SYNTHESIS OF NATURALLY OCCURRING POLYHYDROXYLATED δ--LACTONES, ARYNE MEDIATED SYNTHESIS OF PHENYL INDOLINES AND PD-SBA-TAT CATALYZED C-C CROSS COUPLING REACTIONS

A THESIS SUBMITTED TO THE

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IN THE FACULTY OF SCIENCE

SUBMITTED BY

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CERTIFICATE

CERTIFIED that the work incorporated in the thesis "**Synthesis of Naturally Occurring Polyhydroxylated *δ*-lactones, aryne mediated synthesis of Phenyl indolines and Pd-SBA-TAT catalyzed C-C Cross Coupling Reactions**" submitted by **Ms. Kiran Jawade** was carried out by the candidate at CSIR-National Chemical Laboratory, Pune under my supervision. Such materials as obtained from other sources have been duly acknowledged in the thesis.

(Dr. Pradeep Kumar)

Research Guide **December 2018**

CANDIDATE'S DECLARATION

I hereby declare that the thesis entitled "**Synthesis of Naturally Occurring Polyhydroxylated *δ*-lactones, aryne mediated synthesis of Phenyl indolines and Pd-SBA-TAT catalyzed C-C Cross Coupling Reactions**" submitted by me for the degree of Doctor of Philosophy in Chemistry to the Savitribai Phule Pune University is the record of the work carried out from 6th December, 2010 to 30th August, 2018 under the guidance of Dr. Pradeep Kumar at CSIR-National Chemical Laboratory, Pune, India has not formed the basis of any degree, diploma, associateship, fellowship, titles in this or any other University or other institution of Higher learning.

I further declare that the materials as obtained from other sources have been duly acknowledged in the thesis

Ms. Kiran Jawade (SRF) December, 2018
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Dedicated To

My Beloved Family

Infuse your life with action. Don't wait for it to happen. Make it happen. Make your own future. Make your own hope. Make your own love. And whatever your beliefs, honor your creator, not by passively waiting for grace to come down from upon high, but by doing what you can to make grace happen... yourself, right now, right down here on Earth.

-Bradley Whitford

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Abbreviations

Ac	-	Acetyl
AcOH	-	Acetic acid
Ac_2O	-	Acetic anhydride
Bn	-	Benzyl
BnBr	-	Benzyl bromide
$BH_3 \cdot Me_2S$	-	Boron dimethyl sulfide complex
Boc	-	*tert*-Butoxy carbonyl
$(Boc)_2O$	-	Di-*tert*-butyl dicarbonate
BuLi	-	Butyl lithium
Cat.	-	Catalytic
$CDCl_3$	-	Deuterated chloroform
DBU	-	1,8-Diazabicyclo[5.4.0]undecene-7
DCM	-	Dichloromethane
DDQ	-	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	-	Diisobutylaluminium hydride
DMP	-	2,2-Dimethoxypropane
DMF	-	*N, N′*-Dimethylformamide
DMAP	-	*N,N′*-Dimethylaminopyridine
DMSO	-	Dimethyl sulfoxide
ee	-	Enantiomeric excess
equiv.	-	Equivalents

EtOH	-	Ethanol
Et	-	Ethyl
Et_2O	-	Diethyl ether
EtOAc	-	Ethyl acetate
Et_3N	-	Triethylamine
Hz	-	Hertz
HPLC chromatography	-	High pressure liquid
IBX	-	Iodoxybenzoic Acid
Im	-	Imidazole
LiHMDS	-	Lithium hexamethyl disilazide
m-CPBA	-	*m*-Chloroperbenzoic acid
MeOH	-	Methanol
mg	-	Milligram
min	-	Minutes
mL	-	Millilitre
mmnol	-	Millimole
Mp	-	Melting point
Ms	-	Methanesulfonyl
Me	-	Methyl
MeI	-	Methyl iodide
$NaBH_4$	-	Sodiumborohydride
NaH	-	Sodium hydride
Ph	-	Phenyl
Py	-	Pyridine
PMB	-	*para*-Methoxy benzyl
p-TSA	-	*par*a-Toluenesulfonic acid
RCM	-	Ring closing metathesis
Ts	-	Tosyl

TEA	-	Triethylamine
TBAI	-	Tetra-*n*-butylammonium iodide
TBAF	-	Tetra-*n*-butylammonium fluoride
TBDMS	-	*tert*-Butyldimethyl silyl
TBSCl	-	*tert*-Butyldimethyl silyl chloride
TBDPS	-	*tert*-Butyldiphenyl silyl
TBDPSCl	-	*tert*-Butyldiphenyl silyl chloride
THF	-	Tetrahydrofuran
TPP	-	Triphenylphosphine
p-TSA	-	*p*-Toluenesulphonic acid
TsCl	-	*p*-Toluenesulphonyl chloride

General remarks

- ^{1}H NMR spectra were recorded on AC-200 MHz, MSL-400 MHz, JEOL-400 and DRX- 500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C NMR spectra were recorded on AC-50 MHz, MSL-75 MHz, and DRX-125 MHz spectrometer.
- EI Mass spectra were recorded on Finnigan MAT-1020 spectrometer at 70 *eV* using a direct inlet system.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected.
- All reactions are monitored by Thin layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV light, I_2, ninhydrin and anisaldehyde in ethanol as development reagents.
- All solvents and reagents were purified and dried by according to procedures given in Vogel's Text Book of Practical Organic Chemistry. All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 40 °C.
- Silica gel (60–120) used for column chromatography was purchased from ACME Chemical Company, Mumbai, India.
- All melting points and boiling points are uncorrected and the temperatures are in centigrade scale.

- The compounds, scheme and reference numbers given in each section of chapter refers to that particular section of the chapter only.

Abstract

The thesis entitled "**Synthesis of Naturally Occurring Polyhydroxylated *δ*-lactones, aryne mediated synthesis of Phenyl indolines and Pd-SBA-TAT catalyzed C-C Cross Coupling Reactions"** has been divided into four chapters.

Chapter 1. Introduction to key steps

Chapter 2. Synthesis of Polyacylated-6-Heptenyl-5,6-Dihydro-2H-Pyran-2-Ones

Section A. Synthetic studies towards temporary silicon tethered ring closing directed synthesis of Synparvolide B

Section B. Synthetic studies towards temporary silicon tethered ring closing directed synthesis of Pectinolide C.

Section C. Organocatalytic Approach for the Synthesis of (-)- Cleistenolide

Section D. Organocatalytic Approach for the Synthesis of (+)- Crassalactone A

Chapter 3. Aryne intermediates in the Synthesis of Phenyl Indolines

Chapter 4. Pd-SBA-TAT catalyzed C-C Cross Coupling Reactions

Chapter 1: A brief account of Jacobsen Hydrolytic Kinetic Resolution (HKR), Proline-catalyzed organic transformations and Temporary Silicon-Tethered Ring Closing Metathesis

This chapter gives a brief account of Jacobsen's HKR, Proline catalyzed reactions and Temporary Silicon-Tethered Ring Closing Metathesis reactions.

Jacobsen's HKR[1] has emerged as a powerful tool for synthesis of enantioenriched terminal epoxides in recent times. The hydrolytic kinetic resolution (HKR) of terminal epoxides is catalyzed by chiral (salen) Co (III) OAc complex and affords both recovered unreacted epoxide and 1,2-diol product in highly enantioenriched form. The HKR serves as powerful tool to access useful, highly enantioenriched chiral building that are otherwise difficult to access, from inexpensive racemic materials. The reaction has several attractive from a practical standpoint, including the use of H_2O as a reactant and low loadings (0.2-2.0 mol %) of a recyclable, commercially available catalyst. In addition, the HKR displays extraordinary scope, as a wide array of sterically and electronically varied epoxides can be resolved to >99% ee. The corresponding 1,2-diols were produced in good-to-high enantiomeric excess using 0.45 equiv of H_2O.

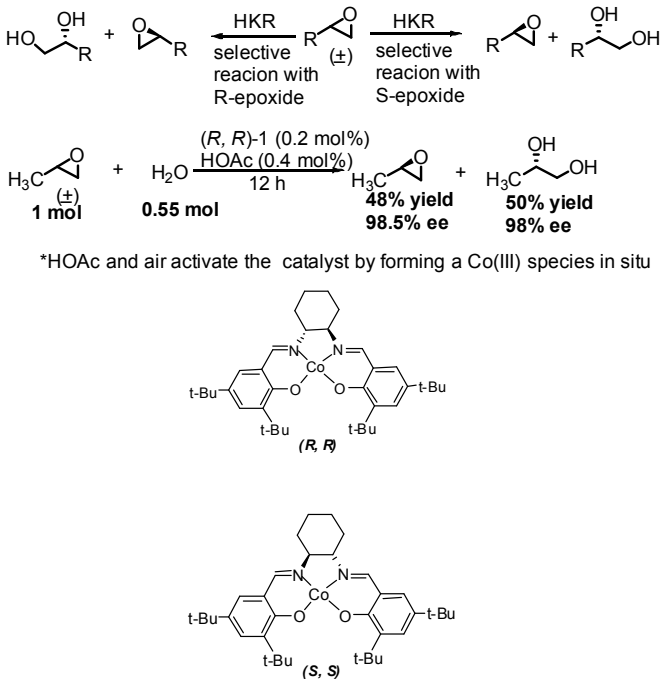

Figure 1: General Scheme for HKR and Co (II) Salen catalyst in both *R* and *S* forms.

Temporary silicon-tethered ring-closing metathesis[2] represents an important cross-coupling strategy for the formation of medium-sized silacycles. These intermediates are valuable synthons in organic synthesis due to their propensity to undergo a facile refunctionalization through protodesilylation, oxidation, silane-group transfer or transmetallation. A particularly attractive utility of this methodology is an application in the synthesis of biologically important natural products. Due to a significant versatility in post-metathesis functionalization, silicon frequently represents "the tether of choice" in many target directed synthesis (vide infra).

In recent years, area of **organocatalysis**[3] has emerged as a promising strategy and as an alternative to expensive protein catalysis and toxic metal catalysis, thus becoming a fundamental tool in the catalysis toolbox available for asymmetric synthesis. Proline has been defined as a "universal catalyst" because of its high utility in variety of asymmetric organic transformations. Proline is the only natural amino acid with a secondary amine functionality, which raises the pKa value and better nucleophilicity as compared to other amino acids. It can act as a nucleophile to carbonyl groups (iminium intermediate) or Michael acceptors (enamines). It can be regarded as a bifunctional catalyst as the secondary amine acts as Lewis base and the acid group acts as Brönsted acid.

References:

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Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. *J. Org. Chem*., **1998**, *63*, 6776; (c) For earlier studies involving (salen) metal-catalyzed reactions of epoxides that served as a foundation for the discovery of the HKR, see: (i) Tekeichi, T.; Arihara, M.; Ishimori, M.; Tsuruta, T. *Tetrahedron,* **1980**, *36*, 3391; (ii) Maruyama, K.; Nakamura, T.; Nakamura, S.; Ogino, A.; Nishinaga, A. *React. Kinet. Catal. Lett.,* **1991**, *45*, 165; (iii) Larrow, J. F., Schaus, S. E., Jacobsen, E. N. *J. Am. Chem. Soc.,* **1996**, *118*, 7420; (d) The HKR is complementary to biocatalytic methods exploiting epoxide hydrolases. For a review, see: Archelas, A.; Furstoss, R. *Trends Biotechnol.,* **1998**, *16*, 108.

2. (a) Amador, M; Ariza, X; Garcia, J; Ortiz, J, *J. Org. Chem.,* **2004**, *69,* 8172; (b) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc*., **1992**, *114*, 5426.
3. List, B. *Tetrahedron,* **2002**, *58*, 5573.

Chapter 2. Synthesis of Polyacylated-6-Heptenyl-5,6-Dihydro-*2 H*-Pyran-2-Ones

This chapter describes synthetic studies towards four naturally occurring δ-lactones and is divided into four sections.

Section A and B: These sections describe synthetic studies towards Synparvolide B and Pectinolide C

Section C and D: These sections describe synthetic studies towards (-)- Cleistenolide and (+)- Crassalactone A

Sections A and B

These sections describe common synthetic strategy involving temporary silicon tethered ring closing metathesis approach for the synthesis of Synparvolide B and Pectinolide C (**figure 2).**

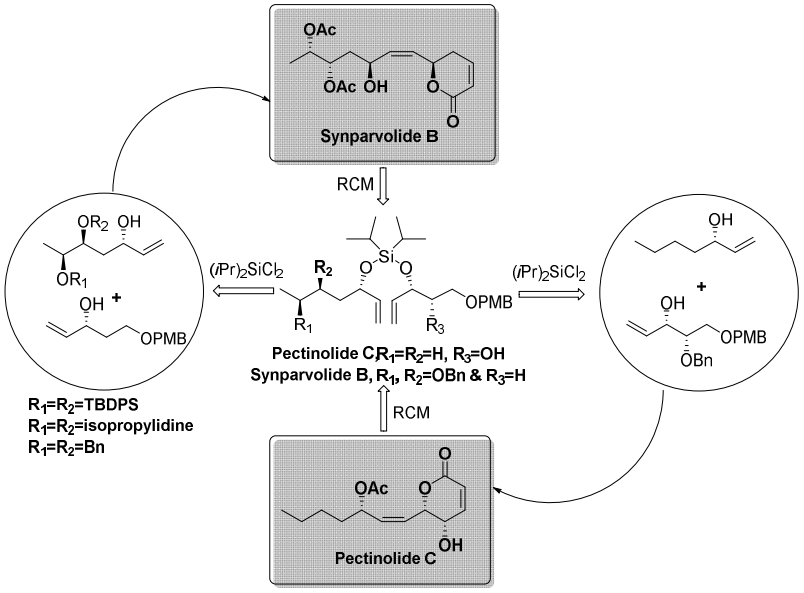


Figure 2: Common strategy for synthesis of Synparvolide B and Pectinolide C

Section A

Synthesis of Synparvolide B:

Introduction:

Synparvolide B[1-7] is one of the naturally occuring *α,β*- unsaturated *δ*- lactones among synparvolide A-C. It has been isolated from the leaves of ***Syncolostemon parviflorus***, a medicinal plant which is used as an emetic to treat loss of appetite. The biological properties of synparvolides have not yet been fully explored.

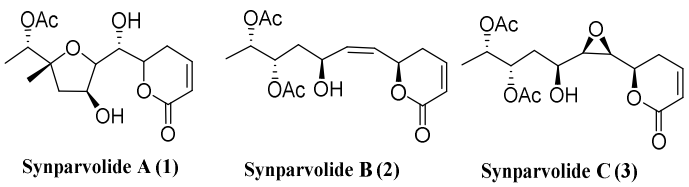


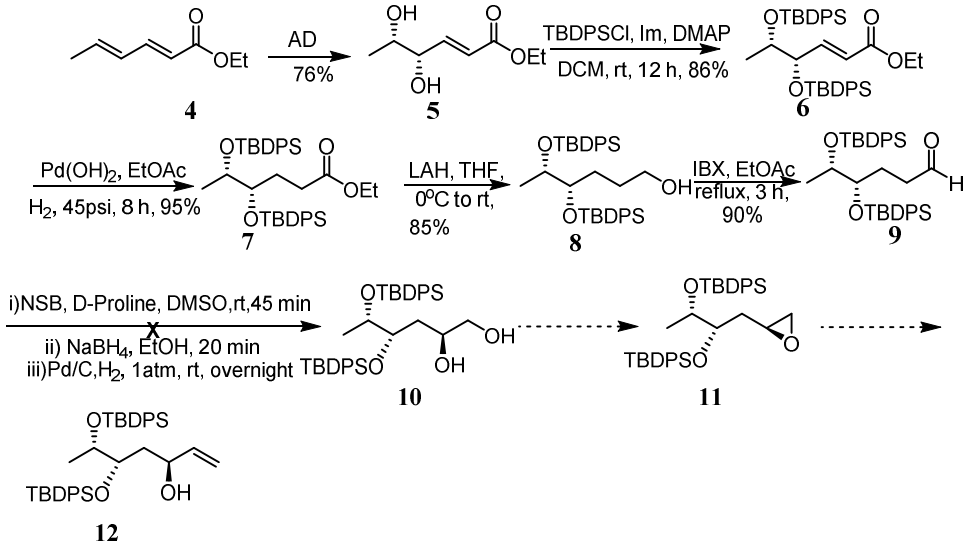
Figure 3: Synparvolides A-C

Till date only two total syntheses of synparvolide A and synparvolide C are known.[5] Hence it becomes important to explore more attractive and efficient synthetic strategy for the synthesis of these structurally varied synparvolides, as a part of our interest in designing attractive and efficient strategy for the synthesis of natural products containing α, β- unsaturated δ-lactones.

