A SYNOPSIS

of the thesis entitled

SYNTHESIS AND STUDY OF HETEROHELICENES

to be submitted
as a partial fulfilment for the award of the degree of

DOCTOR OF PHILOSOPHY

in
CHEMISTRY

by
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under the supervision of
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SYNOPSIS OF THE THESIS

to be submitted to

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for the award of the degree of **DOCTOR OF PHILOSOPHY in CHEMISTRY**

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Title of thesis	**SYNTHESIS AND STUDY OF HETEROHELICENES**
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The thesis will be presented in the form of following chapters –

Chapter 1

Introduction

Chapter 2A

Synthesis and resolution of unsymmetrical 2-aminoaza[6]helicene

Chapter 2B

Accessing optically pure dimethylaza[7]helicene *via* hydrogenative deprotection of chiral helical diamines

Chapter 3

Synthesis and study of symmetrical dicyano containing oxa[7]helicene

Chapter 4

Attempts to synthesize propeller-shaped triple helicenes

Chapter 1

Introduction

Helical structures are very common in nature and are observed in diverse natural formations ranging from macroscopic (sea shells, horns, seed pods, weather patterns, etc.) to microscopic level (DNA double helix).

Design and development of helical structures in various fields of chemistry has surfaced as an ever demanding area of science with a scope of building some new molecules and understanding its properties and applications.

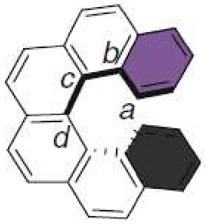
Helicenes are part of an intriguing class of **polycyclic aromatic compounds** formed from ***ortho*-fused** benzene (carbohelicene) or other aromatic rings (heterohelicene) that adopt a helical topology to avoid overlapping of the terminal rings resulting in helically chiral structures.

General properties of helicenes:

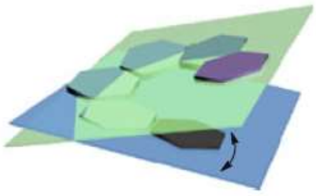
- **Helicity**: The steric hindrance of the terminal rings forces the helicene to wind in opposite directions. This renders them chiral even though they have no asymmetric carbons or other elements of chirality. On the basis of CIP rule, **right-handed helix** is designated as **plus** and denoted as ***P*** whereas **left-handed helix** is designated as **minus** and denoted as ***M***.
- Helicenes show a greater distortion from planarity and the two terms used to explain the extent of distortion are **torsional angle** and **interplanar angle**.
- They are good π-donors and can form **charge-transfer complexes** with many π-acceptors.
- They exhibit **very large specific rotation**.
- Their specific backbone which combines electron delocalization and non-planarity of the p-electron network makes them very stable towards acids, bases and high temperature.

(*M*)-[6]helicene

(*P*)-[6]helicene



Torsional angle



Interplanar angle

Interplanar angle or the **dihedral angle** is the angle between the two terminal rings.
Torsional angle is the dihedral angle of four adjacent inner carbon atoms a, b, c, and d.

Applications of helicenes:

The distinguishing feature of helical molecules is the combination of π-conjugated system and helicity. Hence the applications of helical molecules can be classified on the basis of these two properties. For racemic helicenes, π-conjugated system is responsible for some interesting applications in the field of material science, in liquid crystals, etc. In case of optically pure helicenes, applications are based on its helical chirality in the chiral recognition study, in asymmetric synthesis and also in the field of biological sciences.

