Synopsis of thesis entitled

"Synthesis and Study of Conformationally Twisted Molecules and Chiral Roof Shape Amines"

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in

Chemistry

By

Ms. Riddhi Gupta

Under the guidance of

Prof. Ashutosh V. Bedekar

Department of Chemistry
Faculty of Science
The Maharaja Sayajirao University of Baroda
Vadodara 390 002

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Chapter 1: Introduction

Many molecules, required for life are chiral and exist in two conformations which are non-superimposable mirror images of each other, *i.e.* they are related like our left and right hands. Hence this property is called chirality, from the Greek word '*chiros*' meaning handedness.[1] Chiral molecules are optically active due to the presence of one or more chiral elements namely 1) chiral center 2) chiral axis 3) planar chirality 4) helical chirality 5) spiro center.

Preparing racemates is usually more economical than the synthesis of enantiomers as their separation cannot be efficiently achieved with high yield and purity. The fact that enantiomer pairs possess identical physical properties, but their biological activities and effects can be significantly different has necessitated the growth of symmetric synthesis. More recently, the isolation and purification of single enantiomer products has become an important component of pharmaceutical and fine chemical manufacture industries.

During this Ph.D work, I have focused mainly on the synthesis and study of conformationally twisted small hydrocarbons, resolution of atropisomeric (Axial) molecules leading towards optically pure helicenes and some chiral roof shape secondary amines.

Overall Objective:

Synthesis of distorted nuclei has been challenging task in chemistry. Such skeletal distortions can be introduced easily with higher members of fused ring systems such as helicenes which have six or more aromatic rings, allowing them to exist as two stable enantiomers at room temperature (Chapter-3).[2]

However, as the number of benzene rings decrease, thermal stability of the enantiomers also decreases, causing their rapid racemization at room temperature. Hence, the introduction of distortion in smaller molecules like naphthalenes,[3] phenanthrenes[4] or benzo[c]phenanthrenes[5] is much more difficult. Introduction of bulky substituents at appropriate positions for such smaller molecules leads to an increase in the steric strain within the molecule which is relieved by causing distortion in the molecular skeleton. Such distortions cause the enantiomers to be stable at ambient temperatures and facilitate their separation (Chapter-2).

Synthesis of some molecules with shape resembling to that of roof of a house (more commonly known as roof shape molecules) and study their application as CSA (Chapter-4).[6]

Chapter 2: Introduction to small Twisted Molecules

There are atleast three series of aligned benzenoid compounds: (1) [n]Acenes: formed by linear fusion of benzene rings (2) [n]Phenacenes: formed by linear-angular fused benzene rings and (3) [n]Helicenes: formed by angular fusion of aromatic rings which maybe further subcategorized into (a) carbohelicenes: where the helicene skeleton is made up of all carbon atoms and (b) heterohelicenes: where the helicene skeleton consists of atleast one hetero atom.

Small chiral molecules are important as they prove to be synthetically challenging targets for organic chemists. In medicinal chemistry, the prerequisite for chiral compounds for exploration as drug candidates is the lower molecular weight. Our aim is (i) to synthesize small ring systems with bulky substituents at hindered positions and proving their existence in two enantiomeric forms using various techniques like NMR, HPLC etc. (ii) Growing crystals suitable for Single crystal X-ray analysis to study the degree of twist in the synthesized molecules (iii) Attempting separation of the enantiomers in their optically pure form by introducing functional groups that can act as a handle for efficient separation using various methods such as diastereomer formation, co-crystallization etc.

Distorted Naphthalenes: One of the features that distinguishes naphthalene from benzene is the *peri* relationship between the neighboring positions 1 and 8. The *peri* relationship differs significantly from the ortho relationship between the positions 1 and 2 as the C1-H1 and C8-H8 bonds are parallel and in close proximity as compared to the C1-H1 and C2-H2 bonds in naphthalene. This affects the non-bonding distances (X···X) in 1,8-di-X-naphthalene (**3**) to a greater extent than in 1,2-di-X-naphthalene (**4**). The ($X^1\cdots X^8$) in **3** is much more sensitive to the property of X ($X^1\cdots X^2$) than in **4** (Figure 1).[7]

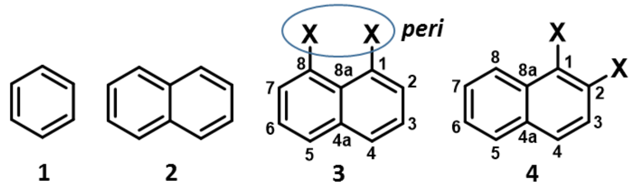


Figure 1: *Peri* interaction in naphthalene

Twisted Phenanthrenes: Phenanthrenes are versatile intermediates toward polycyclic aromatic hydrocarbons which are relevant for materials sciences, as well as toward helicenes, a class of molecules which show remarkable chiroptical properties. For a given pair of substituents X, the internuclear distances for *peri* placed pairs **(5)** is mostly greater than that for *bay* placed (4 and 5 position) pairs in phenanthrenes **(6)** (Figure 2).[8]

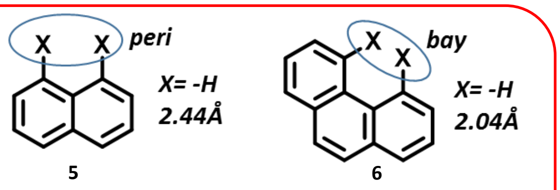


Figure 2: Comparision between the interatomic distances between *peri* substituents in naphthalene and *bay* placed substituents in phenanthrene

Puckered Benzo[c]phenanthrenes: Benzo[c]phenanthrenes and its derivatives are a class of compounds where the molecules are forced into nonplanar conformation due to the intramolecular repulsions between the terminal rings. Deformation of the rings due to substitutions at the 1 and 12 position causes congestion at the fjord region, can affect the chemical and physical properties of such molecules.[9]

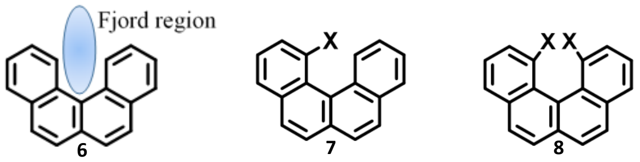
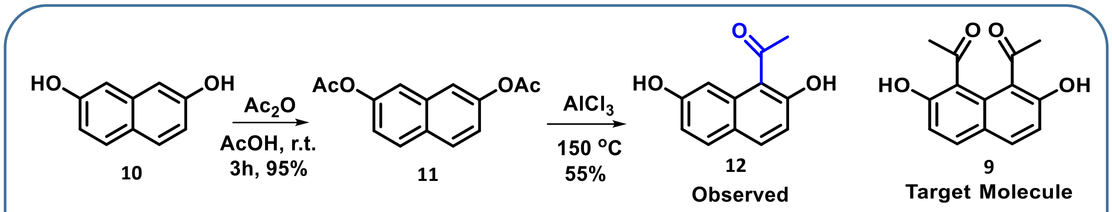


Figure 3: *Fjord* region in benzo[c]phenanthrenes, 1-X-benzo[c]phenanthrene and 1,12-diX-benzo[c]phenanthrene

Present Work:

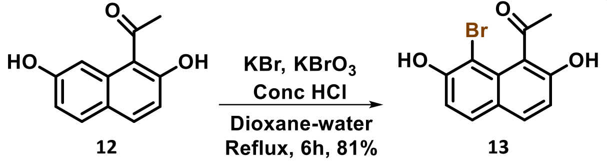
Distorted Naphthalenes: Our aim was to synthesize target molecule 1-(8-bromo-2,7-dihydroxy naphthalen-1-yl)ethan-1-one **(9)**. We started by carrying out O-acetylation of 2,7-dihydroxy naphthalene **(10)** using acetic anhydride followed by Fries rearrangement using anhydrous aluminium chloride at 150°C. However we could obtain Fries rearrangement only at 1 position and the other acetyl group was lost forming 1-acetyl-2,7-dihydroxy naphthalene **(12)** as the only product along with some amount of 2,7-dihydroxy naphthalene **(10)** (Scheme 1).



