CHAPTER I

INTRODUCTION

Supramolecular chemistry has been a subject of intense research interest for better understanding of the recognition phenomena as well as potential applications in separation processes, catalysis, sensing and biochemical studies. A fundamental design principle in the construction of supramolecular assemblies is the alignment of binding groups on a respective molecular platform to achieve complementary binding interactions towards a targeted structure. In regard to host-guest chemistry, the attractive and steric features given by a guest molecule have to be sufficiently matched by a predisposed host. The binding groups are commonly arranged with a distinct conformation controlled by the covalent architecture of the host. The molecular scaffolding and generations of structural diversity involving such scaffolds are the recent advances in this field. An appropriate selection of the molecular scaffold can enable a search of defined conformational space that would lead to the utilization of such scaffold to construct a potential host molecule. The critical aspect of the deliberate design of selective hosts is the selection of interactive arms connected onto a scaffold structure that provides optimal positioning of binding groups for targeted molecules. Nevertheless, this specially selected architecture does not usually allow structural reorganization of the host to accommodate other guests [1], which limited its potential for wide-range applications.

1.1 Chiral recognition

Chiral biomolecules such as proteins, nucleic acids and carbohydrates play the essential roles in all living creatures which have inspired an interest in the design and study of chiral synthetic receptors. Such receptors can find applications in enantioselective catalysis and separation of enantiomers. A good way to obtain a molecular receptor is to mimick the structural key features of the biological systems, thus associating a well-organized binding site to a forming cavity of a host molecule that is able to surround a guest molecule. Hydrogen bonding, capable of showing a high degree of complementarity and directionality, is frequently used as the attractive

interaction for chiral recognition. Most of receptors developed for this purpose usually provided C_1- or C_2-chiral environments with notable examples such as chiral crown ethers and other macrocycles. In recent years, multipodal ligands have been developed to increase diversity, affinity, selectivity and other desired properties by modifying functional groups on a respective scaffold to become alternatives to the macrocyclic hosts. The vast variations of the reported chiral hosts are selectively complied as follow:

1.1.1 C_1-symmetric receptors

In 2004, Oliva and coworkers [2] showed that the combination of *cis*-tetrahydrobenzoxanthene skeleton with a benzoxazole and an amidopyridine **1**, provided an enantioselective receptor for sulfonylamino acids up to K_{rel} value of 18 for chiral recognitions (**Figure 1.1**). The racemic receptor could be suitably resolved through crystallization in the presence of leucine triflate as its guest. Receptor **1** could be used for the enantioselective extraction of sulfonylamino acids from aqueous solutions of their salts. In 2005, Kim and coworkers [3] synthesized chiral aldehyde **2** with three H-bond donating groups. This aldehyde bound a variety of chiral 1,2-amino alcohols in benzene with the same sense of stereoselectivity. Computational and experimental data indicated that one imine bond, one resonance-assisted H-bond to the imine nitrogen, and two H-bonds to the alcoholic oxygen all played an important role in the stereoselective recognition.

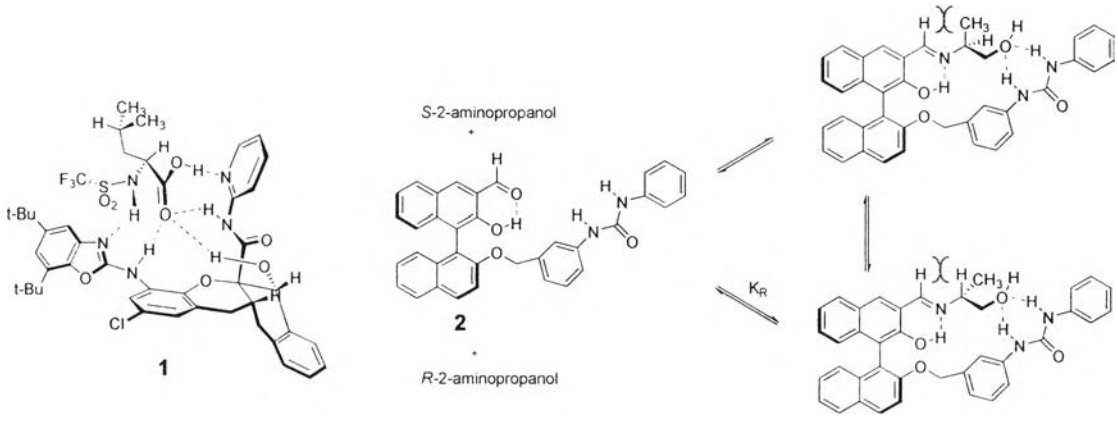


Figure 1.1 The assemblies of C_1-symmetric receptors and chiral guests

1.1.2 C_2-symmetric receptors

In 2005, Yang and coworkers [4] designed a C_2-symmetric carboxylate receptor **3** derived from α-aminoxy acids which showed excellent ability to discriminate the enantiomers of a broad variety of carboxylic acids (**Figure 1.2**). In 2006, González and coworkers [5] synthesized a macrocyclic receptor based on a bischromenylurea and an α,α'-(*o,o*'-dialkyl)diphenyl-*p*-xylylenediamine spacer **(4)** which provided a C_2-chiral cavity to associate the carboxylates by H-bonds. The extent of the selectivity obtained for the racemic receptor **4** and enantiomerically pure (*S*)-naproxen was 7.2:1. Steric repulsions close to the cavity were suggested for the chiral selectivity.

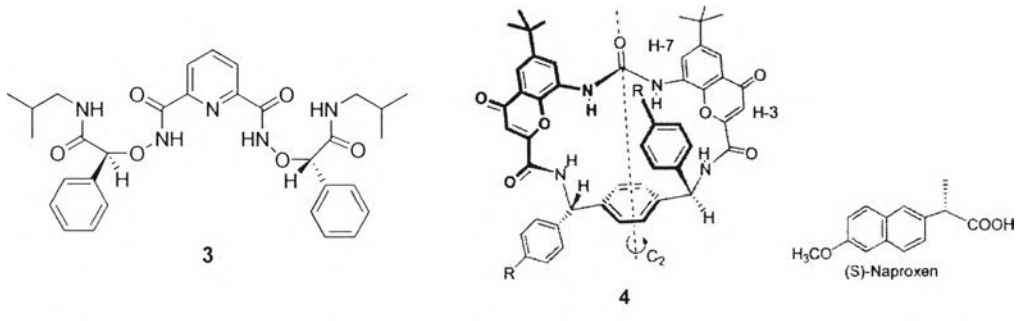


Figure 1.2 C_2-symmetric receptors for the enantiomeric discrimination

In 2008, Kim and coworkers [6] investigated two new anthracene thiourea derivatives **5** and **6** as fluorescent chemosensors for the chiral recognition of the two enantiomers of α-amino carboxylates (**Figure 1.3**). Especially, host **6** displayed K_L/K_D value as high as 10.4 with *t*-Boc alanine. Furthermore, the D/L selectivities of hosts **5** and **6** were opposite, eventhough both hosts bore the same glucopyranosyl units. These intriguing opposite D/L binding affinities by **5** and **6** were supposedly attributed to the CH-π interaction between anthracene moiety and the methyl groups.

