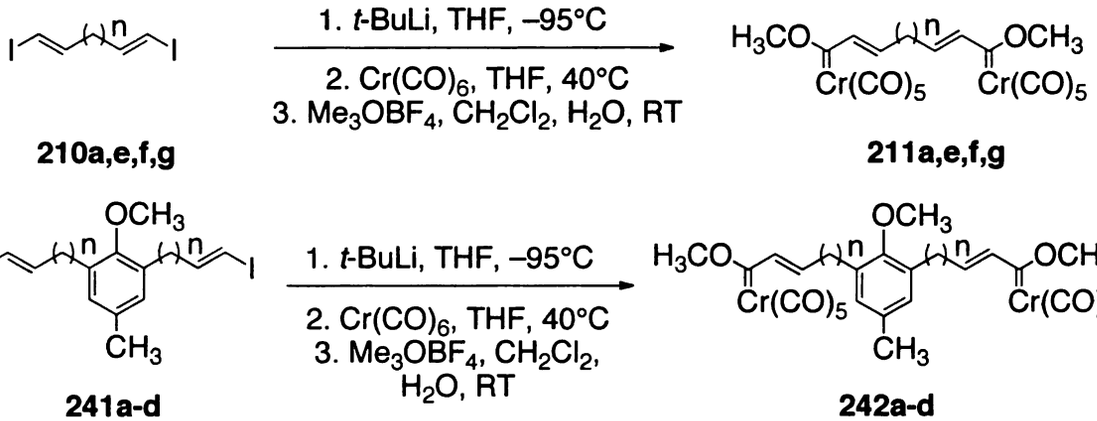
Aromatic vinyl iodide 241b (n = 3) was obtained as a colorless oil (Method B: 77% yield, Method A: 48% yield), R_f 0.70 (5% EtOAc in hexane); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.70 (quint, 4H, *J* = 7.5 Hz), 2.11 (qd, 4H, *J* = 7.3 Hz, 1.3 Hz), 2.25 (s, 3H), 2.58 (t, 4H, *J* = 8.0 Hz), 3.68 (s, 3H), 6.02 (dt, 2H, *J* = 14.3 Hz, 1.3 Hz), 6.54 (dt, 2H, *J* = 14.3 Hz, 7.1 Hz), 6.81 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.82, 29.07, 29.30, 35.81, 61.19, 74.79, 128.52, 133.24, 134.44, 146.21, 154.27; IR (neat) 3046, 3005, 2930, 2858, 2824, 1605, 1477, 1458, 1348, 1282, 1219, 1147, 1130, 1014, 945 cm^{-1}; MS (FAB+, NBA matrix), *m/z* (% rel. intensity) 510 (M^+, 20), 384 (43), 383 (44), 355 (10), 329 (66), 281 (18), 257 (25), 221 (33), 201 (53), 161 (35), 135 (85), 73 (100); HRMS (FAB+, NBA matrix) calcd for M^+ ($C_{18}H_{24}OI_2$) *m/z* 509.9917, found 509.9919.

Aromatic vinyl iodide 241c (n = 5) was obtained as a colorless oil (Method B: 86% yield, Method A: 45% yield), R_f 0.70 (5% EtOAc in hexane); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.35 – 1.47 (m, 8H), 1.59 (quint, 4H, *J* = 7.5 Hz), 2.06 (qd, 4H, *J* = 7.3 Hz, 1.1 Hz), 2.26 (s, 3H), 2.57 (t, 4H, *J* = 7.8 Hz), 3.69 (s, 3H), 5.96 (dt, 2H, *J* = 14.2 Hz, 1.4 Hz), 6.50 (dt, 2H, *J* = 14.3 Hz, 7.3 Hz), 6.82 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ

20.88, 28.18, 28.96, 29.69, 30.54, 35.92, 61.20, 74.36, 128.27, 133.11, 135.08, 146.61, 154.16; IR (neat) 3046, 3005, 2926, 2855, 2824, 1605, 1476, 1350, 1287, 1219, 1144, 1017, 947 cm^{-1}; MS (FAB+, NBA matrix), *m/z* (% rel. intensity) 566 (M^+, 41), 437 (18), 397 (17), 383 (13), 357 (27), 229 (31), 215 (26), 189 (38), 167 (53), 149 (92), 135 (100), 119 (82), 95 (50), 55 (28); HRMS (FAB+, NBA matrix) calcd for M^+ ($C_{22}H_{32}OI_2$) *m/z* 566.0543, found 566.0545.

Aromatic vinyl iodide 241d (n = 11) was obtained as a colorless oil (Method B: 93% yield, Method A: 43% yield), R_f 0.83 (5% EtOAc in hexane); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.25 – 1.40 (m, 32H), 1.59 (quint, 4H, *J* = 7.5 Hz), 2.03 (qd, 4H, *J* = 7.5 Hz, 1.4 Hz), 2.25 (s, 3H), 2.57 (t, 4H, *J* = 8.0 Hz), 3.69 (s, 3H), 5.96 (dt, 2H, *J* = 14.3 Hz, 1.3 Hz), 6.50 (dt, 2H, *J* = 14.3 Hz, 7.5 Hz), 6.82 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.88, 28.33, 28.89, 29.32, 29.49, 29.54, 29.58, 29.82 (integrates to 3 carbons), 30.92, 36.01, 61.19, 74.25, 128.15, 132.96, 135.33, 146.72, 154.13; IR (neat) 3048, 3006, 2924, 2853, 1605, 1466, 1367, 1330, 1288, 1219, 1142, 1019, 945 cm^{-1}; MS (FAB+, NBA matrix), *m/z* (% rel. intensity) 734 (M^+, 30), 608 (8), 467 (3), 441 (7), 314 (10), 275 (2), 175 (20), 149 (100), 135 (76), 119 (56), 55 (26); HRMS (FAB+, NBA matrix) calcd for M^+ ($C_{34}H_{56}OI_2$) *m/z* 734.2421, found 734.2423.

General procedure for preparation of chromium carbene complexes.[170]



Two 250 mL round bottom flasks were charged with the proper diiodide (4 mmol) and chromium hexacarbonyl (16 mmol, 3.52 g), respectively. The diiodide was dissolved in 100 mL of dry THF and chromium carbonyl was dissolved in 50 mL of dry THF (sometimes dissolution is not complete). The flask containing chromium carbonyl was then placed into a 40°C warm water bath. The diiodide solution was cooled down to – 95°C with stirring (acetone – liquid nitrogen bath), and *tert*-butyllithium (16 mmol, 9.4 mL of 1.7M solution in pentane) was added dropwise until the solution color changed abruptly from nearly colorless to yellow (90 – 100% of the *tert*-butyllithium solution is usually added at this point). *Immediately* after this moment, the resulting solution was *quickly* transferred into the vigorously stirred chromium hexacarbonyl solution *via* a large diameter (~ 2 mm, preferably Teflon) cannula (transfer process takes 1 – 2 min). The resulting yellow-orange solution was allowed to stir at room temperature for an additional 30 min, 1 mL of water was added, and then the mixture was evaporated to dryness on a rotovap and dried *in vacuo* for 45 min. The resulting lithium acylate salt was dissolved in a mixture of 75 mL of CH_2Cl_2 and 50 mL of water, and then trimethyloxonium tetrafluoroborate (26 mmol, 3.85 g) was added to the vigorously stirred solution in one portion. The mixture was stirred for 30 min, then poured into 150 mL of ether and water

layer was separated. The organic layer was washed with saturated sodium bicarbonate, brine, dried over $MgSO_4$, and concentrated on a rotovap (bath temperature not above 40°C). The residue was subjected to column chromatography (silica gel, 10% ethyl acetate in pentane for n = 2, 3 and 5, 5% ethyl acetate in pentane for n = 11).

Carbene complex 211a (n = 2) was obtained as a dark-red solid (65% yield), mp 88 – 90°C (dec.), R_f 0.35 (10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.36 – 2.38 (m, 4H), 4.73 (s, 6H), 6.12 – 6.25 (m, 2H), 7.32 (d, 2H, *J* = 14.7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.72, 66.49, 132.90, 144.94, 216.57, 223.87, 335.82; IR (neat) 3049, 2961, 2056, 1912, 1614, 1451, 1333, 1306, 1246, 1171, 1084, 968 cm^{-1}; MS (ES–), *m/z* (% rel. intensity) 549 ($M–H^-$, 100), 520 (4), 373 (8), 257 (5), 132 (8); HRMS (ES–) calcd for $(M–H)^-$ ($C_{20}H_{13}O_{12}Cr_2$) *m/z* 548.9217, found 548.9219.

Carbene complex 211e (n = 3) was obtained as a dark-red solid (71% yield), mp 78 – 80°C (dec.), R_f 0.31 (5% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.68 (quint, 2H, *J* = 7.5 Hz), 2.20 – 2.25 (m, 4H), 4.74 (s, 6H), 6.26 (dt, 2H, *J* = 14.8 Hz, 7.5 Hz), 7.30 (d, 2H, *J* = 15.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.80, 31.56, 66.40, 135.32, 144.70, 216.67, 223.90, 335.97; IR (neat) 3049, 3005, 2961, 2924, 2851, 2060, 1935, 1726, 1456, 1267, 1233, 1171, 1119 cm^{-1}; MS (FAB+, NBA matrix), *m/z* (% rel. intensity) 564 (M+, 17), 452 (12), 424 (33), 368 (46), 340 (90), 312 (100), 284 (54), 248

(19), 181 (5), 154 (24), 120 (16), 90 (10), 52 (24); HRMS (FAB+, NBA matrix) calcd for M^+ ($C_{21}H_{16}O_{12}Cr_2$) *m/z* 563.9452, found 563.9456.

Carbene complex 211f (n = 5) was obtained as a dark-red oil (75% yield), R_f 0.36 (5% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.35 – 1.41 (m, 2H), 1.50 (quint, 4H, *J* = 7.5 Hz), 2.18 (qd, 4H, *J* = 7.3 Hz, 1.1 Hz), 4.73 (s, 6H), 6.29 (dt, 2H, *J* = 14.8 Hz, 7.5 Hz), 7.28 (dt, 2H, *J* = 14.8 Hz, 1.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.01, 28.68, 32.15, 66.35, 136.75, 144.47, 216.74, 223.92, 335.86; IR (neat) 3049, 2919, 2851, 2060, 1933, 1727, 1603, 1456, 1238, 1233, 1170, 978 cm^{-1}; MS (FAB+, NBA matrix), *m/z* (% rel. intensity) 592 (M+, 16), 536 (6), 452 (94), 424 (8), 396 (10), 368 (36), 340 (100), 312 (96), 276 (12), 239 (16), 154 (25), 136 (16), 120 (15), 90 (10), 52 (26); HRMS (FAB+, NBA matrix) calcd for M^+ ($C_{23}H_{20}O_{12}Cr_2$) *m/z* 591.9765, found 591.9767.

Carbene complex 211g (n = 11) was obtained as a dark-red oil (67% yield), R_f 0.48 (5% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.25 – 1.36 (m, 14H), 1.47 (quint, 4H, *J* = 7.3 Hz), 2.17 (q, 4H, *J* = 7.0 Hz), 4.71 (s, 6H), 6.33 (dt, 2H, *J* = 14.8 Hz, 7.3 Hz), 7.28 (d, 2H, *J* = 15.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.23, 29.16, 29.31, 29.41, 29.48, 32.35, 66.24, 137.76, 144.37, 216.78, 223.96, 335.98; IR (neat) 3019, 2930, 2857, 2060, 1923, 1727, 1605, 1453, 1233, 1173, 1086, 978 cm^{-1}; MS (ES–), *m/z* (% rel.

intensity) 675 (M–H$^-$, 100); HRMS (ES–) calcd for (M–H)$^-$ ($C_{29}H_{31}O_{12}Cr_2$) *m/z* 675.0626, found 675.0601.

Aromatic carbene complex 242a (n = 2) was obtained as a dark-red oil (67% yield), R_f 0.21 (5% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.26 (s, 3H), 2.49 (q, 4H, *J* = 7.3 Hz), 2.76 (t, 4H, *J* = 8.0 Hz), 3.70 (s, 3H), 4.72 (s, 6H), 6.35 (dt, 2H, *J* = 14.7 Hz, 7.3 Hz), 6.85 (s, 2H), 7.33 (d, 2H, *J* = 15.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.75, 28.79, 33.20, 61.15, 66.33, 128.79, 133.47, 133.71, 135.98, 144.40, 154.27, 216.71, 223.95, 336.23; IR (neat) 2977, 2926, 2857, 2060, 1943, 1605, 1455, 1328, 1350, 1232, 1152, 1121, 1076, 982 cm^{-1}; MS (ES–), *m/z* (% rel. intensity) 697 (M–H$^-$, 100); HRMS (ES–) calcd for (M–H)$^-$ ($C_{30}H_{25}O_{13}Cr_2$) *m/z* 697.0105, found 697.0095.

Aromatic carbene complex 242b (n = 3) was obtained as a dark-red oil (79% yield), R_f 0.39 (10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.79 (quint, 4H, *J* = 7.5 Hz), 2.24 (q, 4H, *J* = 7.3 Hz), 2.26 (s, 3H), 2.63 (t, 4H, *J* = 7.8 Hz), 3.68 (s, 3H), 4.73 (s, 6H), 6.36 (dt, 2H, *J* = 15.0 Hz, 7.5 Hz), 6.84 (s, 2H), 7.31 (d, 2H, *J* = 15.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.82, 29.34, 29.44, 32.27, 61.25, 66.32, 128.70, 133.48, 134.36, 137.26, 144.51, 154.37, 216.77, 223.93, 336.01; IR (neat) 2928, 2857, 2060, 1925, 1725, 1603, 1478, 1453, 1339, 1231, 1171, 1078, 1015, 974 cm^{-1}; MS (FAB+, NBA matrix), *m/z* (% rel. intensity) 726 (M+, 7), 695 (3), 614 (6), 586 (17), 474 (18), 446

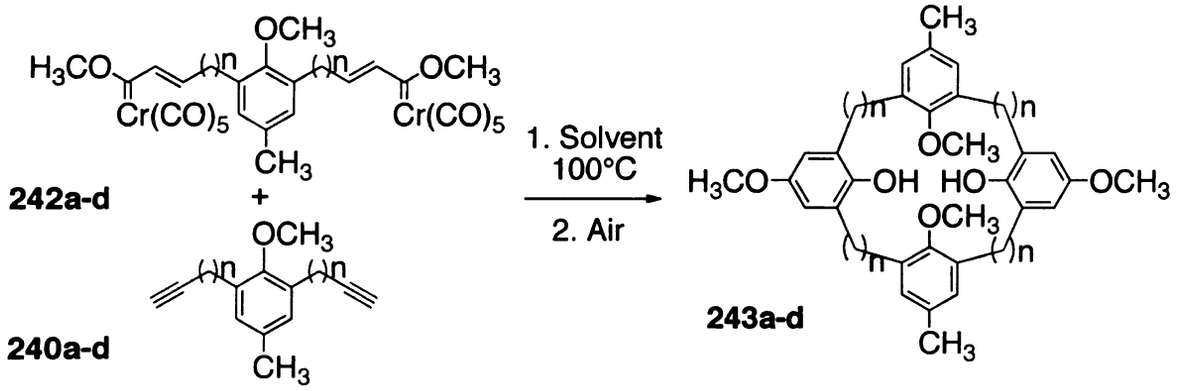
(53), 410 (13), 394 (31), 351 (100), 332 (55), 307 (22), 289 (10), 154 (77), 136 (49), 120 (21), 90 (14), 52 (28); HRMS (FAB+, NBA matrix) calcd for M^+ ($C_{32}H_{30}O_{13}Cr_2$) *m/z* 726.0497, found 726.0494.