Scheme 1: Synthesis of 1-acetyl-2,7-dihydroxy naphthalene **(12)**

We were successful in carrying out bromination at 8th position of 1-acetyl-2,7-dihydroxy naphthalene **(12)** in good yield (Scheme 2). The synthesized compound 1-(8-bromo-2,7-dihydroxy naphthalen-1-

yl)ethan-1-one **(13)** was then subjected to single crystal X-ray diffraction study which showed that the dihedral angle between the two rings of naphthalene was found to be **4.58º** (Figure 4).



Scheme 2: Synthesis of 1-(8-bromo-2,7-dihydroxy naphthalen-1-yl)ethan-1-one **(13)**

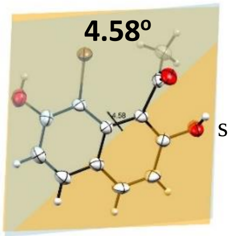
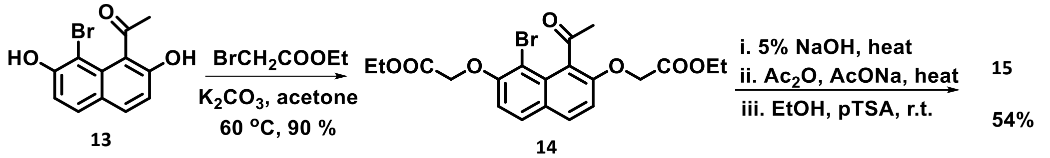


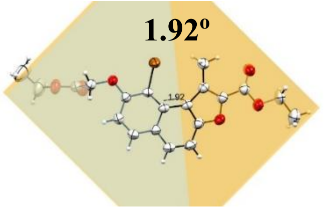
Figure 4: ORTEP diagram of **13** showing inter planar angle to be **4.58º**

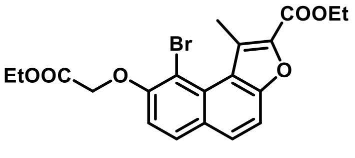
To further increase the distortion in the naphthalene core, 1-(8-bromo-2,7-dihydroxy naphthalen-1-yl)ethan-1-one **(13)** was condensed with bromoethyl acetate which was cyclized to ethyl-9-bromo-8-(2-ethoxy-2-oxoethoxy)-1-methylnaphtho[2,1-b]furan-2-carboxylate **(15)** using *in situ* basic hydrolysis, subsequent cyclisation using sodium acetate and acetic anhydride followed by esterification with ethanol (Scheme 3).



Scheme 3: Synthesis of ethyl-9-bromo-8-(2-ethoxy-2-oxoethoxy)-1-methylnaphtho[2,1-b]furan-2-carboxylate **(15)**

Figure 5: ORTEP Diagram of **15** showing angle between the two planes to be **1.92º**





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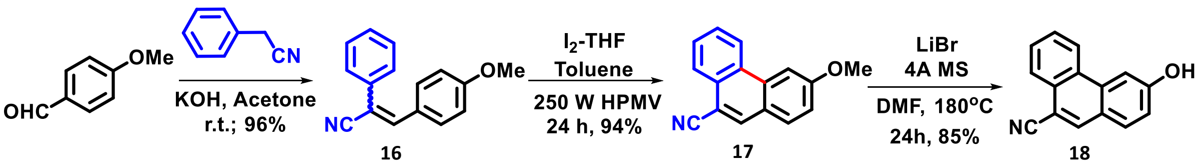
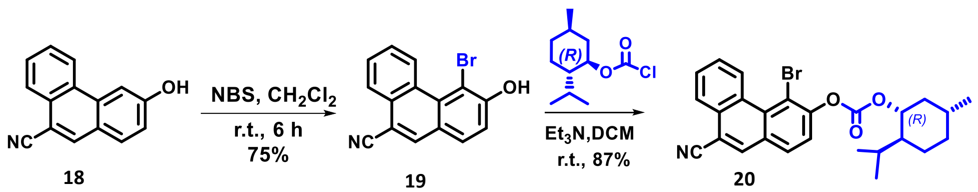
Single Crystal XRD showed that the inter-planar angle between the two terminal rings was reduced to **1.92º** (Figure 5). To further increase the steric bulk, we replaced the furan ring with a benzene ring.

Twisted Phenanthrenes: We carried out Knoevenagel reaction of *p*-anisaldehyde with benzyl cyanide to obtain olefin **(16)** which was subjected to photocyclization to get 3-methoxy phenanthrene-9-carbonitrile **(17)** followed by deprotection of -OMe group under neutral conditions developed during this work to obtain 3-hydroxyphenanthrene-9-carbonitrile **(18)** in good yield (Scheme 4).



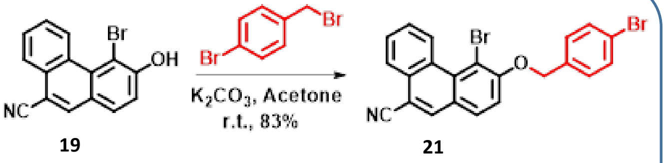
Scheme 4: Synthesis of 3-hydroxyphenanthrene-9-carbonitrile **(18)**

This 3-hydroxyphenanthrene-9-carbonitrile **(18)** was then subjected to bromination using N-bromo succinimide to get 4-bromo-3-hydroxyphenanthrene-9-carbonitrile **(19)**. To test the presence of this compound in two enantiomeric forms, it was converted into its menthyl carbonate derivative **(20)** (Scheme 5). ^{1}H NMR of the carbonate **(20)** did not show any evidence for the presence of diastereomers upto -20°C proving that the twist is not sufficient for the molecule to exist as enantiomers.



Scheme 5: Synthesis of 3-hydroxy-4-methylphenanthrene-9-carbonitrile **(19)** and 4-bromo-9-cyanophenanthren-3-yl ((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl) carbonate **(20)**

4-bromo-3-hydroxyphenanthrene-9-carbonitrile **(19)** was converted into its *p*-bromo benzyl ether **(21)** (Scheme 6) and crystals suitable for single crystal analysis were grown which showed the dihedral angle between the two terminal rings to be **12.04°** (Figure 6).