Results and Discussion:

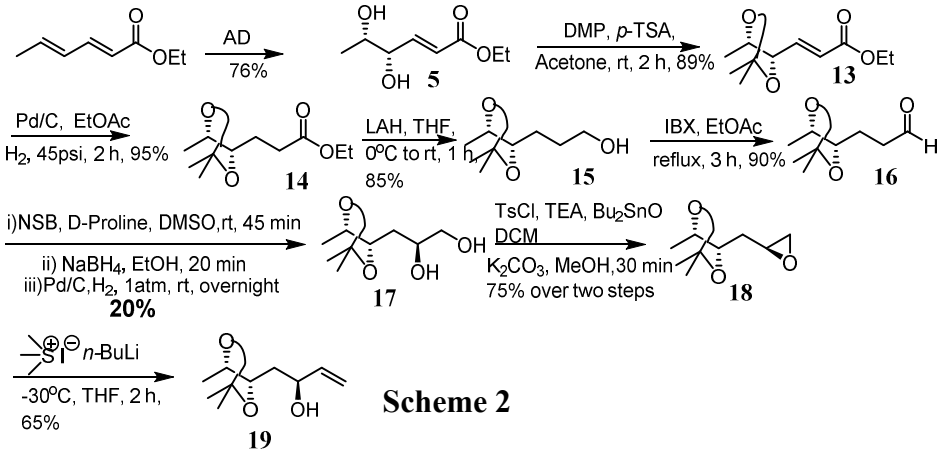
Herein we describe our attempt towards the synthesis of synparvolide B (**2**) from commercially available ethyl sorbate and 3-buten-1-ol employing HKR, AD and silicon tethered RCM as key steps.

Synthesis of Fragment 12



Scheme 1

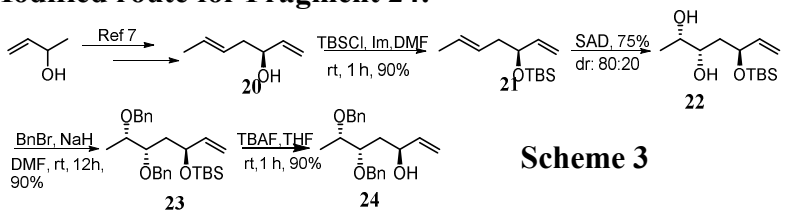
The synthesis of alcohol fragment begins with commercially available ethyl sorbate. The ethyl sorbate was enantioselectively converted to diol **5** under Sharpless asymmetric dihydroxylation condition in 76% yield and 85% e.e.[6] The diol was then protected as TBDPS ether **6** using TBDPSCl/ Imidazole. The TBDPS ether was then subjected to hydrogenation condition using H_2/ $Pd(OH)_2$ to give saturated ester **7** which was then reduced to alcohol **8** using LAH. The alcohol was oxidized to aldehyde **9** using IBX. The aldehyde was then subjected to α-aminoxylation using *D*-proline and nitrosobenzene. This reaction failed to give the desired diol which could have been further converted to epoxide **11** and then to alcohol **12**. The reason behind this failure could be the steric bulk of TBDPS group which inhibits the formation of enamine and hence α-aminoxylation did not occur.Since the α-functionalization of TBDPS protected aldehyde **9** was not successful we changed the strategy employing less bulky protecting group such as acetonide.



Scheme 2

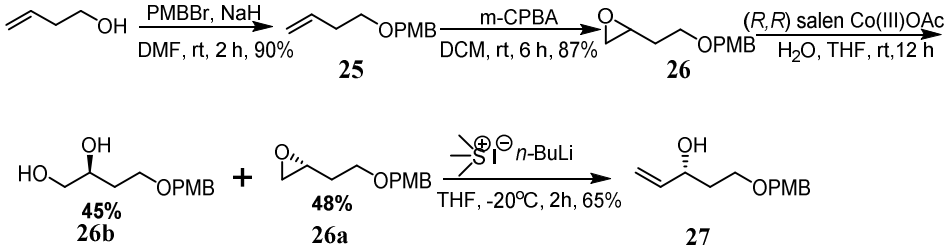
Although we were successful in obtaining allylic alcohol **19** from epoxide **18,** the overall yield was found to be very poor. So in order to obtain desired allylic alcohol in requisite quantities we had to switch to another high yielding reaction sequence.With this aim in mind we started the synthesis with Sharpless kinetic resolution of racemic (*E*)- hepta 1,5-dien-3-ol to yield **20**.[7] Alcohol **20** was protected as its TBS ether **21** and subsequent asymmetric dihydroxylation provided diol **22.** The resultant diol was protected as its dibenzyl ether **23** using BnBr/NaH**.** Then desilylation of compound **23** with TBAF in THF furnished allylic alcohol **24. (Scheme 3)**

Modified route for Fragment 24:



Scheme 3

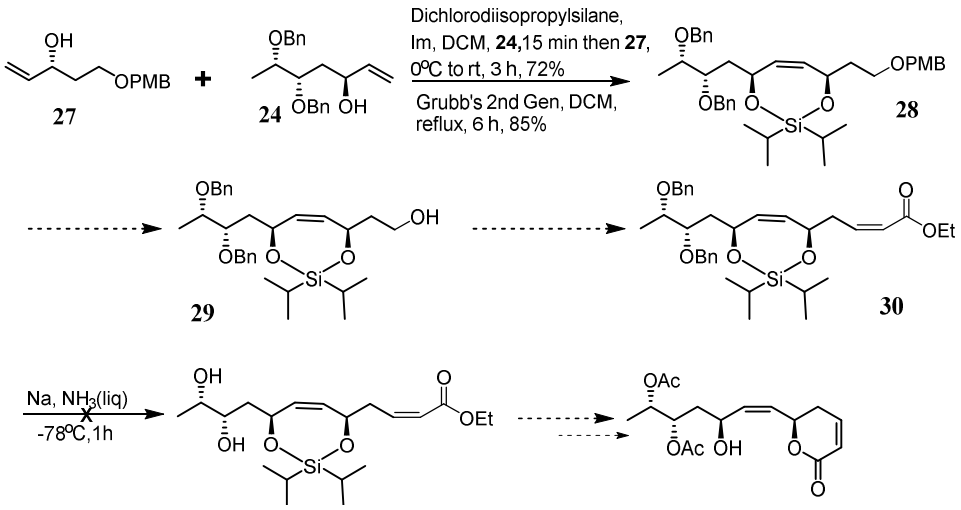
Synthesis of Fragment 27:



Scheme 4

For the synthesis of fragment **27**, 3-buten-1-ol was protected as PMB ether using PMBBr and NaH to furnish olefin **25**. The olefin was converted to epoxide **26** through *m*-CPBA epoxidation. The epoxide was then resolved to *R*- epoxide **26a** (48%) and *S*- diol **26b** (45%) in 99% e.e of each using chiral Salen Co (III) OAc catalyst. The epoxide was then opened with trimethylsulfonium methylide to furnish the allylic alcohol **27**. **(Scheme 4)**

Coupling of Fragments 24 and 27



Scheme 5

With the cross coupling partners in hand, we looked for optimal conditions for the fragment assembly to construct the side chain double bond of the target molecule **1** with *Z*-configuration. To this end, a silyl-tethered RCM was ideally suited to connect the two fragments **24** and **27**. The construction of the mixed *bis*-alkoxy silane **28** was achieved from the allylic alcohol **24** through the treatment with excess diisopropyldichlorosilane to afford the *mono*- alkoxychlorosilane, followed by the removal of the excess silylating agent and addition of the second allylic alcohol **27**. The subsequent RCM proceeded smoothly to furnish **28** in 85% yield. Next we turned our attention to the installation of the pyranone portion of the natural products synparvolide B (1)**.** Removal of PMB group by DDQ resulted the primary alcohol **29** in 90% yield. The alcohol **29** was oxidized to the aldehyde using Dess Martin periodinane in DCM. Olefination with ethyl 2-(bis(*p*-tolyoxylphosphoryl) acetate under Ando condition gave the corresponding unsaturated ester **30**. The stereoselectivity for this olefination step was >20:1 in favour of the Z isomer. The resulting ester was then treated with Na/liq. NH_3. But the reaction resulted in complex mixture of products which could not be characterised. Thus we were successful in construction of framework **28** which can be further manipulated to get the desired natural product Synparvolide B as illustrated in **scheme 5**.

Section B

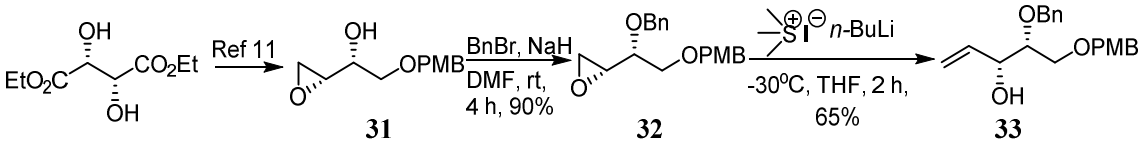
Synthesis of Pectinolide C:

Introduction:

Pectinolides (A-C) belong to a class of antimicrobial 5, 6-dihydro-α-pyrones

isolated from *Hyptis pectinata* in 1993.[9] Chloroform extract of *H. pectinata* leaves was found to show inhibitory activity against several microorganisms. In addition, this extract was cytotoxic (ED_{50}= 2.2 µg/ml) when tested in the in vitro P-388 murine lymphocytic leukemia assay system. The antimicrobial activity has been traced to the mixture of pectinolides A-C by bioassay-directed fractionation using the agar well diffusion method. These novel antimicrobial compounds were tested for cytotoxicity in several tumor cell lines and demonstrated significant activities (ED_{50}, <4 µg/ml).

Results and Discussion:

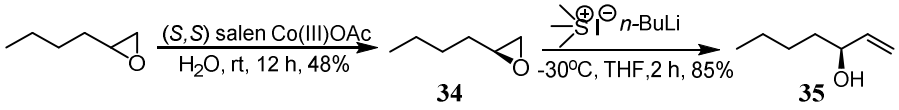


Scheme 6

For synthesis of fragment **33** diethyl *L*-tartarate was first converted to epoxy alcohol **31** using literature reported procedure.[11] The epoxy alcohol **31** was converted to its corresponding benzyl ether **32** using BnBr/NaH in DMF with 90% yield. The benzyl protected epoxy alcohol **32** was homologated to allylic alcohol **33** using trimethylsulfonium ylide in 65% yield**. (Scheme 6)**

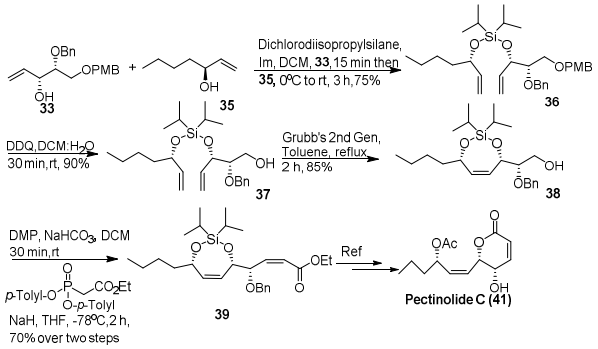
Synthesis of fragment 35:

The fragment **35** was easily obtained from HKR of (±) – 1, 2- epoxyhexane with *(S, S)* Salen Co(III)OAc catalyst to produce epoxide **34** and subsequent homologation with triimethyl sulfonium ylide in 85% yield. **(Scheme 7)**



Scheme 7

Coupling of Fragments 33 and 35

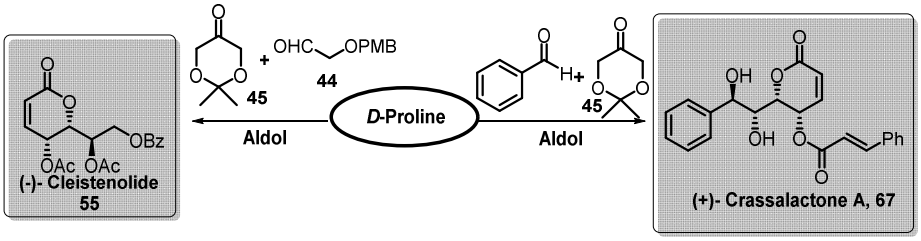


Scheme 8

The construction of the mixed *bis*-alkoxy silane **36** was achieved from the allylic alcohol **33**

through the treatment with excess diisopropyldichlorosilane to afford the *mono*-alkoxychlorosilane, followed by the removal of the excess silylating agent and addition of the secondary allylic alcohol **35**.[8] Removal of PMB group by DDQ resulted in the primary alcohol **37** in 90% yield. The subsequent RCM proceeded smoothly to furnish **38** in 85% yield. Next we turned our attention to the installation of the pyranone portion of the natural products Pectinolide A (2). The alcohol **38** was oxidized to the aldehyde using Dess Martin periodinane in DCM. Olefination with ethyl 2-(bis(*p*-tolyoxylphosphoryl) acetate under Ando condition[12a] gave the corresponding unsaturated ester **39**. The stereoselectivity for this olefination step was >20:1 in favor of the Z isomer. The conversion of resulting ester to Pectinolide C was as reported in the literature.[12b] **(Scheme 8)**

Sections C and D: These sections describe a common organocatalytic approach for the synthesis of Cleistenolide and (+)- Crassalactone A.



Scheme 9

Each section individually describes the synthetic approach for (-)- Cleistenolide and (+)- Crassalactone A involving 2,2-dimethyl-1,3-dioxan-5-one as the common synthon required to synthesize the desired intermediates towards the synthesis of target molecules **(Scheme 9).**

Section C

Synthesis of (-)- Cleistenolide:

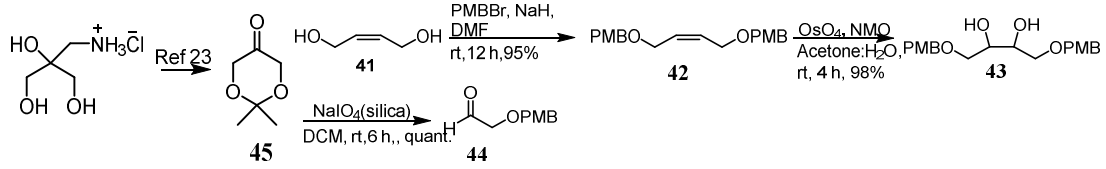
Introduction:

(-)- Cleistenolide is a heptenolide occurring in extracts from fruits, leaves, stem and root barks of ***Cleistochlamys kirkii*** Oliver,[13,14,15,16,19] an Annonaceae species occurring inTanzania an Mozambique.[17] The extract of this plant is used in traditional medicine as a remedy for treatment of wounds, infections, rheumatism, tuberculosis.[18] This heptenolide is known to exhibit antibacterial activity against ***Staphylococcus aureus*** and ***Bacillus anthracis*** as well as antifungal activity against ***Candida albicans.*** Till date nine syntheses have been reported using chiral pool approach[20]. No synthesis has been reported using organocatalytic asymmetric induction. Herein we describe an organocatalytic aldol reaction and subsequent stereoselective reduction for the synthesis of (-) - Cleistenolide.

Results and Discussions:

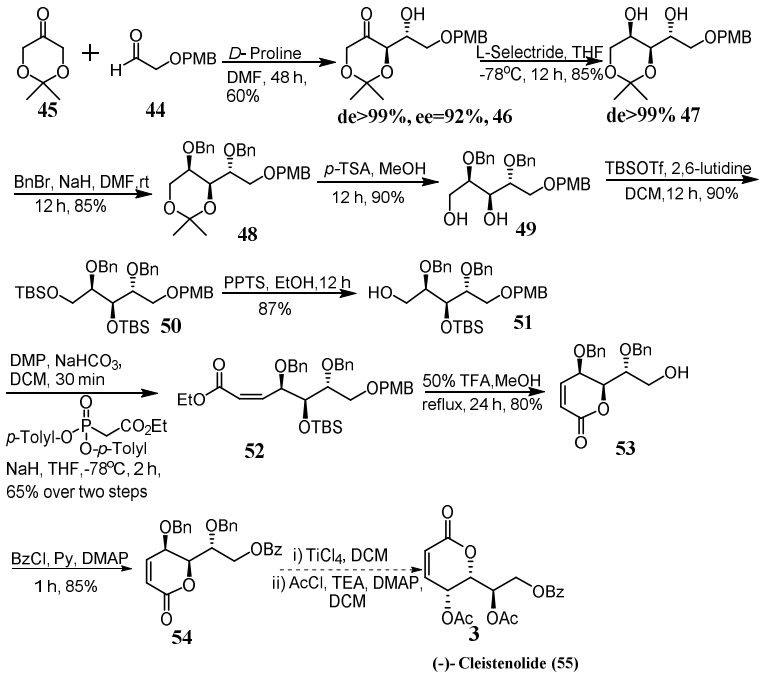
Herein we describe our attempt of organocatalytic aldol reaction and subsequent

stereoselective reduction for the synthesis of (-) - Cleistenolide.