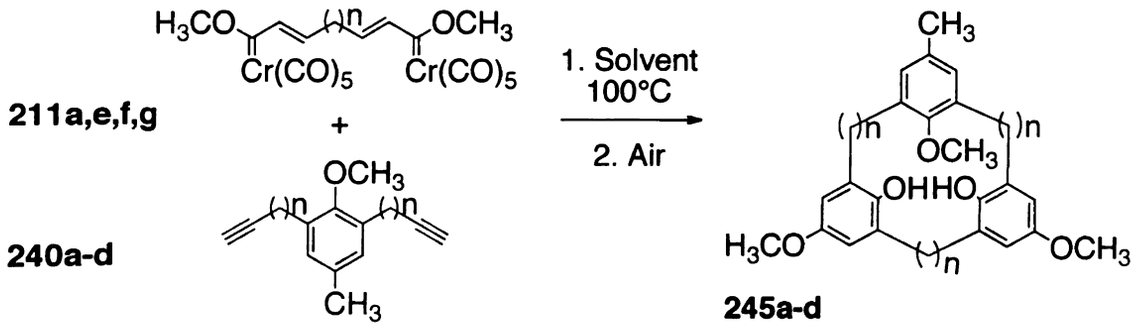
Aromatic carbene complex 242c (n = 5) was obtained as a dark-red oil (68% yield), R_f 0.42 (10% EtOAc in hexane); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.42 (quint, 4H, *J* = 7.3 Hz), 1.53 (quint, 4H, *J* = 7.4 Hz), 1.62 (quint, 4H, *J* = 7.4 Hz), 2.24 (q, 4H, *J* = 7.2 Hz), 2.26 (s, 3H), 2.63 (t, 4H, *J* = 8.0 Hz), 3.69 (s, 3H), 4.73 (s, 6H), 6.32 (dt, 2H, *J* = 15.0 Hz, 7.5 Hz), 6.82 (s, 2H), 7.29 (d, 2H, *J* = 15.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.85, 28.18, 29.33, 29.69, 30.65, 32.31, 61.23, 66.32, 128.31, 133.21, 135.09, 137.36, 144.37, 154.14, 216.76, 223.96, 335.88; IR (neat) 2932, 2856, 2060, 1923, 1603, 1478, 1453, 1289, 1232, 1173, 1084, 1017, 978 cm^{-1}; MS (FAB+, NBA matrix), *m/z* (% rel. intensity) 782 (M+, 5), 698 (5), 642 (14), 586 (3), 558 (10), 530 (27), 502 (100), 450 (40), 419 (8), 388 (21), 357 (7), 307 (10), 289 (8), 185 (14), 154 (38), 136 (28), 91 (10), 52 (22); HRMS (FAB+, NBA matrix) calcd for M^+ ($C_{36}H_{38}O_{13}Cr_2$) *m/z* 782.1123, found 782.1119.

Aromatic carbene complex 242d (n = 11) was obtained as a dark-red oil (49% yield), R_f 0.41 (5% EtOAc in hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.24 – 1.40 (m, 28 H), 1.47 (quint, 4H, *J* = 7.0 Hz), 1.59 (quint, 4H, *J* = 7.4 Hz), 2.24 (qd, 4H, *J* = 7.3, 1.0 Hz), 2.26 (s, 3H), 2.63 (t, 4H, *J* = 8.0 Hz), 3.69 (s, 3H), 4.72 (s, 6H), 6.33 (dt, 2H, *J* = 14.7

Hz, 7.4 Hz), 6.82 (s, 2H), 7.29 (dt, 2H, J = 15.0 Hz, 1.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.85, 28.28, 29.21, 29.37, 29.49, 29.51, 29.55, 29.59, 29.84 (integrates to 2 carbons), 30.95, 32.39, 61.20, 66.27, 128.18, 133.02, 135.37, 137.70, 144.34, 154.17, 216.77, 223.95, 335.93; IR (neat) 2928, 2855, 2060, 1929, 1605, 1454, 1230, 1173, 1142, 1088, 1019, 978 cm^{-1}; MS (FAB+, NBA matrix), *m/z* (% rel. intensity) 866 (M^+–3CO, 3), 835 (2), 810 (1), 760 (1), 670 (100), 618 (18), 541 (10), 289 (8), 149 (82), 135 (78), 119 (62), 91 (44), 52 (45); HRMS (FAB+, NBA matrix) calcd for M^+–3CO ($C_{45}H_{62}O_{10}Cr_2$) *m/z* 866.3153, found 866.3156.

General macrocyclization procedures.





Method A (in THF, freeze-thaw degassing): The proper carbene complex (1 mmol) and the appropriate diyne (1 mmol) were dissolved in 400 mL of freshly distilled anhydrous THF and placed in a 1L Schlenk flask. The flask was then degassed by the freeze-thaw method (3 cycles), warmed up to room temperature, backfilled with nitrogen, and the flask was sealed and heated for 24 h at 100°C in an oil bath. The reaction mixture was then cooled, and the resulting solution was placed in an open 1L beaker in the hood, and stirred open to air overnight. The resulting solution was filtered through a cotton plug to get rid of insoluble chromium-containing material, evaporated to dryness, and subjected to column chromatography (silica gel, 20% ethyl acetate in pentane for n = 2, 3 and 5, 10% ethyl acetate in pentane for n = 11).

Method B (in 1,2-dichloroethane, freeze-thaw degassing): The proper carbene complex (1 mmol) and the appropriate diyne (1 mmol) were dissolved in 400 mL of Aldrich anhydrous 99.8% 1,2-dichloroethane[171], the solution was placed in a 1L Schlenk flask, and the contents of the flask were then degassed by the freeze-thaw method (4-5 cycles), warmed up to room temperature, backfilled with nitrogen, and the flask was sealed and heated for 0.5 – 1 h at 100°C in an oil bath. The reaction mixture was then cooled and the resulting solution was placed in an open 1L beaker in the hood, and stirred open to air overnight. The resulting solution was filtered through the cotton plug to get rid of insoluble chromium-containing material, evaporated to dryness, and subjected to column chromatography.

Method C (in 1,4-dioxane, no freeze-thaw): The proper carbene complex (1 mmol) and the appropriate diyne (1 mmol) were dissolved in 400 mL of 1,4-dioxane which had been freshly dried by passing through an alumina drying column. The solution was placed in a

1L Schlenk flask, and nitrogen was bubbled slowly through it for 3 h. The flask was then sealed and heated for 24 h at 100°C (unless stated otherwise) in an oil bath. The reaction mixture was then cooled, and the resulting solution was placed in an open 1L beaker in the hood, and stirred open to air overnight. The resulting solution was filtered through the cotton plug to get rid of insoluble chromium-containing material, evaporated to dryness, and subjected to column chromatography. In case of the largest macrocycles (n = 11), it was found that cyclization at 115°C gives the best yield of the target product.

Homocalix[4]arene 243a (n = 2) was obtained was obtained as a yellow solid (Method A: 25% yield, Method B: 35% yield, Method C: 22% yield), which can be recrystallized by slow evaporation of a hexane/CH_2Cl_2 (4:1) solution at room temperature to give yellow crystals, mp 180°C, R_f 0.32 (20% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.14 (s, 6H), 2.80 (m, 16H), 3.63 (s, 6H), 3.69 (s, 6H), 5.48 (s, 2H), 6.46 (s, 4H), 6.69 (s, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.71, 30.79, 31.27, 55.60, 61.12, 112.78, 129.13, 129.34, 133.45, 134.37, 146.96, 152.72, 154.27; IR (neat) 3490, 2934, 2856, 1604, 1478, 1348, 1226, 1194, 1143, 1057, 1012 cm^{-1}; MS (ES+) *m/z* (% rel. intensity) 597 ($M+H^+$, 100); HRMS (ES+) calcd for $(M+H)^+$ ($C_{38}H_{45}O_6$) *m/z* 597.3216, found 597.3224.

Homocalix[4]arene 243b (n = 3) was obtained as a yellowish solid (Method A: 25% yield, Method B: 39% yield, Method C: 25% yield), which can be recrystallized by slow evaporation of a hexane/CH_2Cl_2 (4:1) solution at room temperature to give colorless

crystals, mp 155°C, R_f 0.32 (20% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.93 (quint, 8H, J = 7.3 Hz), 2.24 (s, 6H), 2.52 (t, 8H, J = 7.8 Hz), 2.64 (t, 8H, J = 7.3 Hz), 3.55 (s, 6H), 3.74 (s, 6H), 5.67 (s, 2H), 6.54 (s, 4H), 6.83 (s, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.78, 29.54, 29.78, 31.07, 55.61, 60.96, 112.63, 129.18, 130.48, 133.82, 134.72, 146.11, 153.15, 154.16; IR (neat) 3390, 2932, 2850, 1605, 1477, 1439, 1317, 1211, 1190, 1151, 1130, 1061 cm^{-1}; MS (FAB+, NBA matrix), *m/z* (% rel. intensity) 652 (M^+, 100), 531 (4), 397 (8), 339 (6), 325 (12), 299 (6), 257 (13), 173 (40), 135 (68), 95 (62), 55 (92); HRMS (FAB+, NBA matrix) calcd for M^+ ($C_{42}H_{52}O_6$) *m/z* 652.3764, found 652.3768.

Homocalix[4]arene 243c (n = 5) was obtained as a yellowish solid (Method A: 27% yield, Method B: 10% yield, Method C: 17% yield), which can be recrystallized by slow evaporation of a hexane/CH_2Cl_2 (4:1) solution at room temperature to give yellowish crystals, mp 153°C, R_f 0.49 (20% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.40 (quint, 8H, J = 7.4 Hz), 1.62 (sext, 16H, J = 7.5 Hz), 2.25 (s, 6H), 2.53 (t, 8H, J = 7.8 Hz), 2.64 (t, 8H, J = 7.5 Hz), 3.67 (s, 6H), 3.72 (s, 6H), 4.58 (s, 2H), 6.51 (s, 4H), 6.81 (s, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.83, 29.10, 29.66, 29.72, 30.58, 30.77, 55.56, 61.35, 112.80, 128.59, 129.89, 133.30, 135.24, 145.49, 153.11, 154.34; IR (neat) 3453, 2932, 2857, 1601, 1477, 1439, 1348, 1250, 1199, 1152, 1077, 1043, 1005 cm^{-1}; MS (FAB+, NBA matrix), *m/z* (% rel. intensity) 764 (M^+, 70), 391 (10), 307 (40), 289 (28), 219 (34), 154 (100), 136 (100), 119 (62), 105 (50), 91 (71), 81 (57), 69 (77), 55 (82);

HRMS (FAB+, NBA matrix) calcd for M^+ ($C_{50}H_{68}O_6$) *m/z* 764.5016, found 764.5023. Single crystal X-Ray analysis is also available for this molecule (see Appendix).

Homocalix[4]arene 243d (n = 11) was obtained as a colorless oil (Method A: 13% yield, Method C (24 h at 115°C): 18% yield), which can be crystallized from a pentane solution at –20°C to give white crystals, mp 44°C, R_f 0.69 (20% EtOAc in hexane); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.24 – 1.38 (m, 56H), 1.54 – 1.63(m, 16H), 2.25 (s, 6H), 2.53 – 2.58 (m, 16H), 3.69 (s, 6H), 3.74 (s, 6H), 4.29 (s, 2H), 6.53 (s, 4H), 6.82 (s, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.87, 29.41 (integrates to 4 carbons), 29.46, 29.52, 29.66, 29.80, 29.85, 30.51, 30.91, 55.59, 61.21, 112.77, 128.25, 129.26, 133.03, 135.39, 145.34, 153.09, 154.21; IR (neat) 3613, 3480, 2924, 2855, 1707, 1607, 1477, 1466, 1346, 1294, 1219, 1194, 1147, 1095, 1059, 1018 cm^{-1}; MS (FAB+, NBA matrix), *m/z* (% rel. intensity) 1100 (M^+, 100), 550 (2), 391 (2), 289 (6), 219 (10), 189 (12), 175 (26), 161 (32), 151 (92), 149 (84), 135 (84), 119 (56), 105 (38), 91 (30), 81 (27), 69 (36), 55 (43); HRMS (FAB+, NBA matrix) calcd for M^+ ($C_{74}H_{116}O_6$) *m/z* 1100.8772, found 1100.8760.

Homocalix[3]arene 245a (n = 2) was obtained as a white solid (Method A: 9% yield, Method C: 17% yield), which can be recrystallized by slow evaporation of a hexane/CH_2Cl_2 (4:1) solution at room temperature to give colorless crystals, mp 181°C,

R_f 0.39 (20% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.26 (s, 3H), 2.77 – 3.06 (m, 15H), 3.69 (s, 6H), 4.01 (s, 2H), 6.44 (d, 2H, *J* = 3.0 Hz), 6.49 (d, 2H, *J* = 3.3 Hz), 6.95 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.82, 30.50, 30.56, 31.24, 55.58, 61.05, 113.96, 114.14, 129.37, 130.02, 130.33, 134.46, 134.54, 146.26, 153.77, 155.07; IR (neat) 3499, 2924, 2857, 1734, 1605, 1432, 1352, 1307, 1289, 1235, 1196, 1146, 1055, 1007 cm^{-1}; MS (ES+), *m/z* (% rel. intensity) 449 ($M+H^+$, 100), 237 (4); HRMS (ES+) calcd for $(M+H)^+$ ($C_{28}H_{33}O_5$) *m/z* 449.2328, found 449.2320. Single crystal X-Ray analysis is also available for this molecule (see Appendix).

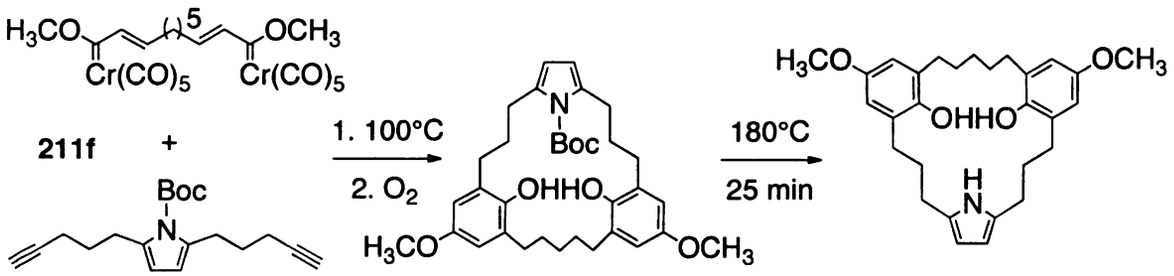
Homocalix[3]arene 245b (n = 3) was obtained as a yellowish solid (Method A: 30% yield, Method C: 31% yield), which can be recrystallized by slow evaporation of a hexane/CH_2Cl_2 (4:1) solution at room temperature to give colorless crystals, mp 159°C, R_f 0.46 (20% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.86 – 1.95 (m, 4H), 2.00 (quint, 2H, *J* = 7.3 Hz), 2.26 (s, 3H), 2.52 – 2.64 (m, 8H), 2.61 (t, 4H, *J* = 7.0 Hz), 3.53 (s, 3H), 3.75 (s, 6H), 5.74 (s, 2H), 6.55 (AB quartet, 4H, *J* = 2.8 Hz, *C* = 2.6 Hz), 6.85 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.80, 29.77, 30.12, 30.19, 30.38, 31.50, 55.56, 60.60, 112.97, 113.37, 129.58, 132.35, 132.83, 134.30, 135.24, 145.86, 153.46, 153.74; IR (neat) 3414, 2920, 2851, 1705, 1603, 1477, 1344, 1203, 1150, 1062, 1012 cm^{-1}; MS (FAB+, NBA matrix), *m/z* (% rel. intensity) 490 (M^+, 32), 460 (4), 391 (2), 341 (2), 307 (30), 289 (16), 219 (10), 154 (100), 136 (63), 117 (12), 107 (18), 89 (14), 77 (13); HRMS (FAB+, NBA matrix) calcd for M^+ ($C_{31}H_{38}O_5$) *m/z* 490.2719, found

490.2722. Single crystal X-Ray analysis is also available for this molecule (see Appendix).

Homocalix[3]arene 245c (n = 5) was obtained as a yellowish solid (Method A: 28% yield, Method C: 25% yield), which can be recrystallized by slow evaporation of hexane/CH_2Cl_2 (4:1) solution at room temperature to give yellowish crystals, mp 142°C, R_f 0.51 (20% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.30 – 1.39 (m, 6H), 1.60 – 1.67 (m, 12H), 2.26 (s, 3H), 2.54 (t, 4H, J = 7.8 Hz), 2.57 (t, 8H, J = 7.8 Hz), 3.65 (s, 3H), 3.73 (s, 6H), 4.77 (s, 2H), 6.51 (s, 4H), 6.81 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.83, 28.10, 28.15, 29.14, 29.61, 29.75, 30.06, 30.13, 30.59, 55.51, 61.53, 112.78, 112.93, 128.66, 130.20, 130.36, 133.57, 135.17, 145.49, 153.31, 154.30; IR (neat) 3455, 2930, 2856, 1604, 1477, 1350, 1215, 1149, 1072, 1040, 1014 cm^{-1}; MS (FAB+, Gly matrix), *m/z* (% rel. intensity) 574 (M^+, 3), 553 (8), 461 (17), 369 (45), 277 (99), 215 (8), 185 (100), 93(100), 75 (86), 57 (70), 45 (56); HRMS (FAB+, Gly matrix) calcd for M^+ ($C_{37}H_{50}O_5$) *m/z* 574.3658, found 574.3662. Single crystal X-Ray analysis is also available for this molecule (see Appendix).