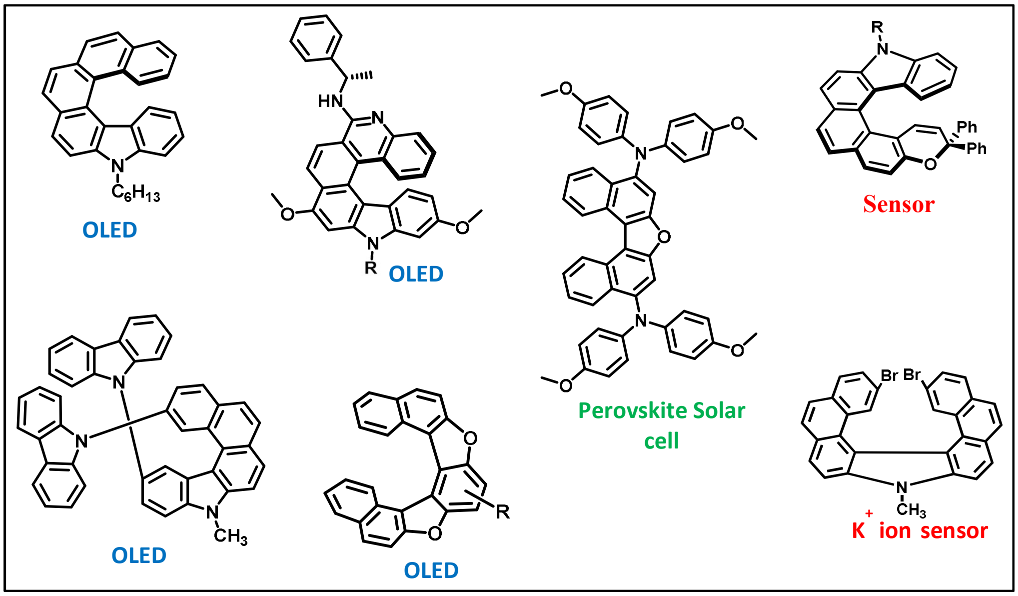


Figure 1: Reported helicenes with interesting applications

Aim and Objectives

Helicenes, with heteroaromatic units incorporated in the p-systems, have been studied due to their interesting self-assembly in the solid state, their ability to behave as organic semiconductors, and their use in optical resolution. The promising applications of such helicenes in various branches of chemistry inspired us to undertake the present research.

The main objectives of this work:

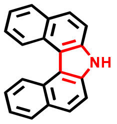
- To synthesize heterohelicene framework, thermally stable at room temperature.
- Characterization of the synthesized helicenes and to study their structural parameters.
- Synthesis of functionalized helical molecules as functionalization of helical compounds is critical in searching applications.
- Resolution or separation of helical isomers and to study their chiroptical properties.

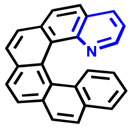
Chapter 2

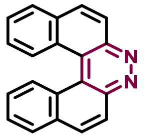
Synthesis and study of aza[n]helicene based chiral amines

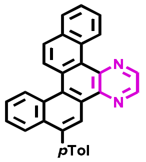
Azahelicene

Azahelicene belong to the subgroup of heterohelicenes. They are composed of *ortho* fused benzene, pyrrole, pyridine, pyridazine, pyrazine or other *N*-heterocyclic rings to form helical framework.









The properties and chemical behaviour of azahelicenes are practically unknown apart from their basicity and few other studies. They can form complexes with transition metal, can assist in the formation of large supramolecular assemblies complexes and they are basic enough to act as enantioselective catalyst. The promising applications of azahelicenes in various branches of chemistry might be investigated and thus there is scope for further research in this field.

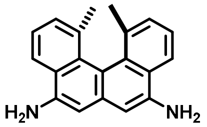
For the synthesis of aza[n]helicenes, carbazole was chosen as our structural motif. As it is:

- Cheap building block
- Three inbuilt rings
- Easy and regioselective functionalization
- Access to gram scale starting material

Chemistry of amino helicenes:

Yamaguchi and group in 2001 reported the synthesis of 5,8-diamino-1,12-dimethyl[4]helicene **1**. It was formed by Curtius rearrangement of its dicarboxylic acid analogue. This helicene was used in the chiral recognition study as it can undergo charge-transfer complexation with electron-deficient helicene.

Later, synthesis of some amino substituted [6]helicenes **2**, **3**, **4**, **5** were also reported by various groups.



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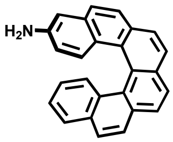

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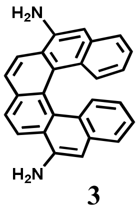

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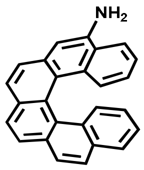

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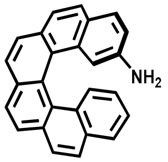

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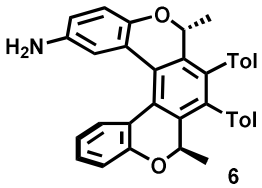
Starý and Stará in 2013, reported a synthesis of enantiopure 2H-pyran-modified amino[5]helicene **6**. It was converted to 1,3-disubstituted imidazolium salts and used as NHC ligand precursors in an enantioselctive [2+2+2] cyclotrimerization of aromatic triynes to obtain helicene derivatives in upto 86% ee.



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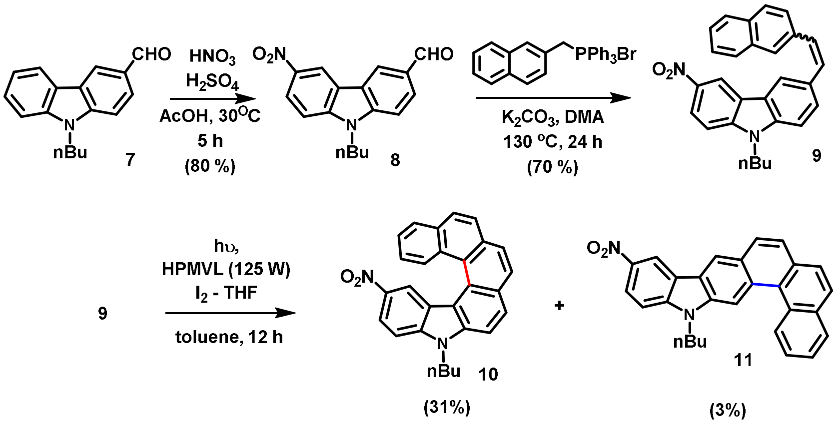
Chapter 2A

Synthesis and resolution of unsymmetrical 2-aminoaza[6]helicene

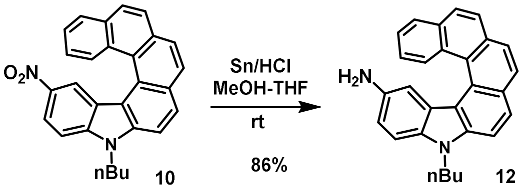
In this chapter, we have synthesized 2-amino-5-aza[6]helicene and efforts to obtain it in optically pure form are discussed.

