Synopsis of the Ph.D thesis entitled

“Synthesis and study of new pyrrolohelicenes and their analogues”

To be submitted to

The Maharaja Sayajirao University of Baroda

For the degree of

DOCTOR OF PHILOSOPHY

in

Chemistry

By

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December 2020

Topic of the Ph.D thesis

The topic of the thesis is broadly related to the study of helical molecules. Helicenes are an intriguing class of polycyclic aromatic compounds formed from ortho annelation of benzene or other aromatic rings which adopts a helical topology due to steric overcrowding of the terminal benzene rings. Helicenes are classified into two groups:

1) Carbohelicenes (composed solely of benzene rings in the back bone)
2) Heterohelicene (containing at least one hetero atom in the back bone or screw shaped skeleton).

In recent years, the preparation of heterohelicenes has been studied extensively in order to exploit the unique properties of these chiral molecules. However, azahelicenes, which are a type of heterohelicenes with nitrogen atoms, have not been elaborated sufficiently, and only a few reports have described the synthesis of nitrogen-containing helicenes, despite their possible applications in various branches of chemistry. So in this research work we have undertook the synthesis of several azahelicenes and studied their structural and photophysical properties. The research done in this field will help us in understanding the chemistry of nitrogen containing helical molecules and in exploring the possible applications of these compounds in various fields of chemistry.

Title of the Ph.D thesis

The previous title proposed was "**Studies of helically chiral compounds**". However during the course of the research work, we have focussed on the synthesis of pyrrole based helical molecules and studied their properties. So we had proposed a change in the title of the thesis to: "**Synthesis and study of new pyrrolohelicenes and their analogues"** which was then approved by the research committee of the Department of Chemistry and Faculty of Science.

Objectives of the study

1. The main objective of our work is to synthesize new pyrrolohelicenes based on carbazole motif.

2. Characterization of the synthesized azahelicenes and to study their stuctural parameters.

3. To install various functional groups in the helix and to study their chemical transformations.

4. To study the photophysical properties of the synthesized pyrrolohelicenes.

5. Resolution of the helicenes into their isomers and to study their chiroptical properties.

In all, the Ph.D. thesis consists of three chapters which are as follows:

Chapter 1: Introduction

Chapter 2: Synthesis and study of pentahelicenes: From stereodynamic to configurationally stable molecules

Chapter 3: Synthesis and study of heptahelicenes

Chapter 1: Introduction

Helical architecture is not an unfamiliar concept as it permeates many diverse natural formations with ubiquitous examples ranging from the sunflower galaxy, weather patterns, tendrils etc. at the macroscopic level to DNA double helix at the microscopic level. 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 or other aromatic rings that adopt a helical topology to avoid overlapping of the terminal rings resulting in helically chiral structures.