Homocalix[3]arene 245d (n = 11) was obtained as a colorless oil (Method A: 10% yield, Method C (24 h at 115°C): 11% yield), which can be crystallized from pentane solution at –20°C to give white crystals, mp 58°C, R_f 0.70 (20% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.22 – 1.38 (m, 42H), 1.55 – 1.62 (m, 12H), 2.25 (s, 3H), 2.53 –

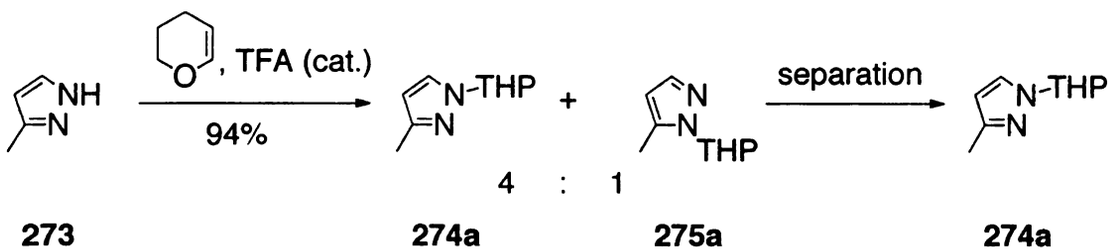
2.58 (m, 12H), 3.69 (s, 3H), 3.73 (s, 6H), 4.29 (s, 2H), 6.53 (s, 4H), 6.82 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.86, 29.26, 29.28, 29.30 (integrates to 5 carbons), 29.32, 29.33, 29.35, 29.42, 29.51, 29.80, 29.81, 29.87, 30.52, 30.86, 55.60, 61.18, 112.81, 112.84, 128.29, 129.28, 133.02, 135.38, 145.38, 153.11, 154.28 (1 aromatic carbon not found); IR (neat) 3616, 3486, 2926, 2853, 1605, 1478, 1346, 1190, 1148, 1055, 1018 cm^{-1}; MS (ES+), *m/z* (% rel. intensity) 828 ($M+H^+$, 100), 814 (1), 510 (3); HRMS (ES+) calcd for $(M+H)^+$ ($C_{55}H_{87}O_5$) *m/z* 827.6554, found 827.6530.



Unprotected Pyrrole Macrocycle 259.[172] Macrocyclization was achieved using Methods B (9% yield) of C (18% yield) (see procedures above). The latter cyclization provided 18% yield of the protected product **258** in pure form as well as 5% yield of a fraction that consisted mainly of the deprotected product **259**. This deprotected material contained unidentified impurities that could not be removed by column purification and was not used further. A solution of product **258** (105 mg, 0.187 mmol) was then evaporated on a rotovap and dried *in vacuo* to afford a thin film in a 250 mL round bottom flask. The flask was then filled with nitrogen and heated at 180°C in an oil bath for 25 minutes, cooled down, and subjected to column chromatography (silica gel, 20%

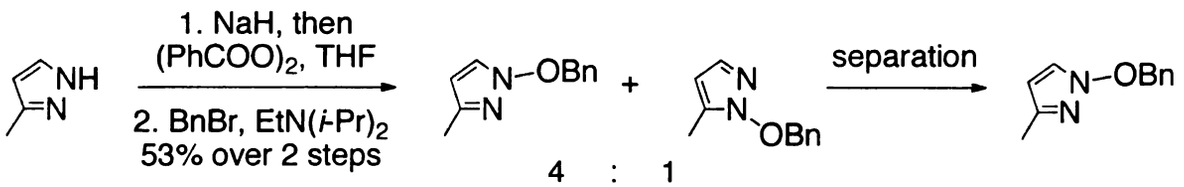
ethyl acetate in hexane). Macrocycle **259** was obtained as a beige solid (76 mg, 0.164 mmol, 88% yield), which can be recrystallized by slow evaporation of a hexane/CH_2Cl_2 (4:1) solution at room temperature to give yellowish crystals, R_f 0.51 (20% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.31 (quint, 2H, *J* = 6.8 Hz), 1.64 (quint, 4H, *J* = 7.3 Hz), 1.90 (quint, 4H, 6.5 Hz), 2.54 (t, 4H, *J* = 7.5 Hz), 2.58 – 2.63 (m, 8H), 3.74 (s, 6H), 4.64 (s, 2H), 5.87 (d, 2H, *J* = 2.5 Hz), 6.54 (AB quartet, 4H, *J* = 3.0 Hz, *C* = 4.8 Hz), 8.64 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.35, 27.13, 29.16, 29.33, 29.39, 30.59, 55.57, 105.94, 113.30, 130.25, 130.61, 130.68, 145.16, 153.91 (1 aromatic carbon not found); IR (neat) 3376, 2926, 2857, 1603, 1476, 1439, 1348, 1335, 1196, 1150, 1067, 1044 cm^{-1}; MS (ES+), *m/z* (% rel. intensity) 464 ($M+H^+$, 100); HRMS (ES+) calcd for $(M+H)^+$ ($C_{29}H_{38}NO_4$) *m/z* 464.2801, found 464.2792. Single crystal X-Ray analysis is also available for this molecule (see Appendix).

3. Procedures for Chapter 4.



273 **274a** **275a** **274a**

3-Methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazole (274a).[173] In a 100 mL round bottom flask, 12.0 mL (12.3 g, 0.15 mol) of 3-methylpyrazole **273**, 20.8 mL g (19.3 g, 0.23 mol) of 3,4-dihydro-2*H*-pyran, and 0.1 mL of trifluoroacetic acid were mixed and refluxed for 12 h under nitrogen atmosphere. The reaction mixture was allowed to cool down to room temperature, 0.6 g of sodium hydride (60% suspension in mineral oil) was added, and the mixture was distilled in vacuo, affording 23.4 g (14.1 mmol, 94%) of 4 : 1 mixture of 3-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazole **274a** (major product) and 5-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazole **275a** (minor product). Pure 3-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazole **274a** can be obtained by column chromatography (silica gel, 35% ether in hexane) as a colorless oil, R_f 0.19 (35% Et_2O in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.55 – 1.60 (m, 1H), 1.65 – 1.72 (m, 2H), 1.95 – 2.06 (m, 2H), 2.08 – 2.15 (m, 1H), 2.30 (s, 3H), 3.65 – 3.70 (m, 1H), 4.05 – 4.09 (m, 1H), 5.28 (dd, 1H, J = 10.5 Hz, 2.5 Hz), 6.07 (d, 1H, J = 2.5 Hz), 7.47 (d, 1H, J = 2.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.52, 22.67, 24.88, 30.37, 67.87, 87.34, 105.65, 128.17, 148.96; IR (neat) 3114, 2942, 2857, 1530, 1443, 1389, 1363, 1279, 1250, 1202, 1177, 1130, 1084, 1042 cm^{-1}; MS (ES+), *m/z* (% rel. intensity) 167 ($M+H^+$, 47), 83 (M–THP+H^+, 100); HRMS (EI) calcd for M^+ ($C_9H_{14}N_2O$) *m/z* 166.1106, found 166.1106.

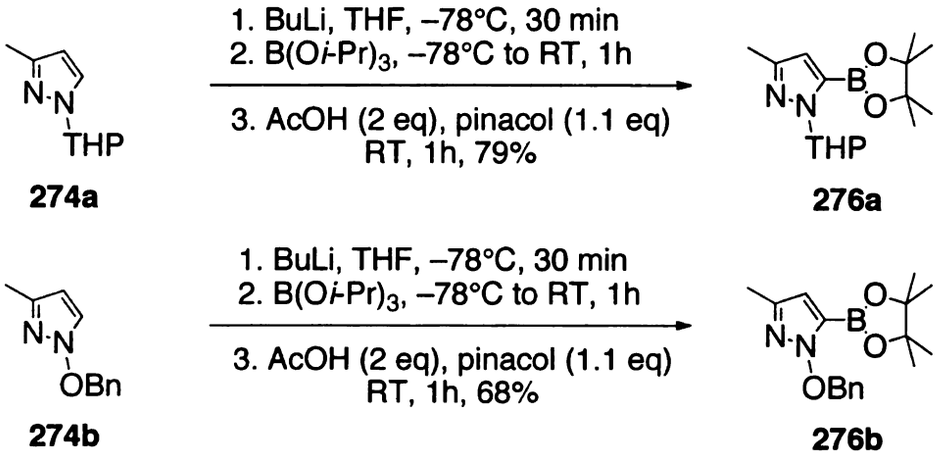


273 **274b** **275b** **274b**

1-(Benzyloxy)-3-methyl-1*H*-pyrazole (274b). A. Pyrazole oxidation.[174] Pure 3-methylpyrazole **273** (12.0 mL, 12.3 g, 0.15 mol) was slowly added *via* syringe to a stirred suspension of 6.6 g (0.165 mol) of sodium hydride (60% suspension in mineral oil, washed 2x50 mL of dry Et_2O) in 250 mL of dry THF at room temperature. After hydrogen evolution had ceased the mixture was cooled to 5°C and a solution of benzoyl peroxide (12.1 g, 0.05 mol, dried overnight *in vacuo* to get rid of water stabilizer) in 250 mL of dry THF was added in such a manner that the temperature of the reaction mixture did not exceed 25°C. After the addition was complete, stirring was continued for 30 min. The reaction mixture was then poured on 150 mL of water, concentrated on a rotovap removing all the THF, and the residue adjusted to pH 10 – 11 with 50% aqueous sulfuric acid (by universal indicator). The unreacted pyrazole was removed by extraction 8x50 mL ethyl acetate. The aqueous phase was then neutralized to pH 7 and the mixture extracted with vigorous shaking 8x50 mL ethyl acetate. The combined extracts were dried over sodium sulfate, evaporated to dryness, and dried *in vacuo* affording 4.3 g (43.9 mmol, 88%) of crude pyrazole oxides mixture (approximately 4 : 1 mixture of 3-methyl-1*H*-pyrazol-1-ol and 5-methyl-1*H*-pyrazol-1-ol, by ^{1}H-NMR), which was used directly in the next step (NOTE: It was found that pyrazole oxides bind to silica gel irreversibly during chromatography, thus, it can cause significant loss of material and is not recommended).

B. Pyrazole oxide benzylation.[175] To a solution of the crude oxide mixture mentioned above (4.3 g, 44 mmol) and N-ethyldiisopropyl amine (9.8 mL, 7.2 g, 56 mmol) in 60 mL of dry CH_2Cl_2 at 0°C was added 6.7 mL (9.6 g, 56 mmol) of benzyl bromide. Stirring

was continued at room temperature for 16 h. The reaction mixture was then concentrated on a rotovap and subjected to column chromatography (silica gel, 20% ethyl acetate in hexane), giving a 5.0 g (26.6 mmol, 53%) of 4 : 1 mixture of 1-(benzyloxy)-3-methyl-1*H*-pyrazole **274b** (major) and 1-(benzyloxy)-5-methyl-1*H*-pyrazole **275b** (minor). Complete separation (several runs through the same large column, 20% Et_2O in hexane as eluent, combining pure fractions) afforded pure 1-(benzyloxy)-3-methyl-1*H*-pyrazole **274b**, R_f 0.38 (20% Et_2O in hexane) as a colorless liquid; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.26 (s, 3H), 5.23 (s, 2H), 5.80 (d, 1H, J = 2.0 Hz), 6.88 (d, 1H, J = 2.0 Hz), 7.30 – 7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.76, 80.27, 102.14, 123.24, 128.51, 129.02, 129.54, 134.05, 142.61; IR (neat) 3142, 3067, 3034, 2928, 2882, 1514, 1499, 1456, 1406, 1346, 1258, 1211, 1188, 1082, 1046, 993 cm^{-1}; MS (ES+), *m/z* (% rel. intensity) 189 ($M+H^+$, 100); HRMS (ES+) calcd for M^+ ($C_{11}H_{12}N_2O$) *m/z* 188.0950, found 188.0951.

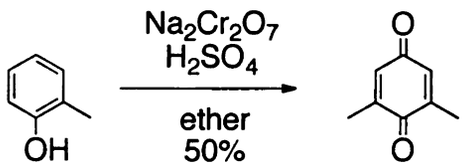


Preparation of pinacolboronate derivatives of protected pyrazoles.[140] Protected pyrazole (10 mmol) was placed in a dry 50 mL round bottom flask and diluted with 15

mL of dry THF. The stirred solution was cooled to –78°C and *n*-butyllithium solution (10.5 mmol, 4.2 mL of 2.5M solution in hexanes) was added dropwise. The mixture was allowed to stir for 30 min at –78°C, after which triisopropyl borate (2.54 mL, 2.07 g, 11 mmol) was added dropwise, and the mixture was allowed to warm up to room temperature and stir for 1 h. Pinacol (1.30 g, 11 mmol) and glacial acetic acid (1.14 mL, 1.20 g, 20 mmol) were added in one portion and the solution was stirred for an additional 1 h at room temperature. The mixture was diluted with 100 mL of ether and 50 mL of water. The organic phase was separated, washed with brine, and dried over magnesium sulfate. The resulting solution was concentrated on a rotovap and subjected to column chromatography (silica gel, 20% ethyl acetate in hexane).

3-Methyl-1-(tetrahydro-2*H*-pyran-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (276a) was obtained as a colorless oil (79% yield), R_f 0.25 (long band; 20% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.33 (s, 12H), 1.51 – 1.55 (m, 1H), 1.64 – 1.78 (m, 2H), 1.90 – 1.95 (m, 1H), 2.02 – 2.08 (m, 1H), 2.29 (s, 3H), 2.40 – 2.48 (m, 1H), 3.62 – 3.69 (m, 1H), 4.07 (dquint, 1H, J = 11.5 Hz, 2.0 Hz), 5.77 (dd, 1H, J = 10.8 Hz, 2.3 Hz), 6.51 (d, 1H, J = 0.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.13, 23.01, 24.45, 24.75, 24.89, 29.91, 67.97, 83.83, 86.13, 115.92, 148.48; IR (neat) 2978, 2940, 2851, 1550, 1466, 1373, 1308, 1271, 1204, 1181, 1144, 1084, 1068, 1043, 1016 cm^{-1}; MS (ES+), *m/z* (% rel. intensity) 293 ($M+H^+$, 100), 209 ($M–THP+H^+$, 69), 127 ($BPin^+$, 24); HRMS (ES+) calcd for $(M+H)^+$ ($C_{15}H_{26}BN_2O_3$) *m/z* 293.2036, found 293.2042.