Scheme 10: Synthesis of ketone 44 and Synthesis of aldehyde 43:

Proline catalyzed aldol reaction was performed to furnish *β*-hydroxy ketone **46** in 65% yield **(de>99).** [13]The *β*-hydroxy ketone was then stereoselectively reduced to diol **47** using L-selectride in THF in 85% yield as single diastereomer. The diol was subsequently protected as it dibenzyl ether **48** using BnBr/NaH in DMF in 87% yield. The acid hydrolysis of dibenzyl ether with *p*-TSA in MeOH furnished diol **49** which was then directly subjected to silyl ether formation using TBSOTf/2,6-lutidine in DCM to afford silyl ether **50**. The silyl ether was then treated with PPTS in EtOH which resulted in selective monodesilylation to produce alcohol **51.** The alcohol **51** was oxidized to the aldehyde using Dess Martin periodinane in DCM. Olefination with ethyl 2-(bis(*p*-tolyoxylphosphoryl) acetate under Ando condition gave the corresponding unsaturated ester **52**. The ester **52** on treatment with 10*N* HCl/THF produced lactone **53.** Lactone **53** was converted to its benzoyl ester **54**. Ester **53** on treatment with $TiCl_4$ and subsequent would lead to (-) Cleistenolide **55. (Scheme 11)**



Scheme 11

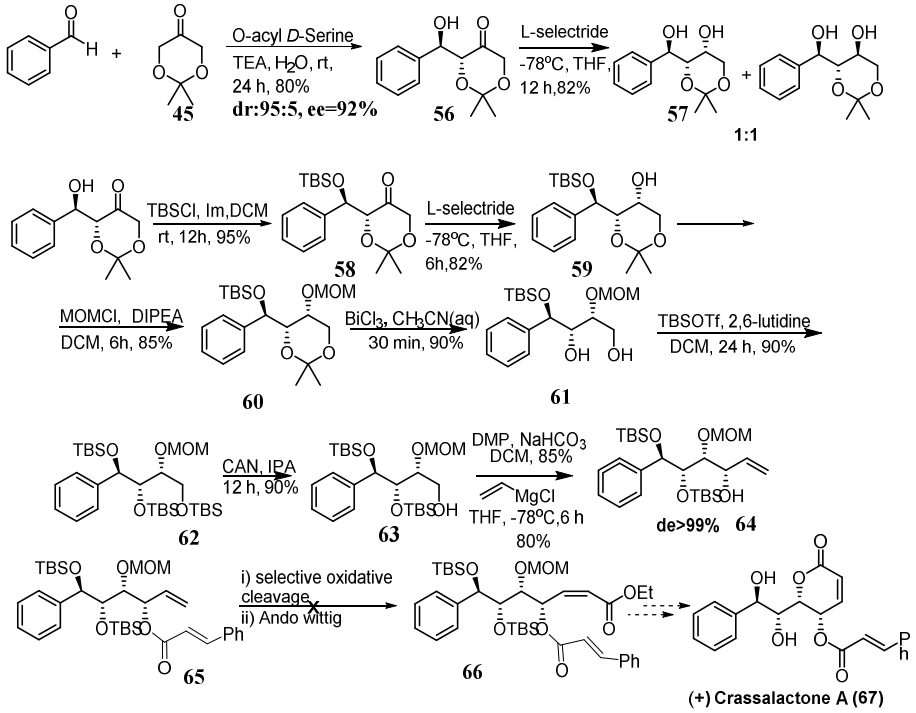
Section D

Synthesis of (+) Crassalactone A

Introduction:

(+) Crassalactone A is a *δ*-pyrone belonging to a group of styryl lactones. These styryl

lactones are an important class of secondary metabolites known for wide variety of medicinal properties. These exhibit significant cytotoxic activity against several human cancer cell lines.[21] The (+)-crassalactone A is isolated from the leaves and twigs of *Polyalthia crassa*.[22] The compound shows cytotoxic activity against a panel of mammalian cancer cell lines.



Scheme 12

Results and Discussion:

Organocatalyzed aldol reaction was carried out to synthesize *β*-Hydroxy ketone **56**.[24,25] This *β*-hydroxy ketone further undergoes stereoselective reduction to generate the third stereocentre. This diol on further synthetic manipulation gives protected tetrahydroxy motif **64.** Alcohol **64** was converted to cinnamate ester **65**. Conversion of intermediate **65** to **66** was unsuccessful. Thus we have achieved the synthesis of intermediate **65** that is desirable towards the synthesis of (+) Crassalactone A **(Scheme 12).**

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Chapter 3: Aryne intermediates in the Synthesis of Phenyl Indolines

Introduction:

3-Substituted indolines occur in many pharmacologically and biologically active components.Vinca alkaloids, including vinblastine, vincristine, vindesine and vinorelbine, are widely used antineoplastic drugs, either as single agents or in combination with other

drugs.The indoline scaffold has been known to occur in numerous bioactive alkaloids such as vinblastine **(1)**[1], strychnine **(2)**[2], (–)-physostigmine **(3)**[3], ajmaline **(4)**[4], and (+)-aspidospermidine **(5)**[5] (**Figure 4**) and is also the structural component of several important pharmaceutically active compounds, such as angiotensin-converting enzyme (ACE) inhibitor and the antihypertensive drug "pentopril" **(6)**[6]**.**

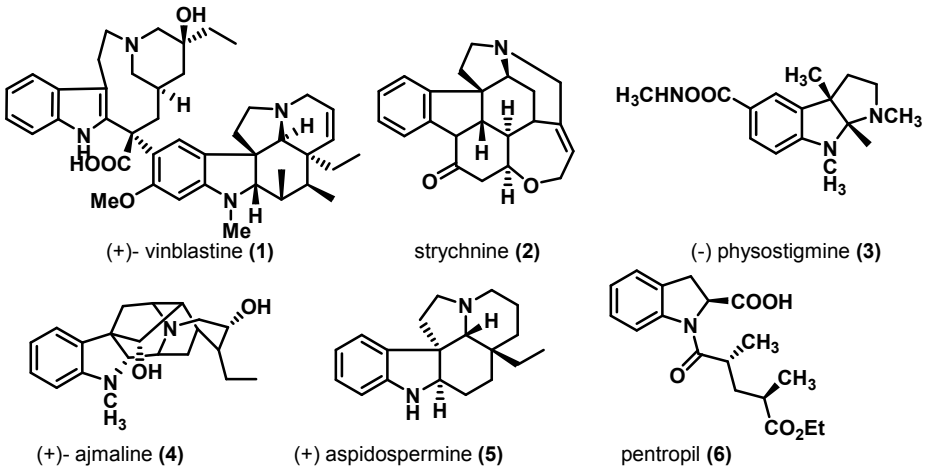
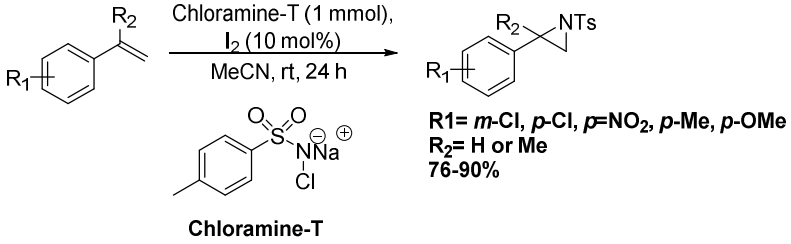


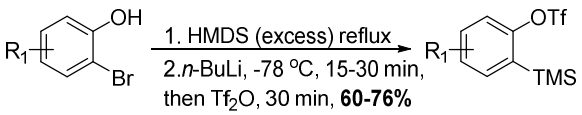
Figure 4

Results and Discussion:

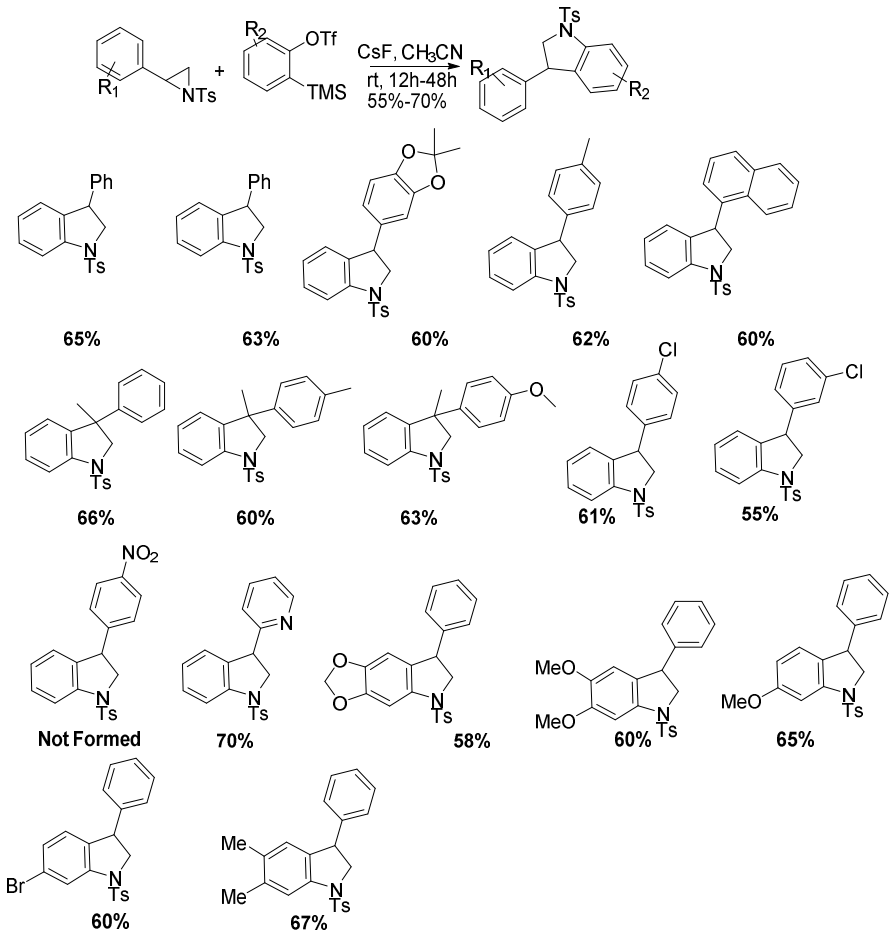
In present work we have applied single step transition metal free approach for synthesis of 3-aryl indolines. Substituted 3-aryl indolines were synthesised in one step using *N*-tosyl phenyl aziridines and substituted 2-(trimethylsilyl) phenyl trifluoromethanesulfonates in moderate to good yields **(Scheme 15).** For this purpose *N*-tosyl aziridines[7] **(Scheme 13)** and 2-(trimethylsilyl) phenyl trifluoromethanesulfonates[8] **(Scheme 14)** were synthesized according to the literature reported procedures.



Scheme 13



Scheme 14



Scheme 15

References:

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Chapter 4: Pd-SBA-TAT catalyzed C-C Cross Coupling Reactions

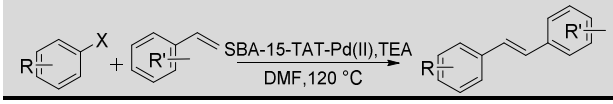
Introduction:

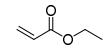
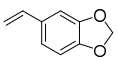
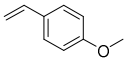
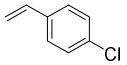
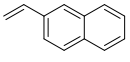
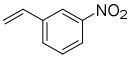
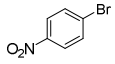
Over the past few years researchers have been successful in synthesizing various heterogeneous palladium catalysts. These include palladium complexes anchored to various inorganic or organic supports like Pd/SiO_2, [1] Pd/C,[2] palladium/resin,[3] palladium/MgO,[4] Pd-montmorillonite,[5] Pd/Al_2O_3,[6] palladium incorporated zeolites,[7] SBA-15 supported palladium catalyst,[8] and many others. These catalysts tend to catalyse only one kind of cross coupling reaction most of the times. Hence it becomes necessary to develop a robust and versatile catalyst which can be employed in most of the cross coupling reactions. In recent times ordered mesoporous materials have been utilized as a solid support in the synthesis of heterogeneous catalysts. Among these materials SBA-15 has triggered the interests of various researchers due to its high thermal stability, high surface areas, ease of accessibility and uniform pores size. The SBA-15 has added advantage that it can be suitably modified to develop various catalysts by functionalizing the organic hydroxyl groups and further the covalent bonding with inorganic support prevents the leaching of active site.

Results and Discussion:

Highly efficient and reusable SBA-15-TAT-Pd(II) catalyst has been synthesized by anchoring 2, 4, 6-triallyloxy-1, 3, 5-triazine (TAT) complex over the organo-functionalized surface of SBA-15.[9] The physiochemical properties of the organo-functionalized catalyst were analyzed by elemental analysis, ICP-OES, XRD, N_2 sorption measurement isotherm, TGA & DTA, solid state ^{13}C, ^{29}Si NMR spectra, FT-IR, XPS, DRS UV-Visible, SEM and TEM. XRD & N_2 sorption analyze to find out textural properties of synthesized catalyst and confirm that ordered mesoporous channel structure was retained even after the multistep synthetic procedures. The electronic environment and oxidation state of Pd in SBA-15-TAT-Pd(II) were monitored by XPS and DRS UV-visible techniques. The catalytic activity of synthesized catalyst SBA-15-TAT-Pd(II) was screened for hydrogenation reactions and shows higher catalytic activity with good turnover numbers (TON) under optimized experimental conditions with the maxima conversion (>99 %) and selectivity (100 %).[9] As the results obtained for hydrogenation reaction were highly exciting and interesting, we aimed at using the same catalyst for various C-C cross coupling reactions. To our delight, we were successful in employing SBA-15-TAT-Pd(II) catalyst for Heck, Sonogashira, Suzuki and Hiyama reactions. The results obtained in the reactions have been summarized in **Tables 1, 2, 3, and 4.**[1]

Table 1:Heck Reaction of various aryl iodides with different olefin[a]



Aryl Iodide	Olefin	Entry	Yield (%)	Time (h)
		1a	95	1
		1b	92	24
		1c	90	30
		1d	95	1
		1e	90	1
		1f	87	1
		1g	85	1
		1h	85	1
		1i	90	1
		1j	85	1
		1k	90	1
		1l	90	1
		1m	80	1
		1n	75	2
		1o	80	6
		1p	75	4
		1q	80	1
		1r	70	1
		1s	75	1
		1t	70	1
		1u	70	2

[a] **Reaction conditions:** Aryl halide (1 mmol), styrene (1.15 mmol), TEA (3 mmol), DMF (3.5 mL), heterogeneous SBA-15-TAT-Pd(II) catalyst (2 mol %) Temperature = 120 °C Isolated yields, product analyzed by GCMS and ^{1}H, ^{13}C NMR spectroscopy.

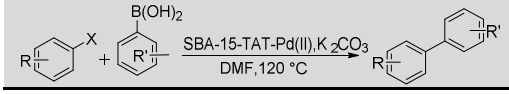
Table 2: Sonogashira Reaction of various aryl iodides with different phenyl acetylene[a]

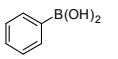
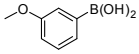
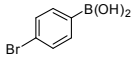
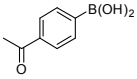
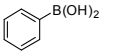
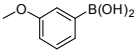
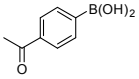
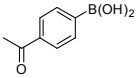
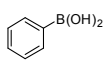
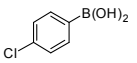
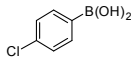
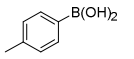
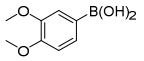
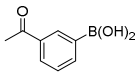
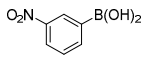
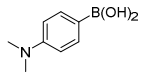
Aryl Iodide	Phenyl acetylene	Entry	Yield(%)	Time (h)
		2a	90	1
		2b	85	1
		2c	82	1
		2d	86	1
		2e	87	1
		2f	90	1
		2g	80[c]	3
		2h	80[b]	3
		2i	80	1

[a] **Reaction conditions:** Aryl halide (1 mmol), phenyl acetylene (1.15 mmol), TEA (3 mmol), DMF (3.5 mL), heterogeneous SBA-15-TAT-Pd(II) catalyst (2 mol%). Temperature = 120 °C Isolated yields, product analyzed by GCMS and ^{1}H, ^{13}C NMR spectroscopy.

[b] CuI (5 mol %) was used.