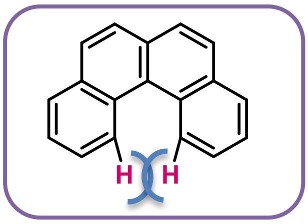


Fig.1: Steric clash caused by terminal rings

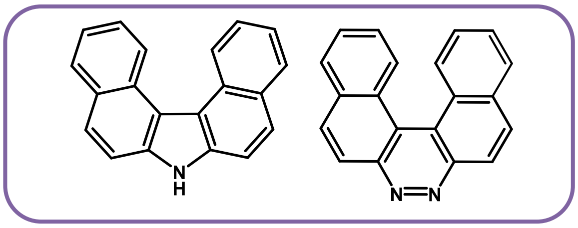


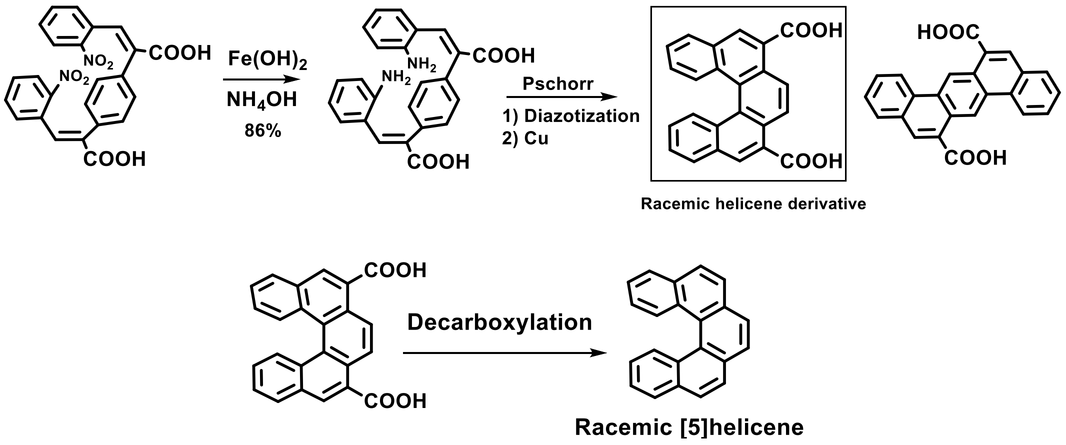
Fig.2: The First Helicenes

The most defining property of a helicene is its helicity which arises due to the steric hindrance of the terminal rings which coerces the molecule to wind in opposite directions. This renders them chiral even though they have no asymmetric carbons or other chiral centre. Right handed helix is designated as plus and denoted as *P* whereas Left handed helix is designated as minus and denoted as *M.* Based on composition of the helical skeleton, they can be broadly divided into two types: Carbohelicenes and Heterohelicenes. Helicenes composed solely of carbon atoms are called carbohelicenes and heterohelicenes have at least one hetero atom like N,S,O,P,B,Si etc.

Helicene structures, incorporating *N* atom are called as azahelicenes. Regarding the properties, nitrogen and its lone pair strongly modify the characteristics of an aromatic ring. The presence of nitrogen changes the inherent properties of the whole ring such as the abundance of electrons and influences its reactivity toward electrophilic reagents. Azahelicenes with fused carbazole cycles, called as Pyrrolohelicenes are known to possess remarkable physical properties like bright emission and hole transporting ability and hence we decided to synthesize some new azahelicenes based on pyrrole motif and explore their properties.

Chapter 2: Synthesis and study of pentahelicenes: From stereodynamic to configurationally stable molecules

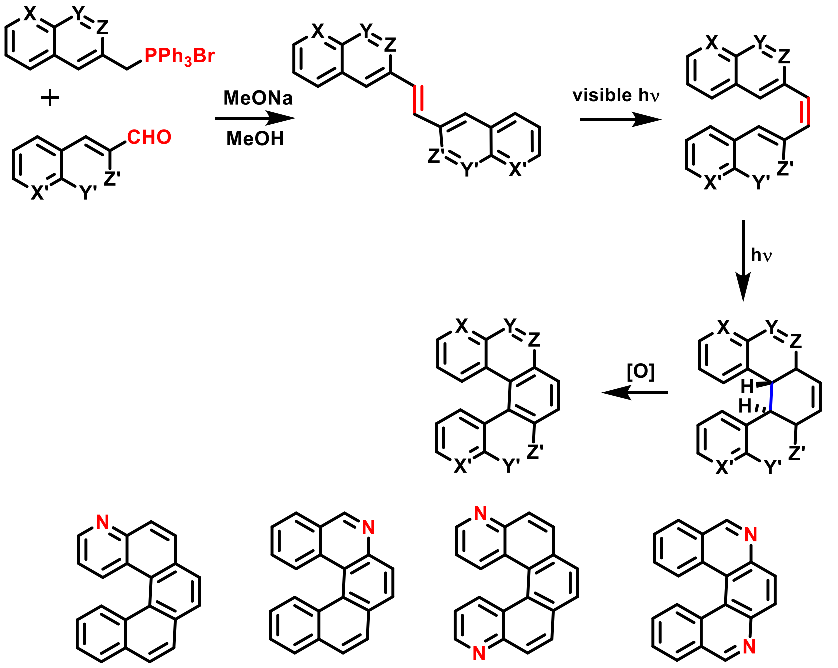
The first two helicenes synthesized were in fact five-membered azahelicenes in 1903 by Meisenheimer and Witte when they studied the reduction of 2-nitronaphthalene (**Figure 2).** The next landmark synthesis of carbo[5]helicene was reported in 1918 by Klingler and group using Pschorr reaction followed by double decarboxylation as shown in **Scheme 1**. However the yield was low due to a competitive formation of linear isomer which made the purification process difficult.



Scheme 1: *First synthesis of carbo[5]helicene in 1918 by Klinger*

The first example of helicenes synthesized by photochemical strategy was reported around the year 1966–1967**.** Mallory *et al*, Carruthers , Scholz *et al*, and Martin *et al* independently reported the first examples of helicenes synthesized by photochemical strategy.