Scheme 6: Synthesis of 4-bromo-3-((4-bromobenzyl)oxy) phenanthrene-9-carbonitrile **(21)**

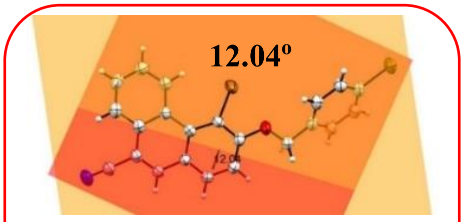
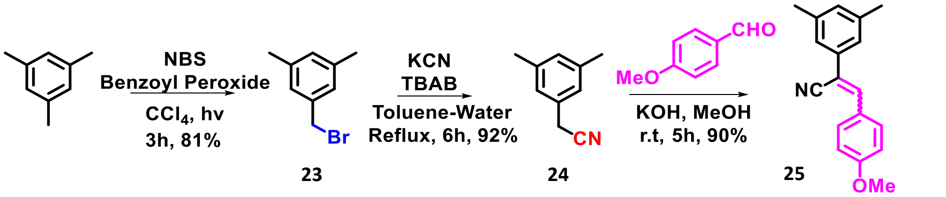


Figure 6: ORTEP Diagram showing inter-planar angle between the two terminal rings to be **12.04°**

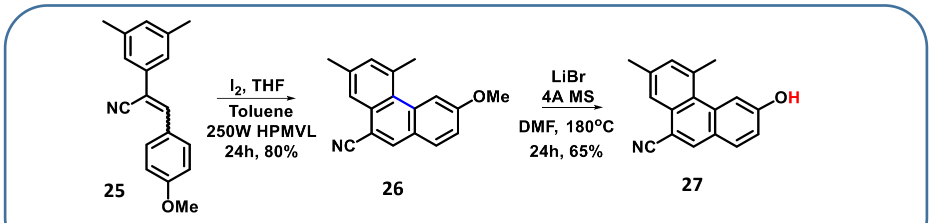
However the steric bulk at 4 and 5 position was not sufficient to render the molecule into two stable enantiomeric forms, we planned to introduce a methyl group at 5th and a bromine atom at 4th position.

Hence for the synthesis of our target molecule 4-bromo-3-hydroxy-5,7-dimethylphenanthrene-9-carbonitrile **(22)** we started with mesitylene, carried out its side chain bromination using NBS with catalytic amount of benzoyl peroxide in CCl$_4$ to obtain 1-(bromomethyl)-3,5-dimethylbenzene **(23)** which was then converted to 2-(3,5-dimethylphenyl)acetonitrile **(24)** by its reaction with potassium cyanide. **24** was then subjected to Knoevenagel condensation with *p*-anisaldehyde to give the corresponding olefin **(25)** (Scheme 7).



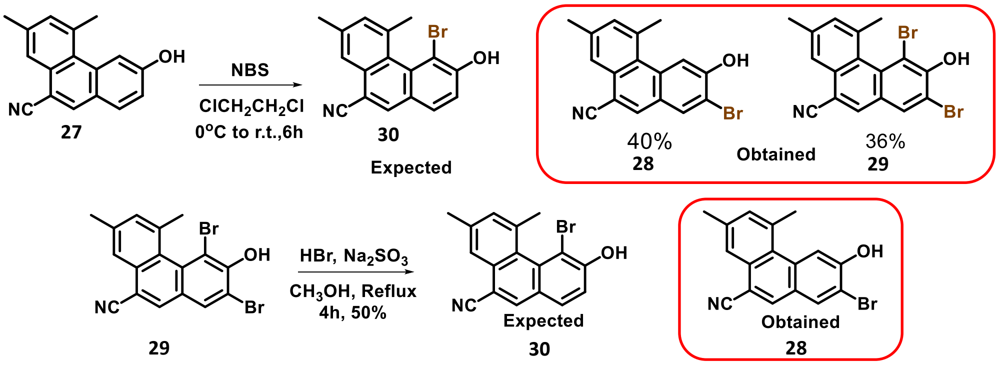
Scheme 7: Synthesis of 2-(3,5-dimethylphenyl)-3-(4-methoxyphenyl)acrylonitrile **(25)**

The olefin **25** was then subsequently subjected to photocyclisation to obtain 3-methoxy-5,7-dimethyl phenanthrene-9-carbonitrile **(26)** in good yield. The –OMe group was cleaved under similar conditions developed earlier to obtain 3-hydroxy-5,7-dimethylphenanthrene-9-carbonitrile **(27)** in moderate yield (Scheme 8).



Scheme 8: Synthesis of 3-hydroxy-5,7-dimethylphenanthrene-9-carbonitrile **(27)**

3-hydroxy-5,7-dimethylphenanthrene-9-carbonitrile **(27)** was then subjected to bromination using NBS which gave us a mixture of 2-bromo-3-hydroxy-5,7-dimethylphenanthrene-9-carbonitrile **(28)** and 2,4-dibromo-3-hydroxy-5,7-dimethylphenanthrene-9-carbonitrile **(29)** but not our target molecule 4-bromo-3-hydroxy-5,7-dimethylphenanthrene-9-carbonitrile **(30)**. Hence we concluded that bromination first occurs at the 2nd position and the second bromination occurs at 4th position when excess of NBS is added. We expected that the debromination of 2,4-dibromo-3-hydroxy-5,7-dimethylphenanthrene-9-carbonitrile **(29)** would result to our target molecule as the bromine atom at the 2nd position is more accessible than that present on the 4th position, but we ended up by obtaining 2-bromo-3-hydroxy-5,7-dimethylphenanthrene-9-carbonitrile **(28)** as the sole product (Scheme 9).



Scheme 9: Attempted synthesis of 4-bromo-3-hydroxy-5,7-dimethylphenanthrene-9-carbonitrile **(30)**

To check the existence of 2,4-dibromo-3-hydroxy-5,7-dimethylphenanthrene-9-carbonitrile **(29)** in two enantiomeric forms, we synthesized its menthyl carbonate derivative **(31)** and *p*-bromo benzyl ether derivative **(32)** using the earlier stated strategy (Figure 7). The carbonate derivative **(31)** was then subjected to low temperature ^{1}H NMR analysis, which showed broadening of the signal for the proton of the chiral center as the temperature was decreased from room temperature to -15°C. Also 2,4-dibromo-3-((4-bromobenzyl)oxy)-5,7-dimethylphenanthrene-9-carbonitrile **(32)** showed two doublets for the methylene protons (Figure 8) which are indicative that they are diastereotopic in nature and we may have achieved sufficient bulk to render the phenanthrene moiety chiral.

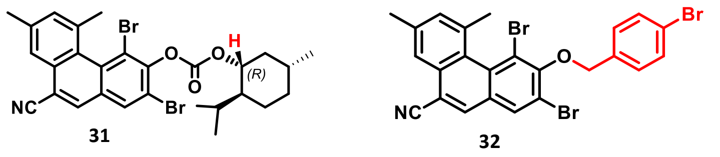
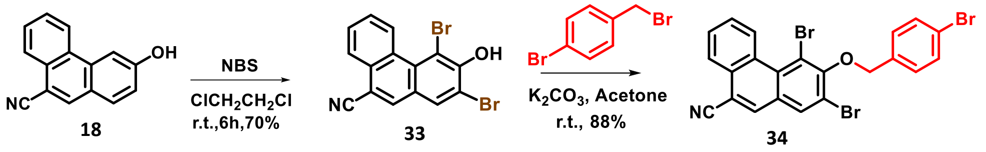


Figure 7: Shows the structure of 2,4-dibromo-9-cyano-5,7-dimethylphenanthren-3-yl((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl) carbonate **(31)** and 2,4-dibromo-3-((4-bromobenzyl)oxy)-5,7-dimethylphenanthrene-9-carbonitrile **(32)**

Figure 8: O-C*H₂*-Ar for **32** in ^{1}H NMR

The role of methyl substituent in the bay region was further confirmed by preparing 2,4-dibromo-3-((4-bromobenzyl)oxy)phenanthrene-9-carbonitrile **(33)** by carrying out bromination **(18)** with excess of NBS and preparing its *p*-bromo benzyl ether **(34)** (Scheme 10).