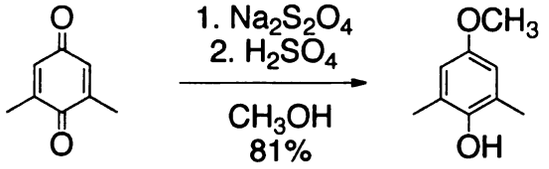
1-(Benzyloxy)-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (276b) was obtained as a colorless oil (68% yield), R_f 0.38 (long band; 20% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.30 (s, 12H), 2.26 (s, 3H), 5.28 (s, 2H), 6.32 (s, 1H), 7.32 – 7.36 (m, 3H), 7.46 – 7.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.12, 24.53, 80.71, 83.86, 111.66, 128.06, 128.62, 129.67, 133.84, 141.92 (1 aromatic C not located); IR (neat) 3067, 3034, 2978, 2932, 2886, 1545, 1460, 1391, 1381, 1373, 1354, 1325, 1294, 1269, 1167, 1143, 1059 cm^{-1}; MS (ES+), *m/z* (% rel. intensity) 337 (M^++Na^+, 65), 315 (M+H^+, 100), 233 (3), 189 (5); HRMS (ES+) calcd for $(M+H)^+$ ($C_{17}H_{24}BN_2O_3$) *m/z* 315.1880, found 315.1873.



267 **268**

2,6-Dimethyl-1,4-benzoquinone (268).[176] A round-bottom flask (1 L) equipped with a dropping funnel with pressure equalizer and big magnetic stirbar, was charged with 2,6-dimethylphenol (164 mmol, 20.0 g), and 250 mL of ether. Jones reagent (a mixture of 110 g $Na_2Cr_2O_7 \cdot 2H_2O$, 150 mL of water, and 70 mL of concentrated H_2SO_4) was added dropwise slowly (3 - 4 h) on cooling in an ice bath. After complete addition the mixture was stirred at room temperature for 48 h, afterwhich it was poured into 900 mL of water.

The ether layer was separated and the water layer was extracted with 2x200 mL of ether. The combined organic extracts were washed with 3x200 mL of water, dried over $MgSO_4$ and evaporated to dryness. The yellow-orange residue was heated with 150 mL of hexane and the solution decanted. This operation was performed 3 more times. The hexane solution was concentrated to 100 mL and left to cool down and crystallize. Filtration and drying *in vacuo* gave 11.2 g (82 mmol, 50%) of 2,6-dimethyl-1,4-benzoquinone as needle-like orange crystals, mp 60 – 66°C (lit.[176] 70 – 72°C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.06 (q, 6H, J = 0.6 Hz), 6.56 (d, 2H, J = 0.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.88, 133.19, 145.71, 187.56, 188.09. These spectral data match those reported for this compound[176].

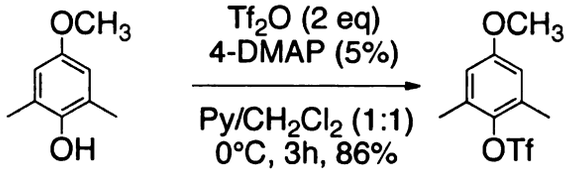


268 **269**

4-Methoxy-2,6-dimethyl-phenol (269). A. Reduction.[176] Fresh[177] sodium dithionite (120 mmol, 21.2 g) was dissolved in 150 mL of water, and 2,6-dimethyl-1,4-benzoquinone (30 mmol, 4.08 g), dissolved in the mixture of 75 mL of ether and 40 mL of methanol, was added at room temperature with stirring. After stirring for 15 min, the solution was extracted with 2x100 mL of ether, combined organic extracts were washed with 100 mL of water, 100 mL of brine, dried over $MgSO_4$, and evaporated to dryness. After drying in vacuo, 3.46 g (25.1 mmol, 84%) of 2,6-dimethyl-1,4-hydroquinone were

obtained as yellowish solid, mp 143 – 146°C (lit.[176] 145 – 148°C); ^{1}H NMR ($CDCl_3$ - DMSO-d_6, 300 MHz) δ 2.13 (s, 6H), 6.34 (s, 2H), 6.90 (s, 1H), 8.17 (s, 1H). These spectral data match those reported for this compound[176].

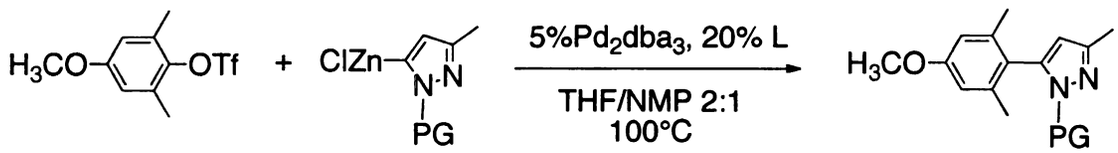
B. Methylation.[178] Round-bottom flask (25 mL) was charged with 1.50 g (10.9 mmol) of 2,6-dimethyl-1,4-hydroquinone, 12 mL of methanol, and 1.5 mL of concentrated sulfuric acid, and refluxed for 1 h. After reaction mixture cooled down to room temperature, 10 g of ice were added, and resulting mixture extracted with 4x10 mL of ether. Combined organic extracts were washed with water (10 mL), brine (10 mL), dried over Na_2SO_4, evaporated to dryness and subjected to column chromatography (silica gel, 20% ethyl acetate in hexane), yielding 1.59 g (10.5 mmol, 96%) of 4-methoxy-2,6-dimethylphenol **269** as beige solid, mp 78°C (lit.[178] 76 – 77°C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.22 (s, 6H), 3.73 (s, 3H), 4.28 (s, 1H), 6.54 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.23, 55.62, 113.76, 124.13, 146.10, 152.97. These spectral data match those reported for this compound[178].



269 **270**

4-Methoxy-2,6-dimethylphenyl trifluoromethanesulfonate (270).[179] A dry round bottom flask was charged with 4-methoxy-2,6-dimethyl phenol **269** (6 mmol, 912 mg), 4-

DMAP (5%, 0.3 mmol, 37 mg), dry dichloromethane (15 mL) and dry pyridine (15 mL). The solution was stirred at 0°C and trifluoromethanesulfonic anhydride (12 mmol, 3.38 g, 2.0 mL) was added dropwise. The stirring continued for 3 h at 0°C, after which all the phenol was consumed (TLC control). The mixture was evaporated to dryness and subjected to column chromatography (3% triethylamine in pentane) to afford 1.67 g (5.88 mmol, 98%) of 4-methoxy-2,6-dimethylphenyl trifluoromethanesulfonate **270** as a colorless liquid; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.34 (s, 6H), 3.76 (s, 3H), 6.61 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.32, 55.41, 114.61, 118.66 (q, $-SO_2CF_3$ carbon, J = 318 Hz), 132.59, 140.39, 158.32; IR (neat) 3007, 2970, 2946, 2845, 1597, 1483, 1404, 1381, 1337, 1292, 1246, 1211, 1189, 1142, 1103, 1061, 1001 cm^{-1}; MS (EI), *m/z* (% rel. intensity) 284 (M^+, 25), 151 (M-Tf, 100), 123 (27), 91 (15), 77 (10), 69 (8); HRMS (EI) calcd for M^+ ($C_{10}H_{11}O_4F_3S$) *m/z* 284.0330, found 284.0332.



270 **274a,b** **277a,b**

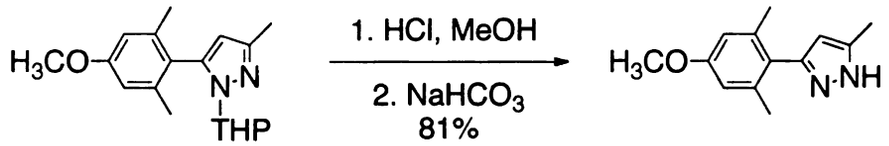
Model Negishi couplings.[145] A dry 25 mL round bottom flask with a stir bar was charged with 1.5 mmol of protected pyrazole (**274a** or **274b**) and 4 mL of dry THF under nitrogen, cooled to –78°C, and *n*-butyllithium solution (1.65 mmol, 0.66 mL of 2.5M solution in hexane) was added dropwise. The reaction mixture was allowed to stir at –78°C for 30 min, after which zinc chloride solution (1.8 mmol, 3.6 mL of 0.5M solution

in THF) was added dropwise. The reaction mixture was then allowed to warm up to room temperature. After being stirred for 10 min at room temperature, the solution of organozinc reagent was transferred *via* cannula into a dry 25 mL Schlenk flask charged with a stir bar, 4-methoxy-2,6-dimethylphenyl trifluoromethanesulfonate **270** (284 mg, 1 mmol), Pd_2dba_3 (46 mg, 0.05 mmol), and 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (93 mg, 0.2 mmol) under nitrogen. The remains of the organozinc reagent were washed from the round bottom flask and transferred using the same cannula and 4 mL of dry 1-methyl-2-pyrrolidinone (NMP). The Schlenk flask was then sealed with Teflon screw cap and heated at 100°C for 24 h with stirring. The reaction mixture was cooled down to room temperature, diluted with 100 mL of ether, and quenched with 50 mL of NH_4Cl (sat.). The organic phase was separated, washed with 50 mL of water, 50 mL of brine, dried over $MgSO_4$, evaporated on rotovap, and subjected to column chromatography (silica gel, 20% ethyl acetate in hexane). (NOTE: Pyrazoles **274a** and **274b** are hard to separate from coupling products **277a** and **277b**, respectively. In the case of PG = THP, the original pyrazole **274a** is volatile under the vacuum of the oil pump, and pure **277a** can be obtained by drying the mixture of **274a** and **277a** (obtained after chromatography) *in vacuo* overnight. In the case of PG = OBn, separation is a lot more tedious, and requires several column separations. For this reason the yields of **277b** given are calculated using NMR signal ratios and the mass of **274b**+**277b** mixtures obtained after chromatography).

5-(4-Methoxy-2,6-dimethylphenyl)-3-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazole (277a) was obtained as a white solid (yield: 79% when 1.5 eq of **274a** used, 90% when 3 eq of **274a** used), mp 104°C, R_f 0.30 (20% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.39 – 1.52 (m, 2H), 1.62 – 1.76 (m, 2H), 1.94 – 1.98 (m, 1H), 1.99 (s, 3H), 2.09 (s, 3H), 2.34 (s, 3H), 2.41 – 2.49 (m, 1H), 3.32 (td, 1H, J = 12.0 Hz, 2.0 Hz), 3.82 (s, 3H), 3.96 – 4.00 (m, 1H), 4.62 (dd, 1H, J = 10.5 Hz, 2.5 Hz), 5.89 (s, 1H), 6.66 (AB quartet, 2H, J = 2.5 Hz, C = 4.3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.92, 20.37, 20.38, 23.07, 24.82, 30.27, 55.07, 67.96, 83.90, 106.33, 112.43, 112.62, 122.45, 139.38, 140.72, 142.19, 149.07, 159.68; IR (neat) 2930, 2847, 1609, 1491, 1458, 1442, 1424, 1395, 1316, 1209, 1198, 1150, 1084, 1063, 1044 cm^{-1}; MS (EI), *m/z* (% rel. intensity) 300 (M^+, 12), 216 (M–THP, 100), 201 (10), 174 (40), 160 (28), 144 (6), 84 (10); HRMS (EI) calcd for M^+ ($C_{18}H_{24}N_2O_2$) *m/z* 300.1838, found 300.1848.

1-(Benzyloxy)-5-(4-methoxy-2,6-dimethylphenyl)-3-methyl-1*H*-pyrazole (277b) was obtained as a colorless oil (yield: 48% when 1.5 eq of **274b** used, 73% when 3 eq of **274b** used), R_f 0.47 (20% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.00 (s, 6H), 2.31 (s, 3H), 3.82 (s, 3H), 5.03 (s, 2H), 5.82 (s, 1H), 6.63 (s, 2H), 6.98 – 7.00 (m, 2H), 7.18 – 7.22 (m, 2H), 7.24 – 7.28 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.95, 20.45, 55.15, 79.92, 103.92, 112.60, 120.76, 128.31, 128.68, 129.21, 133.94, 134.54, 139.92, 141.72, 159.77; IR (neat) 3070, 3034, 2924, 2849, 1607, 1582, 1489, 1456, 1375, 1345, 1318,

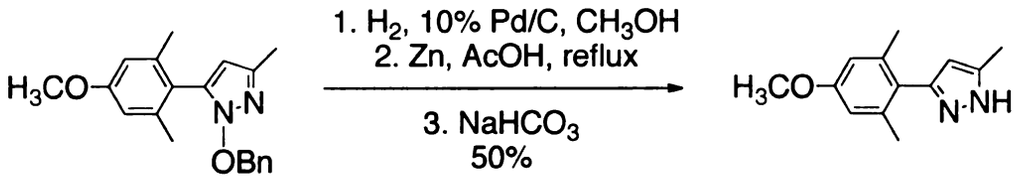
1283, 1203, 1192, 1154, 1069 cm^{-1}; MS (ES+), *m/z* (% rel. intensity) 323 ($M+H^+$, 100); HRMS (ES+) calcd for $(M+H)^+$ ($C_{20}H_{23}N_2O_2$) *m/z* 323.1760, found 323.1753.



277a **279**

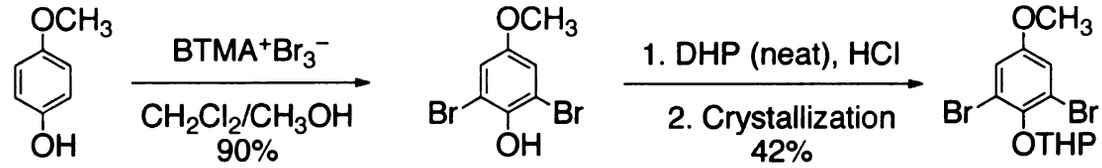
Removal of THP group.[140] Protected pyrazole **277a** (237 mg, 0.79 mmol) was placed in a round bottom flask with a stir bar and 8 mL of stock HCl solution in methanol was added (solution was prepared by slow addition of 10 mL of acetyl chloride to 100 mL of anhydrous methanol on stirring at 0°C). The resulting mixture was stirred at room temperature for 12 hours, after which it was diluted with 50 mL of diethyl ether and vigorously shaken with 50 mL of saturated $NaHCO_3$. The organic phase was separated, water layer extracted with 2x50 mL of ether, combined organic phase washed with brine, dried over magnesium sulfate, concentrated on a rotovap and subjected to column chromatography (silica gel, 40% ethyl acetate in hexane), affording 139 mg (0.64 mmol, 81%) of 3-(4-methoxy-2,6-dimethylphenyl)-5-methyl-1*H*-pyrazole **279** as a yellow solid. The product can be recrystallized by slow evaporation from hexane, affording large yellowish crystals, mp 119°C, R_f 0.25 (30% EtOAc in hexane); ^1H NMR ($CDCl_3$, 500 MHz) δ 2.04 (s, 6H), 2.05 (s, 3H), 3.78 (s, 3H), 5.85 (s, 1H), 6.56 (s, 2H), 12.20 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.77, 20.54, 54.93, 105.16, 112.48, 124.44, 139.23, 144.90, 159.01 (1 aromatic C not located); IR (neat) 3191, 3133, 2923, 2850, 1607, 1462,

1377, 1316, 1289, 1198, 1152, 1080, 1057, 1026, 1009 cm^{-1}; MS (ES+), *m/z* (% rel. intensity) 217 ($M+H^+$, 100); HRMS (ES+) calcd for $(M+H)^+$ ($C_{13}H_{17}N_2O$) *m/z* 217.1341, found 217.1345.



277b **279**

Removal of OBn group.[146] Protected pyrazole **277b** (0.376 mmol, as a mixture with pyrazole **274b**) was dissolved in 10 mL of anhydrous methanol, 120 mg of 10% Pd/C was added, and hydrogen was gently bubbled through the mixture for 5 minutes, after which the reaction flask was sealed with a septum under a balloon with H_2 and stirred overnight. The resulting mixture was filtered to get rid of all solids, the solution was evaporated to dryness, and the residue dissolved in 10 mL of acetic acid, 540 mg of zinc dust was added, and the mixture was refluxed for additional 12 h. The reaction mixture was then cooled down to room temperature, and carefully neutralized by pouring into 100 mL of saturated $NaHCO_3$. The solution was then extracted with 3x50 mL of ether, the combined organic phase washed with brine, dried over magnesium sulfate, concentrated on rotovap, subjected to column chromatography (silica gel, 40% ethyl acetate in hexane) and additionally dried *in vacuo* overnight (to get rid of 3-methylpyrazole) affording 41 mg (0.19 mmol, 50%) of 3-(4-methoxy-2,6-dimethylphenyl)-5-methyl-1*H*-pyrazole **279** as a yellow solid.