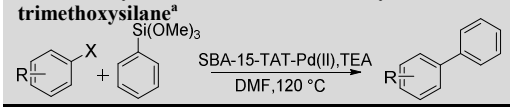
Table 3: Suzuki Reaction of various aryl iodides with different phenyl boronic acids[a]

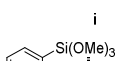
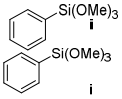
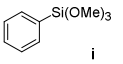


Aryl Iodide	Phenyl boronic acids	Entry	Yield (%)	Time (h)
		3a	90	1
		3b	90	1
		3c	85	1
		3d	82	1
		3e	80	1
		3f	85	1
		3g	85	1
		3h	85	1
		3i	85	1
		3j	85	1
		3k	85	2
		3l	85	1
		3m	80	1
		3n	87	1
		3o	82	1
		3p	86	2

[a] **Reaction conditions:** Aryl halide (1 mmol), phenyl boronic acid(1.15 mmol), K_2CO_3 (3 mmol), DMF (3.5 mL), heterogeneous SBA-15-TAT-Pd(II) catalyst (2 mol%). Temperature = 120 °C Isolated yields, product analyzed by GCMS and ^1H, ^{13}C NMR spectroscopy.

Table 4: Hiyama Reaction of various aryl iodides with phenyl trimethoxysilane[a]



Aryl Iodide	phenyl trimethoxysilane	Entry	Yield (%)	Time (h)
		3a	29	12
		3a	83	8
		3a	98	3
		4a	98	1
		4a	99	2
		4a	99	1
		3i	96	5
		3l	94	4
		4b	89	5

[a] **Reaction conditions:** Aryl halide (1 mmol), phenyl trimethoxysilane (1.5 mmoL), TEA (3 mmol), DMF (3.5 mL), heterogeneous SBA-15-TAT-Pd(II) catalyst (2 mol %). Temperature = 120 °C Isolated yields, product analyzed by GCMS and ^1H, ^{13}C NMR spectroscopy.

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CHAPTER-1

Introduction to

Jacobsen's hydrolytic kinetic resolution,

Silicon tethered ring-closing metathesis reactions and

Proline catalyzed reactions

1.1. JACOBSENS HYDROLYTIC KINETIC RESOLUTION

1.1.1. Introduction:

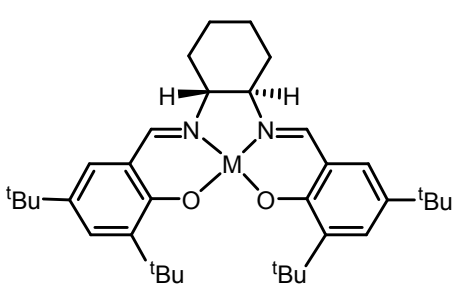
To this date development of new and efficient methods for the synthesis of optically pure compounds remains the most challenging field in the realm of organic synthesis. These methods are important for development of practical and approachable routes for synthesis of various naturally occurring compounds with multiple stereocentres. Amongst the various methods available for synthesis of enantiomerically pure compounds the asymmetric catalysis is the most important one. The asymmetric catalysis involves chiral catalyst driven synthesis of enantio-enriched compounds. The asymmetric catalysis is important from the point of view of cost effectiveness, practicality and efficiency for synthesis of these compounds. The asymmetric catalysis provides an efficient tool for control of stereoselectivity and enantioselectivity in the molecules with multiple stereocentres and varied stereochemical diversity. Although tremendous advances have been made in the field of asymmetric synthesis the field of asymmetric catalysis remains the most explored one since it provides easy access to optically active moieties with greater stereoselectivity and enantioselectivity. With different form of asymmetric catalysis available the kinetic resolution of racemates is the most preferred one for synthesis of enantiomerically pure compounds. The kinetic resolution involves the reaction of a racemic mixture with a chiral catalyst or a chiral reagent to provide the less reactive stereoisomer in enatiomerically enriched form.

Epoxides form a very important class of organic compounds which not only are units in naturally occurring compounds but are also useful synthetic intermediates in multistep synthesis. As optically active epoxides are important intermediates in multistep syntheses there is always growing demand for development of practical and inexpensive methods for the synthesis of same. Out of the numerous methods available for their synthesis the olefin oxidation approach is the most popular one.[1]

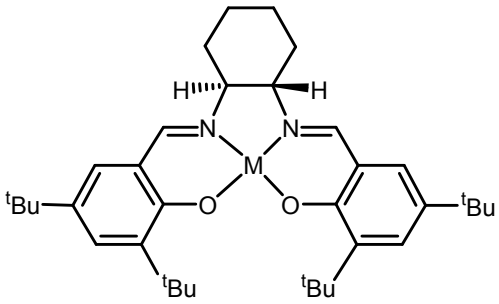
Asymmetric catalysis has provided an important tool for the synthesis of enantio-enriched epoxides using either enantioselective alkene epoxidation approach or kinetic resolution of racemic epoxides. Out of numerous enantioselective alkene epoxidation methods available for optically active epoxides Sharpless epoxidation remains at the forefront in asymmetric catalysis reaction as it provides easy access to a variety of enantiomerically enriched epoxy alcohols.[2] For unfunctionalised conjugated alkenes Jacobsen-Katsuki epoxidation is

employed where chiral Mn (III) - salen complex acts as chiral catalyst providing a certain class of enantio-enriched epoxides.[3] In case of Shi epoxidation, fructose derived dioxirane catalyst is used for epoxidation of various alkenes producing optically active epoxides. Other numerous approaches have also been developed for epoxidation of various classes of alkenes like conjugated enones, cis-enynes and chalcones which furnish a variety of enantiomerically pure epoxides that can be converted to synthetically useful intermediates.[4] Apart from direct methods of synthesis of epoxides indirect methods are also available. These employ halohydrins and cis-1, 2-diols as intermediates which can be further converted to epoxides.[5] Along with these synthetic methods enzymatic methods have also been employed for the synthesis of enantio-enriched epoxides.[6]

Although innumerable synthetic methods have been developed for synthesis of enantio-pure epoxides there is no direct general method for preparation of enantiopure terminal epoxides. As terminal epoxides serve as important motif in organic synthesis that can be converted to synthetically or biologically important intermediates, it becomes necessary to explore methods for their synthesis. In 2001 Jacobsen reported synthesis of enantio-enriched terminal epoxides from their corresponding racemic precursors employing chiral Co (III) – salen complex (**Figure 1)** in presence of H_2O.[7] This method holds great promise as it can be applied to a variety of terminal epoxides and furnishes products with high enantioselectivity as high as $\geq$ 99%. Besides some epoxides which are generally used as precursors for multistep target oriented synthesis like propylene epoxide, glycidol, 1, 2-epoxy styrene, butadiene monoepoxide are commercially available and are inexpensive.[8,9] Also functionalised terminal epoxides can also be synthetically prepared by epoxidation of olefin. Owing to the easy accessibility and inexpensive nature of starting materials this method has been proved highly useful for kinetic resolution of variety of 1-oxiranes.

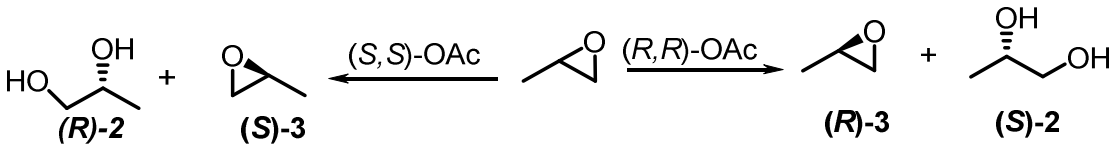


M=Co: (*R, R*)-1
M=Co-OAc: (*R, R*)-1- OAc



M=Co: (*S, S*)-1
M=Co-OAc: (*S, S*)-1-OAc

Figure 1: (Salen) Co complexes



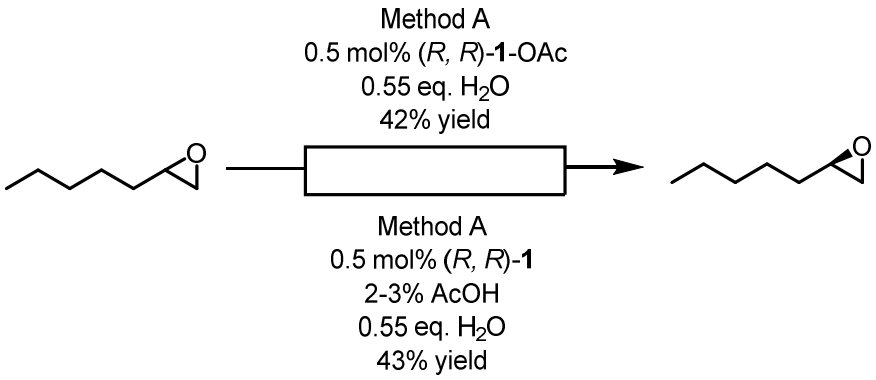
Scheme 1: Jacobsen's Hydrolytic kinetic resolution

Jacobsen's Hydrolytic kinetic resolution has provided a general tool for conversion of racemic terminal epoxides into their corresponding enantio enriched form. This method not only gives enantio enriched terminal epoxide with higher enantioselectivities but also is applicable to practically any kind of terminal epoxides.

1.1.2. Preparation of Catalyst and General Experimental Considerations:

The Co(II)-salen-**1** catalyst is commercially available in both the enantiomeric form or can be synthetically prepared from $Co(OAc)_2$.[10] But this catalyst is inactive for hydrolytic kinetic resolution, hence it has to be converted from Co(II) to Co(III) prior to HKR through one electron oxidation. This can be achieved by subjecting the catalyst **1** to aerobic oxidation in presence of Brönsted acid. For this purpose two methods have been developed for activation of catalyst **1.** Method A involves stirring a calculated amount of catalyst 1 in calc. 1M solution with 2 equiv. of acetic acid under aerobic condition for 30 min upon which the orange coloured catalyst changes to brown coloured solid. All the volatiles are removed under vacuum and a brown coloured solid is obtained. This brown coloured solid, which is the activated form of catalyst **1,** is directly employed in HKR without further purification. In Method B the activated catalyst is generated in situ by stirring a mixture of epoxide or epoxide + solvent under HKR conditions and addition of acetic acid in open atmosphere.

Catalysts obtained by both the methods were employed in HKR of various terminal epoxides. In most of the cases such as HKR of 1, 2-epoxy hexane, catalysts obtained by both the methods were equally efficient in carrying out HKR of varied terminal epoxides with higher enantioselectivities of desired compounds. But in case of less reactive epoxides, method A was much more viable for achieving desired results. When Method B was employed in HKR for less reactive epoxides, optimization of catalyst amount and solvent was required. In a typical experimental procedure the HKR of terminal



Scheme 2: General Reaction for Jacobsen's Hydrolytic Kinetic Resolution

epoxides was carried out by addition of 0.55 equiv. of H_2O and 0.2 mol % of Co (III) –salen catalyst to racemic epoxides and the solution was stirred for 12h-24h under aerobic conditions. In most of the cases no solvent was required for complete resolution but in case of lipophilic substrates solvents such as THF, 2-propanol and 1, 2- hexanediol were crucial for complete resolution of racemic epoxide. Also depending on the complexity and degree of functionalization of epoxides, the catalyst loading varied from 0.2 mol% to 2 mol%.

[(*R*,*R*)-*N*,*N*'-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminato(2-]cobalt(II) ((*R*,*R*)-1). A solution of cobalt(II) acetate tetrahydrate (5.98 g, 24.0 mmol) in MeOH (80 mL) was added to a solution of ligand [(*R,R*)-*N*,*N*'-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine] (10.9 g, 20.0 mmol) in CH_2Cl_2 (80 mL) via cannula under an atmosphere of N_2 with careful exclusion of air. A brick-red solid began to precipitate before addition was complete. The sides of the reaction flask were rinsed with MeOH (20 mL), and the mixture was allowed to stir for 15 min at room temperature and then 30 min at 0 °C. Precipitated solids were isolated by vacuum filtration and rinsed with cold MeOH (2 x 75 mL). The red solid was collected and dried in vacuo to yield [(*R*,*R*)-*N*,*N*'-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminato(2-)]cobalt(II) ((*R*,*R*)-**1**) (11.6 g, 19.2 mmol, 96%).

1.1.3. Mechanistic Aspects of Jacobsen's Hydrolytic kinetic resolution:

The Jacobsen's hydrolytic kinetic resolution displays extraordinary substrate generality and broad substrate scope enabling to achieve enantiomerically pure terminal epoxides with greater stereoselectivity. In almost all the racemic epoxides analysed for HKR the relative rate of reaction with respect to both the enantiomers in the substrate k_{rel} was found to be as high as > 500 in some cases and > 100 in other cases. Kinetic investigation of HKR has revealed that the hydrolytic ring opening of terminal epoxides is essentially a second order reaction which depends on concentration of catalyst and two molecules of catalyst are involved in rate limiting step. The rate limiting step occurs in bimetallic cooperative catalysis mode where one molecule of catalyst activates the epoxide while other molecule activates the H_2O as a nucleophile.

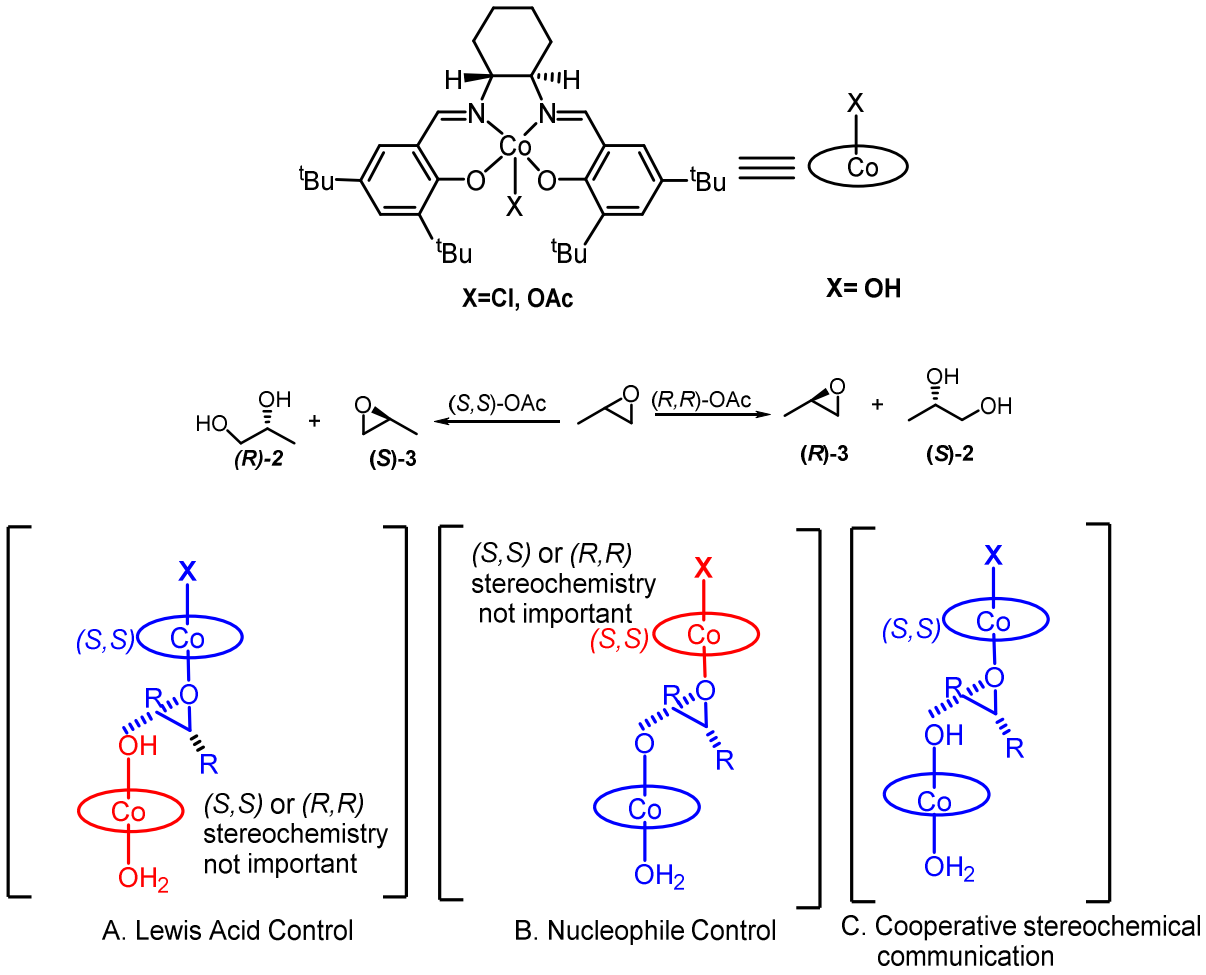
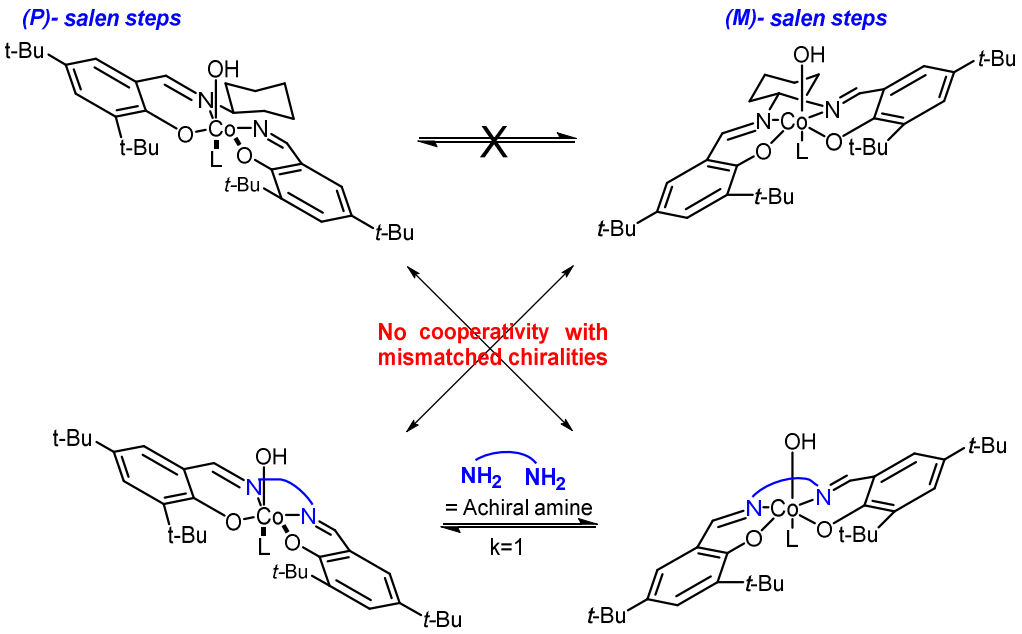


Figure 2: Binding of Salen Co complex with epoxide and nucleophile



P- conformation of formally achiral Co(III) salen complex

M- conformation of formally achiral Co(III) salen complex

Figure 3: Geometries of epoxide complexation to the chiral (salen) Co (III) complex.