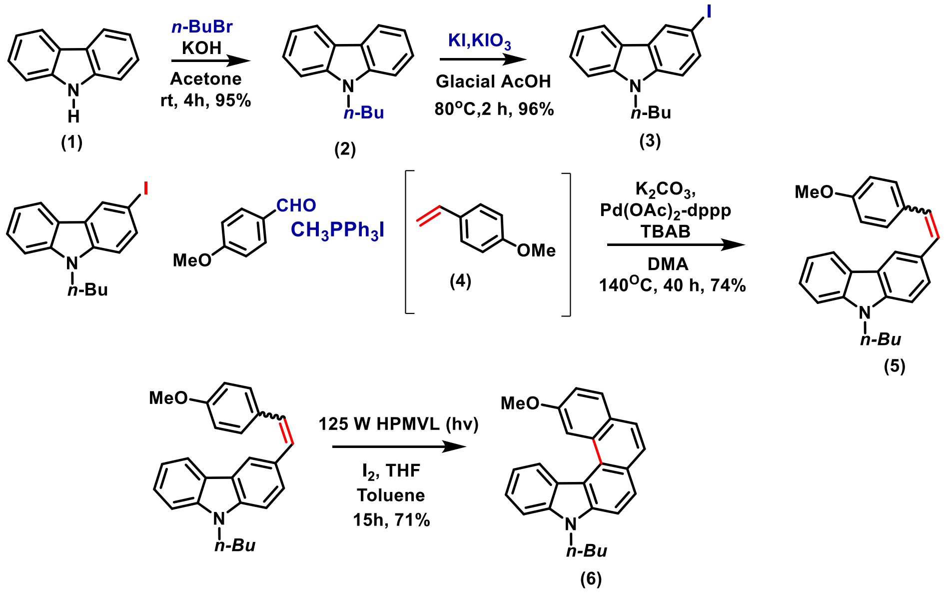
For building azahelicenes by photocyclization, the main approach was based on the stilbene precursors with two aryl groups bearing heteroaromatic ring with N-atom. In 2005, Caronna *et al*. synthesized monoaza and diaza[5]helicenes using the classical oxidative photocyclization of stilbene derivatives. They synthesized the stilbene precursors using Wittig reaction between the corresponding aldehydes and phosphonium salts followed by photocyclization using visible light. The photocyclization proceeds with *trans* to *cis* isomerization of the precursor followed by formation of a dihydroproduct with a trans configuration which was then oxidized to the fully aromatic system in open air as shown in **Scheme 2.**



Scheme 2: *Synthesis of mono and bisaza[5]helicene investigated by oxidative photocyclization*

Present Work:

In the first part, C-2 substituted carbazole based five membered helicene molecules were synthesized by involving Wittig and Heck reaction followed by photocyclization sequence as shown in **scheme 3**. The helical molecules were analysed by usual spectral techniques such as NMR, mass etc. The shape and torsion angle created by the helical form was ascertained by single crystal X-ray diffraction study of this molecule.



Scheme 3: *Synthesis of methoxy-substituted aza[5]helicene*

In order to check the stereodynamicity of this pentahelicene, we carried out HPLC analysis in 97.5:2.5 Hexane-Isopropanol solvent system with IC Chiralpak column. The resulting chromatogram showed a single peak indicating the instability of the isomers at room temperature as shown in figure 4. Hence, our next target was to synthesize configurationally stable five-membered azahelicene.