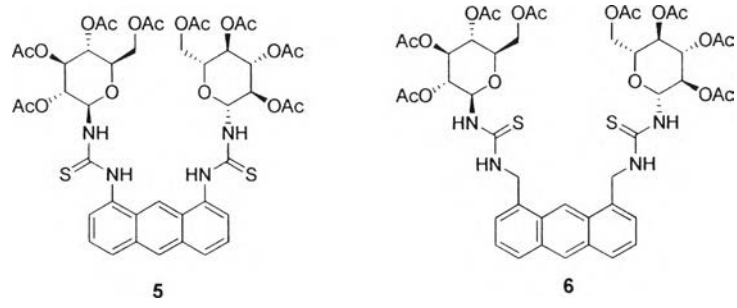


Figure 1.3 The highly enantioselective chemosensors for amino acids

1.1.3 Higher symmetric receptors

In 2002, Lynam and coworkers [7] synthesized *p*-allylcalixarene propranolol amide **7** in 40% yield (**Figure 1.4**). This C_4-symmetric receptor could discriminate between the enantiomers of phenylalaninol through the quenching of the fluorescence emission in methanol. The efficiency of the quenching processes between the fluorophore (host) and the quenching species (guest enantiomer) followed the Stern-Volmer constants (K_{SV}). The K_{SV} ratio (100% *R*/100% *S*) of compound **7** was 1.937 exhibiting significant ability to discriminate between the enantiomers of phenylalaninol (with (*S*)-(-)-phenylalaninol favored). In 2005, the metallocycle **8** showed interesting enantioselective luminescence quenching behavior by chiral amino alcohols in THF [8]. The luminescence signal of enantiopure (*R*)-**8** at 412 nm could be quenched by both enantiomers of 2-amino-1-propanol but at significantly different rates, K_{sv} is 7.35 M^{-1} in the presence of (*S*)-2-amino-1-propanol, and 6.02 M^{-1} in the presence of (*R*)-2-amino-1-propanol. Compound (*R*)-**8** had an enantioselectivity factor $K_{sv}(R\text{-}S)/K_{sv}(R\text{-}R)$ of 1.22 for luminescence quenching in favor of (*S*)-2-amino-1-propanol.

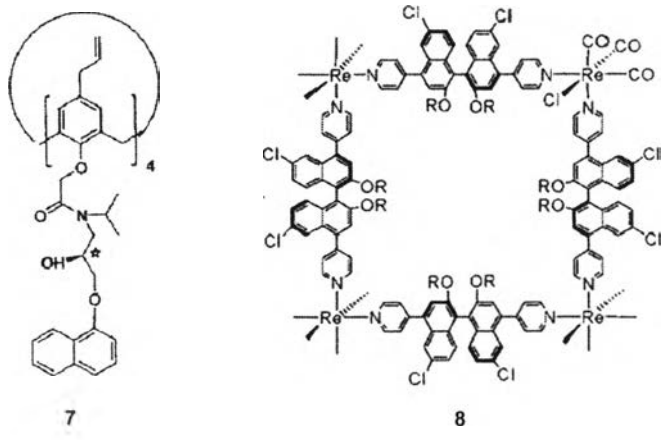


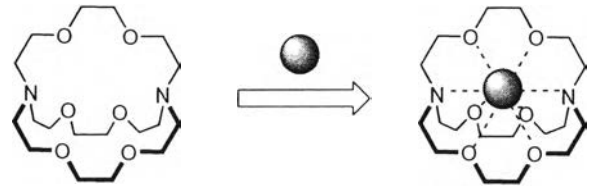
Figure 1.4 Structures of C_4-symmetric chiral molecules **7** and **8**

1.2 Design of ligand system

In host-guest chemistry, it has long been known that binding affinities increased when a collection of donor atoms was structurally constrained to a binding conformation. The concepts of multi-juxtapositional fixedness [9], prestraining [10], preorienting [11], preorganization [12] and predisposition [13] provide two caveats to the general design of effective binding: (i) multidentate ligands are preferred over groups of unidentate ligands and (ii) rigid ligands are preferred over flexible ligands. Synthetic hurdles to achieve these two requirements consequently become the major obstacle to the advance of the field. Besides, conformational flexibility can result in quite different cavity sizes and shapes which may exhibit different guest selectivities.

Design of a targeted ligand towards specific guest discrimination should consider many related factors such as size, charge density, polarizability and shapes [14]. Symmetrically tripodal ligands are among the most frequently investigated host scaffolds that had successfully served the purpose. These so-called "cryptates" are the ideal three-dimensional assemblies which create the very stable inclusion complexes between the caged hosts and their guests [15]. The [2.2.2]cryptands are perhaps one of the simplest molecules prepared that are capable of forming cryptates [16]. They are the macrobicyclic diazo-polyether where the three-coordinated nitrogen atoms provide the vertices of a spheroidal three-dimentional structure (**Scheme 1.1**). Their encapsulated selectivity [17-19] and strength of binding [20-22] were much better

than linear components or macrocycles with an equal number of donor atoms such as podanes or crown ethers.



Scheme 1.1 The three-dimensional assembly of [2.2.2]cryptate

In recent years, preorganized tripodal ligand has been developed to increase diversity, affinity, selectivity and other properties by modifying functional groups on a respective scaffold. The subunits within a molecule obtained and retained a preorganized geometry in a trigonally symmetric conformation. This structural feature is a rigid ligand but relatively flexible resulting in forming quite different cavity sizes and shapes, and possibly good level of discrimination as has been shown upon the binding of targeted molecules. Preorganized tripodal scaffolds have since been of much interest in the construction of various molecular assemblies with many specially desired topologies (**Figure 1.5**). Examples of these scaffolds are steroids **9** [23-24], triazacyclophanes **10** [25-26], Kemp's triacid **11** [27-28], cyclotriveratrylenes **12** [29-30], calixarenes **13** [31-32] and hexasubstituted benzenes **14** [33-34].

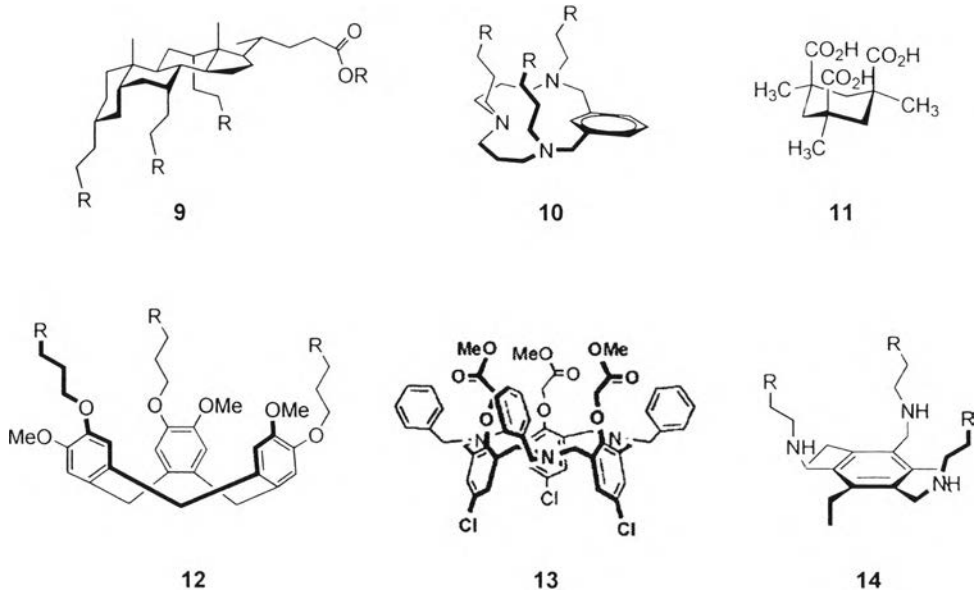


Figure 1.5 Examples of preorganized tripodal scaffolds

1.3 Hexasubstituted benzene

Hexasubstituted benzene had become of particular interest as a favorable platform exploiting "steric gearing" upon the positioning of binding groups. In 1976, McNicol and coworkers were the first group to report the preorganization of the functional groups in hexasubstituted benzene derivatives and determined the molecular structures by X-ray analysis [35-37]. In these systems, six identical subunits within a molecule obtained and retained a preorganized geometry due to the adoption of thermodynamically favored conformation where steric interactions are minimized [38-43]. With the unavoidable steric repulsion between 2 adjacent substituents around the ring, the hexasubstituted benzenes usually arrange themselves in the "*ababab*" configuration, where *a* denotes "above" and *b* denotes "below", as the most thermodynamically stable configuration (**Figure 1.6**). The subunits are oriented in a fully alternated "up-down" arrangement, in which those at the 1, 3 and 5 positions of the central ring all point to the same face of the ring while the rest of subunits turn toward the opposite direction.