Here, the introduction of amino group was achieved via reduction of nitro group, thus we first carried out the synthesis of 2-nitro-5-aza[6]helicene **10**. The synthesis was started from the nitration of readily available 3-formyl-*N*-butyl carbazole **7**, followed by its Wittig reaction with the triphenylphosphonium salt derived from 2-bromomethyl naphthalene. The stilbenoid **9** was then subjected to standard conditions of photochemical cyclodehydrogenation under the irradiation of 125 W HPMVL. This reaction resulted into the formation of the desired angularly cyclized isomer as the major product, while the linear one was also obtained in minor amount (85.5:14.5 as seen on ^{1}H NMR). [Scheme-1]



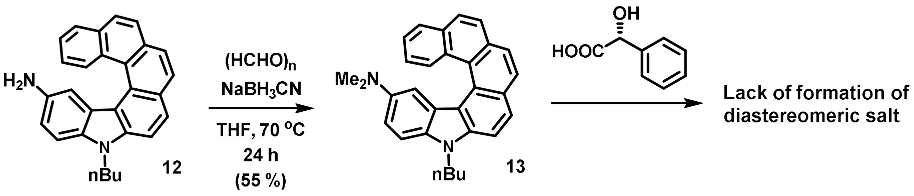
Scheme-1: Synthesis of 2-nitro-5-aza[6]helicene

The compound **10** was also characterized by single crystal X-ray analysis. The nitro helicene 10 was then reduced to the target molecule 12. Various conditions of reduction were carried out, where the best results were obtained using Sn-HCl method. [Scheme-2]



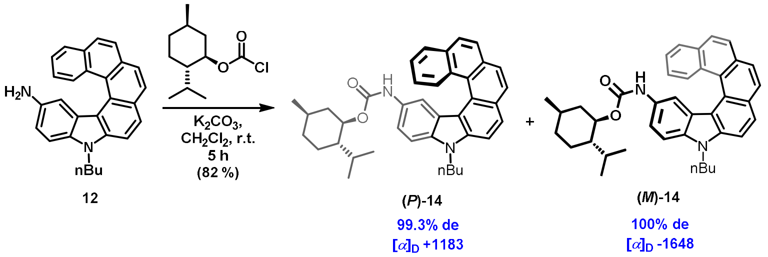
Scheme-2: Reduction of 2-nitro-5-aza[6]helicene

After synthesis, our next target was its resolution. In our first attempt we converted the primary amine **12** to its *N,N*-dimethylamino derivative **13** which was then subjected to co-crystallization with chial acids in different solvents. Here, either amorphous solid fell out or oily mass was obtained. Analysis of this material indicated lack of enrichment of one of the isomers. [Scheme-3]



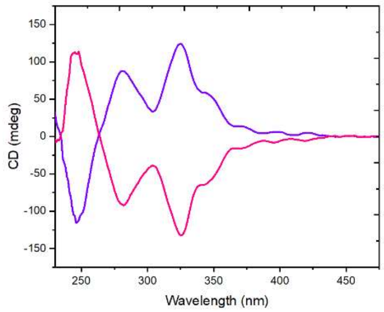
Scheme-3: Diastereomeric salt formation with chiral acid

Then we changed our approach, where the primary amino group was converted into the diastereomeric menthyl carbamates by attaching the chiral auxiliary (*R*)-(-)-menthylchloroformate. The diastereomers were separated by alumina column chromatography and were analysed by HPLC analysis and their SOR were measured. [Scheme-4]

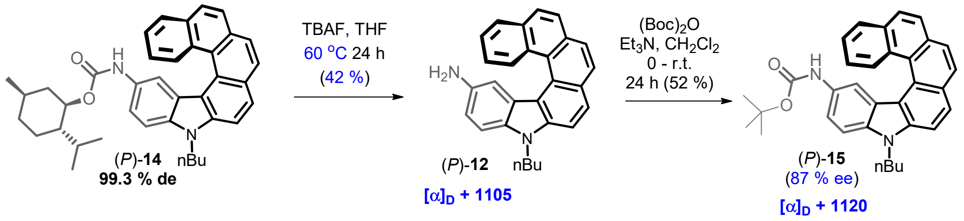


Scheme-4: Formation of diastereomers by reaction with chiral auxiliary

The separated diastereomers were further analyzed by circular dichroism spectroscopy where they displayed opposite Cotton effect. Since the menthyl group showed no significant response in this particular UV-visible range this mirror image relationship was purely due to the helical framework of the two isomers. CD Spectra of diastereomeric carbamates (*P*)-**14** and (*M*)-**14** was recorded in (1.0 x 10^{-5} M in $CHCl_3$).