After careful investigation of calculated transition structures it was found that there is very little or no spatial interaction of bimetallic assembly with the organic fragment in epoxides. The stereochemical outcome of the reaction solely depends on the chiral stepped conformation of salen ligand **(Figure 3)**. The salen step is an important feature of (salen) Co (III) complexes regardless of whether the ligands are derived from chiral amines. The geometry of the transition state when epoxide binds to Co (III) centre of the complex is the same irrespective of the nature of epoxide substituent. Hence in most of the cases desired results were obtained without selectivity factor dropping below 50.The sole role of epoxide substituent is to position the less substituted electrophilic reactive site with respect to catalyst. This explains the higher enantioselectivity and broader substrate scope in HKR.

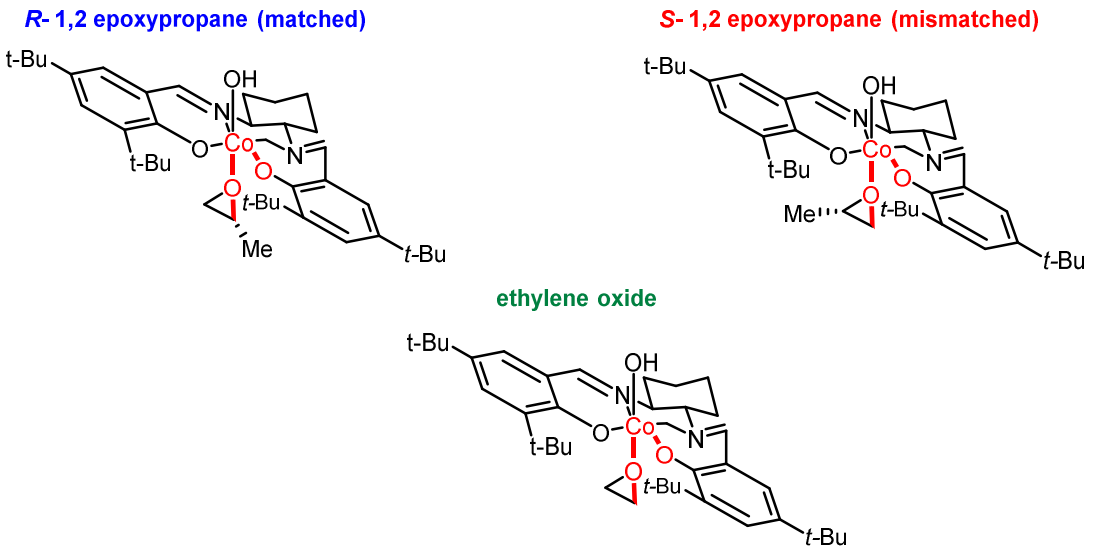


Figure 4: Chiral stepped conformation of salen ligand

Different mechanistic aspects of HKR were investigated by Jacobsen and co-workers to explain the effect of catalyst concentration, structure of racemic epoxides and orientation of ligands around the metallic centre on the outcome of HKR.[11] Using different experimental and computational techniques it was found that the hydrolytic ring opening reaction of epoxide proceeded through bimetallic Co (III) complex where one part acts as Lewis acid while the other part is the nucleophile. For appreciable hydrolysis to occur it was necessary that the absolute stereochemistry of Lewis acid catalyst matched with absolute stereochemistry of nucleophilic catalyst **(Figures 3 and 4)**. The monometallic complexes either in the form of Lewis acid catalyst or nucleophilic catalyst were incapable of rendering desired results.

1.2. SILICON TETHERED ASSISTED RING-CLOSING METATHESIS REACTIONS

1.2.1. Introduction to Silicon Tethered Reactions

Intramolecular reactions have been widely explored for the synthesis of complex target molecules owing to their efficiency to provide higher regio and stereoselectivity. This

exploration has given rise to the field of tethered reactions where the intermolecular reaction is converted to corresponding intramolecular variant by employing a temporary tether. These tether reactions often resemble to enzymatic reactions where the enzyme binds to the active site of specific substrate. After the formation of product the enzyme dissociates itself from the active site of substrate thus illustrating temporary nature of the enzyme-substrate complex.[12, 13] Tethers serve the same purpose in target oriented synthesis where the reactive sites are temporary held together to achieve desired reaction. The choice of tether plays an important role with respect to ease of anchoring the reactive partners to the tether and conversion of tether to appropriate intermediates to provide desired products.

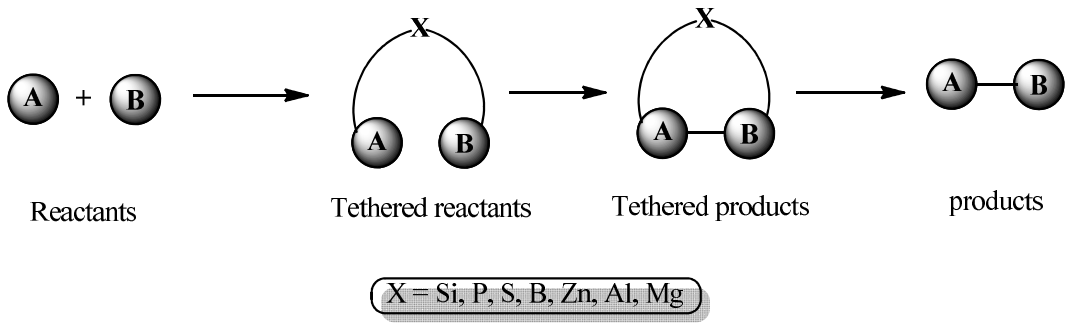


Figure 5: Application of temporary tethers in organic synthesis.

The tethers offer the benefit of converting intermolecular reaction into their intramolecular variant. This enhances the rate reaction considerably due to close proximity of reacting partners ensuring their higher effective concentration thereby lowering the activation entropy. Also due to considerable conformational restriction in the transition state, the reaction results in higher regio- and stereoselectivity.

1.2.2 Silicon as ideal tether of choice:

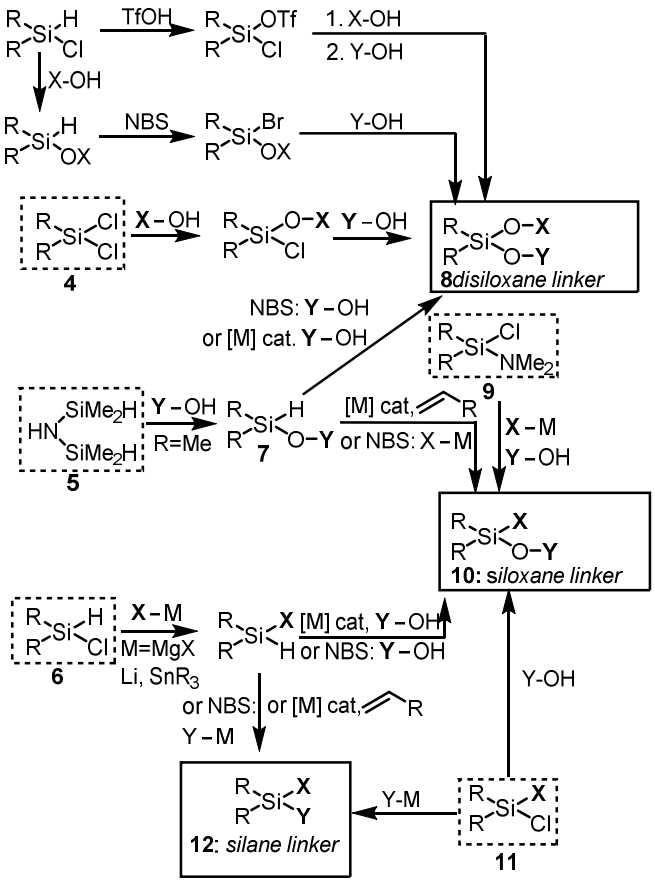
Out of the various linker atoms available for tethering, silicon tethering has been the most explored method of tethering. Silicon tethers are easily accessible through formation of siloxanes or disiloxanes (**Figure 6**).[14] Furthermore these tethers can be functionalized to synthetically useful intermediates through protodesilylation, oxidation, silane-group transfer or transmetallation.

siloxanes **disiloxanes**

Figure 6: Siloxanes and Disiloxanes

The first report of silicon tether appeared in mid 1980's by the independent study of Nishiyama and Stork where in silicon tether was utilized in the context of free radical addition.[15]With the advancement of research, silicon tether was incorporated in cross-coupling reactions[16], hydrosilylation[17] and [4+2] cycloadditions.[18] The recent literature has reported the use of silicon tether in transition-metal-catalyzed cycloisomerization and ring-closing metathesis reactions.[19]

Amongst the available methods of tether incorporation, the widely used method for tether incorporation is the formation of disilioxane using dichlorodialkyl silanes through sequential addition of reacting partners. Using the appropriate dichlorodialkyl silanes, the disilioxane motif is synthesized through sequential addition of two alcohols. The single substitution occurs at silicon when one of the alcohols is added to excess dichlorodialkyl silane. The excess reagent facilitates formation of monosiloxane fragments and overcomes the obvious problem of disubstitution. The excess reagent is removed in vacuo followed by the addition of second alcohol. This single step sequential addition gives access to disiloxane **8** in good yields. This is the general method for introducing silicon tether where volatile dichlorodialkyl silanes are involved. For the non volatile variants of dichlorodialkyl silanes stepwise procedure is required for tether incorporation. In such cases tetraalkyldisilazanes **12** or chlorosilanes **11** will silylate alcohols to give intermediate siloxanes **10**[20, 21] which can be reactivated to a second nucleophilic displacement using halide electrophiles, or perhaps more appealingly can undergo metal-catalysed Si–O bond formation.[22]



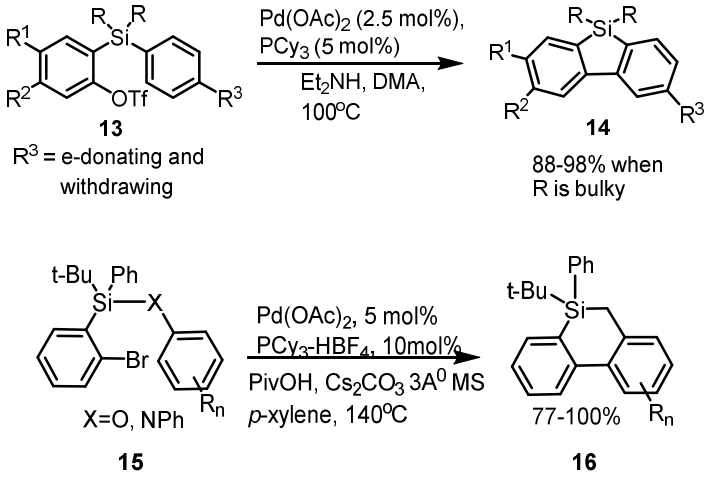
Scheme 3: Common routes for TST construction

1.2.3 Silicon-tethered Reactions:

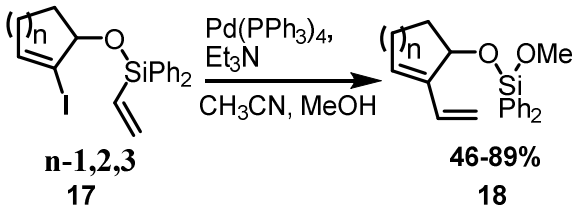
In recent times silicon tether has been employed in a variety of metal mediated reaction such as alkene metathesis, hydrosilylation, carbosilylation, cross-coupling and Heck chemistry and allylation reactions.

1.2.3.1. Palladium-catalysed cross-coupling reactions:

One of the most emerging fields in the area of synthetic organic chemistry is C-H activation. The discovery of silicon tethers have led to whole new arena of C-H activation wherein synthesis of dibenzosiloles have been achieved using a silicon tether. When tethered aryl triflates **13** were treated with $Pd(OAc)_2/PCy_3$, silicon-bridged biaryls (dibenzosiloles) were obtained. Different dibenzosiloles were synthesized having both electron donating and electron withdrawing substituents. Young and co-workers developed a silicon-tethered version of Heck reaction, allowing a vinyl substituent to be readily attached to a 5, 6 or 7-membered ring.[23]The reaction is useful for alkenylation of five- and six-membered rings, but less efficient for medium rings **(Scheme 4)**.[16]



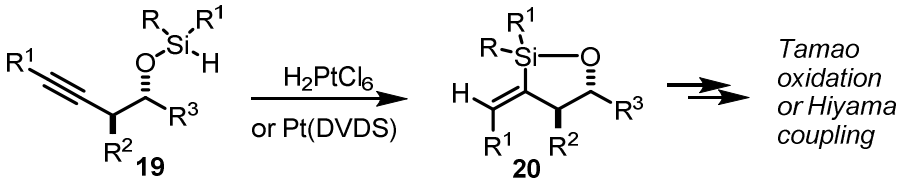
Scheme 4: Synthesis of silicon-bridged biaryls via C–H activation (Hiyama)



Scheme 5: Silicon-tethered Heck reaction

1.2.3.2 Hydrosilylation and carbosilylation[17]:

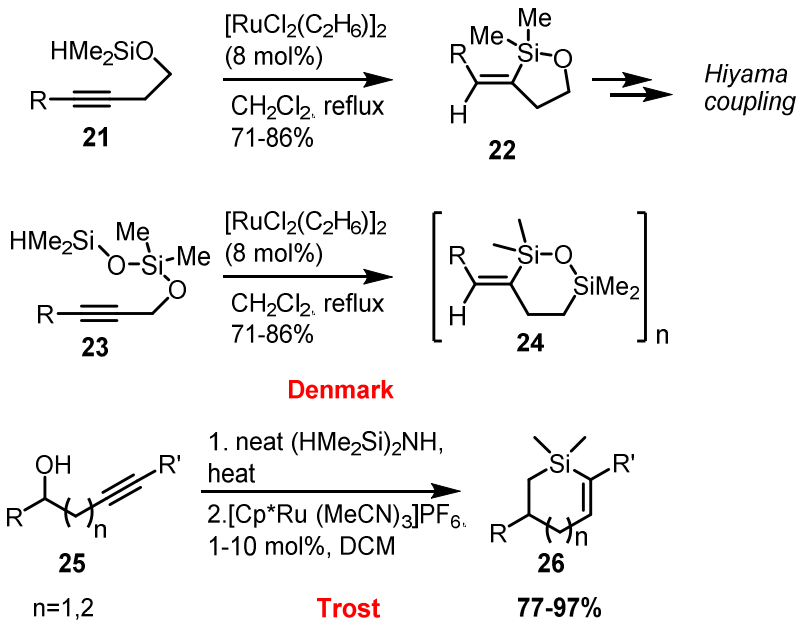
Hydrosilylation of acetylenes is an important approach for the synthesis of vinylsilanes which serve as important intermediates in multistep organic synthesis. The intramolecular version of hydrosilylation provides an important tool to furnish products with higher region and stereoselectivity. Since the first report of alkyne hydrosilylation reaction by the Tamao group in 1988, several methods have been developed to access a variety of vinylsilanes with all the



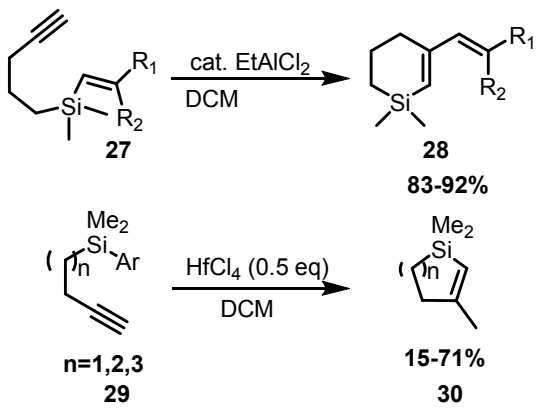
Scheme 6: Platinum-catalysed (syn, exo) hydrosilylation

possible stereochemistries. A wide range of transition metal catalysts have been employed to carry out the transformation of hydrosilanes with homopropargyl moiety to silioxanes. The outcome of reaction largely depends on the transition metal catalyst employed in the reaction.