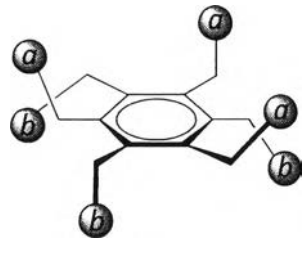


Figure 1.6 *ababab*-Configuration of the hexasubstituted benzene scaffold

1.3.1 Stereochemistry of hexasubstituted benzenes

The static and dynamic stereochemistry of hexaethylbenzene **(15)** was analyzed in great detail by Iverson and coworkers [38]. Molecular mechanic calculations have indicated that the fully alternated conformation gave the lower energy than a nonalternated conformation (ca. 3.46 kcal mol^{-1}) which possessing two pairs of *ortho*-substituents oriented toward the same face of the benzene ring where its associated steric interaction (a *syn* interaction) is repulsive. All ethyl groups are perpendicular to the central ring, giving eight possible different diastereomeric forms.

Calculation has shown that relative steric energies of these forms increased roughly with the number of *syn* interactions present (none, two, four or six; **Figure 1.7**).

As a further test of stereochemistry of **15**, relative energy levels for the eight structures were computed by the extended Hückel method. Such hybrid EFF (BIGSTRN-2) [39] and EFF-EHMO [40] calculations showed the fully alternated form remained the ground state conformer (**Figure 1.8**). Both methods of calculations therefore predicted the same ground state conformation as found from the X-ray structure [38] and indicated that the solution of **15** contained more than 99% of this conformer at equilibrium under normal conditions. Higher energy conformers could be implicated as intermediates in the degenerate conformational rearrangement (topomerization) of the fully alternated conformer.

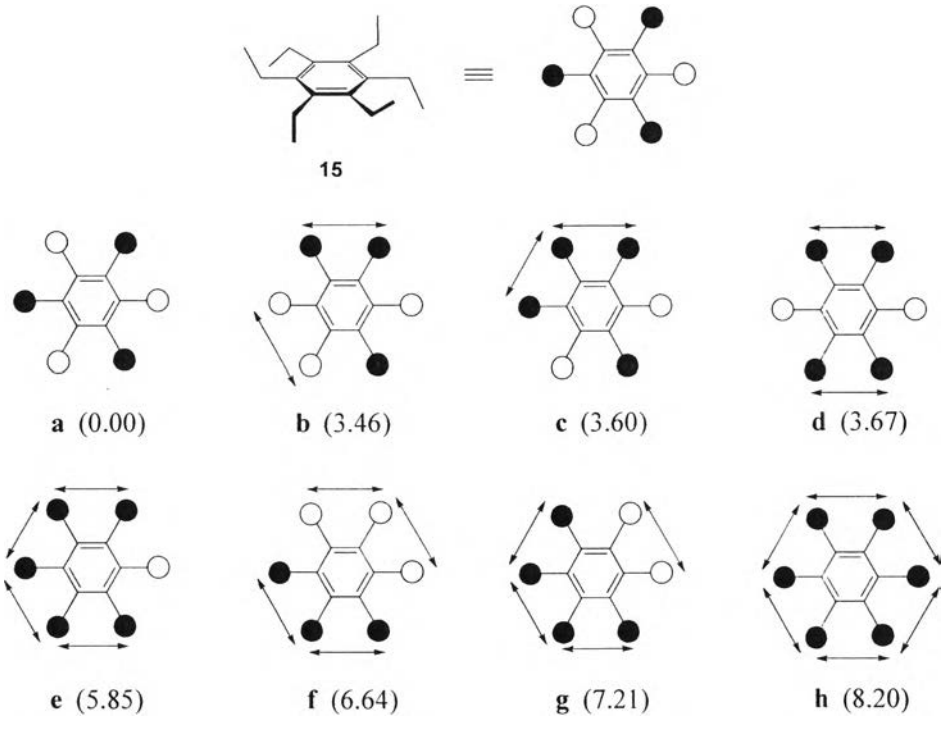


Figure 1.7 The eight ideal up-down forms of hexaethylbenzene **(15)** and their calculated EFF (BIGSTRN-2) relative steric energies (kcal mol^{-1}) (filled and empty circles represent ethyl groups pointing to or away from the observer; a double arrow denotes a *syn* arrangement of two *ortho* ethyl groups).

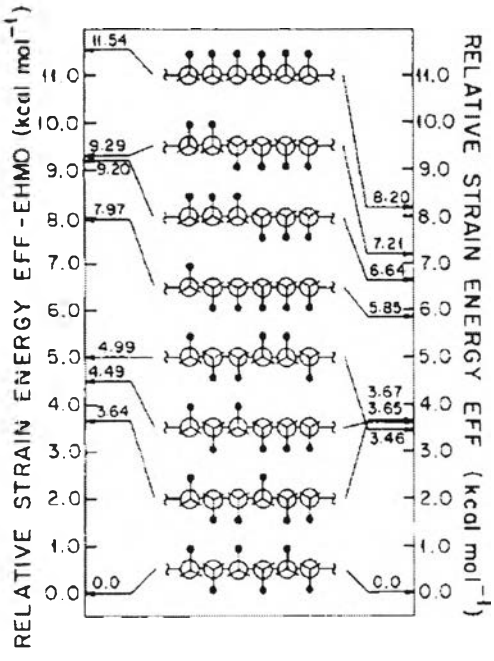


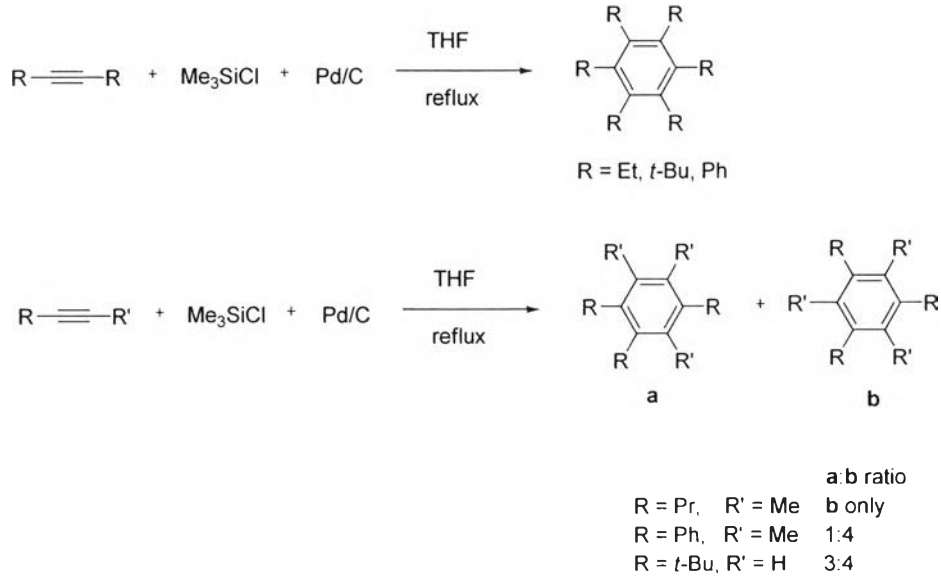
Figure 1.8 The eight up-down isomers of **15**. Each schematic projection represents a view around the perimeter of the benzene ring. The heavy dots stand for methyl groups. The scales on the right and left of the diagram indicate relative energies calculated by the EFF (BIGSTRN-2) and EFF-EHMO methods, respectively.