For accessing optically pure amine, pure sample of (*P*)-**14** was subjected to standard conditions of deprotection using TBAF. The reaction was sluggish at ambient temperature but proceeded smoothly at elevated temperature. The amine sample being less stable was converted to its *N*-Boc derivative to study its optical purity. *N*-Boc derivative of the amine obtained after cleavage at lower temperature showed optical purity of **87%**, while the one obtained from the amine derived at higher temperature showed only 56% ee. [Scheme-5]



Scheme-5: Deprotection of diastereomer 14

As we could observe that the racemization might have occurred during the deprotection of carbamate, we tried other methods of deprotection at lower temperatures, but none of them resulted into the cleavage.

In this chapter we have synthesized amino derivatives of aza[6]helicene where the helical core was synthesized using carbazole as the structural motif and the basic strategy utilized was the photochemical cyclodehydrogenation. The 2-amino-5-aza[6]helicene was converted to diastereomeric carbamate by reaction with (*R*)-(-)-menthyl chloroformate, which could be physically separated by column chromatography. The optically pure amines were regenerated and their chiroptical properties were measured. The diastereomeric derivatives were analyzed by CD spectroscopy to observe opposite Cotton effect, while the 2-nitro-5-aza[6]helicene and 2-*N*,*N*,-dimethylamino-5-aza[6]helicene were characterized by single crystal X-ray diffraction analysis.

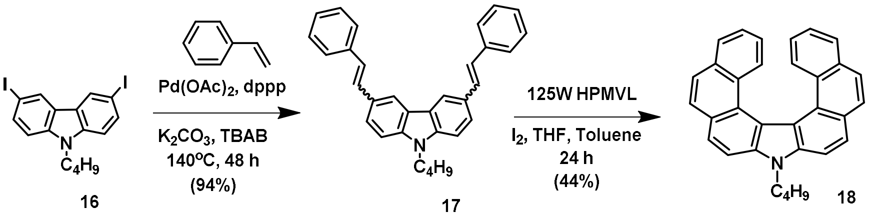
Chapter 2B

Accessing optically pure dimethylaza[7]helicene *via* hydrogenative deprotection of chiral helical diamines

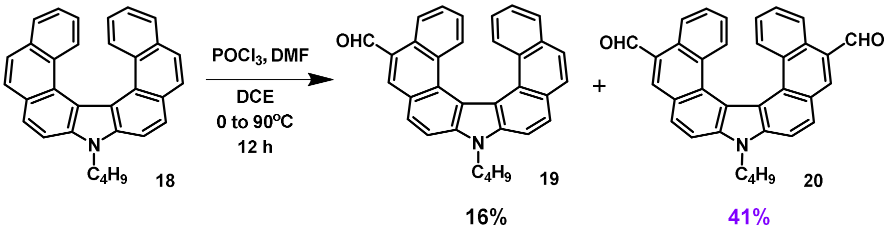
In this chapter, we have discussed a new method for obtaining optically pure helicene with methyl substituent by the selective hydrogenative deprotection of the diastereomeric helical diamines.
We started with the synthesis of 5,13-diformyl-9-butyl-az[7]helicene.

Approach-1: By formylation of 9-butyl-9*H*-aza[7]helicene

Aza[7]helicene was synthesized by the photocyclization of bis-stilbene derivative **17** obatined by Heck olefination of 3,6-diiodo-*N*-butylcarbazole 16 with styrene.



This aza[7]helicene was subjected to Vilsmeier-Haack formylation, where the TLC of the reaction mixture showed the presence of multiple spots. The desired diformyl derivative **20** was isolated in very less amount.



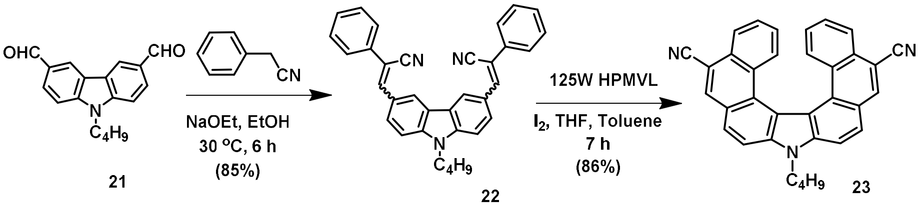
Drawbacks of this approach:

- Low yielding photocyclization reaction
- Long duration of photocyclization reaction
- Low yield of **20**

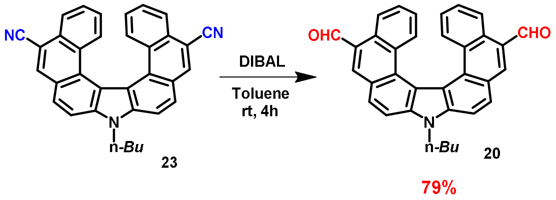
Thus we changed our approach towards the synthesis of helicene **20**.