When platinum based catalyst was employed [(H_2PtCl_6) or Pt (1,1,3,3-tetramethyl-1,3-divinyldisiloxane)] *syn* hydrosilylation was observed leading to the formation of *E*-vinyl siloxanes in a exo-addition of Si–H **(Scheme 9)**.[24]In contrast to these results Denmark and co-workers[25] found that when ruthenium catalyst ($[RuCl_2(C_2H_6)]_2$) was employed for the same reaction, the reaction proceeded in *anti*, exo-dig manner. In another studies Trost and co-workers[26] discovered formation of siloxanes in *endo-dig* manner when a different ruthenium catalyst ($[Cp^*Ru(MeCN)_3]PF_6$) was involved **(Scheme 7)**.



Scheme 7: Ruthenium-catalysed *exo*-dig and *endo*-dig hydrosilylation



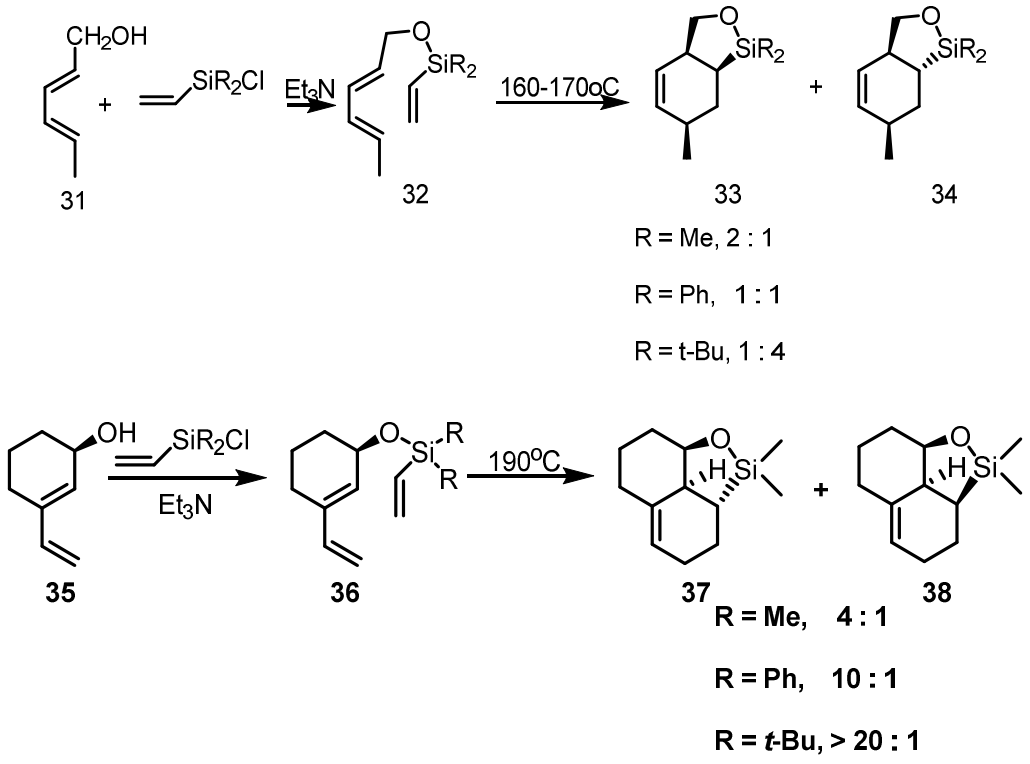
Scheme 8: Lewis Acid catalyzed stereoselective carbosilylation.

Along with hydrosilylation a *trans* carbosilylation process has also been reported by the Yamamoto group.[27]In this process silicon-tethered alkynylvinylsilanes are converted to corresponding six-membered silacycles in the presence of Lewis acid such as s $EtAlCl_2$ .A

variety of silylated carbocycles and silacycles were synthesized bearing five, six and seven membered rings with good yields and high regio- and stereoselectivity which were not easily accessible by previous methodologies. The reactions proceeded via *exo*-dig cyclisation to predominantly form the *trans* aryl silylated products **(Scheme 8)**.

1.2.3.3: Cycloaddition

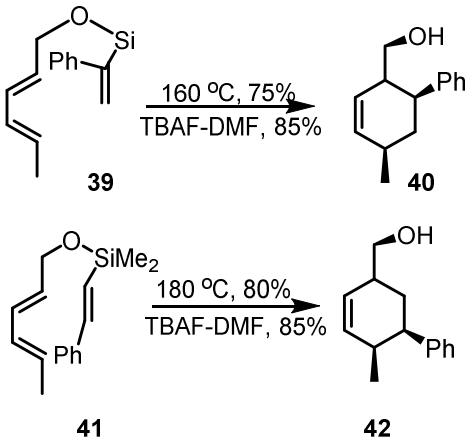
Cycloaddition reactions have played an important role in the construction of various cyclic compounds as they allow formation of C-C bonds in a concerted manner. In earlier reports a variety of intermolecular versions of cycloadditions have been explored for C-C bond formation. But with the advent of silicon tethers intramolecular variant of the same has been explored for the construction of cyclic system. The silicon tethers not only bring the reaction partners in close proximity but also provide rigid conformational structure in transition state so as to furnish product with higher regio- and stereoselectivity **(Scheme 9)**.



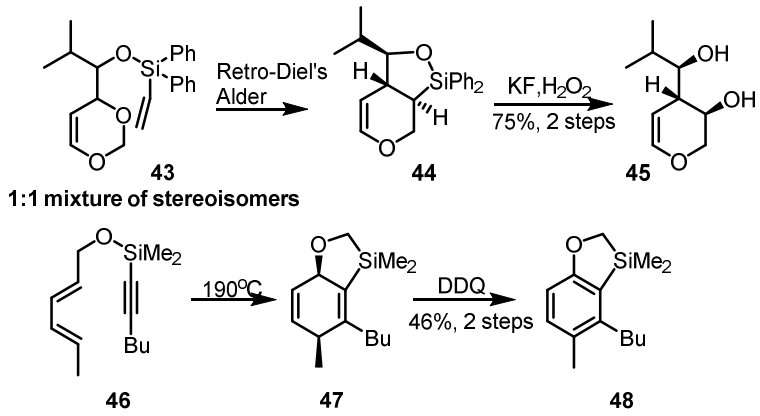
Scheme 9: Silicon Tethered [4+2] cycloadditions.

These cyclic siloxanes post desilylation furnish synthetically important intermediates which can be employed in multistep target oriented synthesis.[28]Also it was found that post desilylation the product obtained was a single isomer although the precursor was a mixture of

diastereomers **(Scheme 9)**. This selectivity can be attributed to the rigidity provided by the cyclic siloxanes in the transition state.[29]

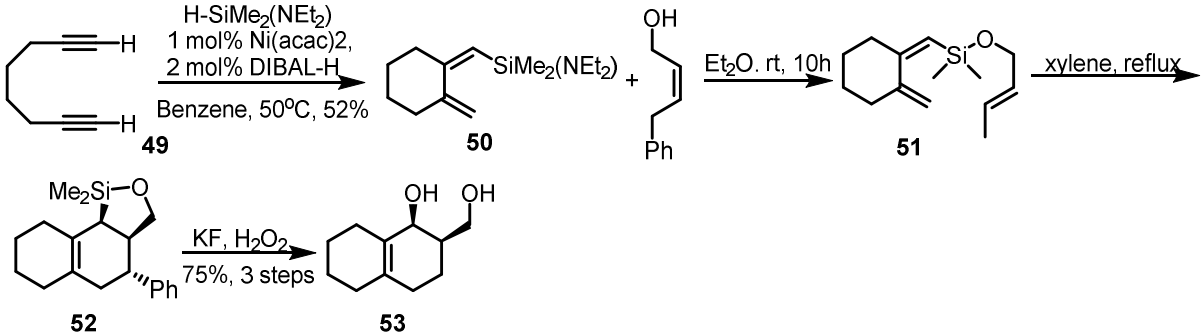


Scheme 10: Stereoselectivity and regioselectivity in silicon tethered cycloadditions.

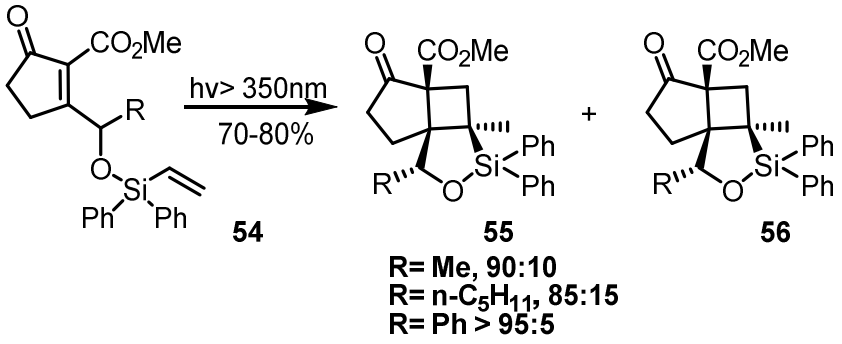


Scheme 11: Silicon Tethering in hetero Diels Alder reaction.

The silicon tethered version for all carbon Diels Alder reaction was also applied to hetero Diels Alder reaction and similar results were found as in case all of carbon Diels Alder reaction **(Scheme 11)**.[30]

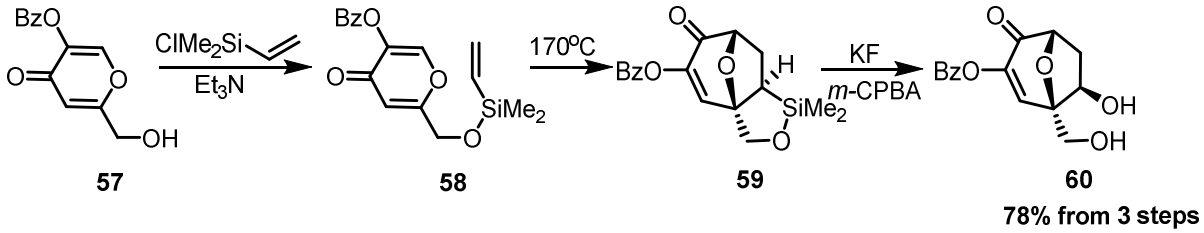


Scheme 12: Functionalization of cyclic siloxanes

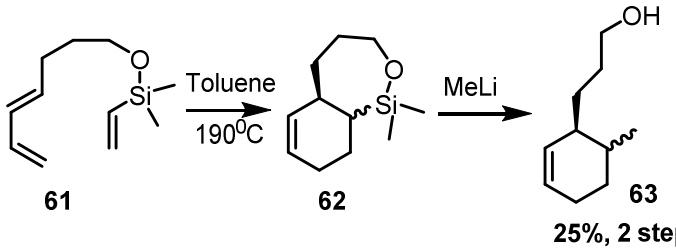


Scheme 13: Photochemical [2+2] cycloadditions

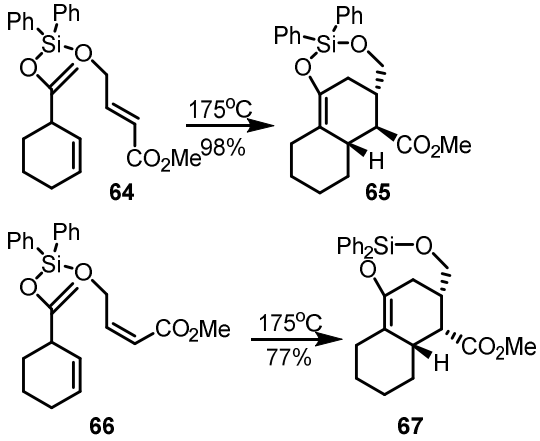
Apart from the usual [4+2] silicon tethered cycloadditions photoinduced [2+2] silicon tethered cycloadditions were also observed **(Scheme 13).**[31]

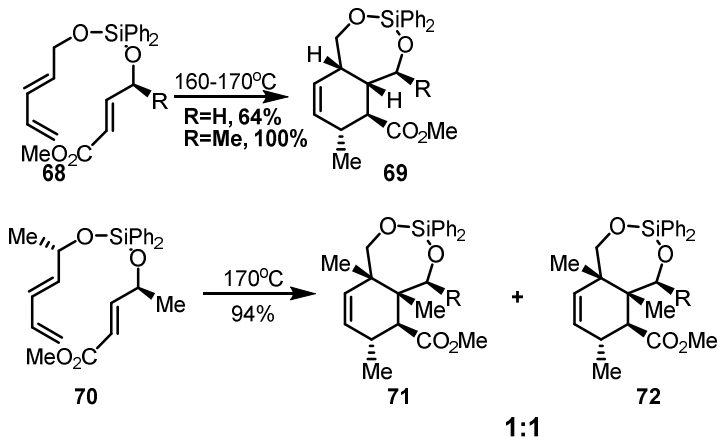


Scheme 14: [5+2] Cycloaddition reaction[32a]

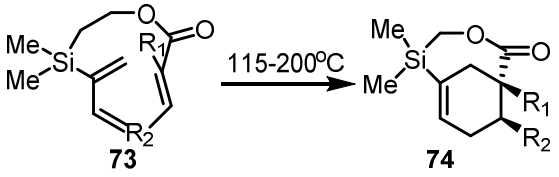


Scheme 15: Diels Alder to form 6-atom Silicon Tether[32b]



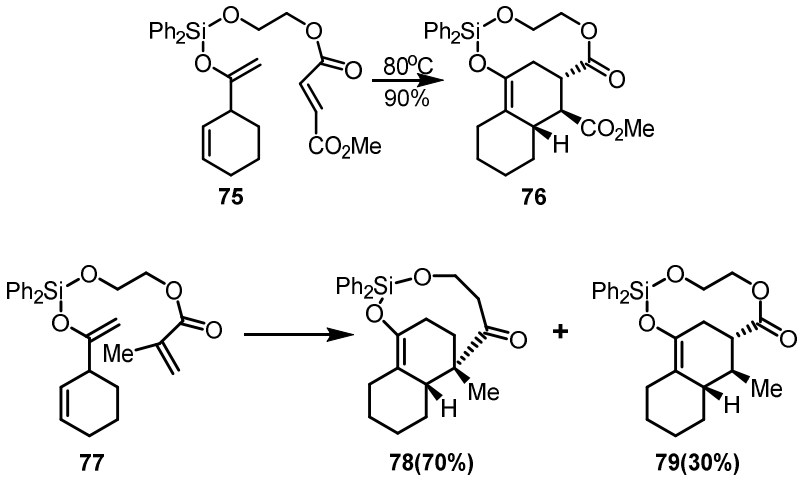


Scheme 16: Silyl acetal 7-atom Tether Ring[32c]



R_1	R_2	Yield (%)
H	H	98
Me	H	88
H	Me	78
H	Ph	93
Me	Me	65
CN	Pr	53

Scheme 17: Type II Diels Alder 8-atom Tether Ring[33]