1.3.2 Synthesis of hexasubstituted benzenes

1.3.2.1 Cyclotrimerization

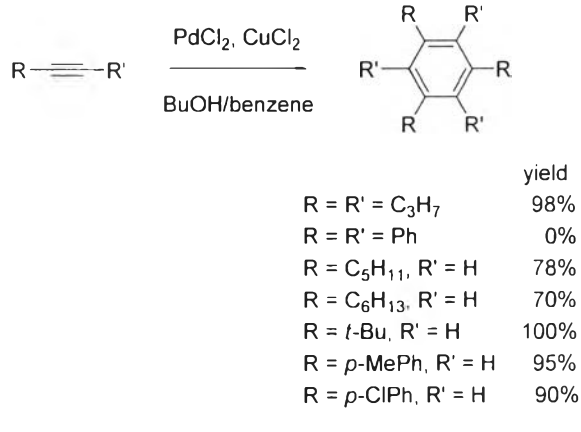
A variety of homogeneous transition metal carbonyl complexes could be employed for the preparative cyclotrimerization of alkynes to hexasubstituted benzene derivatives [44-47]. Examples of these complexes were Ziegler catalyst (*i*-Bu_3Al and $TiCl_4$), Bis(benzonitrile)palladium chloride, $NaBH_4$ with $NiCl_2$, Ta_2Cl_6(tetrahydro-thiophene)$_3$ and Nb_2Cl_6(tetrahydrothiophene)$_3$. Many of these methods produced complex reaction mixtures which afforded low yields of the desired trimers while very stringent reaction conditions were mostly required. In 1987, during an attempted addition of trimethylsilyl chloride to alkynes in the presence of Pd/C, Jhingan and Maier [48] observed the formation of hexasubstituted benzene derivatives from symmetrical alkynes in high yields (**Scheme 1.2**). Furthermore, trimerization of the unsymmetrical alkynes produced the asymmetric trimer and the trimerization of

terminal alkyne was selected to probe the sensitivity of the reaction to steric effects. The unsymmetrical 1,2,4-trimer was obtained as a minor product.



Scheme 1.2 Cyclotrimerization of alkynes with Pd catalyst

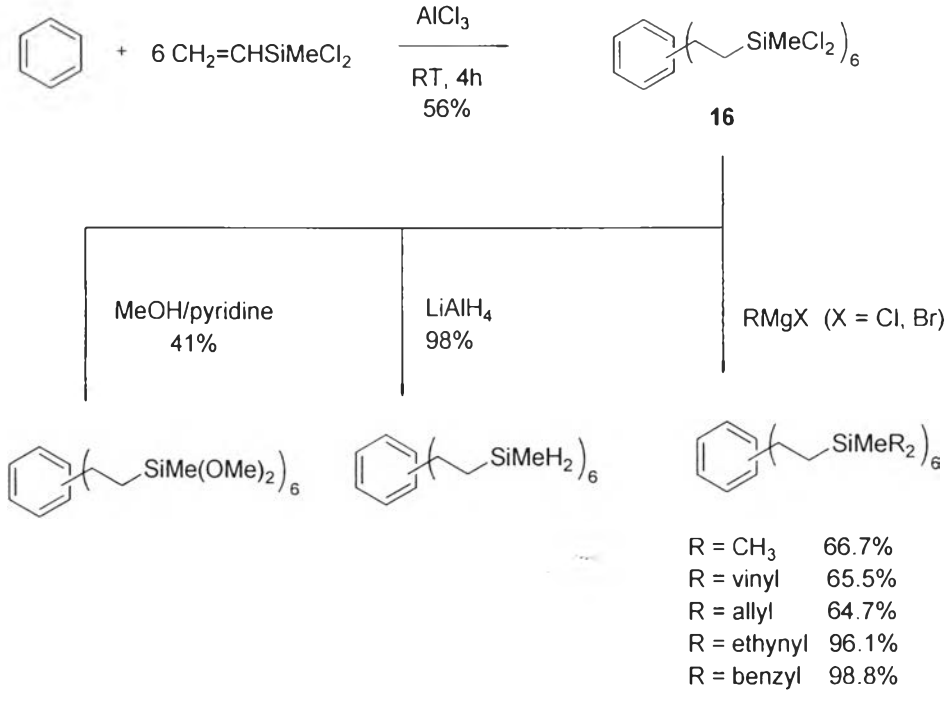
In 2001, Jiang and coworkers [49] presented a regioselective and highly chemoselective method for preparing hexasubstituted benzene derivatives via $PdCl_2$ catalyzed cyclotrimerization of alkynes in the presence of $CuCl_2$ (**Scheme 1.3**). They found that a symmetrically internal alkyne except diphenylacetylene was cyclotrimerized in high yield in the presence of $PdCl_2$-$CuCl_2$ in BuOH/benzene at room temperature. The cyclotrimerization did not yield benzene derivatives without adding $CuCl_2$ as the oxidant.



Scheme 1.3 $CuCl_2$-induced regiospecific cyclotrimerization of alkynes

1.3.2.2 Benzene substitution

Friedel-Crafts alkylation of vinyldichloromethylsilane to benzene in the presence of aluminum chloride catalyst at room temperature gave hexakis((dichloro-methylsilyl)ethyl)benzene **16** in 56% yield [50]. The chlorosilyl group can easily react with organometallic reagents, alcohols and amines to afford useful new organosilicon compounds which could be served as possible precursors for new silicon-containing materials. Compound **16** was treated with a variety of reagents such as methyl, vinyl, allyl, ethynyl, and benzyl Grignard reagents, methanol, and $LiAlH_4$ to give the corresponding derivatives (**Scheme 1.4**) in good to excellent yields.