Approach-2: By reduction of 5,13-dicyano-9-butyl-9*H*-aza[7]helicene

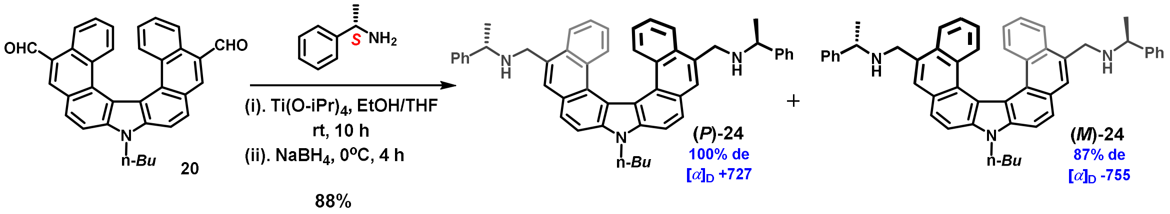
5,13-dicyano-9-butyl-9*H*-aza[7]helicene was synthesized by the photocyclization of bis- olefin **22** which was synthesized by the Knovaenegel condensation of 3,5-diformyl-N-butylcarbazole **21** with benzyl cyanide.



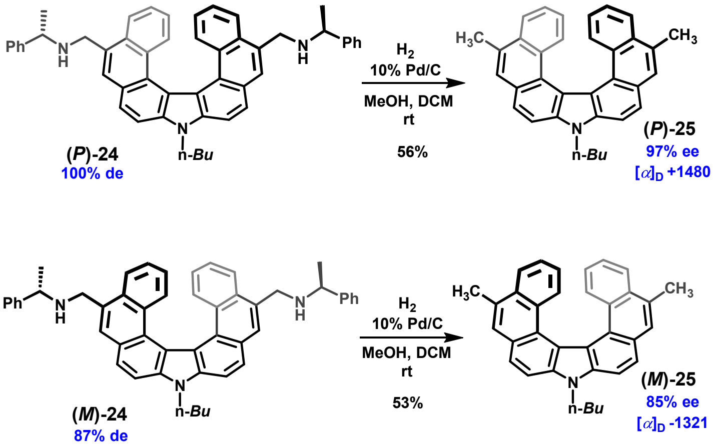
The dicyanohelicene 23 was subjected to reduction using DIBAL which is a selective reagent for the reduction of cyano goup to aldehyde group. Here, the desired diformyl helicene **20** was obtained in good yield. Compound **20** was analysed by single crystal X-ray analysis.

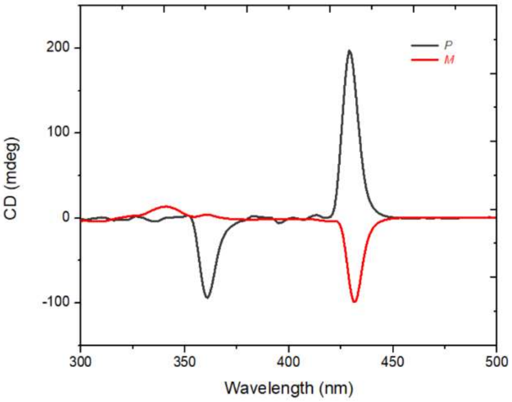


Reductive amination of helicene 20 with titanium isopropoxide and sodium borohydride was carried out to obtain the diastereomeric mixture of helical diamines which were separated by alumina column chromatography. The isomers were then analysed by HPLC analysis and their SOR were recorded.



Then, we attempted hydrogenation of the separated diastereomers. The palladium-on-carbon catalyzed hydrogenative deprotection of one the *N*-benzyl group occurred selectively, leading to the formation of optically pure 5,13-dimethylaza[7]helicene.





The isomers (*P*)-**25** and (*M*)-**25** were also analysed by the CD spectroscopy where they displayed opposite Cotton effect.

In this chapter the synthesis of diamino derivative of aza[7]helicene by reductive amination of 5,13-diformyl-aza[7]helicene using (*S*)-α-methylbenzylamine will be discussed in detail. The hydrogenative deprotection of these diastereomeric amines to give optically pure helicene with methyl substituents will be described further.

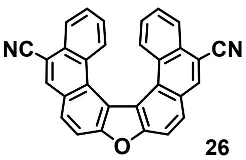
Generally, the cleavage of chiral auxiliary from diastereomers leaves the helicene with functional group intact. In this method we obtained optically pure helicene with methyl substituents, after the cleavage of chiral auxiliary. Thus, this becomes a new method of accessing optically pure helicene with methyl substituent. All the compounds were well characterized by various spectroscopic techniques. The 5,13-diformyl-aza[7]helicene was characterized by single crystal X-ray diffraction analysis and the enantiomerically pure dimethyl derivatives were analysed by CD spectroscopy.