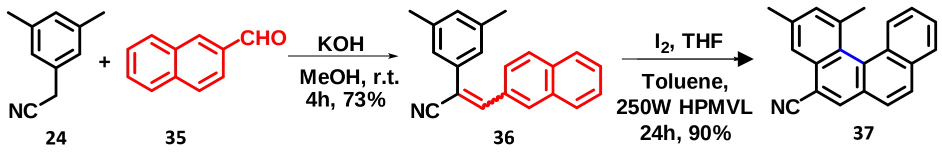
Scheme 10: Synthesis of 2,4-dibromo-3-((4-bromobenzyl)oxy)phenanthrene-9-carbonitrile **(34)**

Figure 9: O-C*H₂*-Ar for **34** in ^{1}H NMR

The ^{1}H NMR for 2,4-dibromo-3-((4-bromobenzyl)oxy)phenanthrene-9-carbonitrile **(34)** showed a sharp singlet for the methylene protons proving the necessity of presence of methyl group at 5-position.

Puckered Benzo[c]phenanthrenes: We synthesized three molecules with a methyl group placed at C-1 position and studying the effect of presence (C-5 or C-6) or absence of –CN group on crystal packing and other intermolecular interactions.

2-(3,5-dimethylphenyl)acetonitrile **(24)** and 2-naphthaldehyde **(35)** were condensed in presence of KOH to obtain the corresponding olefin **(36)** which was subjected to photocyclization to obtain 1,3-dimethylbenzo[c]phenanthrene-5-carbonitrile **(37)** in good overall yield.



Scheme 11: Synthesis of 1,3-dimethylbenzo[c]phenanthrene-5-carbonitrile **(37)**

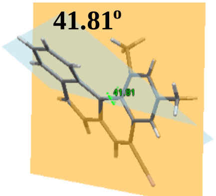
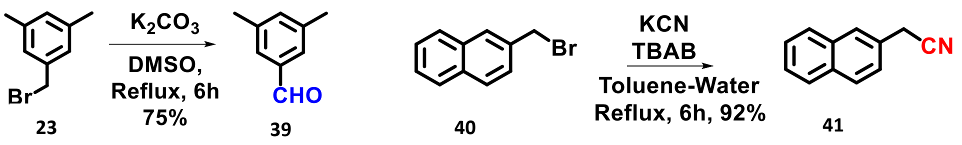


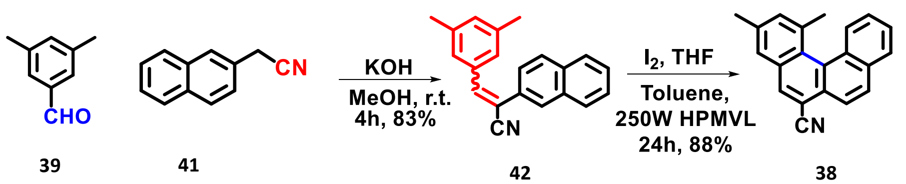
Figure 10: ORTEP diagram of **37** showing interplanar angle between two terminal rings is 41.81°.

To further study the effect of position of cyano group on the crystallization pattern, our target was to synthesize compound **38** for which a similar retrosynthetic scheme can be designed, by just changing the coupling partners. The mesityl bromide **(23)** which we had synthesized in the earlier scheme, was subjected to Kornblum oxidation to give 3,5-dimethylbenzaldehyde **(39)** in moderate yield. Similarly, bromomethyl naphthalene **(40)** was converted into its corresponding cyano derivative 2-(naphthalen-2-yl) acetonitrile **(41)** by reaction with KCN (Scheme 12).



Scheme 12: Synthesis of 3,5-dimethylbenzaldehyde **(24)** and 2-(naphthalen-2-yl) acetonitrile **(40)**

These two newly synthesized coupling partners were then subjected to Knoevenagel condensation to give the olefin **42**, which was then cyclized under similar conditions used earlier to obtain the final target molecule 1,3-dimethylbenzo[c]phenanthrene-6-carbonitrile (**38)** in 88% yield (Scheme 13).



Scheme 13: Synthesis of 1,3-dimethylbenzo[c]phenanthrene-6-carbonitrile **(38)**

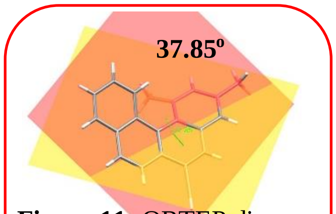
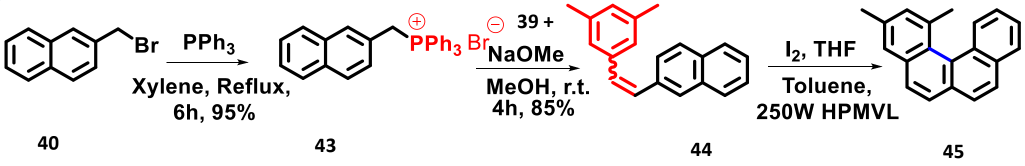


Figure 11: ORTEP diagram of **38** showing interplanar angle between two terminal rings is **37.85°**.

Following a slightly modified strategy to obtain the required olefin **(44)** without a cyano group, the bromomethyl naphthalene **(40)** was subjected to Wittig salt **(43)** formation by reaction with triphenyl phosphine in refluxing xylene. **43** was then subjected to Wittig reaction with 3,5-dimethylbenzaldehyde **(39)** in presence of freshly prepared sodium methoxide in dry methanol to give the olefin **44** in good yield. The olefin was then subjected to photocyclization using similar methods used before, to give the 1,3-dimethylbenzo[c]phenanthrene **(45)** in moderate yield (Scheme 14).



Scheme 14: Synthesis of 1,3-dimethylbenzo[c]phenanthrene **(44)**

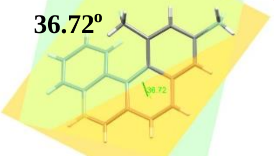
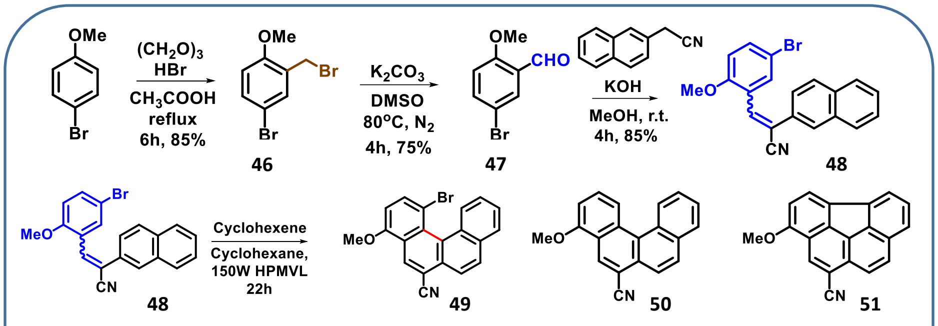


Figure 12: ORTEP of **45** showing inter planar angle between two terminal rings is **36.72°**.

All the three derivatives of [4]helicene were subjected to low temperature HPLC and all the molecules showed almost baseline separation at a temperature of -20°C. Hence we conclude that the enantiomers of these compounds were stable at low temperature but racemize at room temperature.

Hence to increase the steric bulk on the 1-position of benzo[c]phenanthrene, we wanted to introduce a bulky bromine atom in the Fjord region and compare the properties of this compound with previously synthesized compounds. We started our synthetic scheme with *p*-bromo anisol, carrying out its bromomethylation to get 4-bromo-2-(bromomethyl)-1-methoxybenzene **(46)** which was then subjected to Kornblum oxidation to obtain 5-bromo-2-methoxybenzaldehyde **(47)**. The synthesized aldehyde **(47)** and the previously synthesized naphthyl cyanide **(41)** were then subjected to Koevenagel condensation to obtain the desired olefin 3-(5-bromo-2-methoxyphenyl)-2-(naphthalen-2-yl) acrylonitrile **48** in good yield. The olefin was then subjected to photocyclization using cyclohexene in cyclohexane using 150W HPMVL (Scheme 15).