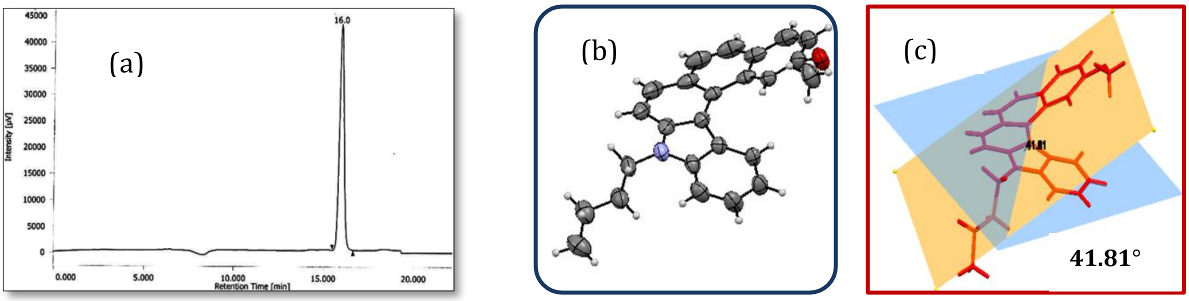
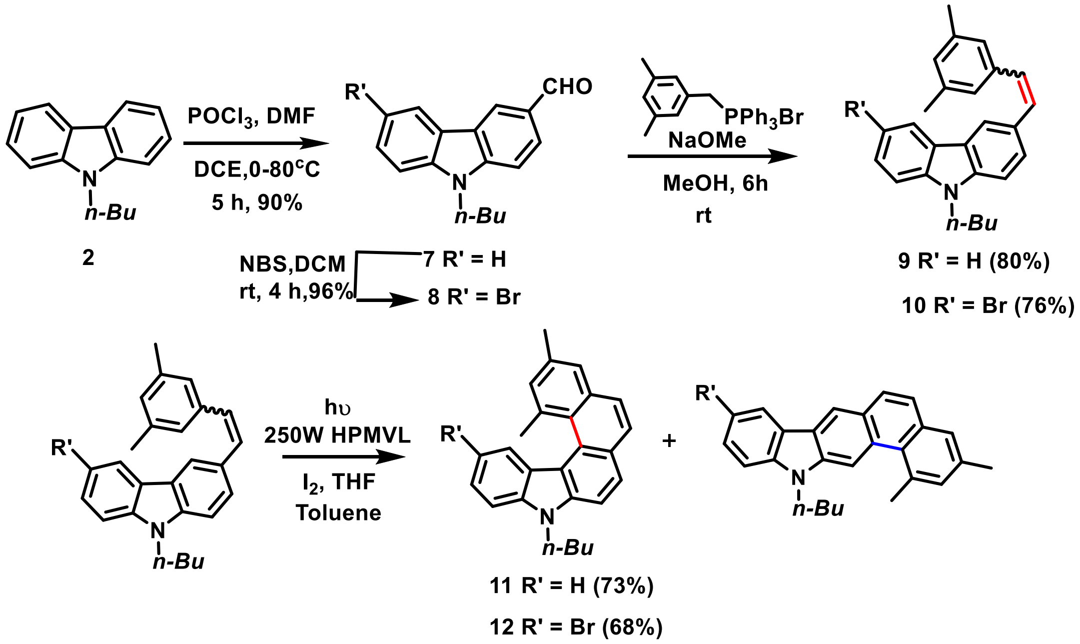


Fig.3: (a) HPLC Chromatogram showing single peak (b) ORTEP plot (c) Dihedral angle of compound 6

To synthesize a configurationally stable pentahelicene, it is necessary to install the substituent at C-1 position to increase the steric bulk. Even a mono-methyl substituent installed in the fjord region sufficiently raises the barrier of racemization by a considerable extent. So we designed a simple approach to introduce a methyl substituent by Wittig reaction and thereby subject it to photocyclodehydrogenation conditions as shown in **scheme 4**.



Scheme 4: *Synthesis of C-1-substituted aza[5]helicene 11 and 12*

However the ^{1}H NMR analysis of the product of photoreaction of the dimethyl stilbene derivative, showed a mixture of angular and linear isomers as shown in **scheme 4**. We tried to repeat the photoreaction in very low concentration but our efforts were in vain. So we redesigned the scheme by introducing a bromo substituent on the carbazole ring and followed the same subsequent steps for the synthesis. This time the linear isomer was separated by crystallization and thus we were successful in synthesizing a C-1 substituted pentahelicene which on HPLC analysis rendered two stable, resolvable peaks indicating stable conformers at room temperature.

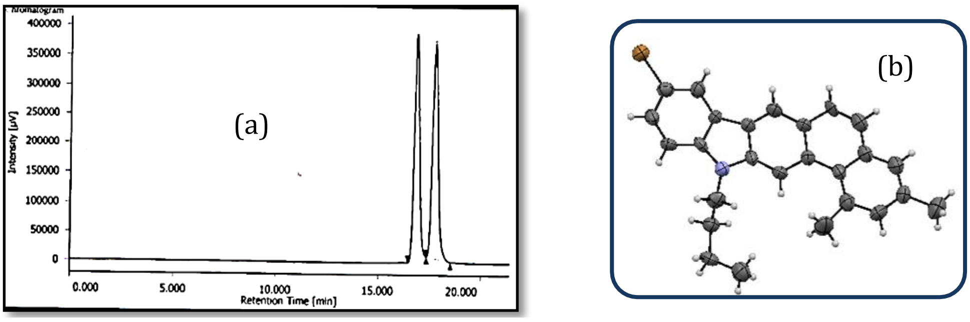
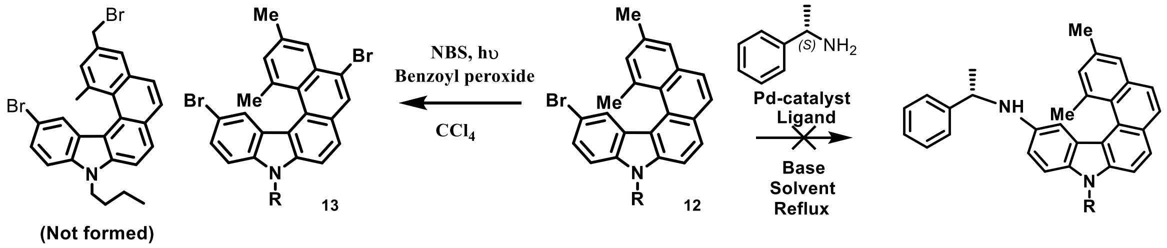