Chapter 3

Synthesis and study of symmetrical dicyano containing oxa[7]helicene

In this chapter 6,12-dicyano-9-oxa[7]helicene was synthesized in order to study the phenomenon of spontaneous resolution.

Our group has already synthesized two CN containing heterohelicenes, **26** and **27**. We did not observe spontaneous resolution in **26**, while it was seen in compound **27**. We proposed the structure **28** in order to vary the electronic property of the hydrogen attached *ortho* to the CN group, which may influence the supramolecular interaction during process of molecular recognition and aspects of crystal engineering.



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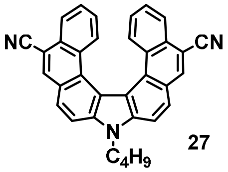

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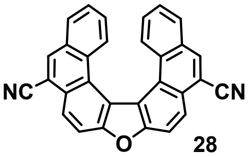

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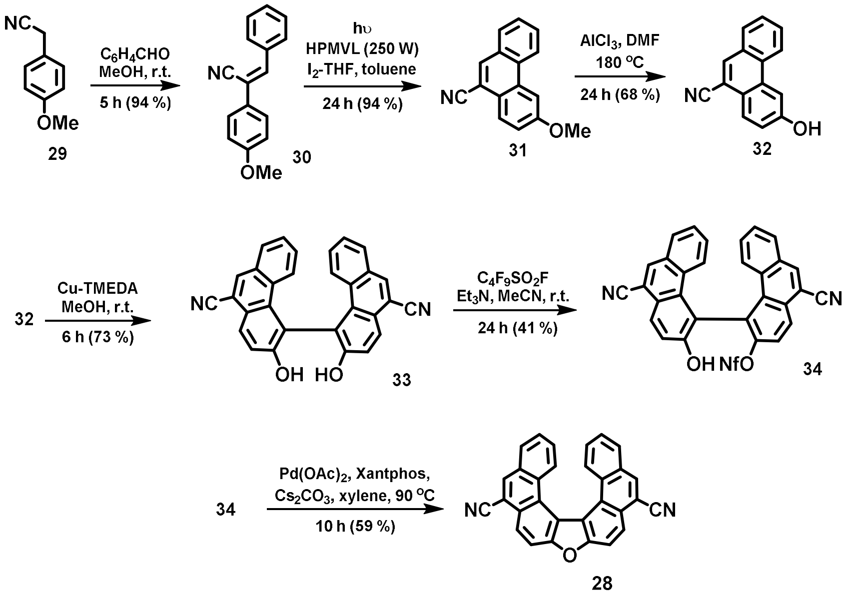
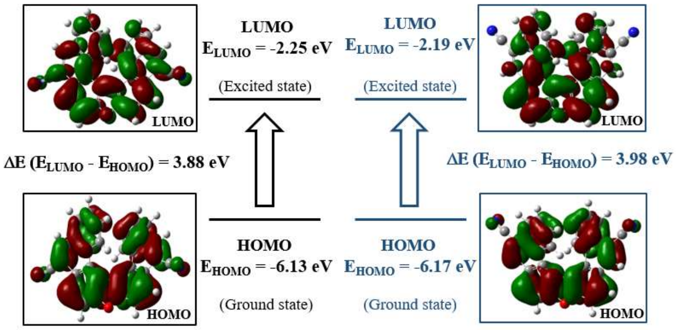
In order to extrapolate this study of spontaneous resolution, synthesis of this target molecule **28** will be carried out further in this chapter.

The synthesis of 6,12-dicyano-9-oxa[7]helicene **28** was started from the Knovaenegel condensation of 4-methoxybenzyl cyanide and benzaldehyde. The olefin obtained was further subjected to photocyclization under the irradiation of 250 W HPMVL to obtain methoxy phenanthrene derivative in good yield. Several known methods of cleavage of methoxy group were employed, where BBr_3 did not show any conversion, LiBr in DMF and HBr in glacial acetic acid offered lower yields. The best results were obtained using $AlCl_3$ in DMF. Homocoupling of 3-hydroxyphenanthrene-10-carbonitrile proceeded smoothly with the standard reagent of Cu-TMEDA to obtain one of the diol **17** regioselectively. It was followed by Pd catalysed cyclization after due activation of diol **17**. This activation was achieved by converting one of the hydroxyl group to nonafluorobutanesulfonate which was further reacted with $Pd(OAc)_2$, xantphos and Cs_2CO_3 system, where the desired target molecule was obtained in good yield.



The characterization of the synthesized molecule will be discussed in detail. The comparision of the synthesized helicene **28** with the one synthesized earlier will be discussed in different aspects. The ^{1}H NMR of the compound **28** showed shifting of signal of proton *ortho* to cyano group in the upfield region compared to **26** which was in agreement to our expectation by changing the position of cyano groups. Difference was also observed in the solubility of both the compounds. Various attempts made towards the crystallization will be discussed further. The crytals obtained in toluene were analysed by HPLC where we could not observe any enrichment of the isomers. Also, its single crystal X-ray analysis showed that the molecule is racemic.
The phophysical properties of both the compounds were studied. The emission maxima was almost identical for both, difference of 12 nm was observed in their absorption maxima values, which further leads to the difference in their Stokes shift.
For helicenes, the frontier molecular orbital (FMOs) distributions and energy gap (HOMO-LUMO gap) are closely associated to electronic and optical properties. Thus the energy of their HOMO and LUMO orbitals were calculated using B3LYP/631-G level of theory.