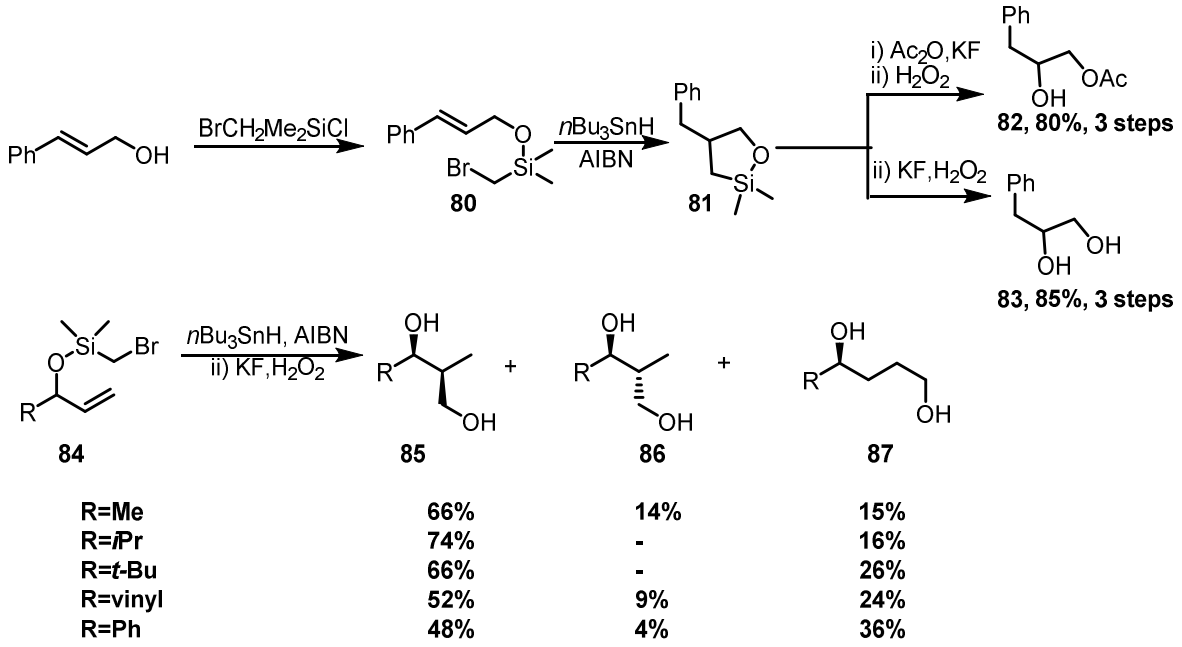


Scheme 18: Formation of longer Silicon Tether Rings

Along with 5-atom silicon tether ring which have been employed in [4+2], [2+2] and [5+2] cycloaddition reactions larger silicon tether rings[33] were also reported **(Scheme 14 to Scheme 18).** These silicon tethers not only facilitate the formation of desired product as compared to intermolecular version but also provided greater stereoselectivity. In some cases where intermolecular reaction failed to furnish desired product, the silicon tethering helped in easy access to product in good yield **(Scheme 12).**

1.2.3.4: Radical Reactions promoted by Silicon Tethers

The Silicon Tether chemistry was also applied for the synthesis of a variety of 1, 3 – diols.[34]Under the radical reaction conditions involving tributyltin hydride and AIBN, the vinylsiloxy ether **80** was converted to cyclic silyl tether **81.** The tether upon oxidation with KF and H_2O_2 provided corresponding diol **83**. It was observed that the rate of 5-*exo*-tri cyclization was relatively slower when radical was α to silicon thus 6-*endo* cyclization becoming a competing pathway. In case of phenyl substitution, the stable benzyl radical formed from 5-*exo* cyclization precluded the formation of 6-*endo* product **(83,** when **R=Ph)**.



Scheme 19: Radical cyclization to form 1, 3- diols.

1.2.4. Modern Application of Silicon Tethers: Ring-Closing Metathesis Reaction

a) The introduction of olefin metathesis in the field of synthetic organic chemistry has given rise to altogether a new era of C-C bond formation. The reaction predominantly involves metal mediated exchange of metal alkylidene species and tethered dienes where there is redistribution of fragments of alkene by scission and rearrangement to form new C-C bonds. The olefin metathesis reaction has proven to be immensely useful in the construction of various carbo and heterocycles.[35]

b) The extraordinary applicability displayed by olefin metathesis reaction can be attributed to high functional group tolerance, well defined catalyst, higher catalytic activity of catalyst and sustained thermal stability.

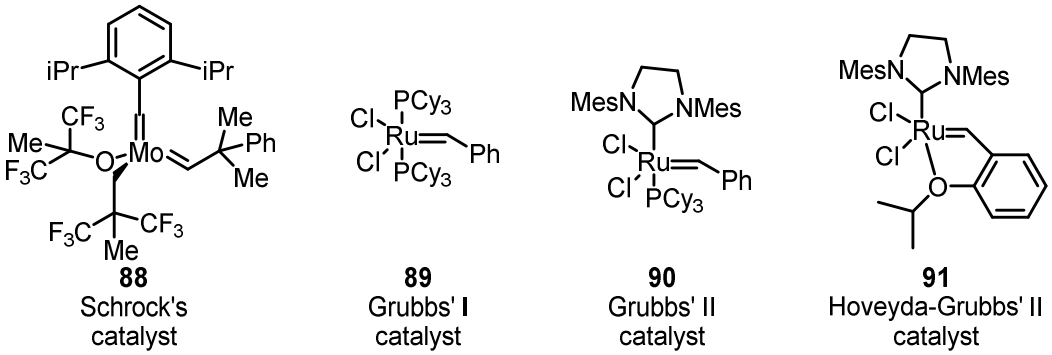


Figure 7: Some of the most heavily used metal-alkylidene metathesis catalysts.

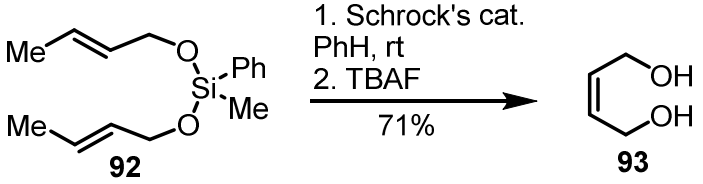
Inspite of the numerous advantages, the metathesis reaction suffers from the lack of ability to offer E/Z stereoselectivity in the formation of medium and larger rings. The metathesis reaction for the formation of medium and large rings suffers poor E/Z stereoselectivity due to the large enthalpy and entropy value and unfavourable transannular interactions.

To overcome this stereoselectivity problem a temporary silicon tether incorporation followed by ring closing metathesis serves as an important tool in formation of Z-selective olefin bond in most medium rings. The gem dialkyl substitutents on silicon atom further help in bringing the two reactive alkenes by distorting the angles between them. This distortion of bond angles also known as Thorpe-Ingold effect[36] immensely facilitates formation of cyclic system in tethered compounds. Furthermore the ruthenium based metathesis catalysts also display occasional intolerance towards strongly coordinating heteroatoms and enhanced reactivity towards differently substituted alkenes. As more and more efforts are employed in this interest it has lead to the advent of systems with a broader functional group tolerance and

enhanced reactivity. Therefore the use of temporary silicon tethering-ring closing metathesis strategy has proven useful in the synthesis of biologically important and complex natural products.

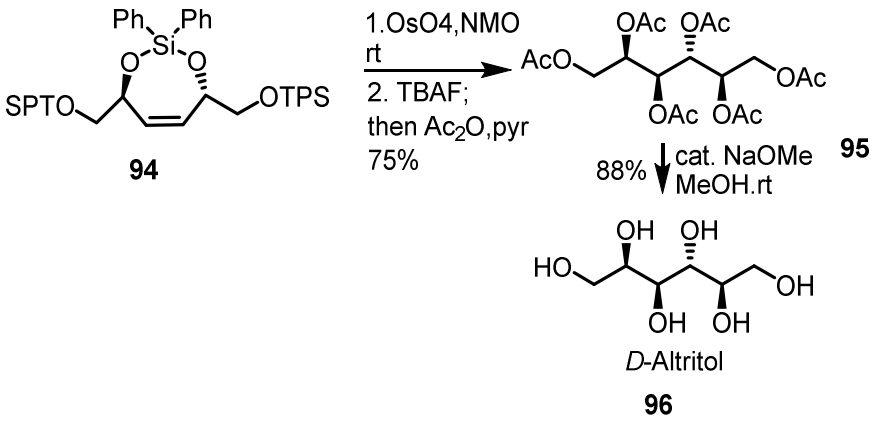
1.2.4.1. Alkene RCM of Substrates Containing O-Si-O Linkage: Symmetrical Silaketals

The enantioselective synthesis of C_2 symmetric 1, 4-diols have aroused interest of synthetic organic chemist owing to their applicability as precursors to a variety of useful intermediates for two-directional synthesis.[37]As a part of this research, Grubb and Fu employed a temporary silicon tethering and subsequent ring closing metathesis strategy for the construction of achiral 1, 4-diols.[38] The method employed formation of bisalkoxy siloxane by simple silylation of hydroxyl group with appropriate dialkyl dichlorosilane reagent. The highlight of this method involves the tolerance of sensitive bisalkoxy siloxane to cyclization process. As the cyclized silaketal was sensitive during purification process, the crude cyclic silaketal was subjected to desilylation using tetra-n-butylammonium fluoride (TBAF).



Scheme 20: Construction of achiral 1,4-diols.

The C_2 symmetric ketals synthesized employing TST-RCM strategies have proven to be useful in the synthesis of many complex molecules. Once such synthetic utility is demonstrated in the synthesis of *D*-altritol by Evans and co-workers and the library of long-chain-linked disaccharides.[39] Also a variety of medium sized ring were synthesized with satisfactory Z-olefin selectivities using TST-RCM method by Hoye and Promo.[40]



Scheme 21: Synthesis of *D*-Altritol

1.2.4.2. Alkene RCM of Substrates Containing O-Si-O Linkage: Unsymmetrical Silaketals

With initial exploration of TST-RCM strategy for symmetrial silaketals, it was followed by the synthesis of unsymmetrical silaketals and its application in organic synthesis. The synthesis of mixed bisalkoxy silanes is carried out by first reacting the alcohol with excess of dichlorodialkylsilane under dilute condition, removal of unreacted dichlorodialkylsilane in vacuo followed by addition of second alcohol. Although this is a very common method for prepartion of mixed bisalkoxy silanes it suffers from following disadvantages:

1. It requires removal of excess of dichlorodialkylsilane in vacuo from monochlorosilane
2. The synthesis of heavier bisalkoxy silanes employs higher boiling dichlorodialkylsilanes as silylating agent due to which this method becomes impractical.

   Several elegant and practical approaches are emplyoyed to circumvent these shortcomings. [41]

A comparative study was done by Mioskowski and co-workers in the cyclization of various heterodienes using ring closing metathesis method employing Schrock's alkoxy imidomolybdenum, Grubbs' first- and second-generation catalysts.[42]

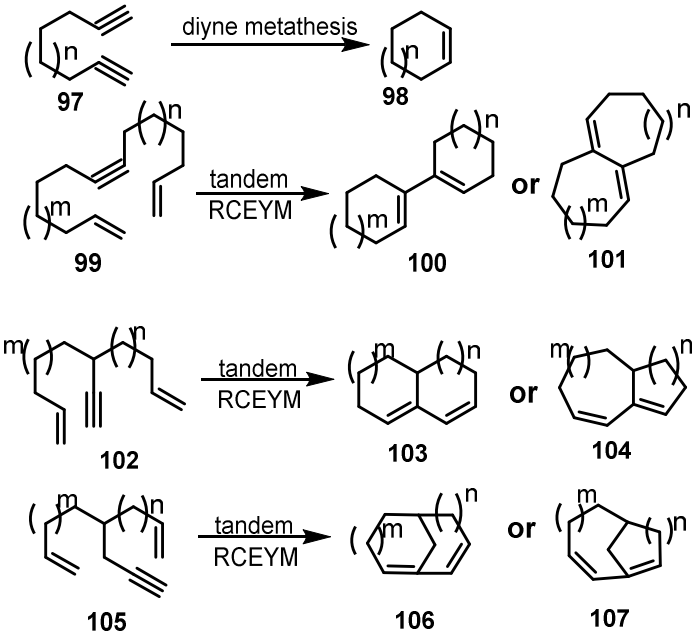
As a part of further studies, the TST-RCM strategy was utilized by Eustache and co-workers for the synthesis of spiro [5,5] ketal fragment of okadaic acid.[43] (*Z*)-2-ene-1,5-diol moiety which was synthetically transformed into desired dihydroxylactone, which was further converted to okadaic acid through acid catalyzed spiro ketalization was synthesized using

TST-RCM approach. The robustness of this approach was demonstrated unambiguously as it was utilized for the total synthesis of the spiroketal-containing natural product, attenol A.[44]

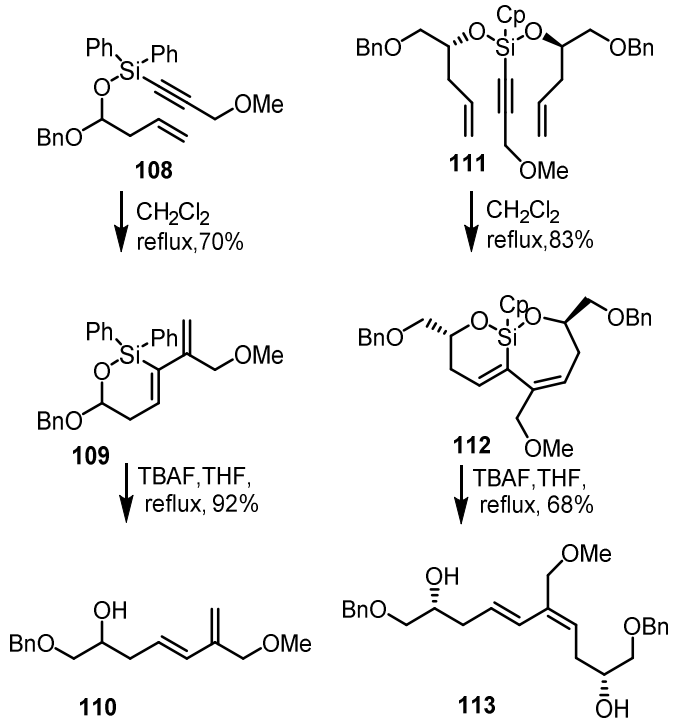
Evans and co-workers further expanded the utility of the TST-RCM sequence in the total synthesis of the potent antitumor agent (−)-mucocin.[45]

1.2.4.3. Enyne RCM of Substrates Containing O-Si-O Linkage: Symmetrical and Unsymmetrical Silaketals

Enyne metathesis has been of great importance in the realm of olefin metathesis due to its unique ability to form a new substrate from altogether different starting materials. In contrary to alkene metathesis which is widely explored area in C-C bond forming reactions, its enyne counterpart still remains to be explored. There are very few reports regarding the formation of small to medium sized rings (n=5 to 9) and sixteen membered rings through enyne metathesis, formation of ten membered to fifteen membered macrocycles has yet to be subjected to extensive studies. The enyne metathesis suffers a major drawback regarding the regio and stereocontrol in the formation of cyclic systems as well as undefined mechanistic aspects of ring closing enyne metathesis.



Scheme 22: General Scheme for Ring Closing Enyne Metathesis



Scheme 23: Enyne Metathesis of Siloxane Products

To overcome the regio- and stereocontrol problem as well as to have insights to mechanistic aspects for enyne metathesis researchers have dedicated a tremendous amount of efforts for the development of general methodology for the synthesis of stereodefined dienes. Temporary silicon tethers have offered a reliable solution to the above mentioned shortcomings and have helped to achieve the stereoselective construction of silacyclic dienes. Temporary silicon tether assisted enyne metathesis have led to synthesis of various important intermediates containing 1,2- or 1,3- or 1,4-substituted 1,3-dienes. Since 1, 4-substitution is more frequently seen in natural products, tandem enyne RCM of silaketal-based dienynes provides an effective method for the synthesis of various naturally occurring compounds and other useful intermediates.[46]

Temporary silicon-tethered ring-closing metathesis (TST-RCM) has rapidly established as a powerful tool for the formation of C-C bonds. With the advent of well-defined transition-metal catalysts that display a high reactivity and functional group tolerance, it has led to the further exploration of this strategy. With its major advantage of forming C-C bonds in regio and stereocontrol fashion temporary silicon-tethered ring-closing metathesis strategy suffers from drawback due to low thermal stability of siloxane moiety and sensitivity toward the strongly coordinating functional groups.

1.3. PROLINE CATALYZED REACTIONS

1.3.1. Introduction to Organocatalysis

Reactions involving small organic molecules to carry out organic transformations have progressively become an important area of research in enantioselective synthesis. The intermediates synthesized by enantioselective method have found relevance in the field of medicinal chemistry, electrochemistry and polymer chemistry. Organocatalysis, the term first introduced in 2000, involves use of purely organic moiety not containing any metal atom to execute organic transformations and has progressively become the most explored field in enantioselective synthesis. Since the first report of synthesis involving organic entity appeared in 1860 from Leibig *et al,* more and more reports have surfaced illustrating importance of organocatalysis in synthetic organic chemistry.[47]

Although the first report of organocatalysis appeared in 1860, the field of organocatalysis displayed a surge of exploratory research activities only in 1900's with respect to academic and industrial research. In 1971 organocatalysis saw a breakthrough in the form of Hajos–Parrish–Eder–Sauer–Wiechert reaction which featured synthesis of optically active diketol and developed by two independent groups Hajos and Parrish [48]and the group of Eder, Sauer, and Wiechert [49] .The synthetic transformation was carried out by using (*S*)- proline as catalyst for aldol reaction of a triketone.