Scheme 15: Synthesis of 1-bromo-4-methoxybenzo[c]phenanthrene-6-carbonitrile (**49**)

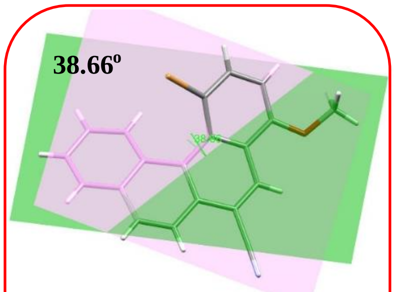


Figure 13: ORTEP of **49** showing inter planar angle between two terminal rings is **38.66°**.

The photocyclization however gave a mixture of products along with the desired product by carrying out repeated purification using column chromatography. The desired product 1-bromo-4-methoxybenzo[c]phenanthrene-6-carbonitrile (**49**) was obtained in 33% yield along with debrominated product 4-methoxybenzo[c]phenanthrene-6-carbonitrile **(50)** and a perylene type compound 3-methoxybenzo[ghi]fluoranthene-1-carbonitrile **(51)**. Single Crystal X-ray diffraction analysis for **49** shows the interplanar angle between the two terminal rings is **38.66°** (Figure 13) and chiral HPLC analysis showed two well resolved peaks at room temperature indicating that the compound exists in two enantiomeric forms which are stable at room temperature.

Chapter 3: Introduction to Oxa-helically chiral molecules:

Historically, the efforts towards heterohelicenes were focused mainly on azahelicenes. Over the years, considerable attention has also been devoted to thiahelicenes; however, comparatively few oxahelicenes have been synthesized and studied to date. That may be partially because oxa-heterohelicenes are stereochemically less stable. The presence of furan results in smaller in-plane angle (θ), compared to the corresponding analogues having six member aromatic ring (Figure 14).[10]

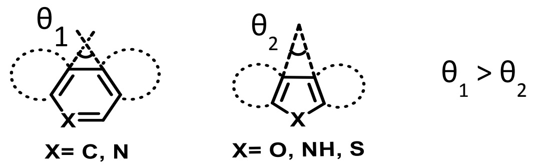
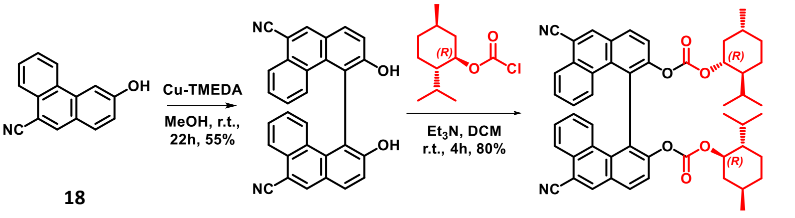


Figure 14: Shows a comparison between the in-plane angle for six membered and five membered ring

Oxygen-containing polycyclic aromatic compounds, especially furan-containing polycyclic aromatics, are expected to provide relatively high HOMO levels and offer utility in electronic devices, such as organic light-emitting diodes (OLEDs)[11] and organic field-effect transistors (OFETs).[12]

Present Work:

Starting with 9-cyano-3-hydroxy phenanthrene **(18)** which we have already synthesized in chapter-2, was subjected to oxidative homo coupling to the corresponding 3,3′-dihydroxy-4,4′-biphenanthryl **(52)** analogous to synthesis of BINOL from β-naphthol.[13] The racemic bis-phenanthrol **(52)** was subjected to the bis-carbonate formation with (–)-menthyl chloroformate to obtain diastereomeric mixture of **53** which was subjected to crystallization (Scheme 16).[14] The single-crystal X-ray analysis of the solid compound obtained clearly established the stereochemistry of the chiral axis to be "*S*" of the bis-carbonate (Figure 15), and the soluble portion after the crystals were separated contains the other diastereomer in 96 % diastereomeric excess as confirmed by ^{1}H NMR analysis.



18 **52** **53**

Scheme 16: Synthesis of 9,9'-dicyano-[4,4'-biphenanthrene]-3,3'-diyl bis((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl) bis(carbonate) **(53)**

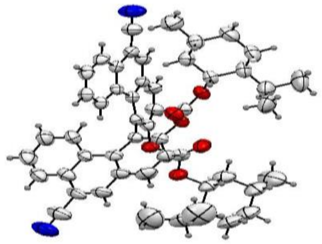
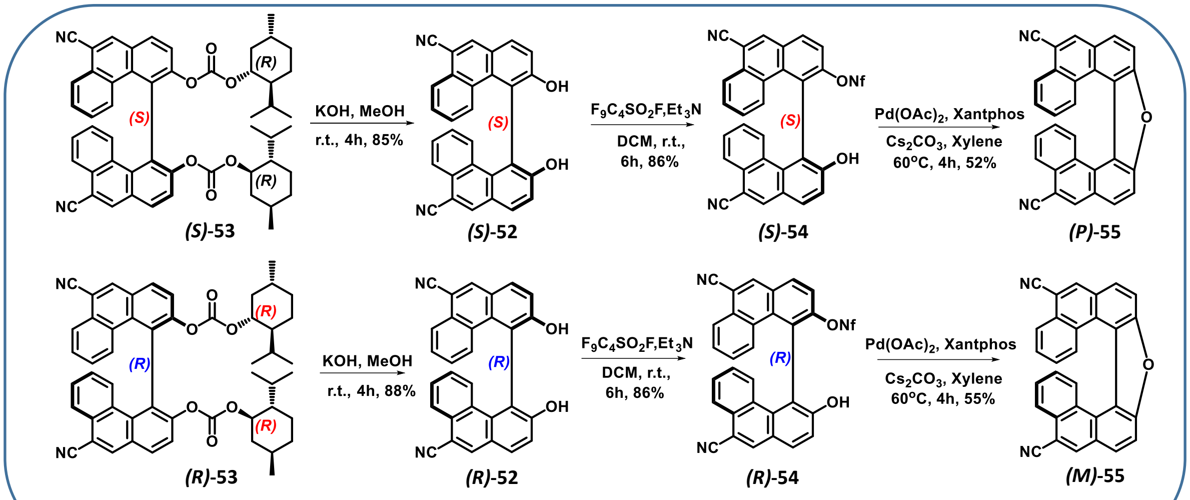


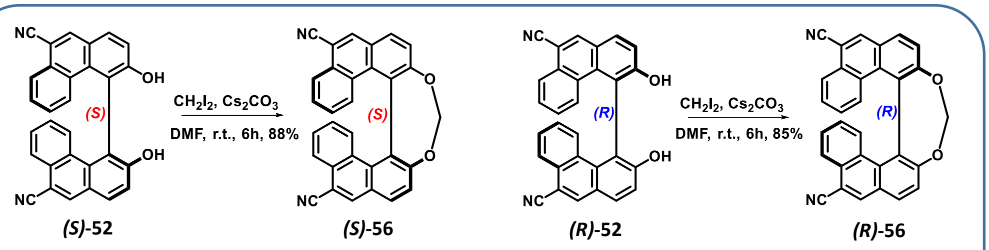
Figure 15: ORTEP Diagram of ***(S)*-53** showing the stereochemistry between two phenanthrene units to be **(*S*)**

The optically pure diastereomers were then subjected to alkaline hydrolysis to generate chirally enriched diol **(*S*)-52** and **(*R*)-52** with no loss of optical purity of the atropisomeric diol, as confirmed by HPLC analysis on chiral phase column. Optically pure **52** was converted to its mono nonafluoro sulfonate **(54)** by the known procedure and subjected to cyclization with palladium acetate-xantphos catalyst system.[15] The cyclized product 5,13-dicyano-9-oxa[7]helicenes (**55)** was isolated in moderate yield (Scheme 17).