Compound	Band gap calculated from UV-Vis absorption edge	Theoritical Band gap
28 (Present work)	3.13 eV	3.88 eV
26	3.03 eV	3.98 eV

Thermal properties of the helicene **28** were studied by TGA and DSC analysis. The helicene **28** possessed a high thermal-decomposition temperature (***T*d**) of **328 °C**. It is to be noted that a high T_d value is an asset to OLED applications. DSC scans were performed, where the sample was heated at the rate of 10 °C/min from 40 to 280 °C under N_2 atmosphere. During this heating process, an endothermic peak was not observed which indicates that the melting point of compound **28** is greater than 280 °C. The thermal analysis data indicated high thermal stability of compound **28**.

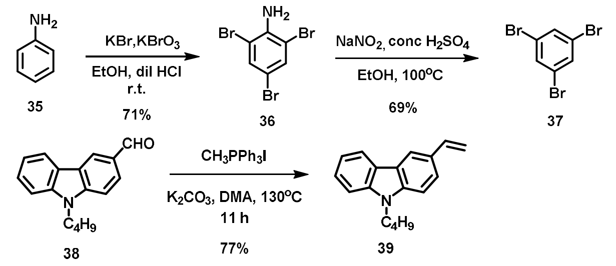
This chapter describes the synthesis of 6,12-dicyano-9-oxa[7]helicene Pd catalyzed intramolecular cyclization of the activated bis-phenanthrol derivative as well as its characterization by single crystal X-ray analysis and other usual spectral methods.
In comparision with its analogue 5,13-dicyano-9-oxa[7]helicene, we observed changes in the overall solubility of the compound, its photophysical properties and shifting of signals in the ^{1}H NMR. However, our efforts to effect separation of isomers by spontaneous resolution did not meet with success. Its geometry optimization was carried out using B3LYP/6-31G level of theory and its HOMO-LUMO energy gap was calculated. The synthesized helicene showed good thermal stability.

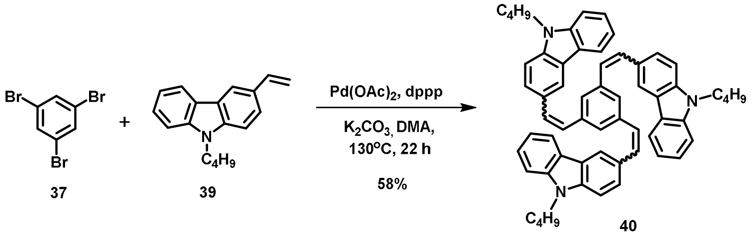
Chapter 4

Attempts to synthesize propeller-shaped triple helicenes

In this chapter, various attempts made to synthesize triple helicenes will be discussed.

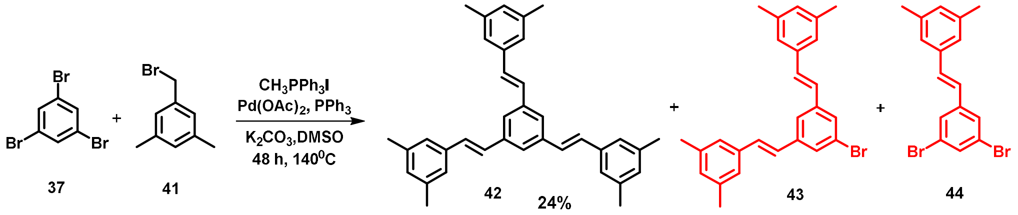
Our first attempt was to synthesize triple aza[6]helicene. In order to synthesize the target molecule, tris-olefin derivative **40** was synthesized by the heck reaction between 1,3,5-tribromobenzene and 3-vinyl-*N*-butylcarbazole.