Fig.4: (a) HPLC Chromatogram of compound 12 showing two peaks (b) ORTEP plot of the linear regiomer of compound 12

After successfully separating the angular and linear regiomers, we tried to carry out side chain bromination on the mono-bromo dimethyl derivative. However it was confirmed from ^{1}H-NMR analysis that the product obtained was the result of electrophilic aromatic bromination. We tried to carry out Buchwald-Hartwig amination reaction but could not detect the formation of product in any of the conditions.



Scheme 5: ***Functionalization on aza[5]helicene 12***

We were able to get fine crystals of compound 13 and thus we were able to compare the structural parameters for this C-1 substituted pentahelicene. As can be seen from the XRD data, instalment of substituent on C-1 position sufficiently increases the torsional angle and dihedral angle.

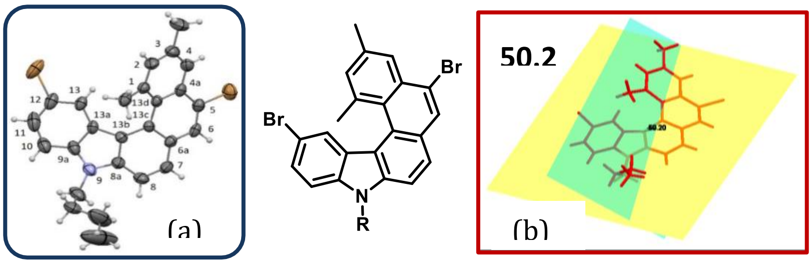
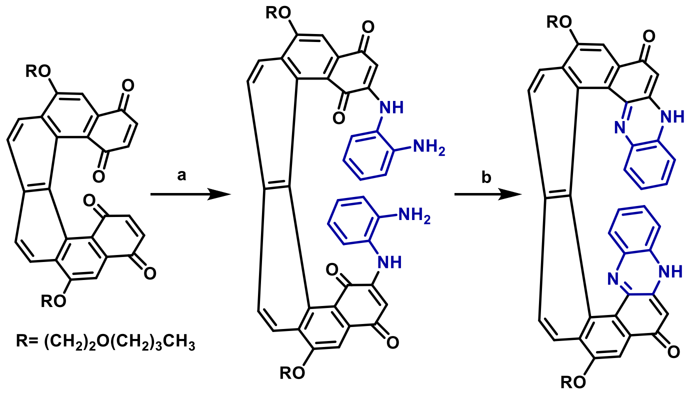


Fig.5: (a) ORTEP Plot of compound 13 (b) Dihedral angle of compound 13

Chapter 3 : Synthesis and study of heptahelicenes

Helicenes belonging to the higher order(n>6), comprises of a very stable helical scaffold with greater racemization barriers and most significantly exhibit modified properties due to the extension of the helical framework. Hence, various strategies have been developed and explored to extend the helical core from pre-existing skeletons by, for instance, addition of ortho-fused rings at terminal ends as shown in **scheme 6**.