285 **286** **263b**

2-(2,6-dibromo-4-methoxyphenoxy)tetrahydro-2*H*-pyran (263b).

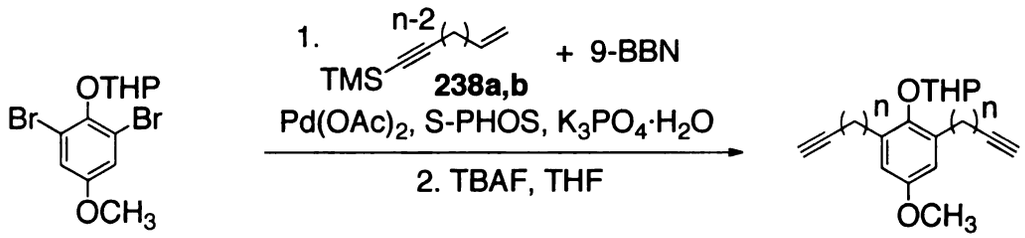
A. Benzyltrimethylammonium tribromide.[180] In a 2 L glass equipped with a large stir bar hydrobromic acid (48%, 1.2 mol, 203 g) was added to a stirred solution of benzyltrimethylammonium chloride (0.4 mol, 74.4 g) and potassium bromate (0.133 mol, 22.2 g) in 450 mL of water. The resulting precipitate was filtered off, washed with water (5x100 mL) and pressed onto a filter to maximum dryness. The resulting solid was dissolved in CH_2Cl_2 on heating, dried with magnesium sulfate, filtered hot and cooled down in an ice bath. The resulting crystals were collected, the mother liquor concentrated and cooled down to 0°C again. Two crops were combined and dried in vacuo to afford 126.3 g of benzyltrimethylammonium tribromide as large orange crystals.

B. 2,6-Dibromo-4-methoxyphenol.[180] To a vigorously stirred solution of 4-methoxyphenol (0.147 mol, 18.2 g) in 1300 mL of CH_2Cl_2 and 500 mL of dry methanol benzyltrimethylammonium tribromide (126.3 g, 0.323 mmol) was added. The resulting solution was stirred for 2 h, after which the mixture was evaporated to dryness and extracted with 6x100 mL of ether (vigorous shaking). The combined organic extracts were dried with magnesium sulfate, evaporated on a rotovap, filtered through a thick pad of silica gel (using ether as eluent) and evaporated to dryness to afford 2,6-dibromo-4-

methoxyphenol **286** (37.2 g, 132 mmol, 90%) as a tan solid that can be used in the next step directly.

C. 2-(2,6-Dibromo-4-methoxyphenoxy)tetrahydro-2*H*-pyran.[150] Obtained 2,6-dibromo-4-methoxyphenol **286** (37.2 g, 132 mmol) was mixed with 3,4-dihydro-2*H*-pyran (14.4 g, 172 mmol) and 0.3 mL of concentrated HCl, and vigorously stirred overnight. The reaction mixture was then dilute with 300 mL of ether, washed with 5x100 mL of 5% aqueous NaOH, dried over potassium carbonate, and solvent was removed on a rotovap. The remaining oil was dissolved in 75 mL of pentane and placed in –20°C freezer overnight, producing large yellow crystals. The mother liquor was removed using nitrogen pressure and a thick cannula, and the product was dried *in vacuo*, affording 20.3 g (55.5 mmol, 42%) of 2-(2,6-dibromo-4-methoxyphenoxy)tetrahydro-2*H*-pyran **263b** as yellow crystals. (NOTE: chromatography of the product should be avoided because of its significant instability towards acids). The compound can be further purified by dissolving it in a 10:1 mixture of pentane and CH_2Cl_2 on heating, and letting the solution crystallize at –20°C overnight. This affords 2-(2,6-dibromo-4-methoxyphenoxy)tetrahydro-2*H*-pyran **263b** as white crystals, mp 78°C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.62 – 1.68 (m, 3H), 1.88 – 1.94 (m, 1H), 1.95 – 2.04 (m, 1H), 2.12 – 2.17 (m, 1H), 3.59 – 3.63 (m, 1H), 3.74 (s, 3H), 4.35 – 4.40 (m, 1H), 5.30 (t, 1H, J = 3.5 Hz), 7.07 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.90, 25.02, 30.33, 55.87, 63.69, 103.02, 118.11, 118.36, 146.30, 156.04; IR (neat) 3083, 2975, 2946, 2851, 1591, 1547, 1488, 1431, 1391, 1356, 1289, 1227, 1202, 1186, 1124, 1111, 1040, 1022 cm^{-1}; MS (ES+), *m/z* (% rel. intensity) 283

(M–THP+H$^+$, 35), 281 (M–THP+H$^+$, 100), 279 (M–THP+H$^+$, 38); HRMS (EI) calcd for (M–THP+H)$^+$ ($C_7H_6O_2{}^{79}Br_2$) *m/z* 279.8735, found 279.8735.



263b **264b,c**

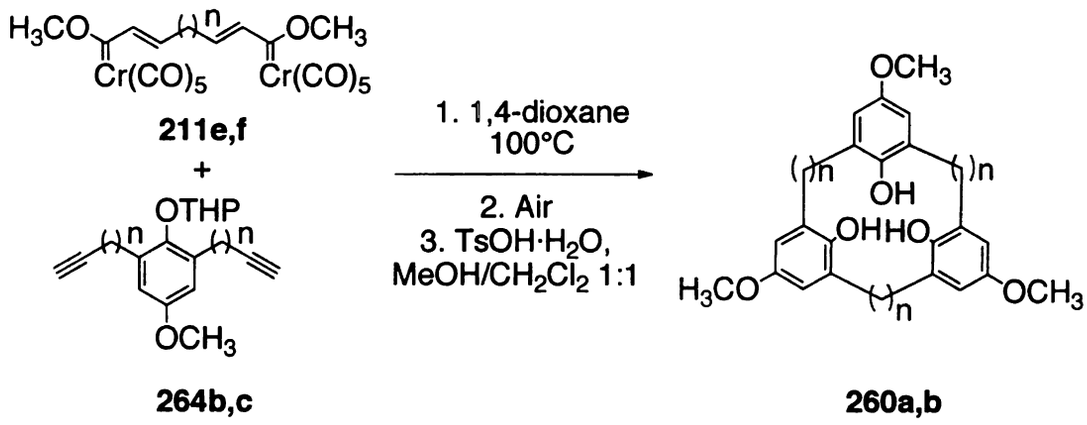
Preparation of THP-protected diynes 264. TMS-protected enyne (**238a** or **238b**, 40 mmol) was put in a dry 100 mL Schlenk flask with a stir bar and 9-BBN (40 mmol, 80.0 mL of 0.5 M solution in THF) was added under nitrogen. The resulting solution was heated and stirred at 70°C for 2 h, cooled down to room temperature and transferred *via* cannula to a 250 mL Schlenk flask containing 2-(2,6-dibromo-4-methoxyphenoxy)tetrahydro-2*H*-pyran **263b** (20 mmol, 7.32 g), potassium phosphate monohydrate (40 mmol, 9.20 g), palladium acetate (0.64 mmol, 143 mg) and S-PHOS ligand (1.28 mmol, 530 mg) under a nitrogen atmosphere. The Schlenk flask solution was then degassed using the freeze-thaw method (3 cycles), warmed up to room temperature, back-filled with nitrogen, sealed and heated at 70°C for 4 h. Reaction mixture was poured over a Celite pad which was then rinsed with 4x25 mL of ether. The solvent was removed on a rotovap and the residue was subjected to column chromatography (silica gel, 5% EtOAc in hexane). (NOTE: In this coupling it was found that column purification of intermediate silylated diyne cannot be avoided, in contrast to analogous preparations for diynes **240**). The protected diyne obtained after column chromatography was then

dissolved in 100 mL of THF. TBAF (9 mmol, 3.3 mL of 75% solution in water) was added and the mixture was stirred for 1 h (controlled by TLC). The reaction mixture was then extracted with 100 mL of water, the organic layer was separated, and the water layer was extracted with 50 mL of ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, concentrated on a rotovap, and subjected to column chromatography (silica gel, 5% ethyl acetate in hexane).

2-(4-Methoxy-2,6-di(pent-4-ynyl)phenoxy)tetrahydro-2*H*-pyran (264b, n = 3) was obtained as a transparent yellowish oil (3.40 g, 10.0 mmol, 50% yield), R_f 0.22 (5% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.53 – 1.61 (m, 3H), 1.80 – 1.88 (m, 5H), 1.91 – 2.02 (m, 2H), 1.97 (t, 2H, J = 2.5 Hz), 2.20 – 2.24 (m, 4H), 2.66 – 2.74 (m, 2H), 2.77 – 2.84 (m, 2H), 3.44 – 3.49 (m, 1H), 3.75 (s, 3H), 4.01 – 4.06 (m, 1H), 4.70 (dd, 1H, J = 6.5 Hz, 2.5 Hz), 6.58 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.21, 20.86, 25.10, 29.06, 29.96, 31.44, 55.24, 64.74, 68.46, 84.38, 103.80, 112.91, 135.99, 148.11, 155.61; IR (neat) 3293, 2944, 2865, 2840, 2116, 1603, 1468, 1441, 1379, 1358, 1215, 1198, 1178, 1146, 1101, 1072, 1032 cm^{-1}; MS (ES+), *m/z* (% rel. intensity) 341 ($M+H^+$, 100), 309 (5), 118 (13); HRMS (ES+) calcd for $(M+H)^+$ ($C_{22}H_{29}O_3$) *m/z* 341.2117, found 341.2120.

2-(2,6-Di(hept-6-ynyl)-4-methoxyphenoxy)tetrahydro-2*H*-pyran (264c, n = 5) was prepared as a transparent yellowish oil (4.12 g, 10.4 mmol, 52% yield), R_f 0.31 (5%

EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.44 – 1.50 (m, 4H), 1.52 – 1.65 (m, 11H), 1.78 – 1.86 (m, 1H), 1.93 (t, 2H, J = 2.5 Hz), 1.92 – 1.98 (m, 2H), 2.19 (td, 4H, J = 7.0 Hz, 2.5 Hz), 2.57 – 2.64 (m, 2H), 2.64 – 2.72 (m, 2H), 3.44 – 3.49 (m, 1H), 3.75 (s, 3H), 4.02 – 4.07 (m, 1H), 4.68 (dd, 1H, J = 6.5 Hz, 2.0 Hz), 6.55 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.32, 20.93, 25.19, 28.37, 28.77, 29.91, 30.69, 31.51, 55.31, 64.75, 68.08, 84.67, 103.82, 112.48, 136.91, 148.08, 155.62; IR (neat) 3295, 2938, 2861, 2116, 1605, 1468, 1441, 1379, 1354, 1213, 1198, 1178, 1148, 1103, 1072, 1036 cm^{-1}; MS (ES+), *m/z* (% rel. intensity) 397 ($M+H^+$, 100), 379 (16), 235 (5), 118 (28); HRMS (ES+) calcd for $(M+H)^+$ ($C_{26}H_{37}O_3$) *m/z* 397.2743, found 397.2749.



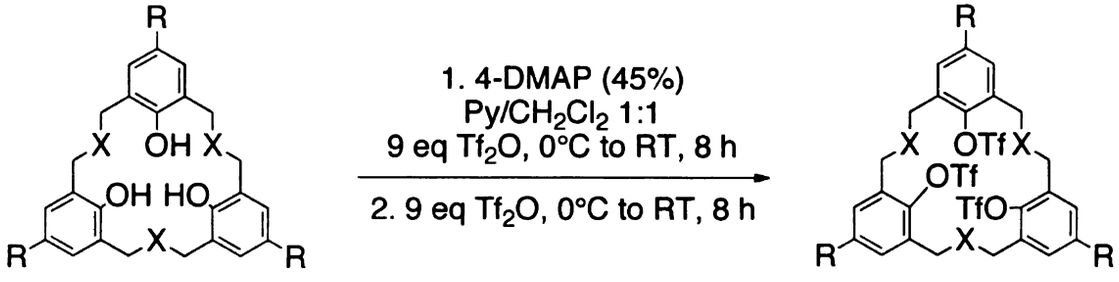
Large-scale preparation of C_3-symmetric macrocycles 260. A round bottom oven-dried three-necked 5 L flask was equipped with a reflux condenser and a nitrogen inlet, charged with Teflon boiling chips (ca. 50 pieces, approx 1 mm in size) and cooled by a stream of nitrogen. Then, from the solvent purification apparatus in which 1,4-dioxane (~ 4.5 L) was refluxed over sodium metal for several hours, the solvent was distilled out into

the 5 L flask using a Teflon tube. (Overall, about 4 L of oxygen-free, dry 1,4-dioxane were placed into the flask). The solvent was then cooled down in the mild flow of nitrogen, and carbene complex **211** (10 mmol) and diyne **264** (10 mmol) were added to the 5 L flask. Nitrogen was then vigorously bubbled through the deep red solution for additional 2 h, the flask was sealed using glass stoppers with Teflon sleeves and Teflon film, and the solution was refluxed under positive nitrogen pressure using heating mantle for 24 h. The resulting yellow solution was placed in two large crystallizer dishes and allowed to oxidize in the air for 2 days (with occasional stirring). The remaining mixture was then filtered through cotton to get rid of insoluble chromium residue, evaporated to dryness on 50 g of silica gel, and washed off the silica gel on a glass filter using ethyl acetate. The filtrate was concentrated on a rotovap and dissolved in 30 mL of CH_2Cl_2 and 30 mL of methanol. To this solution, *p*-toluenesulfonic acid monohydrate (0.25 g, 1.3 mmol) was added[151], the mixture was stirred for 4 h at room temperature, evaporated on a rotovap, and subjected to column chromatography (silica gel, 20% EtOAc in CH_2Cl_2 for **260a**, 20% EtOAc in hexane for **260b**).

Homocalix[3]arene 260a (n = 3) had to be additionally purified after the column due to its extremely poor solubility in most organic solvents. The product after the column was taken up in 30 mL of ethyl acetate and 500 mL of dichloromethane, and concentrated on a rotovap to approximately 50 mL. Filtration afforded **260a** as white crystalline powder (24% yield), mp 171°C, R_f 0.58 (10% EtOAc in CH_2Cl_2); ^{1}H NMR (C_5D_5N, 500 MHz) δ 2.09 (quint, 6H, J = 7.0 Hz), 2.71 (t, 12H, J = 7.3 Hz), 3.55 (s, 9H), 5.50 (s, 3H), 6.68

(s, 6H); ^{13}C NMR (C_5D_5N, 125 MHz) δ 30.99, 31.19, 55.48, 113.93, 133.06, 147.39, 153.90; IR (KBr pellet) 3446, 3405, 3054, 2961, 2933, 2871, 2863, 2834, 1606, 1478, 1437, 1342, 1326, 1297, 1256, 1222, 1199, 1174, 1151, 1122, 1070, 1063, 1038 cm^{-1}; MS (ES+) *m/z* (% rel. intensity) 985 ($2M+H^+$, 90), 510 (8), 493 ($M+H^+$, 100), 338 (16); HRMS (ES+) calcd for $(M+H)^+$ ($C_{30}H_{37}O_6$) *m/z* 493.2590, found 493.2582.

Homocalix[3]arene 260b (n = 5) was obtained as yellowish solid (20% yield), which can be recrystallized by slow evaporation of hexane/CH_2Cl_2 (10:1) solution at room temperature to give colorless crystals, mp 155°C, R_f 0.34 (20% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.40 (quint, 6H, *J* = 7.0 Hz), 1.65 (quint, 12H, *J* = 7.5 Hz), 2.57 (t, 12H, = 7.8 *J* Hz), 3.74 (s, 9H), 4.83 (s, 3H), 6.52 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.66, 29.19, 29.61, 55.53, 112.98, 129.92, 145.21, 153.42; IR (neat) 3397, 2930, 2857, 1603, 1478, 1350, 1194, 1150, 1071, 1040 cm^{-1}; MS (ES+) *m/z* (% rel. intensity) 1153 ($2M+H^+$, 27), 577 ($M+H^+$, 100), 343 (6); HRMS (ES+) calcd for $(M+H)^+$ ($C_{36}H_{49}O_6$) *m/z* 577.3529, found 577.3538.