Scheme 17: Synthesis of 5,13-dicyano-9-oxa[7]helicenes (**55**)

Another class of helicene-like compounds diarylated [*d*,*f*][1,3]dioxepine analogues are also subject of the present study. Thus, the diol **52** was subjected to diether formation with diiodomethane and Cs_2CO_3 as base. The dioxepine derivative **56** was obtained as single compound in good yield (Scheme 18).[16]



Scheme 18: Synthesis of diphenanthro[3,4-d:4',3'-f][1,3]dioxepine-5,15-dicarbonitrile (**56**)

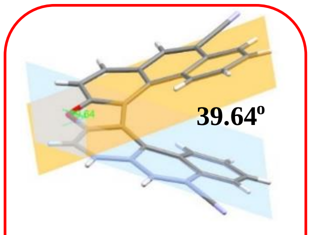


Figure 16: Single Crystal XRD of **55**

One of the important properties of optically pure helical compounds is their high optical rotation ($[\alpha]_D$) and molecular optical rotation ($[\varphi]_D$). Both the isomers of chirally pure sample of **52** showed much less rotation, which changed considerably when converted to helicene-like compounds **56**. When the helical compound **55** was synthesized, there was considerable increase in the value of optical rotation as well as molecular rotation. The sample of (*S*)-**52** with OR of +157 and molecular OR of +685 was converted to (*P*)-**55**, the values changed to +790 and +3306, respectively.

The separated enantiomers were characterized by optical rotation, UV-Vis and fluorescence spectroscopy, CD spectroscopy and circularly polarized luminescence. Both sets of enantiomers, (*P*)-/(*M*)-**55** and (*R*)-/(*S*)-**56**, showed a mirror-like CPL signal with opposite g_{lum} values around the emission maximum, which correspond to the typical range of similar chiral molecules.

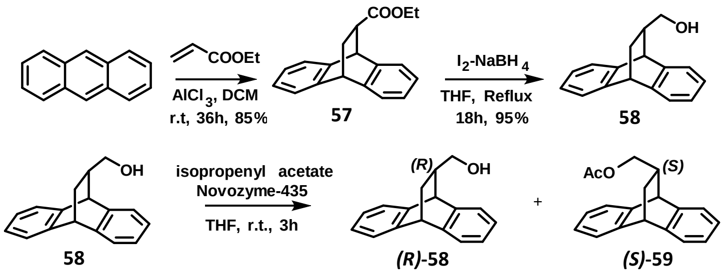
Chapter 4: Introduction to Roof shape molecules:

A novel class of compounds resembling the shape of a roof was introduced and studied by Weber, while searching their applications as clathrate hosts with inclusion properties. Such molecules find few applications in different areas ranging from medicinal chemistry, material science to being used as chiral auxiliary for asymmetric synthesis of α-halo acids and as chiral solvating agents for discrimination of the signals of some optically active compounds in NMR spectroscopy.

Present Work:

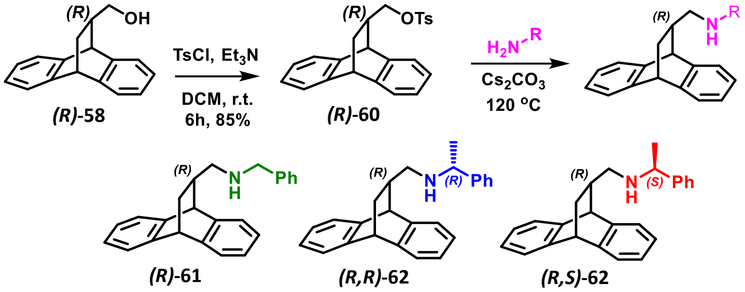
In the present study, we have prepared optically pure roof shape secondary amines and evaluated them as chiral solvating agents for the discrimination of signals of chiral acids by NMR spectroscopy.

The cycloaddition reaction of anthracene and ethyl acrylate to furnish adduct **57** which was subsequently reduced with I_2-$NaBH_4$ method to furnish roof shape alcohol **58**. The alcohol **58** was then resolved using enzymatic transesterification using Novozyme-435 and isopropenyl acetate as acyl donor in THF (Scheme 19). The absolute configuration of enantiomerically pure **58** was established by comparison of its specific optical rotation with literature values and also by carrying out it chiral HPLC under known conditions.[17]



Scheme 19: Synthesis and resolution of 9,10-dihydro-9,10-ethanoanthracen-12-ylmethanol (**58**)

The chiral alcohol ***(R)*-58** was converted to its tosylate ***(R)*-60**, and it was then treated with benzyl amine, (*R*)-α-phenylethylamine and (*S*)-α-phenylethylamine to furnish chiral secondary amine ***(R)*-61**, ***(R,R)*-62** and its diastereomer ***(R,S)*-62** (Scheme 20).

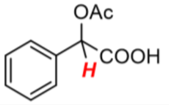
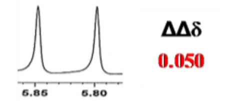
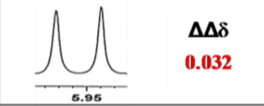
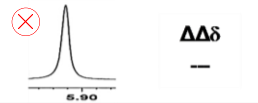
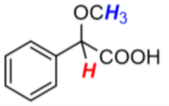
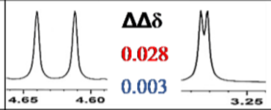
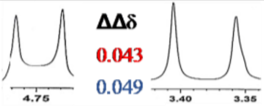
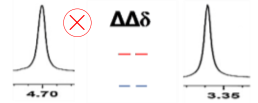
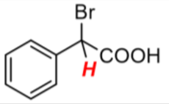
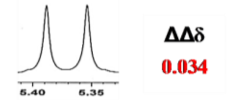
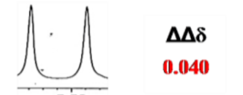
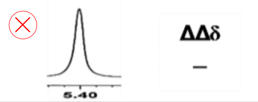
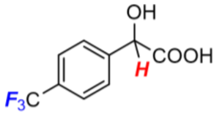
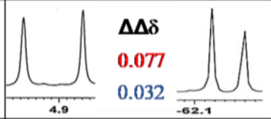
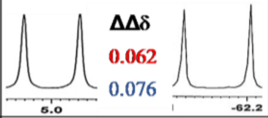
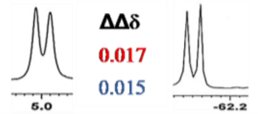
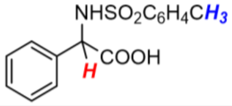
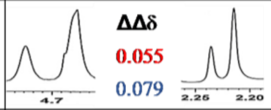
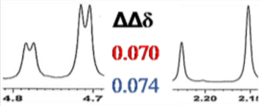
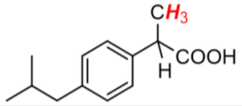
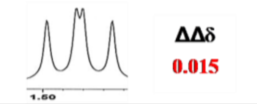
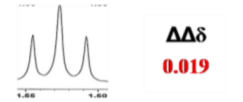
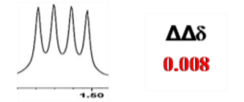
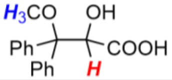