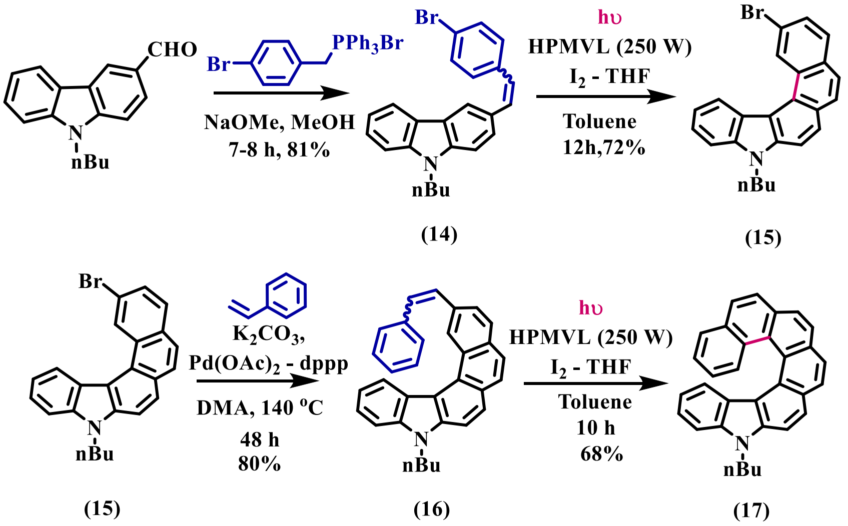
(a) 1,2-phenylenediamine, $Cu(OAc)_2$, 1:1 MeOH-CH_2Cl_2, 2.5h (b) AcOH, reflux, 2.5h

Scheme 6: *Helicene growth by terminal ends elongation from [6] to [8]helicene*

In the first part of this chapter we have designed a simple protocol for the functional elongation of pentahelicene to synthesize a seven-membered helical molecule.

Present Work:

Heptahelicene derivative was synthesized from pentahelicene as shown in **scheme 7** by following a Heck reaction and photocyclization of the bromo-functionalized pentahelicene. The helical molecule was analysed by usual spectral techniques such as NMR, mass etc.



Scheme 7: *Synthesis of aza[7]helicene from aza[5]helicene*

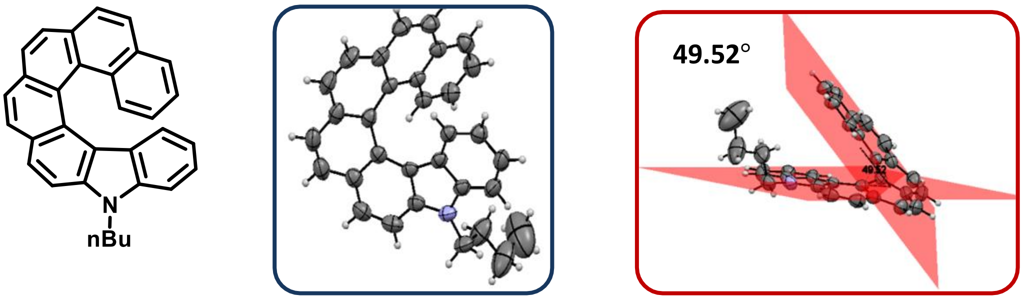
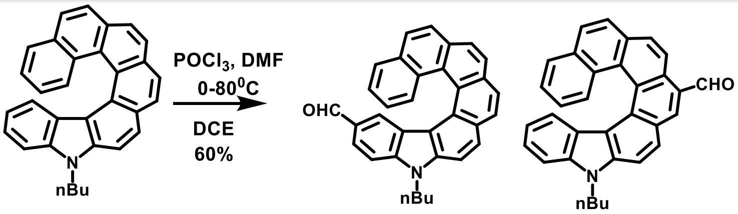


Fig.6: (a) ORTEP plot of compound 17 (b) Dihedral angle of compound 17

This compound was further functionalized by Vilsmaeyer-Haack formylation giving rise to two products as shown in **scheme 8**. Both the formylated derivatives were well characterized and we were able to obtain good quality single crystals for both so the structural parameters were studied by X-ray diffraction analysis.



17

18

19

Scheme 8: *Scheme for the synthesis of formylated derivatives of aza[7]helicene*

Sr. No.	$POCl_3$: DMF	REACTION TIME	YIELD (%)18	YIELD (%) 19
1.	2:5	12h	TRACE	74
2.	2:5	20h	14	58
3.	10:10	12h	TRACE	20

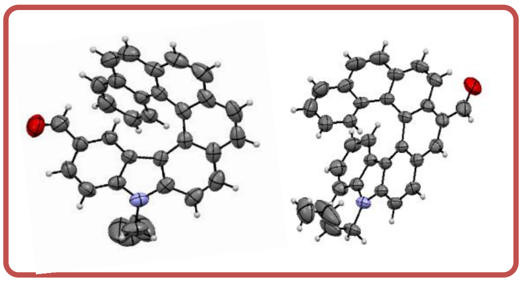
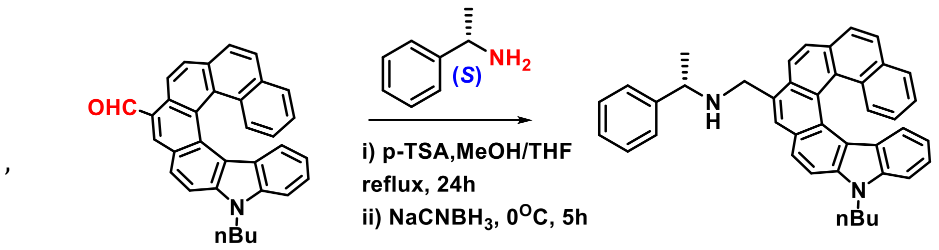