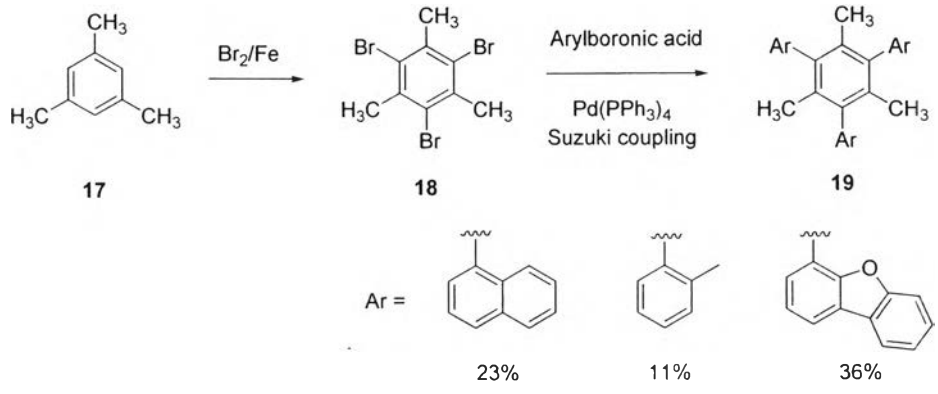


Scheme 1.4 Syntheses and structures of the hexa(methylsilylated)benzenes

1.3.2.3 Substitution on 1,3,5-trialkylbenzene

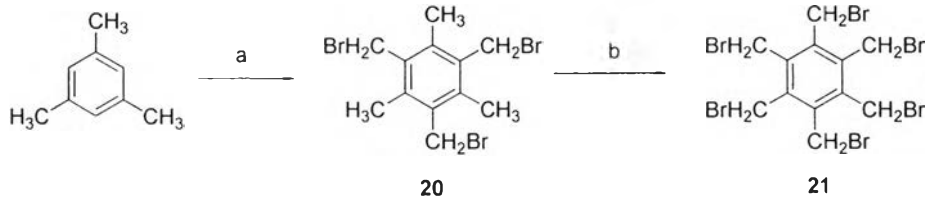
Mesitylene **17** was used to synthesize triarylmesitylenes **19** using the Pd-catalyzed Suzuki coupling via tribromomesitylene **(18)** with arylboronic acid obtaining the product **19** in low yield [51] (**Scheme 1.5**). The minor all-*syn* isomer of compound **19** was isolated and studied the kinetics of interconversion of rotational isomers and found that the methyl groups on compound **19** did provide a sufficient

barrier to aryl-aryl bond rotation to prevent rapid isomer interconversion at room temperature.



Scheme 1.5 Synthesis of triarylmesitylenes derivatives **19**

In 1993, van der Made and coworkers [52] discovered an easy synthetic route to threefold bromomethylation of mesitylene that led straightforward to the 1,3,5-tribromomethyl-2,4,6-trimethylbenzene **(20)** using paraformaldehyde in acid. In 1994, Závada and coworkers [53] presented the methodology to prepare an important intermediate, hexabromomethylbenzene **(21)** for further modification to various hexasubstituted benzene derivatives (**Scheme 1.6**).

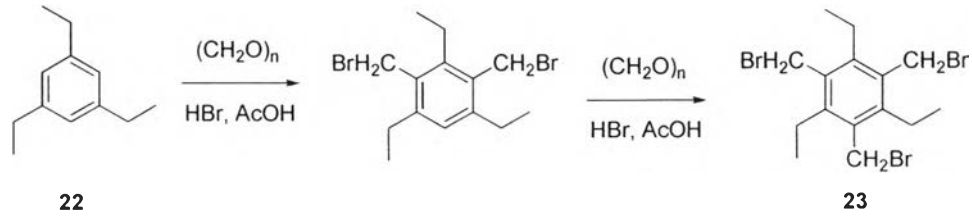


(a) $(CH_2O)_n$, KBr, $AcOH/H_2SO_4$, 95 °C, 6 h 97% (b) $Br_2/BrCH_2CH_2Br$, reflux, 20 h 97%

Scheme 1.6 Synthesis of hexabromomethylbenzene **(21)**

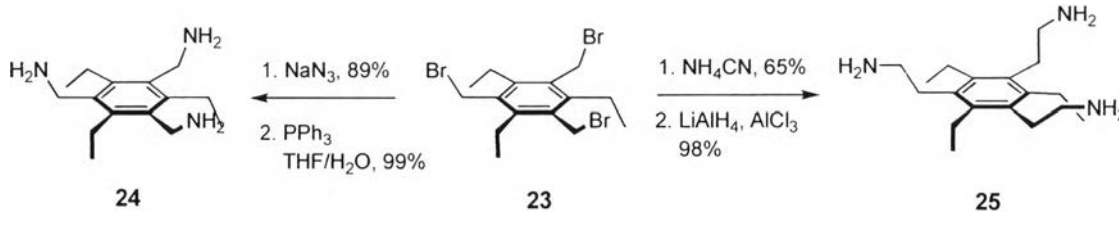
Walsdorff, Metzger and their coworkers [54-55] improved the synthesis of hexasubstituted benzene derivatives through 1,3,5-tribromomethyl-2,4,6-triethylbenzene **(23)** from 1,3,5-triethylbenzene **(22)**. Compound **23** could be synthesized in one step following the approach outlined in **Scheme 1.6**, but due to purification problems, they chose to use the route shown in **Scheme 1.7** yielding

compound **23** in greater than 53% yield over two steps. This product could be used as the main precursor to synthesize various ligand systems through functionalizations on bromomethyl groups.



Scheme 1.7 Two-steps synthesis of 1,3,5-tribromomethyl-2,4,6-triethylbenzene **(23)**

For instance, compound **23** was the precursor to be converted into the tris-amines **24** and **25** through functionalizations on bromomethyl groups (**Scheme 1.8**). Azide substitutions were performed on compound **23** in which the azide product was reduced into tris-amine **24** [55]. Compound **25** was formed by cyanations followed by reductions [56]. These amines could also be used as the starting materials, like compound **23**, for various ligand systems through functionalizations of amino groups.



Scheme 1.8 Synthetic pathways to tris(aminoalkyl)triethylbenzenes **24** and **25**

The applications of the hexasubstituted benzene scaffold in supramolecular chemistry have emerged rapidly. Several receptor molecules for chiral guests have been designed by placing various binding groups around the benzene ring. In Anslyn's group, 1,3,5-trisubstituted triethylbenzene derivatives have been extensively explored as receptors for polyfunctional, biorelevant, anionic guest molecules. Different functional groups are predisposed around the benzene core to match with the functionalities and geometries given by the targeted guest as showed in **Figure 1.9**. By employing a colorimetric competition assay method, a chemosensor was

established using the bowl shaped host **26** that bound inositol triphosphate in buffered water with a binding constant of $2.2x10^4$ M^{-1}. In their competition assay, an indicator dye bound to the receptor was displaced by a stronger binding guest molecule. As a consequence, the indicator's microenvironment changed as it was released from the host into the solution, which affected its fluorescent properties [57].