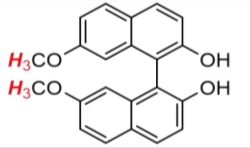
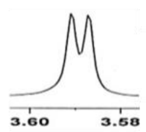
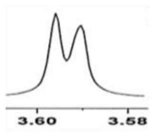
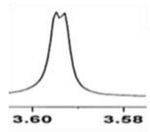
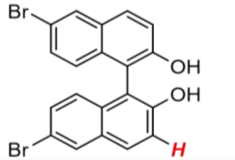
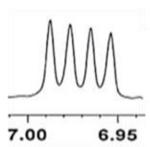
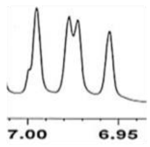
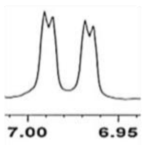
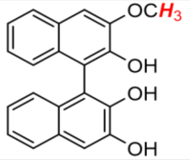
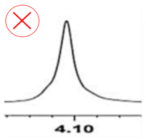
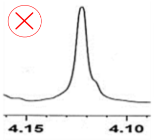
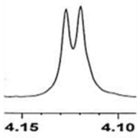
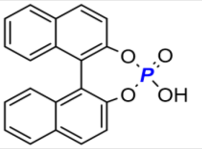
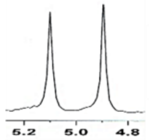
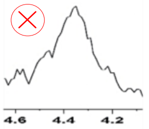
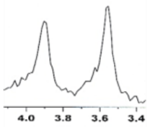
Scheme 20: Synthesis of chiral roof shape amines

The three roof-shape secondary amines ***(R)*-61**, ***(R,R)*-62**, and ***(R,S)*-62** were used as host for different acidic substrates for determination of optical purity of the guest analytes. The recognition study was conducted in $CDCl_3$ (400 MHz; 20 mM concentration; ratio of 1:1) using various racemic mandelic acid and its derivatives as well as weakly acidic BINOL derivatives.

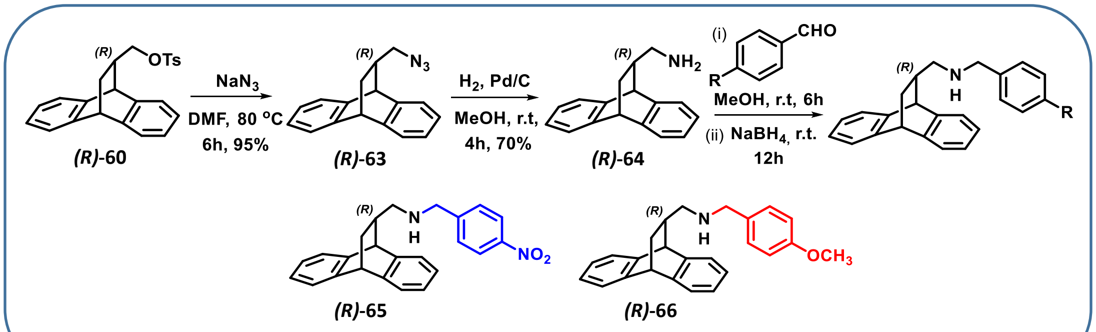
Although CSAs ***(R)*-61** and ***(R,R)*-62** were almost equally effective showing baseline separation of signals, the CSA ***(R,S)*-62** showed relatively poor resolution for all mandelic acid derivatives, N-tosyl phenylglycine, ibuprofen, naproxen and 2-hydroxy-3-methoxy-3,3-diphenylpropanoic acid, which is an intermediate for few pharmaceuticals. However, for BINOL all three were ineffective in separating the signals but, structurally similar 2,2′,7,7′-tetrahydroxy-1,1′-binaphthyl and its derivatives lead to better interactions with the CSA. The CSAs ***(R)*-61** and ***(R,S)*-62** were able to separate the signal of the most shielded hydrogen attached to the C8 position while CSA ***(R,R)*-62** failed to resolve them. Hence, ***(R,S)*-62** proved to be slightly superior class of CSA for binaphthyl system, while its diastereomer ***(R,R)*-62** was found more effective in the chiral recognition of derivatives of mandelic acid. Such match-mismatch effect for controlling supramolecular interactions between diastereomeric chiral solvating agents for molecular recognition is noteworthy (Table 1).

Table 1: Enantiodescrimination of acidic substrates with our synthesized chiral roof shape amines

Substrates	***(R)*-61**	***(R,R)*-62**	***(R,S)*-62**
	 ΔΔδ 0.050	 ΔΔδ 0.032	 ⊗ ΔΔδ —
	 ΔΔδ 0.028 0.003	 ΔΔδ 0.043 0.049	 ⊗ ΔΔδ – – – –
	 ΔΔδ 0.034	 ΔΔδ 0.040	 ⊗ ΔΔδ —
	 ΔΔδ 0.077 0.032	 ΔΔδ 0.062 0.076	 ΔΔδ 0.017 0.015
	 ΔΔδ 0.055 0.079	 ΔΔδ 0.070 0.074	 ΔΔδ 0.049 0.031
	 ΔΔδ 0.015	 ΔΔδ 0.019	 ΔΔδ 0.008
	 ΔΔδ 0.039 0.016	 ΔΔδ 0.146 0.079	 ΔΔδ 0.006 0.013

Substrates	*(R)*-61	*(R,R)*-62	*(R,S)*-62
	 ΔΔδ 0.004	 ΔΔδ 0.005	 ΔΔδ 0.002
	 ΔΔδ 0.011	 ΔΔδ 0.018	 ΔΔδ 0.005
	 ΔΔδ --	 ΔΔδ --	 ΔΔδ 0.007
	 ΔΔδ 0.205	 ΔΔδ --	 ΔΔδ 0.341

We then planned to introduce electron withdrawing group or electron releasing group to the benzyl moiety and study the effect on their activity as CSAs. The tosyl derivative ***(R)*-60** was converted into azide ***(R)*-63** which was further reduced to amine ***(R)*-64** in presence of Pd-C and hydrogen. Roof shape amine ***(R)*-64** was condensed with *p*-nitro benzaldehyde and *p*-methoxy benzaldehyde to form imines, which were in-situ reduced to corresponding secondary amines ***(R)*-65** and ***(R)*-66** (Scheme 21).

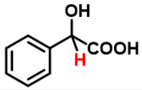
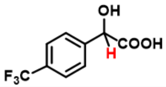
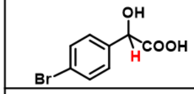
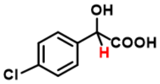
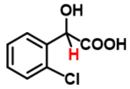
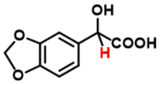
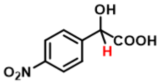
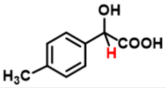
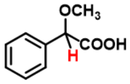
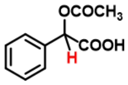
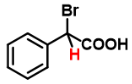
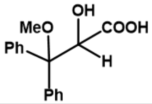
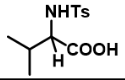
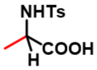
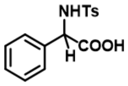


Scheme 21: Synthesis of chiral roof shape amines

We then compared the extent of molecular recognition for ***(R)*-65** and ***(R)*-66** with the earlier synthesized derivative ***(R)*-61**. We scanned all the three derivatives as CSA for racemic mandelic acid and its analogues as well as some N-protected amino acid derivatives as test analytes (Table 2).