Table 1: Optimization conditions for formylated derivatives Fig.7: ORTEP plots of compound 18 and 19

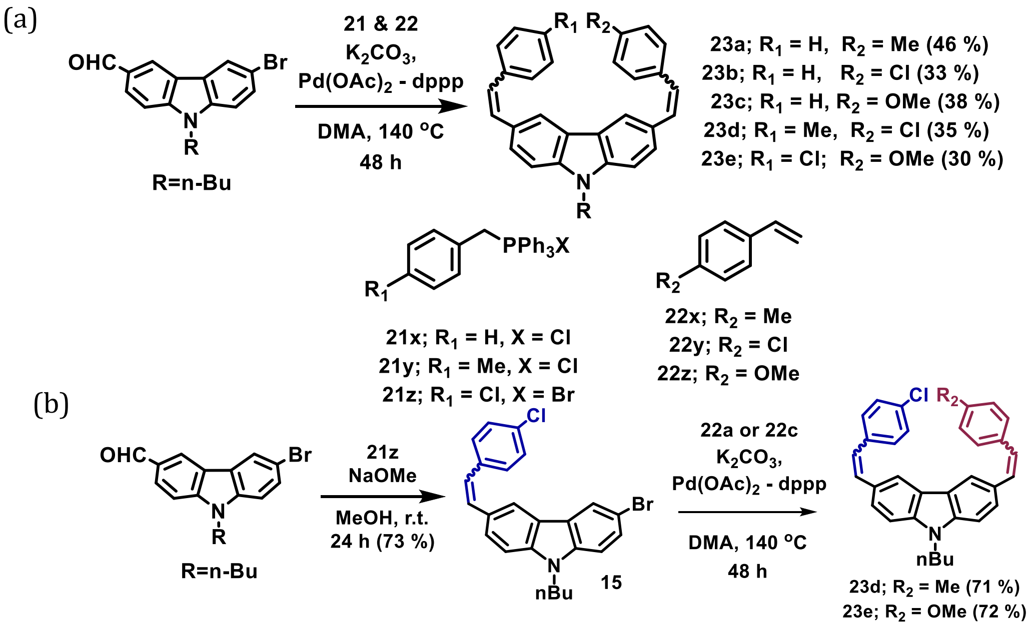
The conditions for the formation of the formylated derivatives was studied and it was observed that in all the conditions the 9-substituted product was obtained as the major product. The 9-formyl helicene was also transformed into the corresponding amine ligand using (S)-phenylethylamine. Resolution of this diastereomeric ligand is under progress.



Scheme 9: *Synthesis of amine ligand of aza[7]helicene*

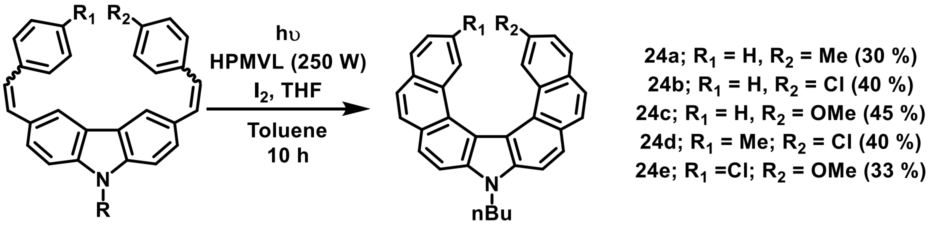
So in this part on the study of heptahelicenes, we were able to develop an easy protocol for the synthesis of heptahelicene from pentahelicene scaffold. We have also functionalized the molecule into its formylated derivated and synthesized amine ligand by a reductive amination reaction using (S)-phenylethylamine. All the compounds were well characterized by various spectral techniques.