Calixarene triflate preparation. Homocalix[3]arene (0.407 mmol) and 4-DMAP (22 mg, 0.183 mmol) were placed in a dry pear shaped flask with a triangular stir bar under nitrogen, and dissolved in 3 mL of dry pyridine and 3 mL of dry CH_2Cl_2. The solution was then cooled down to 0°C, and trifluoromethanesulfonic anhydride (0.62 mL, 1.03 g, 3.66 mmol) was added dropwise *via* syringe. The solution was then allowed to warm up to room temperature and stirred for 8 h, after which cooled down to 0°C again, and second portion of trifluoromethanesulfonic anhydride (0.62 mL, 1.03 g, 3.66 mmol) was added. The reaction mixture was stirred for another 8 h, and then diluted with 50 mL of ether and poured into 50 mL of water. Layers were separated, and water layer extracted with 2x50 mL of ether. Combined organic extracts were then washed with 50 mL of 2M HCl, 50 mL of brine, dried over magnesium sulfate, concentrated on a rotovap, and subjected to column chromatography (silica gel, 10% EtOAc in hexane for *paco*-**280**, 20% EtOAc in hexane for *paco*-**266a** and **266b**).

***Paco*-triflate 280 (X = O, R = CH_3)** was obtained as a white solid (80% yield), which can be recrystallized by slow evaporation of hexane/CH_2Cl_2 4:1 solution to give large colorless crystals, mp 154°C, R_f 0.58 (10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.20 (s, 6H), 2.39 (s, 3H), 4.07 (d, 2H, J = 13.5 Hz), 4.26 (t, 4H, J = 13.5 Hz), 4.54 (d, 2H, J = 13.5 Hz), 4.64 (d, 2H, J = 14.0 Hz), 4.97 (d, 2H, J = 13.0 Hz), 6.98 (d, 2H, J = 2.5 Hz), 7.19 (d, 2H, J = 1.5 Hz), 7.24 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.50, 20.54, 64.26, 67.66, 68.16, 118.59 (q, $-SO_2CF_3$ carbon, J = 318 Hz), 118.61 (q, two $-SO_2CF_3$ carbons, J = 318 Hz), 129.44, 130.80, 130.88, 131.49, 131.56, 132.69,

138.23, 138.58, 140.04, 142.56; IR (neat) 2938, 2876, 1603, 1462, 1399, 1300, 1246, 1211, 1140, 1092, 1011 cm^{-1}; MS (ES+) *m/z* (% rel. intensity) 864 ($M+NH_4^+$, 100), 847 ($M+H^+$, 65), 613 (6), 338 (9); HRMS (ES+) calcd for $(M+H)^+$ ($C_{30}H_{28}O_{12}F_9S_3$) *m/z* 847.0599, found 847.0588.

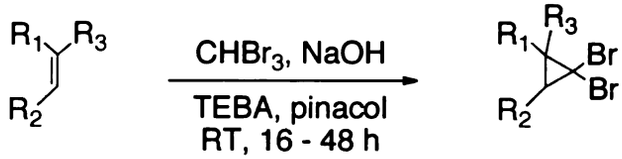
***Paco*-triflate 266a (X = CH_2, R = OCH_3)** was obtained as a colorless oil solidifying on standing (78% yield), which can be recrystallized (50 mL of boiling hexane per 400 mg, cooled to RT) to give white needle-like crystals, mp 149°C, R_f 0.31 (20% EtOAc in hexane); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.50 – 1.67 (m, 1H), 1.90 – 2.38 (m, 9H), 2.42 – 2.54 (m, 2H), 2.58 – 2.70 (m, 2H), 2.72 – 2.84 (m, 2H), 2.87 – 2.96 (m, 2H), 3.76 (s, 6H), 3.78 (s, 3H), 6.63 (s, 4H), 6.69 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.88, 27.51, 28.30, 28.48, 29.68, 55.34, 55.41, 112.60, 113.34, 117.87 (q, $-SO_2CF_3$ carbon, J = 319 Hz), 118.31 (q, two $-SO_2CF_3$ carbons, J = 318 Hz), 135.15, 135.39, 136.94, 138.23, 138.90. 159.00, 159.02 (1 aromatic C not located); IR (neat) 2942, 2876, 2847, 1593, 1484, 1398, 1348, 1321, 1246, 1213, 1187, 1148, 1100, 1065, 1047, 1033 cm^{-1}; MS (ES–) *m/z* (% rel. intensity) 933 ($M+COOH^-$, 100); HRMS (ES–) calcd for $(M+COOH)^-$ ($C_{34}H_{34}O_{14}F_9S_3$) *m/z* 933.0967, found 933.0948.

Triflate 266b (X = $(CH_2)_3$, R = OCH_3) was obtained as a colorless oil solidifying on standing (95% yield), which can be recrystallized (30 mL of boiling hexane per 1g,

cooled to RT, then to 0°C) to give white needle-like crystals, mp 118°C, R_f 0.42 (20% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.23 (quint, 6H, *J* = 7.3 Hz), 1.54 (quint, 12H, *J* = 7.5 Hz), 2.64 (t, 12H, = 7.5 *J* Hz), 3.76 (s, 9H), 6.57 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.84, 29.57, 30.63, 55.42, 113.72, 118.51 (q, $-SO_2CF_3$ carbon, *J* = 318 Hz), 137.17, 139.16, 158.57 ; IR (neat) 3003, 2938, 2863, 1593, 1464, 1441, 1401, 1345, 1213, 1167, 1140, 1100, 1036 cm^{-1}; MS (ES+) *m/z* (% rel. intensity) 973 ($M+H^+$, 25), 886 (13), 883 (19), 849 (26), 827 (90), 613 (23), 475 (12), 338 (100), 271 (14), 212 (18), 155 (23), 110 (27); HRMS (ES+) calcd for $(M+H)^+$ ($C_{39}H_{46}O_{12}F_9S_3$) *m/z* 973.2008, found 973.1985.

4. Procedures for Chapter 5.

(Please note: Chapter 5 is included as a collection of preliminary results. The compounds described in Chapter 5 lack full characterization data and the procedures are included "as is").



291a-h **292a-h**

Typical experimental procedure for the synthesis of 1,1-dibromocyclopropanes.[162]

Alkene (100 mmol) was mixed with bromoform (4 equivalents, 400 mmol, 35.0 mL), benzyltriethylammonium chloride (5 mmol, 1.29 g) and pinacol (13 mmol, 1.53 g). A

solution of sodium hydroxide (400 mmol, 50% solution, 16.0 g NaOH in 16 mL of water) was carefully added to the stirred organic mixture and stirring was continued for 16 h. Reaction mixture was then poured into 100 mL of water and extracted with 3x50 mL of dichloromethane. The combined organic extracts were dried over magnesium sulfate and filtered. Dichloromethane and most of bromoform were removed on a rotovap (90°C bath). The residue was purified by crystallization or distillation in vacuo.

9,9-Dibromobicyclo[6.1.0]nonane (292a).[161] Distillation (85°C/0.15 mm Hg, lit.[161] 80 – 82°C/0.1 mm Hg) gave 26.2 g (93%) of 9,9-dibromobicyclo[6.1.0]nonane **292a** as colorless liquid.

***Trans*-1,1-dibromo-2,3-dipropylcyclopropane (292b).**[181] Distillation (67 – 69°C/0.1 mm Hg) gave 25.8 g (91%) of trans-1,1-dibromo-2,3-dipropylcyclopropane as a yellowish liquid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.97 (t, J = 7.2 Hz, 6H), 1.08 (m, 2H), 1.38 - 1.63 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.82, 21.51, 34.61, 36.78, 39.33. These spectral data match those reported for this compound[181].

***Trans*-1,1-dibromo-2,3-diphenylcyclopropane (292c).**[182] Column chromatography (short pad of silica gel, hexane/dichloromethane 10:1) gave 18.1 g (49%) of colorless oil, which solidified in the refrigerator to give *trans*-1,1-dibromo-2,3-diphenylcyclopropane as an off-white solid, mp 59°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.25 (s, 2H), 7.37 (m,

10H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 36.71, 40.00, 127.81, 128.42, 128.87, 135.87. These spectral data match those reported for this compound[182].

1,1-Dibromo-2-phenylcyclopropane (292d).[161] Distillation (89 – 92°C/0.1 mm Hg, lit.[161] 90 – 91°C/0.1 mm Hg) gave 16.6 g (60%) of 1,1-dibromo-2-phenylcyclopropane as a yellowish liquid.

1,1-dibromo-2,2-diphenylcyclopropane (292e).[161] Recrystallization from 10:1 pentane/dichloromethane mixture gave 31.4 g (89%) of 1,1-dibromo-2,2-diphenylcyclopropane as off-white powder (mp 152°C, lit.[161] 154 – 156°C).

13,13-Dibromobicyclo[10.1.0]tridecane (292f).[183] Distillation (100 – 105°C/0.1 mm Hg) gave 26.2 g (93%) of 13,13-dibromobicyclo[10.1.0]tridecane as a colorless oil.

1,1-Dibromo-2-hexylcyclopropane (292g).[161] Distillation (69 – 70°C/0.1 mm Hg, lit.[161] 70°C/0.1 mm Hg) gave 25.2 g (89%) of 1,1-dibromo-2-hexylcyclopropane as a colorless liquid.

1-Cyclohexyl-2,2-dibromocyclopropane (292h).[184] Distillation (72 – 73°C/0.1 mm Hg) gave 19.4 g (69%) of 1-cyclohexyl-2,2-dibromocyclopropane as a colorless liquid.

292a-h **293a-h**

Typical experimental procedure for the synthesis of allenes.[163] A stirred solution of substituted 1,1-dibromocyclopropane (10 mmol) in dry tetrahydrofuran (20 mL) was treated with ethylmagnesium bromide (13 – 20 mmol, 13.0 – 20.0 mL of 1M solution in THF; 3M solution also was successfully used) at room temperature (higher scale preparations require cooling with an ice bath). Stirring was continued for 30 min - 1 h, after which water (3 mL) was added. The organic layer was separated. The water suspension of the magnesium salt was dissolved in a small amount of 4M HCl and extracted with 2x20 mL of petroleum ether. Combined organic extracts were dried over magnesium sulfate, filtered, and evaporated. The residue was dissolved in 10 mL of petroleum ether, filtered through 15 g of silica gel, and evaporated again. The product was purified by crystallization or distillation *in vacuo*.

Cyclonona-1,2-diene (293a).[161] 9,9-Dibromobicyclo[6.1.0]nonane **292a** (16.9 g, 60 mmol) was treated as above with 3M ethylmagnesium bromide (40.0 mL, 120 mmol) and stirred for 1 h. Distillation (65°C/10 mm Hg) afforded 5.03 g (68%) cyclonona-1,2-diene **293a** as a colorless liquid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.30 – 1.81 (m, 10H), 2.14 – 2.25 (m, 2H), 5.23 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.28, 27.33, 27.96, 92.39, 205.55. These spectral data match those reported for this compound[161].

Nona-4,5-diene (293b).[181] *Trans*-1,1-dibromo-2,3-dipropylcyclopropane **292b** (8.52 g, 30 mmol) was treated as above with 1M ethylmagnesium bromide (60.0 mL, 60 mmol) and stirred for 1 h. Distillation (55°C/10 mm Hg) afforded 3.00 g (81%) of nona-4,5-diene **293b** as a colorless liquid.

1,3-Diphenyl-1,2-propadiene (293c).[185] *Trans*-1,1-dibromo-2,3-diphenylcyclopropane **292c** (7.04 g, 20 mmol) was treated as above with 1M ethylmagnesium bromide (26.0 mL, 26 mmol) and stirred for 30 min. Removal of solvent on a rotovap and drying the residue in vacuo afforded 3.47 g (90%) of 1,3-diphenyl-1,2-propadiene **293c** as a white solid. The compound is rapidly dimerizing at room temperature and must be stored in the dark at –20°C and used ASAP.

Phenyl-1,2-propadiene (293d).[161] 1,1-Dibromo-2-phenylcyclopropane **292d** (13.8 g, 50 mmol) was treated as above with 3M ethylmagnesium bromide (22.0 mL, 65 mmol) and stirred for 30 min. Distillation (65 – 70°C/10 mm Hg) afforded 4.9 g (85%) of phenyl-1,2-propadiene **293d** as yellowish liquid. It is sensitive to oxidation and should be stored under nitrogen.

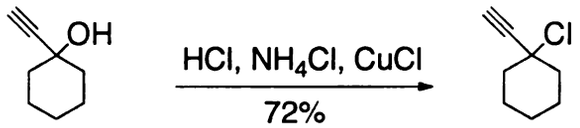
1,1-Diphenyl-1,2-propadiene (293e).[161] 1,1-Dibromo-2,2-diphenylcyclopropane **292e** (7.04 g, 20 mmol) was treated as above with 1M ethylmagnesium bromide (26.0 mL, 26 mmol) and stirred for 30 min. Removal of solvent on a rotovap and drying the residue in

vacuo afforded 3.71 g (96%) of 1,1-diphenyl-1,2-propadiene **293e** as yellow oil. The compound is rapidly dimerizing at room temperature and must be stored in the dark at – 20°C and used ASAP.

Cyclotrideca-1,2-diene (293f).[183] 13,13-Dibromobicyclo[10.1.0]tridecane **292f** (20.3 g, 60 mmol) was treated as above with 3M ethylmagnesium bromide (40.0 mL, 120 mmol) and stirred for 1 h. Distillation (60 - 62°C/0.1 mmHg) afforded 4.50 g (42%) cyclotrideca-1,2-diene **293f** as colorless liquid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20 – 1.63 (m, 16H), 1.95 – 2.15 (m, 4H), 5.07 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.43, 26.67, 27.02, 27.11, 27.39, 91.28, 204.21. These spectral data match those reported for this compound[183].

Nona-1,2-diene (293g).[161] 1,1-Dibromo-2-hexylcyclopropane **292g** (14.2 g, 50 mmol) was treated as above with 3M ethylmagnesium bromide (28.3 mL, 85 mmol) and stirred for 1 h. Distillation (53 - 55°C/10 mmHg) afforded 5.00 g (81%) of nona-1,2-diene **293g** as colorless liquid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, 3H, J = 2.1 Hz), 1.23 – 1.42 (m, 8H), 1.99 (m, 2H), 4.64 (m, 2H), 5.09 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.05, 22.64, 28.28, 28.78, 29.10, 31.68, 74.45, 90.07, 208.51. These spectral data match those reported for this compound[161].

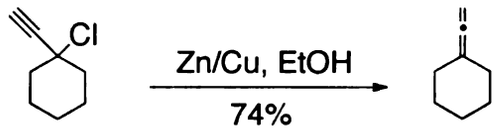
1-Cyclohexyl-1,2-diene (293h).[186] 1-Cyclohexyl-2,2-dibromocyclopropane **292h** (8.74 g, 31 mmol) was treated as above with 3M ethylmagnesium bromide (17.6 mL, 53 mmol) and stirred for 1 h. Distillation (57 – 58°C/10 mm Hg) afforded 2.20 g (58%) 1-cyclohexyl-1,2-diene **293h** as colorless liquid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.04 - 1.35 (m, 5H), 1.60 - 1.80 (m, 5H), 1.98 (m, 1H), 4.68 (m, 2H), 5.08 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.99, 26.13, 32.96, 36.60, 75.35, 96.03, 207.40. These spectral data match those reported for this compound[186].