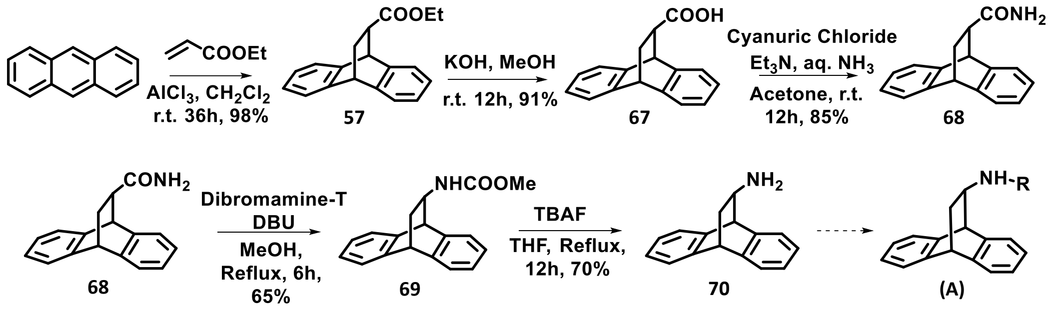
***(R)*-65** bearing electron withdrawing group, proved to be better CSA for most of the mandelic acid derivatives under study showing complete base line separation for the signal of α-H and hence, proving to be effective as CSA for the determination of the optical purity of such acidic analytes. We also tested certain α-substituted phenyl acetic acids as substrates for which ***(R)*-61** proved to be superior CSA as compared to the other two derivatives. We used our present set of CSAs for the enatiodiscrimination of N-tosyl derivatives of some amino acids like Phenylglycine, Valine and Alanine. In all the cases, ***(R)*-66** bearing electron releasing group proved to be best choice of CSA among the CSAs under study.

Table 2: Enantiodescrimination of acidic substrates with our synthesized chiral roof shape amines

Substrates:	***(R)*-61**	***(R)*-65**	***(R)*-66**
	ΔΔδ: 0.123 49.2 Hz	✓ ΔΔδ: 0.146 58.4 Hz	ΔΔδ: 0.037 14.8 Hz
	✓ ΔΔδ: 0.077 30.8 Hz	ΔΔδ: 0.022 8.8 Hz	ΔΔδ: 0.041 16.4 Hz
	ΔΔδ: 0.004 1.6 Hz	✓ ΔΔδ: 0.042 16.8 Hz	--
	ΔΔδ: 0.008 3.2 Hz	--	ΔΔδ: 0.007 2.8 Hz
	ΔΔδ: 0.034 13.6 Hz	✓ ΔΔδ: 0.064 25.6 Hz	ΔΔδ: 0.058 23.2 Hz
	ΔΔδ: 0.027 10.8 Hz	✓ ΔΔδ: 0.119 47.6 Hz	ΔΔδ: 0.092 36.8 Hz
	--	✓ ΔΔδ: 0.014 5.6 Hz	ΔΔδ: 0.005 2.0 Hz
	ΔΔδ: 0.010 4.0 Hz	✓ ΔΔδ: 0.063 25.2 Hz	ΔΔδ: 0.014 5.6 Hz
	✓ ΔΔδ: 0.028 11.2 Hz	ΔΔδ: 0.021 8.4 Hz	ΔΔδ: 0.015 6.0 Hz
	✓ ΔΔδ: 0.050 20.0 Hz	ΔΔδ: 0.029 11.6 Hz	ΔΔδ: 0.047 18.8 Hz
	✓ ΔΔδ: 0.034 13.6 Hz	ΔΔδ: 0.016 6.4 Hz	ΔΔδ: 0.017 6.8 Hz
	ΔΔδ: 0.039 15.6 Hz	ΔΔδ: 0.003 1.2 Hz	✓ ΔΔδ: 0.050 20.0 Hz
	ΔΔδ: 0.087 34.8 Hz	ΔΔδ: 0.145 58.0 Hz	✓ ΔΔδ: 0.167 67.0 Hz
	ΔΔδ: 0.012 4.6 Hz	ΔΔδ: 0.013 5.2 Hz	✓ ΔΔδ: 0.018 7.2 Hz
	ΔΔδ: 0.055 22.0 Hz	--	✓ ΔΔδ: 0.056 22.4 Hz

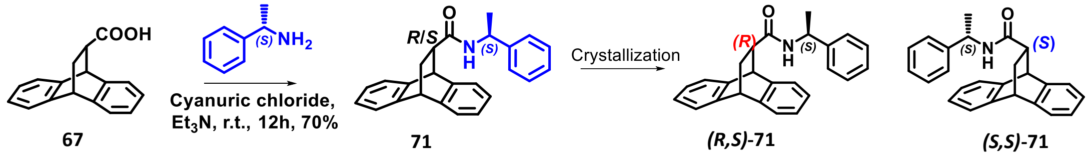
In all the above studies, the chiral center associated with the roof shape moiety is one sp^3 carbon away from the amine functionality. Hence, we wanted to synthesis amines where the amino group is directly attached to the chiral center of the roof shape molecule and compare their CSA activities with molecules synthesized earlier. We expect that this would result in a more rigid geometry as the amine would be attached directly to the bicyclic framework providing better stereocontrol and hence improved molecular recognition as CSA.

The roof shape ester **(57)** which was synthesized by Diels-Alder reaction between anthracene and ethyl acrylate, is then hydrolyzed to acid in basic condition by using KOH in methanol to access roof shape acid **(67)** in excellent yield. We have successfully converted **67** to its corresponding amide **(68)** using cyanuric chloride, triethylamine and liquor ammonia in acetone. Which was then subjected to Hoffmann rearrangement using dibromamine-T and DBU in methanol to obtain corresponding carbamate derivative **(69)**. This carbamate derivative **69** can then be hydrolyzed to yield roof shape primary amine **70**, which will be later utilized to synthesize secondary amine derivatives (Scheme 22).



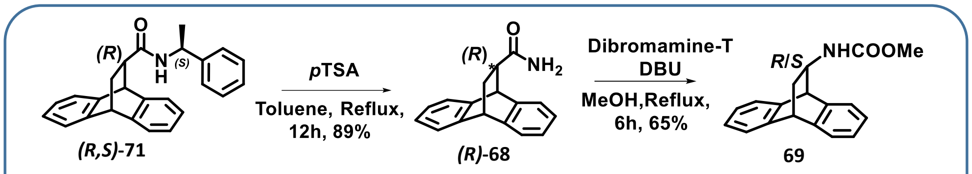
Scheme 22: Synthesis of chiral roof shape amine

To access both the enantiomers of **70** in their optically pure form, we started by converting racemic **67** into its diastereomeric amide by its reaction with optically pure (*S*)-α-methylbenzyl amine using cyanuric chloride and triethylaminne. The two diastereomers ***(R,S)*-71** and ***(S,S)*-71** hence obtained were subjected to crystallization where one of the diastereomers ***(R,S)*-71** crystallized out from the racemate whereas the other diastereomer ***(S,S)*-71** remained in the mother liquor (Scheme 23). The absolute configuration of the chiral center associated with the roof shape moiety was found to be *R* with respect to the known chiral center of the amine which was determined by carrying out single crystal XRD for ***(R,S)*-71**.



Scheme 23: Resolution of **67** by diastereomer formation

The synthesized chiral amide ***(R,S)*-71** was successfully hydrolysed using *p*-toluenesulfonic acid in refluxing toluene to obtain enantiomerically pure (***R*)-68** which was confirmed by HPLC. The optically pure (***R*)-68** was then subjected to Hoffmann rearrangement conditions as mentioned for the preparation of **69** from **68** (Scheme 24).



Scheme 24: Attempted synthesis of optically pure **69**.

The conversion occurred in good yield, however leading to complete racemization of the product. Hence, we were unsuccessful in obtaining enantiomerically pure **69** from (***R*)-68**. Efforts for developing suitable reaction conditions to prevent racemization is under progress.

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2. Gupta, R.; Cabreros, T. A.; Muller, G.; Bedekar, A. V. *Eur. J. Org. Chem.* **2018**, 5397.

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Ms. Riddhi Gupta
(Ph.D Student)

Prof. A.V. Bedekar
(Guide)

Prof. S. R. Shah
Head (*I/c*)
Department of Chemistry