In the second part on the study of heptahelicenes, various functionalized unsymmetrical heptahelicene derivatives were synthesized by involving Wittig and Heck reaction followed by photocyclization sequence. The helical molecules were analysed by usual spectral techniques such as NMR, mass etc. The shape and torsion angle created by the helical form was ascertained by single crystal X-ray diffraction study of these molecules.



Scheme 10: *Synthesis of bis-olefin derivatives by (a) one-pot Wittig Heck reaction (b) step-wise method*

Various functionalized bis-olefin derivatives were synthesized by a one-pot Wittig-Heck methodology and also by stepwise reaction by various combination of Wittig salt and substituted styrenes. All the corresponding stilbene derivatives were then subjected to oxidative photocyclization condition to yield the corresponding mono and di-functionalized heptahelicene derivatives.



Scheme 11: ***Photocyclization of the bis-olefin derivatives***

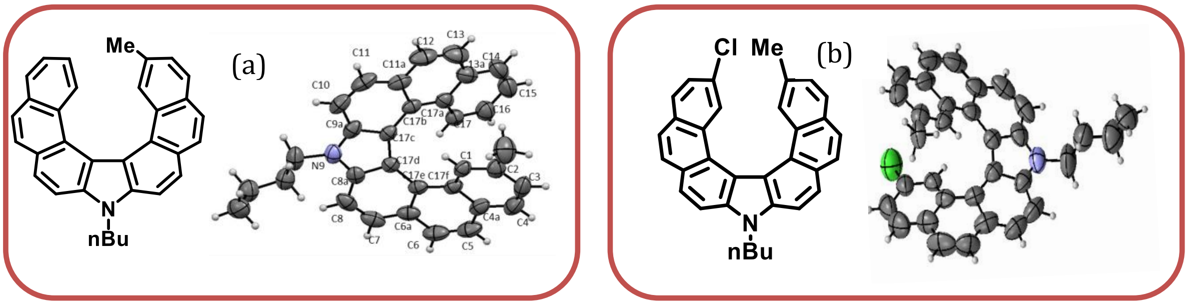
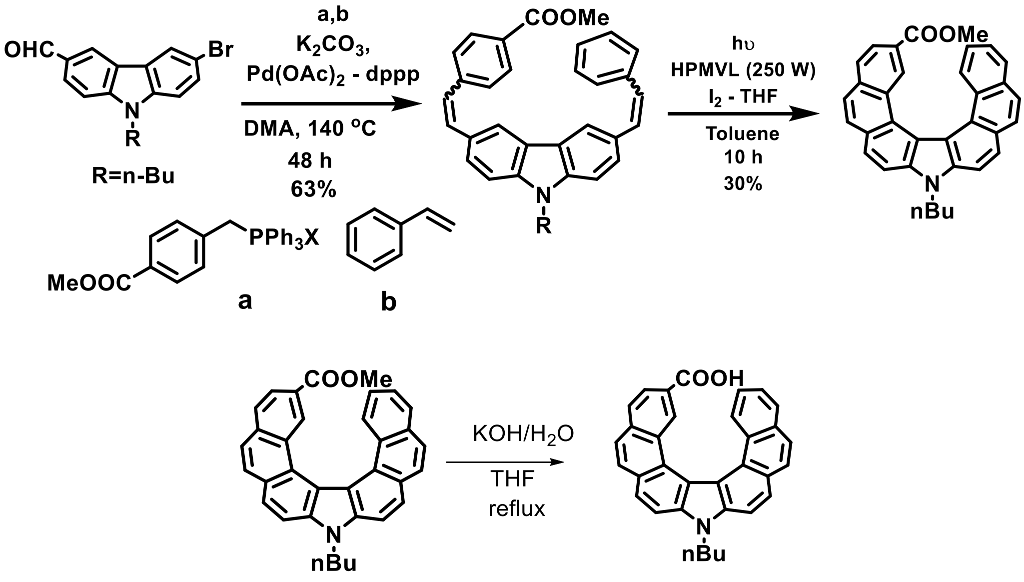


Fig. 8: ORTEP plot of (a) 24a (b) 24d

In order to carry out resolution studies of the heptahelicene, we have also synthesized a helicene carboxylic acid . So for that helicene containing ester group was synthesized which was then hydrolysed to get the product.



Scheme 12: ***Synthesis of aza[7]helicene carboxylic acid***

The diasteromeric resolution of this racemic acid using various chiral base is under progress.

Publication from this work:

"Synthesis of unsymmetrical aza[7]helicenes by one-pot Wittig-Heck and photodehydrogenation sequence"

Blessy Rajan, A V Bedekar, *Synlett* **2017**, *28*, 2262

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