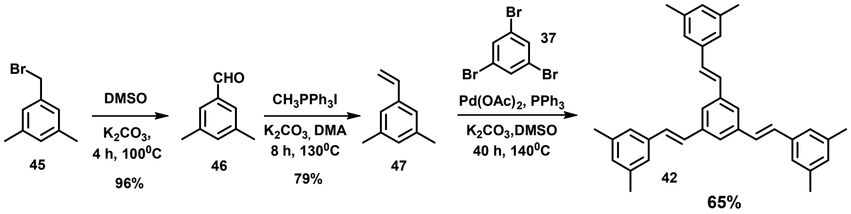




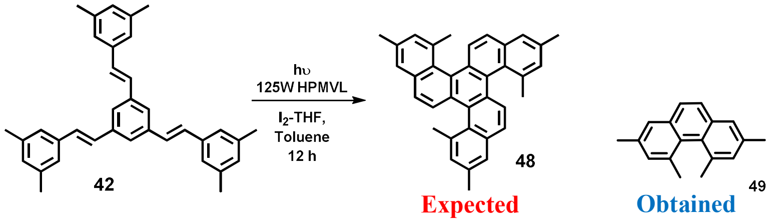
The formation of the olefin **40** was confirmed by its ^{1}H NMR. Only one set of signals in the aliphatic region indicated that the Heck reaction has occurred on all the three possible sites. The presence of a doublet with coupling constant of 16.4 Hz further confirmed its formation. This olefin was then subjected to standard conditions of photocyclization. Reaction was carried out under the presence of 125 W as well as 250 W HPMVL using different concentrations of the starting material, but in none of these cases the desired product was formed. A black sticky mass was obtained, the analysis of which showed the disappearance of the olefinic protons but the other distinct protons to be involved in the photocyclization were still present. We were unable to predict the exact structure of this molecule. We believe that these difficulties in the photocyclization reaction might have occurred because of the presence of three bulky carbazole groups on the benzene ring.

Thus, triple 1,3-dimethyl[4]helicene was chosen as our next target molecule, which is comparatively a smaller molecule with lesser steric strain. Smaller helicenes like [4]helicene without any substitution, does not intrinsically adapt the helical topology due to lack of overlap of the terminal rings. They have flat structures. Introducing a methyl substituent in the fjord region sufficiently raises the barrier of racemization by a considerable extent. In order to reach to our target molecule, we first synthesized the tris-olefin **42**. Initially, a one pot oxidation-Wittig-Heck reaction was carried out, where the desired olefin was obtained in lower yield along with the other side products. Then, the stepwise reactions were performed where the 3,5-dimethylstyrene was isolated, purified and then subjected to Heck olefination reaction to obtain the tris-olefin in good yield.



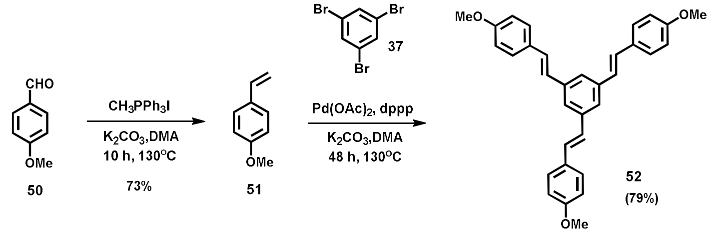


The formation of this olefin **42** was confirmed by its ^{1}H NMR which was same as that in the literature. This olefin was subjected to photocyclization under the irradiation of 125 W HPMVL . The reaction resulted into the formation of 2,4,5,7-tetramethylphenanthrene **49** instead of our expected product.

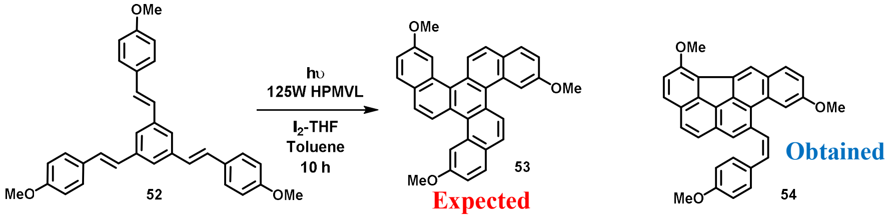


The formation of **49** was confirmed by single crystal X-ray analysis. The possible mechanism for the formation of this unusual product will be described in this chapter.

Later, another such target molecule was designed where a [4]helicene **53** was one of the desired intermediate. Here, triple olefin **52** was first synthesized. 4-methoxybenzaldehyde was subjected to Wittig reaction to form 4-methoxystyrene which was further reacted with 1,3,5-tribromobenzene in Heck olefination conditions to obtain the desired olefin 52 in good yield.



The formation of this olefin **52** was confirmed by the ^{1}H NMR. This olefin on cyclization resulted in some unusually cyclized product instead of the desired expected product **53**.



In this chapter, the attempts for the synthesis of some propeller-shaped triple helicenes will be discussed. The photocyclization of tris-olefin **40** did not result into the formation of the desired triple aza[6]helicene. The steric strain caused by the bulky carbazole group might have hindered the usual cyclization process. So, the triple 1,3-dimethyl[4]helicene, a comparatively smaller moiety with lesser steric strain was chosen as our next target molecule. In the process of synthesizing this target molecule, we obtained some undesired compound which was confirmed by single crystal X-ray analysis to be 2,4,5,7-tetramethylphenanthrene. We believe that instead of normal electrocyclic ring closing reaction, the olefin **42** might have undergone an intermolecular [2+2] cycloaddition followed by cyclobutane ring fission which might have led to the formation of this unusual product during photocyclization step. In order to check whether intermolecular reaction occurs in such type of systems, we designed another such molecule with methoxy substituent **53**, where we failed to get any such observation. However, we could not obtain our desired compound. Some unusually cyclized product **54** was obtained as evident from ^{1}H NMR as well as mass spectra.

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