294 **295**

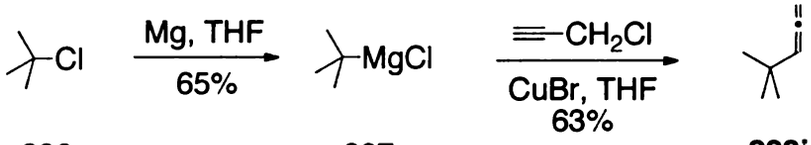
1-Chloro-1-ethynylcyclohexane (295).[164] Powdered ammonium chloride (0.37 mol, 20 g), copper (I) chloride (0.03 mol, 2.7 g), copper bronze (0.4 g) and 90 mL of concentrated HCl were cooled to –15°C. Hydrogen chloride gas (generated by slow addition of 50 g of concentrated sulfuric acid to 60 g of solid NaCl on heating) was slowly bubbled through the stirred mixture, until 18 g (0.50 mol) of HCl were dissolved (flask weight was occasionally checked). Ethynylcyclohexanol **294** (0.20 mol, 25 g) was added in one portion, and stirring continued for 1.5 h at 0 to –5°C. After this period ice-cold water (just enough to dissolve the salts) and small amount of pentane were added, the upper layer was separated and the lower layer was extracted with 20 mL of pentane. Combined solutions were washed with water and dried over magnesium sulfate. After removal of the pentane on a rotovap, the remaining liquid was carefully distilled through a 20-cm

Vigreux column to afford 1-chloro-1-ethynylcyclohexane **295** as a yellowish liquid, bp 55 – 56°C/15 mm Hg (20.53 g, 72%).



295 **293i**

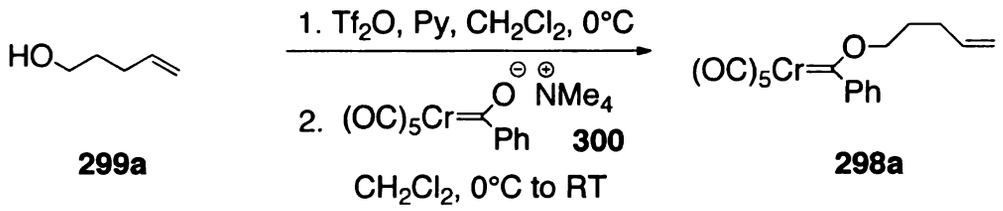
Vinylidenecyclohexane (293i).[164] To a suspension of freshly prepared zinc-copper couple (11.4 g) in 20 mL of absolute ethanol, was added at room temperature 1-chloro-1-ethynylcyclohexane **295** (2.0 g). After a few minutes an exothermic reaction started and the temperature rose to 45 - 50°C (if temperature does not rise, mixture should be gradually warmed, until a further rise of the temperature is observed). When this reaction subsided, the mixture was cooled to 35 - 40°C, and the rest (8.0 g) of the acetylenic chloride **295** was added over 15 min, while maintaining the temperature around 40°C. After the addition, stirring was continued for 30 min at 65°C, then the mixture was cooled to room temperature and the upper layer was decanted off. The black slurry of zinc was rinsed five times with 10 mL portions of diethyl ether. The alcoholic solution and the extracts were combined and washed with 3x30 mL of 2M HCl, saturated with ammonium chloride. After drying over magnesium sulfate most of diethyl ether was removed on a rotovap. The remaining liquid was distilled at 15 mmHg through 20 cm Vigreux column. The (single) receiver was cooled in an ice bath. The allene **293i**, bp 32-35°C/15 mm Hg, was obtained as colorless liquid (5.6 g, 74%).

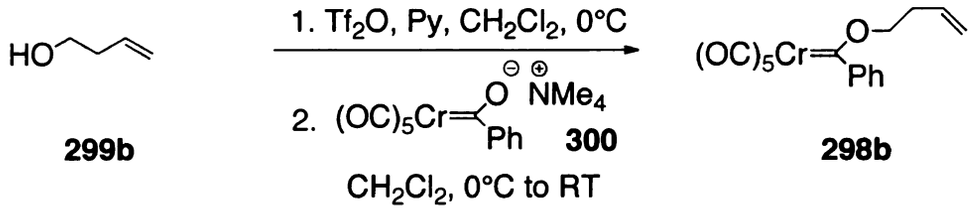


296 **297** **293j**

4,4-Dimethylpentadiene-1,2 (*tert*-butylallene, 293j). A. *Tert*-butylmagnesium bromide.[166] A three-necked 1 L flask was equipped with dropping funnel (with a pressure equalizer), thermometer, reflux condenser, magnetic stirring bar, and nitrogen inlet (connected to dropping funnel). Tetrahydrofuran (80 mL) and magnesium turnings (0.92 mol, 22 g) were added, stirring started, and 1,2-dibromoethane (4 g) was introduced. When ethylene evolution stopped and the temperature had dropped to 50°C (without using a cooling bath!), 80 mL of tetrahydrofuran were added. From the dropping funnel, containing 2-chloro-2-methylpropane **296** (0.62 mol, 57 g, 68 mL), 10 mL were added. The flask was immersed in a water bath of the same temperature as that of the reaction mixture. This bath was removed as soon as the temperature became 2°C higher (if there's no rise in temperature, a 55°C or 60°C water bath should be applied). After the temperature dropped below 50°C, the remainder of the chloride was added during 1.5 h. The reaction temperature was kept in 40 - 50°C range during all the addition. After the addition the flask was warmed for an additional 40 min at about 50°C. The mixture was then cooled down to 30 - 35°C, and transferred into another flask in a stream of nitrogen. The excess of magnesium was rinsed with 3x20 mL of tetrahydrofuran and the rinsing was added to the main solution. The resulting grey solution was used in the next step without any analysis or purification. It can be stored for very long times, although at room temperature part of the Grignard compound crystallizes out. The precipitate dissolves again when solution is heated to 35 - 40°C.

B. 4,4-Dimethylpentadiene-1,2 (*tert*-butylallene).[166] A mixture of dry tetrahydrofuran (50 mL), propargyl chloride (0.33 mol, 23.0 g), and copper (I) bromide (0.005 mol, 0.7 g) was cooled to –40°C. A solution of *tert*-butylmagnesium chloride **297** (all from the previous preparation, about 0.37 - 0.40 mol) was added using the dropping funnel over a period of 1 h. The reaction temperature was gradually raised from –20°C to 0 - 10°C to make stirring possible (if stirring is still difficult, more of the dry THF can be added). After the addition of the Grignard solution stirring was continued for an additional 30 min, then the mixture was poured into 300 mL of ice-cold 3M HCl. About 100 mL of dodecane were added, and organic layer was washed with 10x100 mL 3M HCl. The combined aqueous layers were washed once with 50 mL of dodecane, which also was washed with 5x15 mL of 3M HCl. The combined organic extracts were dried over magnesium sulfate and decanted into 500 mL flask. After adding some boiling stones the flask was connected to a 20 cm Vigreux column, condenser and receiver cooled at –70°C and the system was evacuated (10 mmHg) whilst the flask was heated in a water-bath. The "distillation" stopped when the temperature in the top of the column reached 55 - 60°C. Redistillation of the contents of the receiver through a 20 cm Vigreux column at normal pressure gave *tert*-butylallene **293j** (18.5 g, 63%) as colorless liquid, bp 79 – 80°C.





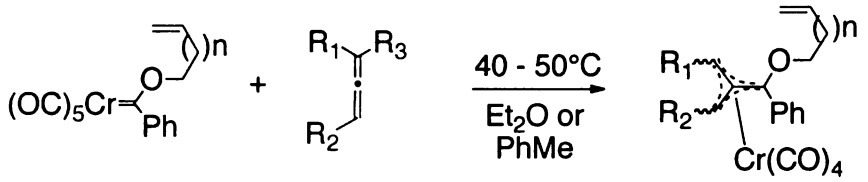
Carbene complexes 298. A. Triflates. Freshly distilled trifluoromethanesulfonic anhydride (12 mmol, 2.0 mL) was diluted with 15 mL of dry dichloromethane and cooled to 0°C. A mixture of alcohol (10 mmol) and pyridine (10 mmol, 0.80 mL), diluted with 5 mL of dry dichloromethane, was added to the stirred solution of triflic anhydride dropwise over a period of 15 min. The mixture was allowed to stir for 15 min at 0°C, afterwhich it was filtered through a thick pad of silica gel (on a Schott filter). The filter cake was flushed with 50 mL of dry dichloromethane, and the combined filtrates were concentrated on a rotovap (cold water bath) and kept there for 1 h. The resulting triflate is pure enough for the next reaction.

B. Carbene complexes. Pentacarbonyl [tetramethylammonium (phenyl)carbenyl oxide]chromium(0) **300** (8 mmol, 2.97 g) was dissolved in 35 mL of dry dichloromethane and cooled down to 0°C. Triflate (9 mmol) diluted with 5 mL of dry dichloromethane was added in one portion, and the reaction mixture was stirred for 3 h, gradually warming up to room temperature. The solution was then diluted with 100 mL of ether, and washed subsequently with 100 ml of saturated sodium bicarbonate, 100 mL of water, and 100 mL of saturated brine. The resulting solution was dried over magnesium sulfate, evaporated, and subjected to column chromatography (silica gel, pentane/ether 10:1). These

complexes are temperature-sensitive and should be handled at room temperature or below only.

Pentacarbonyl[(4-penten-1-yloxy)(phenyl)carbene]chromium(0) (298a) was prepared as deep-red oil (2.81 g, 96%) that is unstable at room temperature and should be stored frozen in benzene solution at –20°C or used immediately; ^{1}H NMR (C_6D_6, 300 MHz) δ 2.10 – 2.21 (m, 2H), 2.31 – 2.37 (m, 2H), 4.82 (s, 2H), 5.10 – 5.23 (m, 2H), 5.80 – 5.85 (m, 1H), 7.21 – 7.28 (s, 2H), 7.38 – 7.45 (m, 3H); ^{13}C NMR (C_6D_6, 75 MHz) δ 28.43, 29.90, 80.24, 116.08, 122.27, 128.04, 129.78, 136.51, 153.58, 216.07, 224.19, 349.38. These spectral data match those reported for this compound[167].

Pentacarbonyl[(3-buten-1-yloxy)(phenyl)carbene]chromium(0) (298b) was prepared as deep-red oil (2.20 g, 78%) that is unstable at room temperature and should be stored frozen in benzene at –20°C or used immediately; ^{1}H NMR (C_6D_6, 300 MHz) δ 2.74 – 2.79 (m, 2H), 4.89 (t, 2H, J = 7.0 Hz), 5.20 – 5.30 (m, 2H), 5.90 – 5.93 (m, 1H), 7.21 – 7.28 (m, 5H); ^{13}C NMR (C_6D_6, 75 MHz) δ 33.85, 79.77, 118.54, 122.68, 128.09, 130.12, 132.85, 153.60, 216.14, 224.32, 349.55. These spectral data match those reported for this compound[167].



298 **293** **303**

Typical experimental procedure for trimethylenemethane complexes preparation.[158] In a 50 mL Schlenk flask, carbene complex (1.00 mmol) and allene (2.00 mmol aliphatic, 3.00 mmol aromatic) were dissolved in 5.0 mL of dry solvent (ether for aliphatic, toluene for aromatic). The solution was degassed using the freeze-thaw technique and stirred for 2 h at 50°C (ether) or 40°C (toluene). Reaction mixture was then cooled down, solvent was removed in vacuo, and 25 mL of degassed hexane added to the reaction mixture. The resulting solution was carefully transferred to the top of silica gel column that was deoxygenated (the column is evacuated using oil pump and held for 30 min, then back-filled with nitrogen; operation repeated twice more) and eluted with 6:1 mixture pentane-dichloromethane. The bright-yellow band (R_f ~ 0.65, pentane/ether 10:1) was collected, concentrated (rotovap back-filled with nitrogen), and dried in vacuo. In order to obtain good NMR, deoxygenated mixture of C_6D_6/CS_2 (1:1) or deoxygenated pure C_6D_6 were used.

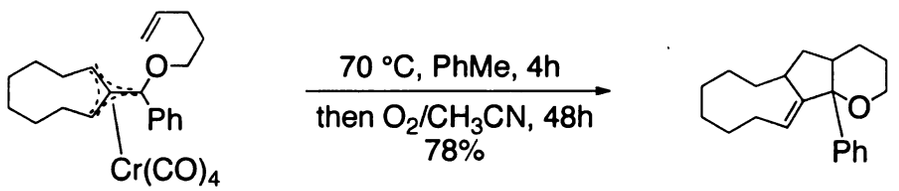
TMM complex 303a was obtained in 65% yield as yellow-orange oil; ^{1}H NMR (C_6D_6-CS_2 (1:1), 300 MHz) δ 1.20 – 1.70 (m, 9H), 1.72 – 2.05 (m, 6H), 2.25 – 2.40 (m, 2H), 2.95 – 3.04 (m, 1H), 3.05 – 3.15 (m, 1H), 3.75 – 3.84 (m, 1H), 4.80 – 4.92 (m, 2H), 5.50

– 5.60 (m, 1H), 7.03 – 7.20 (m, 3H), 7.25 – 7.40 (m, 2H); ^{13}C NMR (C_6D_6-CS_2 (1:1), 75 MHz) δ 26.77, 27.06, 28.79, 28.82, 29.26, 30.58, 32.33, 32.49, 71.34, 71.86, 75.20, 90.47, 115.15, 124.58, 128.10, 128.38, 131.71, 136.32, 137.85, 237.37.

TMM complex 303d was obtained in 54% yield as yellow-orange oil; ^{1}H NMR (C_6D_6, 500 MHz) δ 0.90 – 1.18 (m, 4H), 1.20 – 1.36 (m, 4H), 1.48 – 1.54 (m, 2H), 1.56 – 1.68 (m, 2H), 1.68 – 1.75 (m, 2H), 1.82 – 1.89 (m, 2H), 1.97 (d, 1H, J = 13.0 Hz), 3.10 – 3.17 (m, 1H), 3.17 – 3.24 (m, 1H), 3.84 (dd, 1H, J = 10.5 Hz, 2.0 Hz), 4.84 – 4.94 (m, 2H), 5.50 – 5.60 (m, 1H), 6.95 – 7.10 (m, 3H), 7.40 – 7.43 (m, 2H); ^{13}C NMR (C_6D_6, 125 MHz) δ 26.14, 26.22, 26.50, 28.99, 30.34, 34.28, 38.68, 40.78, 45.02 (1 CH_2 carbon not found; note hindered cyclohexyl rotation), 71.03, 82.37, 90.70, 115.14, 128.29, 128.80, 130.67, 135.66, 137.86, 238.00.

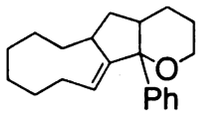
TMM complex 303f was obtained in 29% yield as yellow-orange oil; ^{1}H NMR (C_6D_6-CS_2 (1:1), 300 MHz) δ 1.20 – 1.65 (m, 8H), 1.86 – 2.05 (m, 5H), 2.25 – 2.40 (m, 2H), 2.95 – 3.07 (m, 1H), 3.10 – 3.20 (m, 1H), 3.80 – 3.88 (m, 1H), 4.80 – 4.92 (m, 2H), 5.45 – 5.60 (m, 1H), 7.00 – 7.14 (m, 3H), 7.28 – 7.37 (m, 2H); ^{13}C NMR (C_6D_6-CS_2 (1:1), 75 MHz) δ 26.78, 27.07, 28.80, 28.82, 32.34, 32.50, 34.40, 71.36, 71.91, 75.33, 90.49, 116.92, 124.29, 128.12, 128.41, 131.71, 134.72, 136.20, 237.29.