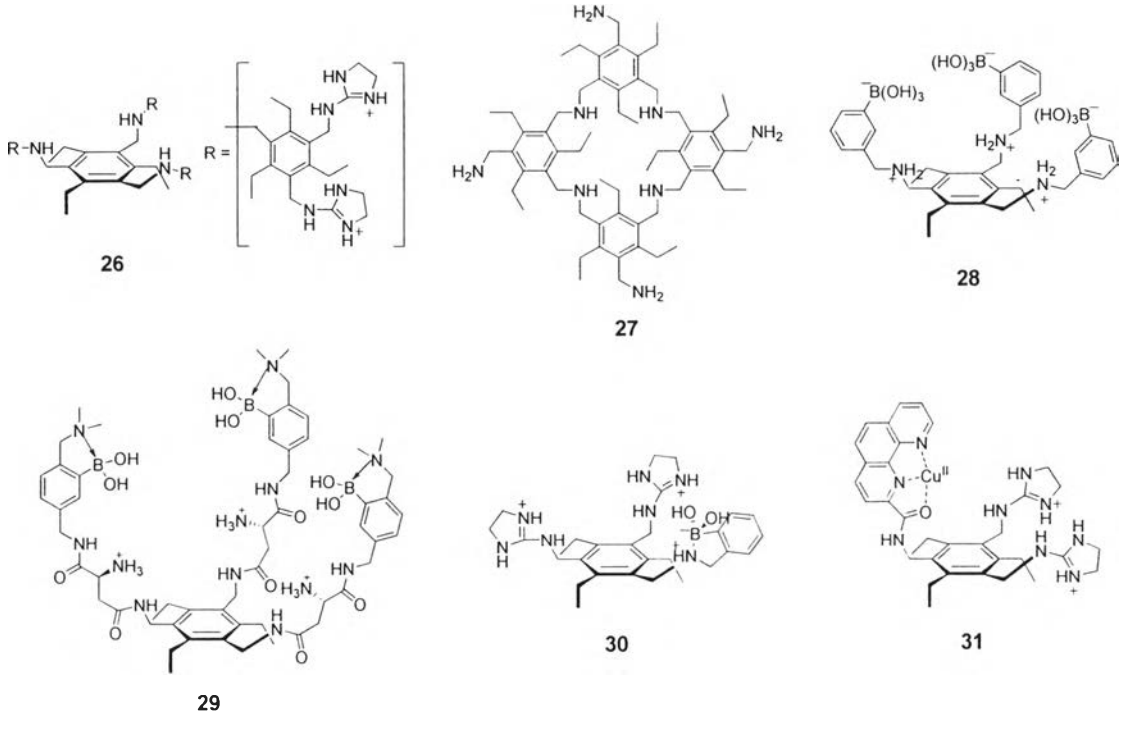


Figure 1.9 1,3,5-Trisubstituted-2,4,6-triethylbenzene based receptors **26-31** for biorelevant anionic guests

Addressing the same type of guests, they synthesized aza-calixarene **27** that formed a large cavity. Again, in fluorimetric competition assays, selective bindings of inositol triphosphate ($K_a = 2.4x10^5$ M^{-1}) and fructose-1,6-diphosphate ($K_a = 25.0x10^4$ M^{-1}) were obtained in aqueous solution [58]. Similarly, the use of a dye displacement assay with the tris-boronic acid receptor **28** revealed selective binding of glucose-6-phosphate over glucose and phosphate in 30% water/methanol [59]. Receptor **29**, possessing groups of ammoniums and boronic acids, showed good affinity and selectivity for heparin over similar polysaccharides using an indicator-displacement assay (IDA). The binding constant (K_{assoc}) between **29** and heparin was $3.8x10^4$ M^{-1} in

a 1:1 (v/v) water/methanol solution buffered with 10 mM HEPES at pH 7.4 [60]. The mono-Boc protection of compound **24** has been used as a starting material for several receptors. This gives access to triethylbenzene with different functional groups in the 1,3-versus 5-positions. Tartrate and malate bound to the imidazolinium portions of receptor **30** through their carboxyl groups with additional binding to the boronic acid side with the hydroxyl functional group. Receptor **29** was also used in a chemosensor ensemble to measure the amount of tartaric acid and malic acid in wine at high accuracy [61]. The metalloreceptor **31** functioned as a fluorescent sensor for citrate which coordinated to both imidazolinium groups and the Cu(II) center [62].

A different approach to analyte sensing was taken by attaching two tripeptide side arms onto the benzene scaffold bound to a resin (**Figure 1.10**). On the solid support, a library of approximately 3600 receptors with different peptide side arms was scanned by looking for a fluorescent response in the presence of fluorophore-labeled ATP (adenosine triphosphate). The ATP was found to bind cooperatively to Ser-Tyr-Ser peptide arms and the guanidinium functions of compound **32**. The fluorescent receptor system **32** was synthesized by attaching fluorescent end groups to the Ser-Tyr-Ser peptide arms, which displayed the best selectivity and sensitivity among all tripeptides. Hence, the sensor ensemble obtained could distinguish between ATP, AMP and GTP with only ATP inducing a 1.5-fold fluorescence enhancement upon binding [63].

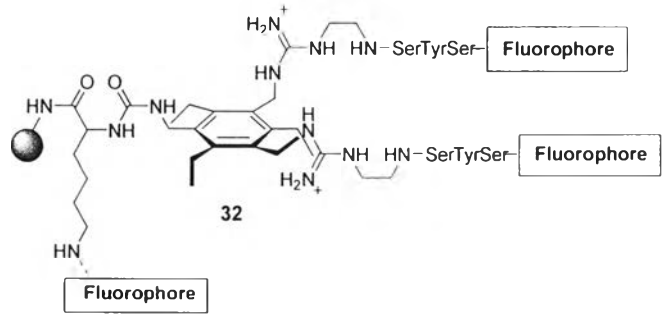


Figure 1.10 ATP-selective resin bound chemosensor ensemble

Rebek and coworkers took advantage of the predisposition of three glycoluril groups around 1,3,5-trisubstituted triethylbenzenes to achieve the formation of

dimeric, hydrogen-bonded capsules [64-65]. The supramolecular assemblies formed by the two complementary "half-bowl" monomers **(33** and **34)** were capable, according to the size of the cavities and the guest molecules, of encapsulating and re-releasing the guest reversibly (**Figure 1.11**).

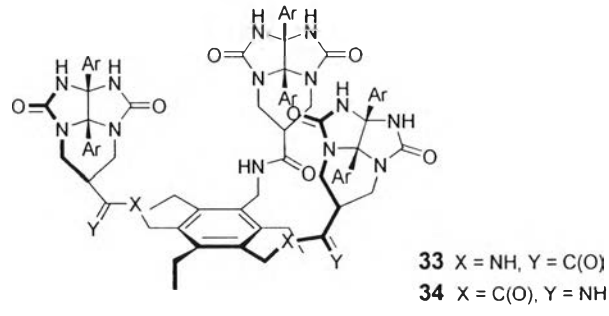
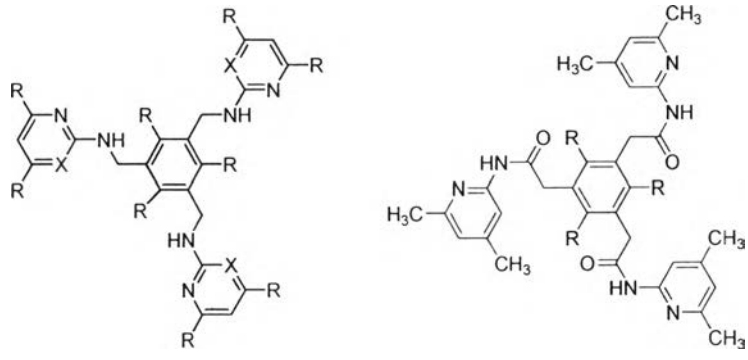


Figure 1.11 Monomers **33** and **34** that self-assembled into dimeric capsules

The tripodal receptor for molecular recognition of carbohydrates, especially monosaccharide, is an actively investigated topic in bioorganic chemistry. The prototypical host featured a 1,3,5-trisubstituted triethylbenzene scaffold bearing three convergent H-bonding units. Mazik and coworkers' systematic studies toward recognition for carbohydrates showed that aminopyridines, aminopyrimidines and amidopyridines provided an excellent structural motif for binding carbohydrates, associated with the ability to form cooperative and bidentate hydrogen bonds with the sugar OH groups. Aminopyridine receptors based on a trimethylbenzene **35**, triethylbenzene frame **36** and trimethylaminopyrimidine **37** showed high β versus α-anomer binding selectivity in the recognition of glucopyranosides [66-70] (**Figure 1.12**). Amidopyridine receptors **38** and **39** displayed high efficiency and an inverse selectivity in favor of α-anomer. The possible binding modes between the acyclic receptors and monosaccharides were analyzed on the basis of chemical shift changes in ^{1}H-NMR spectra and molecular modeling calculations.

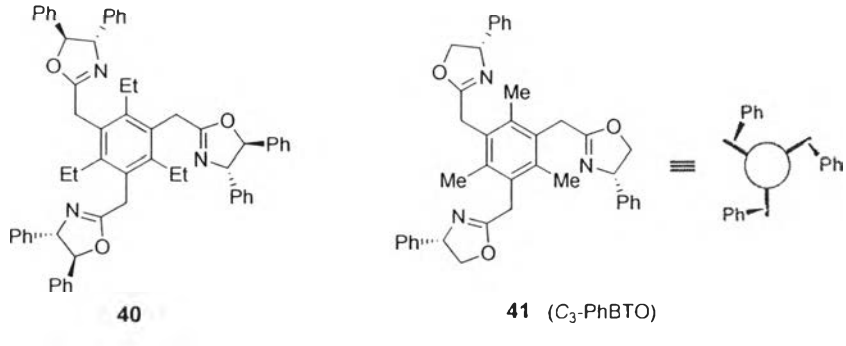


35 X = CH, R = CH_3
36 X = CH, R = CH_2CH_3
37 X = N, R = CH_2CH_3

38 R = CH_3
39 R = CH_2CH_3

Figure 1.12 Tripodal receptors for molecular recognition of monosaccharides

The hexasubstituted benzene-based tripodal tris(chiral-oxazolines) derivatives were synthesized for selective recognition of linear alkylammonium ions, *n*-$BuNH_3^+$, *sec*-$BuNH_3^+$, *t*-$BuNH_3^+$ and $Ph(CH_2)_2NH_3^+$. Receptor **40** gave the selectivity ratio of *n*-$BuNH_3^+$/*t*-$BuNH_3^+$ as high as 4000 [71] (**Figure 1.13**). In 2002-2003, Kim, Ahn and their coworkers reported the C_3-symmetric enantiomeric recognition of α-, β-, and α,β-chiral primary ammonium ions with phenylglycinol-derived tripodal oxazoline receptors **41** (C_3-PhBTO). A good level of chiral discrimination was observed which has been elucidated from different binding studies and X-ray crystallographic analyses for both diastereomeric inclusion complexes utilizing bifurcated H-bonding [72-73]. Moreover, receptor **41** showed chiral discrimination in a fluorescence assay study upon binding enantiomeric guests [74].



40

41 (C_3-PhBTO)

Figure 1.13 The chiral tripodal receptors for molecular recognition of primary ammonium ions

In 2005, C_1-PhBTO receptor **42** was synthesized and studied its enantioselective recognition toward α–chiral primary ammonium ions (**Figure 1.14**). C_1-PhBTO receptor showed higher selectivity with an opposite sense of enantio-discrimination compared to other C_1-symmetric analogues examined, but lower selectivity with the same sense of enantioselection compared to its C_3-symmetric analogue. Binding studies indicated that the C_1-symmetric receptors, particularly C_1-PhBTO, interacted with the guests in a 2:1 host-guest complex mode in stark contrast to its C_3-symmetric analogs [75]. In 2006, They have constructed homochiral coordination cages **43** by Pd(II)-mediated dimerization of C_3-symmetric tripodal oxazoline units bearing pyridine pendant groups. A binding study indicated that the cages could recognize organoammonium ions, including chiral samples [76].

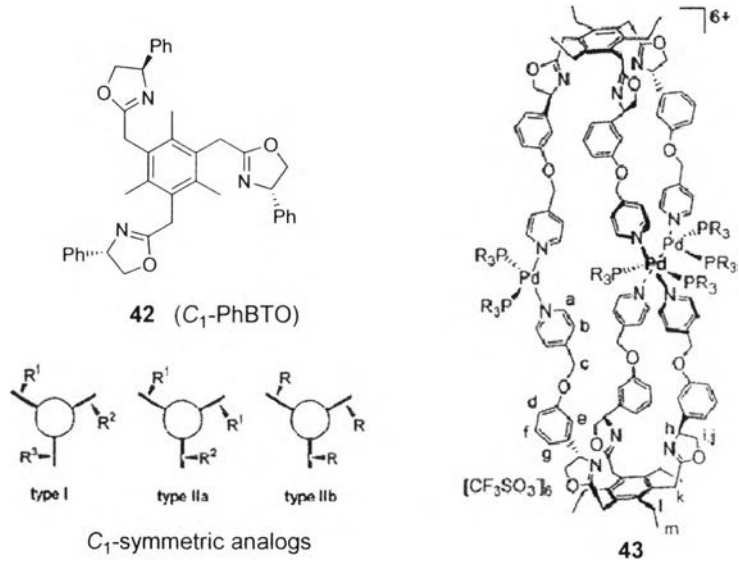
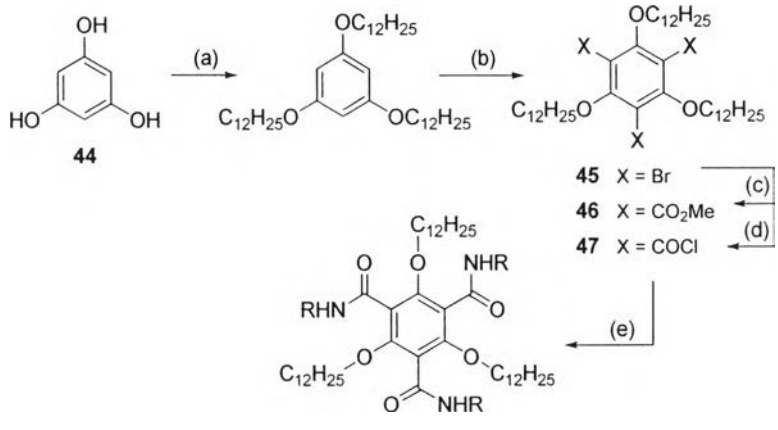


Figure 1.14 Enantioselective receptors for chiral ammonium ions

1.3.2.4 Substitution on phloroglucinol

In 2001, Nuckolls and coworkers synthesized hexasubstituted benzene derivatives using phloroglucinol **44** as the starting material, which was proceeded by triple *O*-alkylations and brominations to compound **45**. Then triple lithium/halogen exchanges at -78 °C and quenching the reaction with methyl chloroformate obtained compound **46** in 30% yield [77] (**Scheme 1.9**). The targeted derivatives of structures **48** were then synthesized in three steps: saponification, conversion to **47** and reaction

with primary amines (75-81% yields). These products were studied upon their self-assembled ability into column together with their relevant physical properties.