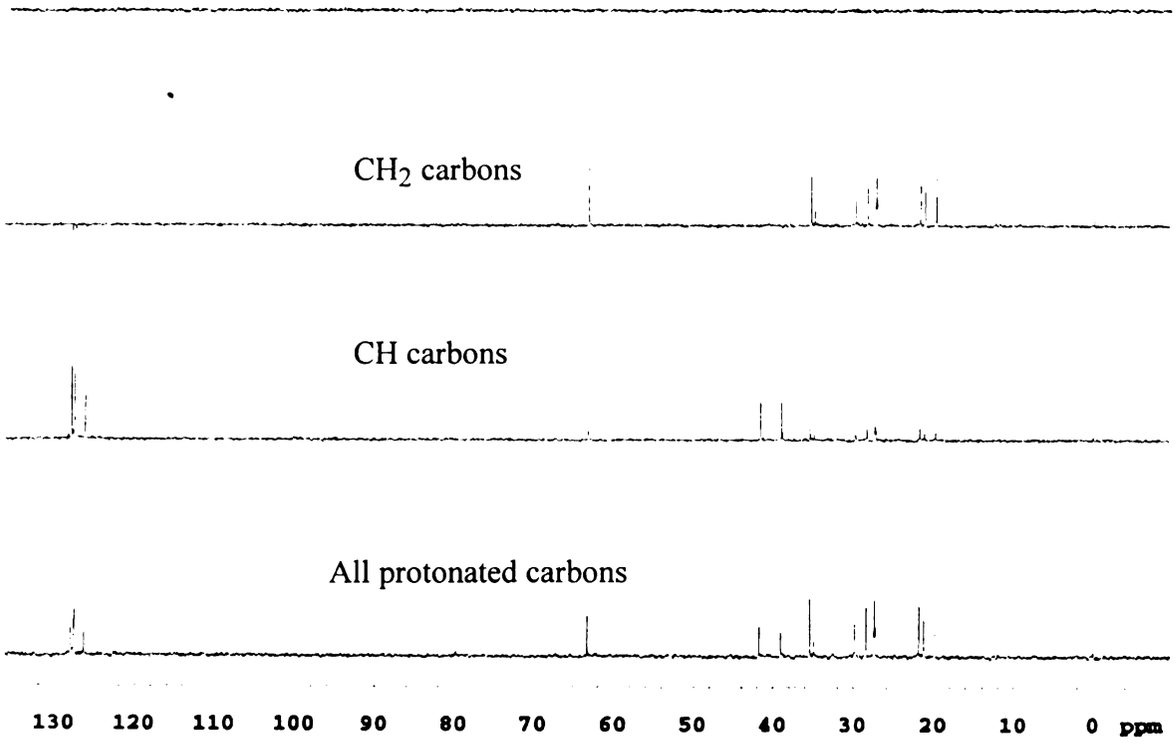
Typical experimental procedure for cyclization of trimethylenemethane complexes and following oxidation. In a 50 mL Schlenk flask, TMM complex (1.5 mmol) was dissolved in 15 mL of dry deoxygenated toluene. The solution was degassed using the freeze-thaw technique (3 repetitions) and stirred for 4 h at 70°C. Reaction completion results in a change from yellow-orange to a faint yellow color. The solution was then evaporated to dryness on a rotovap and the residue was dissolved 50 mL of dichloromethane. The solution was stirred for 2 days with air slowly bubbling through it. When the oxidation was complete (checked by TLC, pentane/ether 10:1), solution was evaporated to dryness, and the residue subjected to column chromatography.

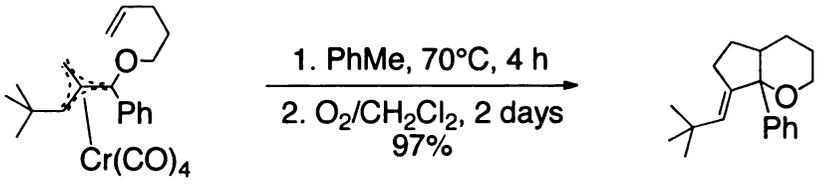


303a **304a**

Cycloadduct 304a was obtained in 78% yield as a colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.10 – 1.20 (m, 1H), 1.27 – 1.70 (m, 10H), 1.80 – 2.20 (m, 7H), 2.53 – 2.70 (m, 2H), 3.40 (td, 1H, J = 11.7 Hz, 1.5 Hz), 3.74 (dd, 1H, J = 11.6 Hz, 4.4 Hz), 4.62 – 4.70 (m, 1H), 7.20 – 7.25 (m, 1H), 7.35 – 7.43 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.84, 21.24, 21.85, 27.34, 27.42, 28.39, 29.85, 35.01, 35.49, 39.06, 41.73, 63.32, 86.89, 126.34, 127.62, 127.65, 128.07, 141.27, 153.67; MS (EI), *m/z* (% rel. intensity) 296 (M^+, 100), 253 (4), 225 (35), 219 (38), 212 (27), 199 (10), 173 (7), 131 (5), 105 (15).

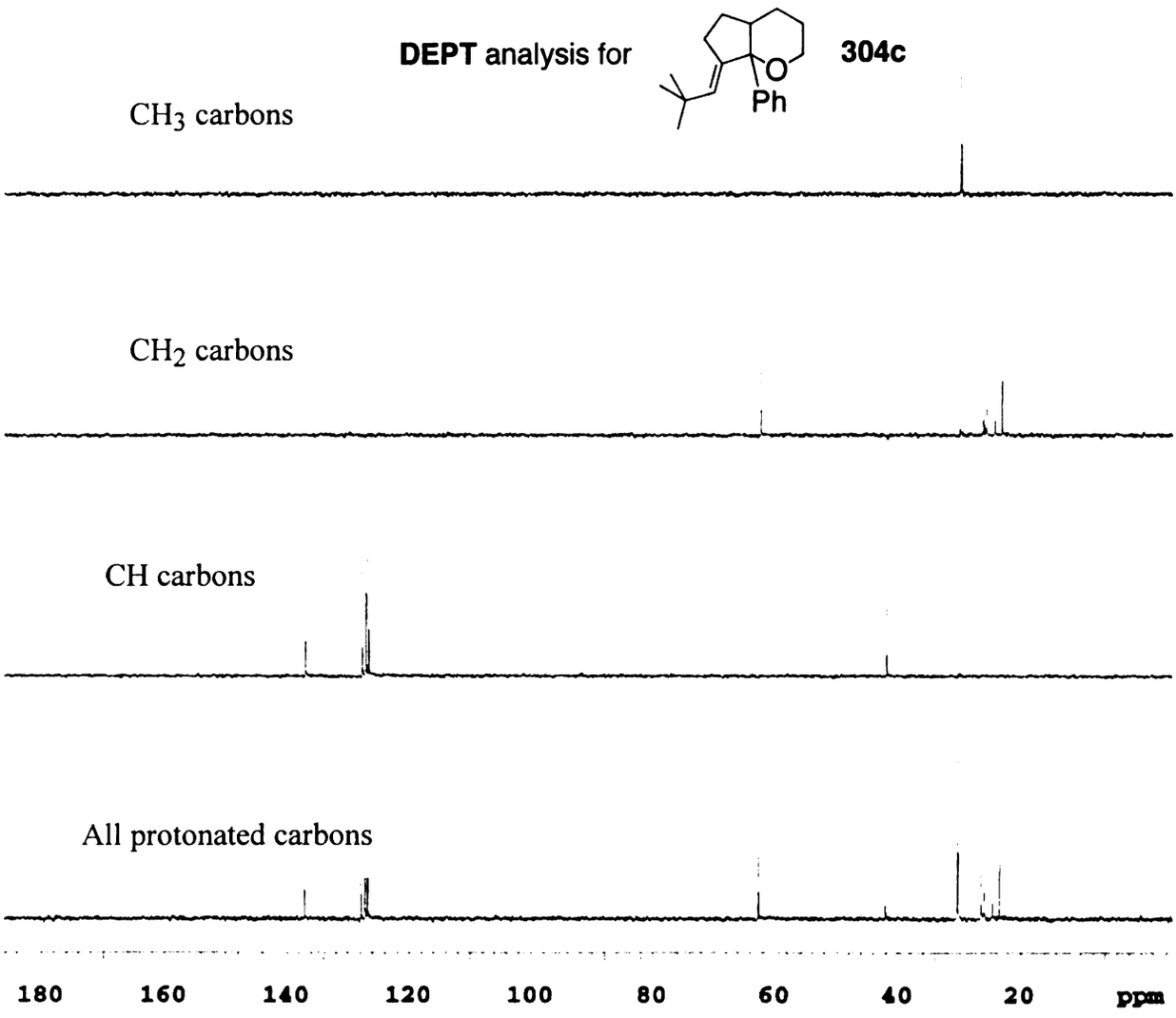
DEPT analysis for  **304a**

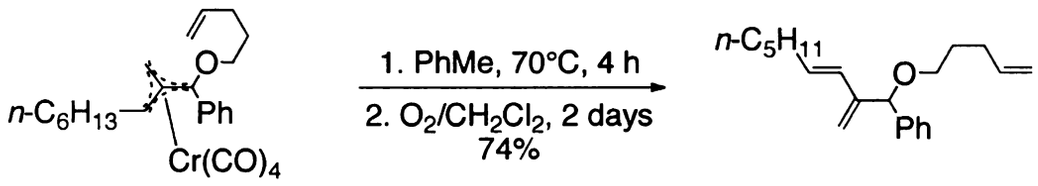




303e **304c**

Cycloadduct 304c was obtained in 97% yield as a colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.10 (s, 9H), 1.40 – 1.75 (m, 6H), 2.18 – 2.27 (m, 1H), 2.40 – 2.53 (m, 1H), 2.68 – 2.82 (m, 1H), 3.60 – 3.75 (m, 2H), 5.24 (t, 1H, J = 2.7 Hz), 7.18 – 7.43 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.41, 24.56, 25.93, 26.42, 30.27, 33.11, 42.00, 62.60, 87.48, 126.70, 127.16, 127.84, 137.10, 138.56, 145.02; MS (EI), *m/z* (% rel. intensity) 270 (M^+, 1), 254 (3), 213 (M-*t*Bu$^+$, 100), 193 (12), 145 (7), 105 (17), 77 (12).

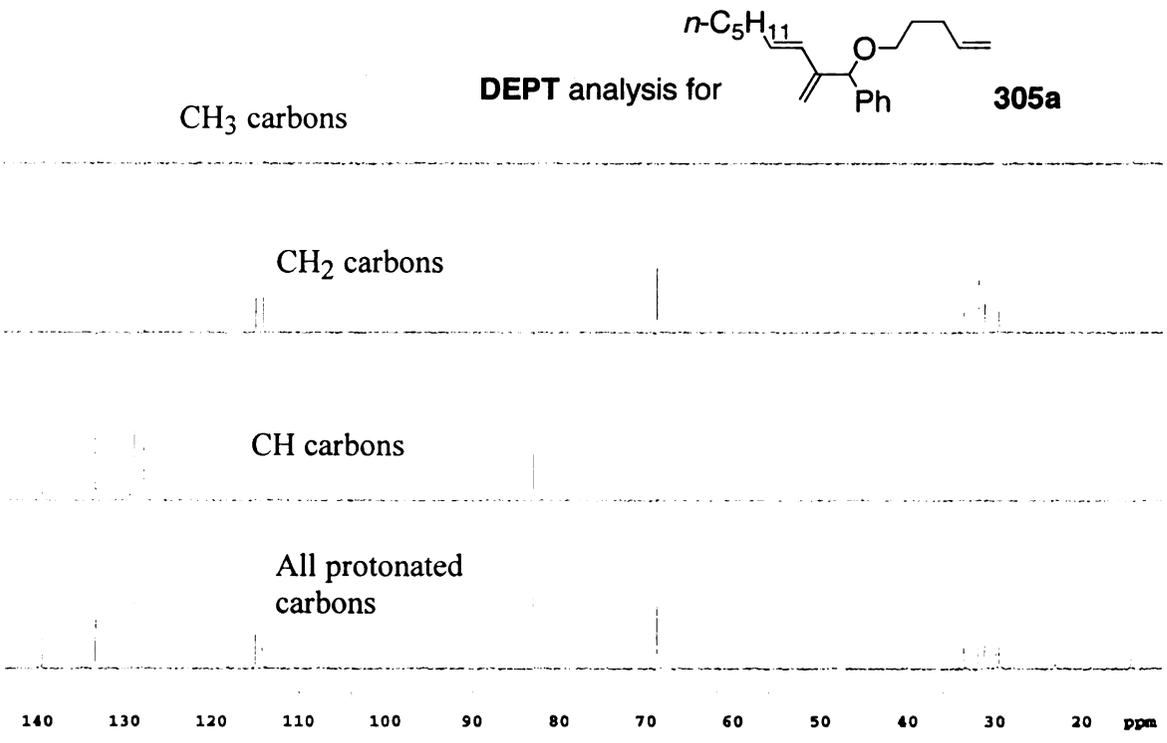


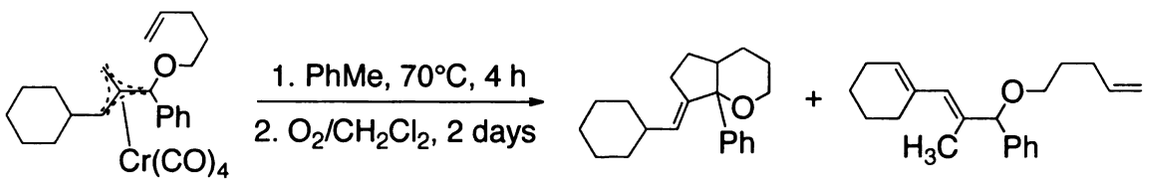


303c **305a**

Triene 305a was obtained in 74% yield as a colorless oil; ^{1}H NMR (CD_3CN, 500 MHz) δ 0.89 (t, 3H, J = 7.3 Hz), 1.15 – 1.37 (m, 6H), 1.67 – 1.75 (m, 2H), 1.98 – 2.05 (m, 2H),

2.15 – 2.20 (m, 2H), 3.38 – 3.43 (m, 1H), 3.49 – 3.55 (m, 1H), 4.96 – 5.07 (m, 3H), 5.22 – 5.24 (m, 2H), 5.85 – 6.03 (m, 3H), 7.27 – 7.43 (m, 5H); ^{13}C NMR (CD_3CN, 125 MHz) δ 14.34, 21.18, 29.62, 29.98, 31.22, 31.92, 33.63, 68.85, 83.03, 114.27, 115.10, 127.97, 128.24, 128.99, 129.52, 133.42, 139.57, 142.31, 147.22; MS (EI), *m/z* (% rel. intensity) 298 (M^+, 30), 213 (100), 175 (60), 143 (25), 107 (50), 69 (12).

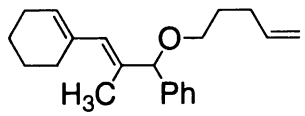




303d **304b,** 17% **305b,** 56%

Cycloadduct 304b was obtained was obtained in 17% yield as a colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 – 1.80 (m, 16H), 2.03 – 2.18 (m, 1H), 2.25 – 2.40 (m, 2H), 2.55 – 2.65 (m, 1H), 3.50 – 3.62 (m, 1H), 3.67 – 3.78 (m, 1H), 5.00 (dt, 1H, J = 9.0 Hz, 2.7 Hz), 7.20 – 7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.86, 24.13, 25.73, 26.23, 26.27, 26.39, 32.69, 33.00, 38.61, 42.55 (1 CH_2 carbon not resolved; note hindered cyclohexyl rotation), 63.18, 86.19, 126.93, 127.38, 128.22, 133.19, 141.88, 144.06; MS (EI), *m/z* (% rel. intensity) 296 (M^+, 2), 213 (100), 167 (3), 137 (5), 105 (10), 77 (8).

Triene 305b was obtained in 56% yield as a colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.50 – 1.80 (m, 9H), 2.07 – 2.20 (m, 6H), 3.32 – 3.55 (m, 2H), 4.66 (s, 1H), 4.93 – 5.08 (m, 2H), 5.63 – 6.02 (m, 3H), 7.20 – 7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.25, 22.13, 22.94, 25.63, 29.15, 29.22, 30.54, 67.66, 87.37, 114.55, 126.40, 126.89, 127.59, 127.95, 130.76, 134.59, 134.99, 138.54, 141.51; MS (EI), *m/z* (% rel. intensity) 296 (M^+, 100), 227 (35), 210 (15), 171 (18), 128 (10), 105 (35), 91 (22), 77 (30).

DEPT analysis for  **305b**

CH_3 carbons

CH_2 carbons

CH carbons

All protonated carbons

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170. For earlier methods of bis-vinyl Fischer carbene complexes preparation, see a) procedure in Dr. Gopalsamuthiram's Ph.D. dissertation, Ref. 118, p. 176; b) procedure in Dr. Wang's Ph.D. dissertation, Ref. 113, p. 150.

171. The quality of 1,2-dichloroethane was found to be extremely important for the success of the "triple annulation" benzannulations. Only the anhydrous Aldrich 99.8% 1,2-DCE was found suitable; even after being distilled from CaH_2, reagent grade 1,2-DCE repeatedly lead to reaction failures.

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