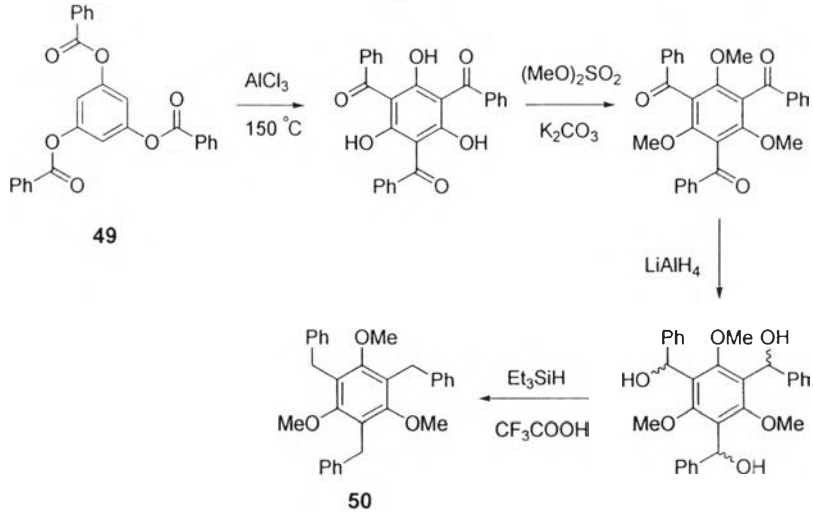


48 R = $C_{12}H_{25}$, CH_2CH_2Ph, GlyO*t*-Bu

(a) K_2CO_3, $C_{12}H_{25}I$, reflux; (b) $Br_2/FeCl_3$; (c) *i*.*t*-BuLi; *ii*.$ClCO_2Me$; (d) *i*.NaOH, reflux; *ii*.$SOCl_2$, reflux; (e) RNH_2/Et_3N

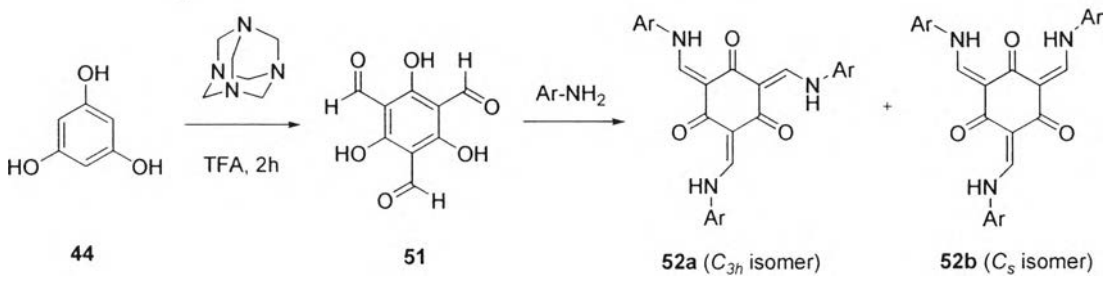
Scheme 1.9 Synthetic pathway to hexasubstituted benzenes from phloroglucinol

In 2003, Biali and coworkers [78] used 1,3,5-tribenzoyloxybenzene **(49)** as the starting material to synthesize compound **50** as shown in **Scheme 1.10**. The triester **49** was rearranged followed by protection of the resulting phenolic hydroxyl groups by methylations. The three carbonyls were then reduced to methylenes in two-step sequence.



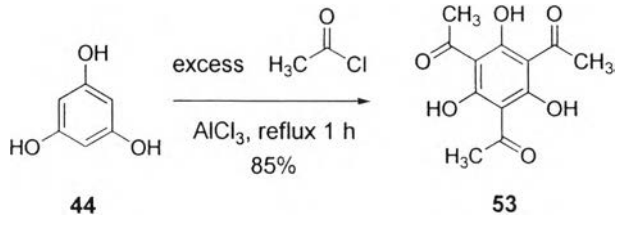
Scheme 1.10 Synthetic pathways to hexasubstituted benzene from 1,3,5-tribenzoyloxybenzene **(49)**

Tripodal ligands were synthesized using 1,3,5-triacyl-2,4,6-trihydroxy benzenes as new scaffolds. The route toward 1,3,5-triformyl-2,4,6-trihydroxybenzene **(51)** was discovered by MacLachlan's group as the one step synthesis from the reaction of phloroglucinol **(44)** with hexamethylenetetramine (HMTA) in trifluoroacetic acid (Duff reaction) (**Scheme 1.11**). Precursor **51** was converted to tris(*N*-salicylideneaniline) derivatives **52** by reacting with excess aromatic amines. ^{1}H-NMR spectra were very complicated, showing that all-keto-enamine (NH form) was present in a mixture of two geometric isomers **(52a** and **52b)**. The imines tautomers (OH form) were not observed in the solid state [79].



Scheme 1.11 Synthesis of tris(*N*-salicylideneaniline) derivatives **52**

The 1,3,5-triacetyl-2,4,6-trihydroxybenzene **(53)** has been synthesized by an easy synthetic route through triple *O*-alkylations of phloroglucinol **(44)** using excess acetyl chloride at reflux temperature [80] (**Scheme 1.12**). The *O*-acetylated intermediate presumably formed initially underwent Fries rearrangements into the hexasubstituted products upon treatment with $AlCl_3$ as the acid catalyst. Compound **53** was generated in this one step process in 85% yield.



Scheme 1.12 Synthesis of 1,3,5-triacetyl-2,4,6-trihydroxybenzene **(53)**

Compound **53** has inspired an interest in the design and study of synthetic tripodal ligands. It could be used as starting material for development of various types of tripodal ligands by attaching similar or different binding groups on the opposite faces of phenyl ring and displaying *ababab*-facial segregation around the central phenyl plane. The functionalizations have been done in three pathways: (i) alkylations on the phenolic hydroxy groups, (ii) substitutions at α-carbon atoms of the ketone groups and (iii) additions on the carbonyl of the ketone groups (**Figure 1.15**).

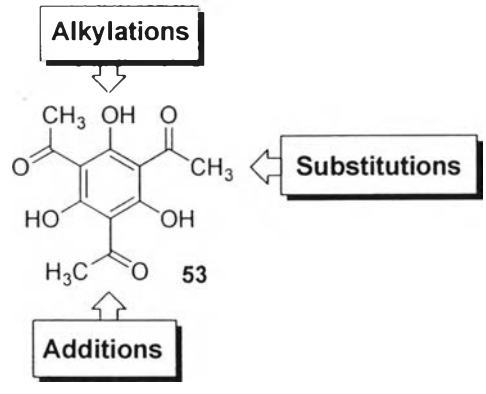


Figure 1.15 Three pathways for functionizations on compound **53**

1.4 Objective

The parent 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene **(23)** had been the most used starting material for its various generations of host structures. Several receptor molecules have been designed by placing the corresponding binding groups around the phenyl platform (see **Section 1.3.2.3**). The major limitation for a wider use of 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene scaffold **(23)** was the difficulty to attach the binding arms with different functionalities onto the highly steric central phenyl ring.

By the independent discovery of easy synthetic routes to 1,3,5-triacetyl-2,4,6-trihydroxybenzene **(53)**, this compound could be used as the more readily accessed starting material for the development of tripodal ligands displaying facial segregation in which, not only the 1, 3 and 5-positions on the central phenyl ring are functionalized, but also at the 2, 4 and 6-positions that point toward the opposite face of the ring with similar or different functionalities. This structural feature is a rigid

ligand but relatively flexible resulting in forming quite different cavity sizes and shapes, with possibly good level of enantio-discrimination. Therefore, scaffold **53** would potentially expand the design and synthesis of various types of tripodal ligands for molecular recognition and chiral discrimination. The functionalizations could be made with readily available chiral amines such as the β-amino alcohols, amino acids and their derivatives into chiral tris-amine derivatives. Eventually, the chiral recognition study with application toward enantiomeric resolution would be pursued following the successful synthesis of the targeted ligand.