Since the dawn of organocatalysis it has brought in the complementary mode of catalysis which has bestowed with the advantages of savings on cost, time and energy, easy experimental procedures and reduction in chemical wastes. Apart from the green advantages organocatalysis offers, the organocatalytic approach is also important since it provides flexibility in organic synthesis. With more and more efforts are employed in the design and synthesis of organic synthesis that provide better efficiency, new reactivities and greater turnover numbers, organocatalysis has become an important tool in organic synthesis. The tremendous efforts put towards the development of organocatalysis in recent years will be fruitful in putting the field of organocatalysis at the same level of transition metal catalysis.

1.3.2: Classification of Organocatalyst:

Most but not all organocatalysts can be broadly classified as Lewis bases, Lewis acids, Brønsted bases, and Brønsted acids.The corresponding (simplified) catalytic cycles are shown in Scheme 1. Accordingly, Lewis base catalysts (B:) initiate the catalytic cycle via nucleophilic addition to the substrate (S). The resulting complex undergoes a reaction and

then releases the product (P) and the catalyst for further turnover. Lewis acid catalysts (A) activate nucleophilic substrates (S:) in a similar manner. Brønsted base and acid catalytic cycles are initiated via (partial) deprotonation or protonation, respectively.

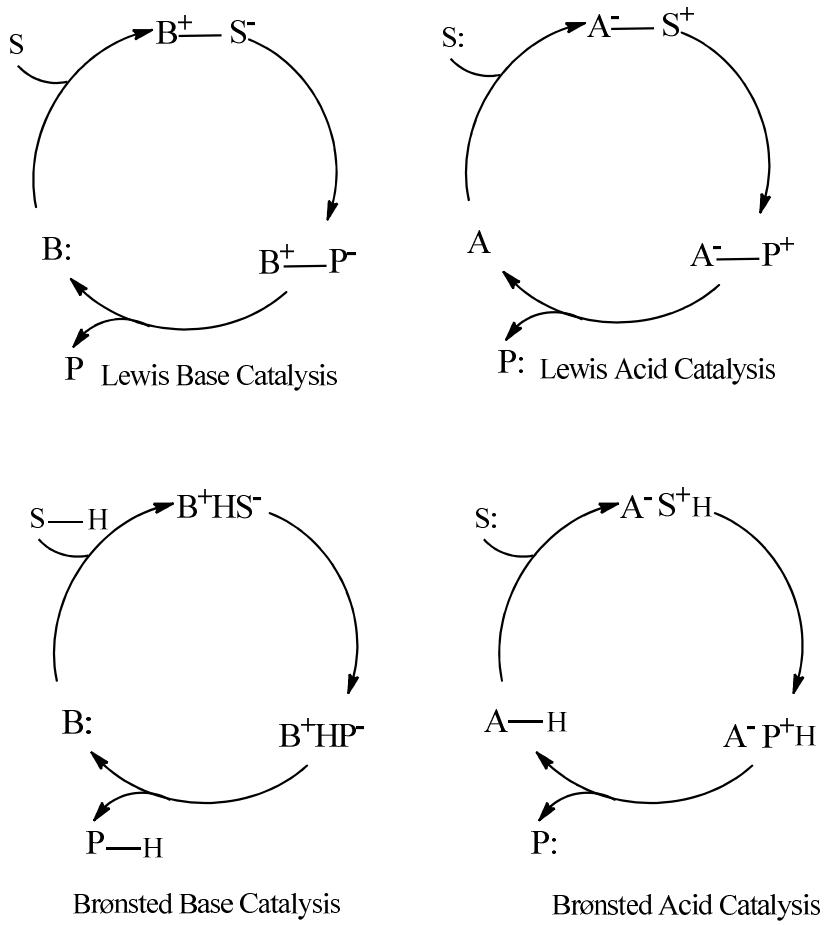


Figure 8: Organocatalytic cycles

1.3.3. Proline as Universal Catalyst:

Since the discovery of Hajos–Parrish–Eder–Sauer–Wiechert reaction, proline has proved as an important organocatalyst for various organic transformations. Proline is the sole naturally occurring amino acid which bears secondary amine functionality and both the enantiomers of proline are readily available. Proline has an asymmetric centre next to the functional group which makes it feasible to attach to reactive substrate in different ways. The presence of both acid and amine functionality, proline can act as either a nucleophile to carbonyl group (iminium catalysis) or Michael acceptor (enamine catalysis).

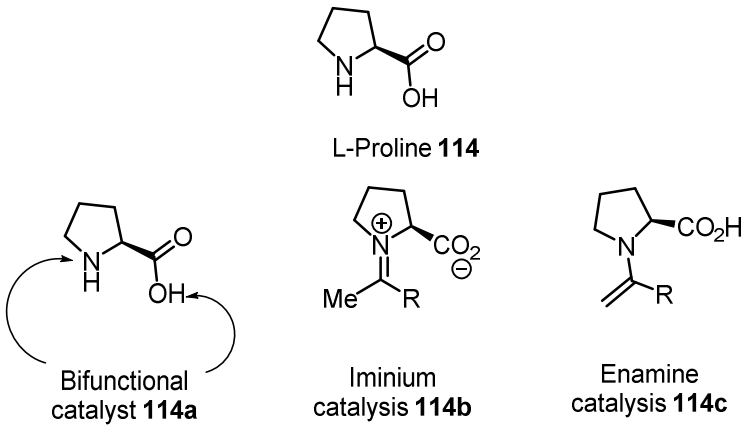


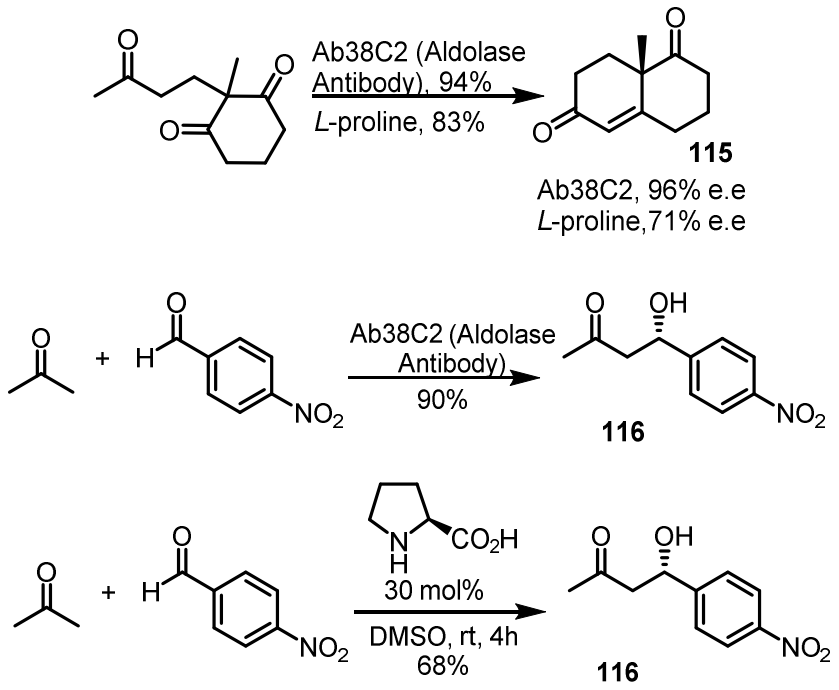
Figure 9: Modes of proline catalysis

Proline acts as a bifunctional catalyst due to the presence of both carboxylic acid and secondary amine groups. It serves as a versatile organocatalyst which offers higher stereoselectivities and enantioselectivities through the formation of organised transition state with the help of hydrogen bonding. Since the discovery of proline as an organocatalyst it has been known to effectively catalyze reactions like aldol[50], Diels-Alder[51], Michael addition[52] and α-functionalization of aldehydes and ketones[53]among many other organic transformations.[54]

1.3.3. Proline catalyzed reactions

1.2.3.1 Proline catalyzed aldol reaction

Since the discovery of aldol reaction involving reaction proline as catalyst by two independent groups Hajos and Parrish[48]and the group of Eder, Sauer, and Wiechert[49] researchers have explored the proline catalyzed aldol involving various substrates. In 2000 List reported intermolecular aldol reaction involving acetone and *p*-nitrobenzaldehyde which furnished optically active *β*-hydroxy alcohol.[50]The product was obtained in excellent yield and ee>90%. The optically active *β*-hydroxy alcohol obtained in this reaction serves as an important intermediate in the synthesis of polyhydroxylated compounds. The results obtained sparked interest of various researchers to further explore this reaction. Although the first reported proline catalyzed aldol involved an intramolecular version, intermolecular version which was reported in 2000 is much more explored than its intramolecular counterpart.

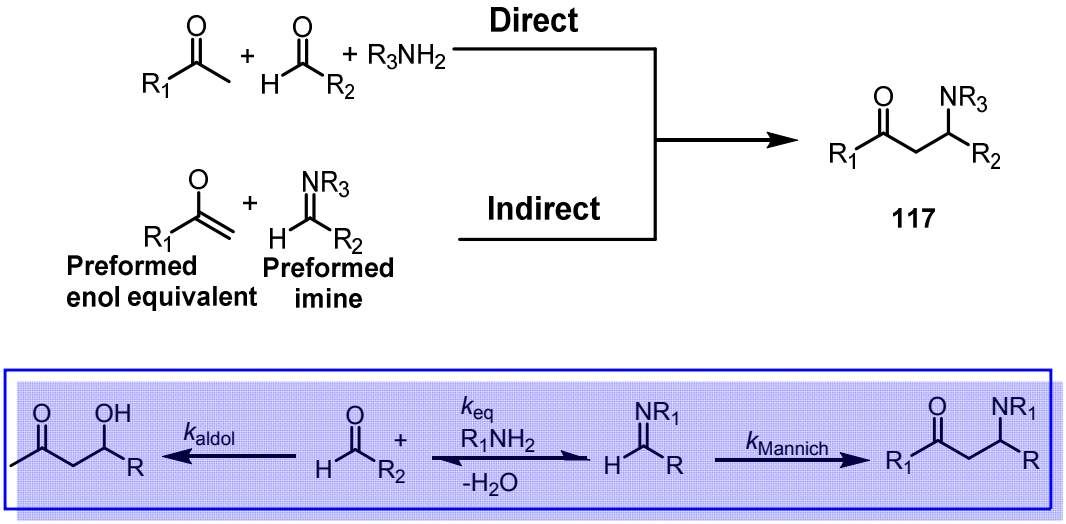


Scheme 24: Proline catalyzed aldol reaction

1.2.3.2 Proline catalyzed Mannich reaction

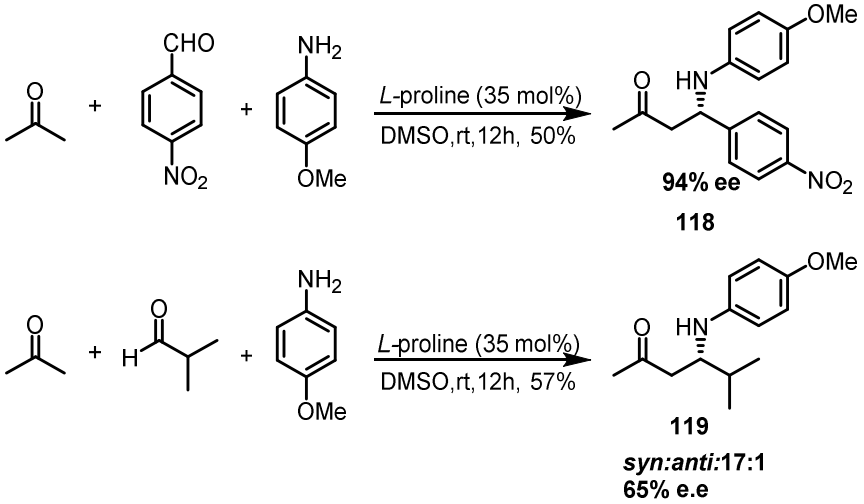
Mannich reaction has played an important role in the field of synthetic organic chemistry for the construction of various nitrogeneous compounds. The Mannich reaction essentially involves the condensation of primary or secondary amine or ammonia with compounds containing α- acidic hydrogen leading to the formation of β-amino ketone. The nitrogeneous compounds synthesized using Mannich reactions have found to be important in the field of natural product synthesis and medicinal chemistry. Although there are numerous methods reported for the synthesis of β-amino ketone very few mention the synthesis of optically active β-amino ketones.[55]

With the advanced research towards the development of Mannich reaction with the enantioselective version, various reports have surfaced over the period of times illustrating both the catalytic and non-catalytic techniques.[56] The earlier reports mentioning enantioselective Mannich reaction highlighted the use of stoichiometric amount of chiral reagent which included addition of preformed enamines to amines.[57] The results obtained in non-catalytic approach for Mannich reaction led the scientists to design catalytic methods for Mannich reaction. Out of the fewer methods reported for catalytic enantioselective Mannich reaction most of them describe the synthesis of β-amino ketones through indirect approach.



Scheme 25: Direct and Indirect modes of Mannich reaction

The use of aldolase antibody 38C2 in many condensation reactions acted as foundation for the further exploration of catalytic methods for Mannich reactions.[56]The aldolase antibody facilitated the formation of enamine first and subsequent nucleophilic attack of enamine on aldehyde followed by hydrolysis furnishes the desired product. Taking a clue from this bio-catalytic transformation, List and co-workers developed a direct method for Mannich reaction involving a three component reaction of acetone, *p*-nitrobenzaldehyde and *p*-anisole using *L*-proline as catalyst.[57]



Scheme 26: Direct Mannich reaction

The direct Mannich reported by List holds importance in the field of synthetic chemistry from the point of view that it does not require preformed imine for the synthesis of *β*-amino ketones. It not only furnishes products with higher enantioselectivities but also offers substrate scope ranging from aromatic aldehydes to branched chain aliphatic aldehydes.

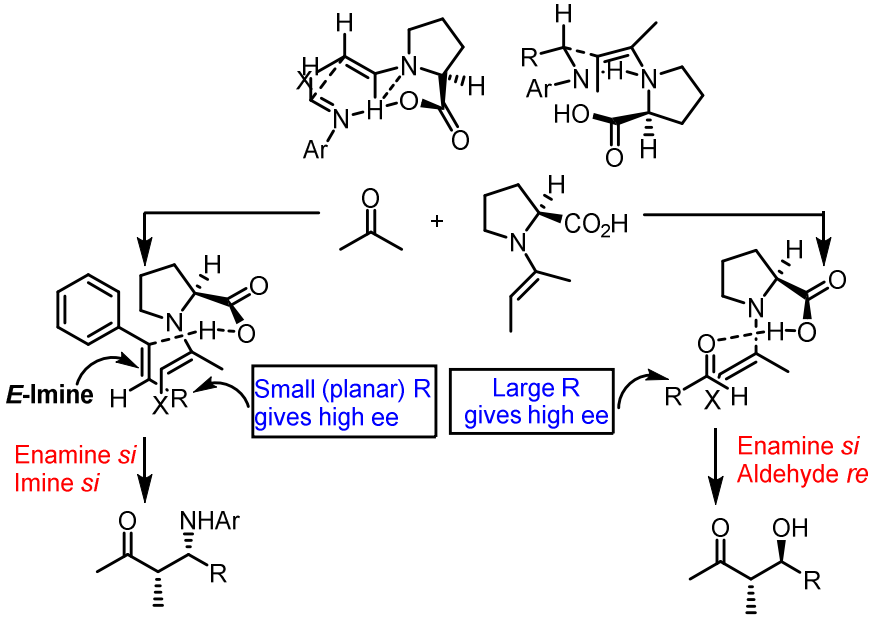
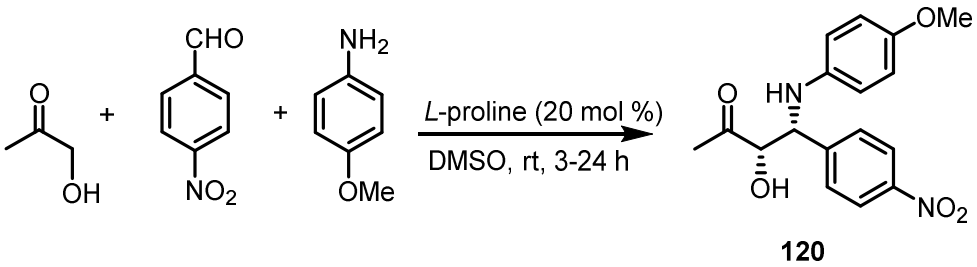


Figure 10: Mechanism for direct Mannich reaction



120

Scheme 27: Direct Mannich reaction of hydroxy acetone

Table 1: Mannich reaction of hydroxy acetone with aromatic aldehydes

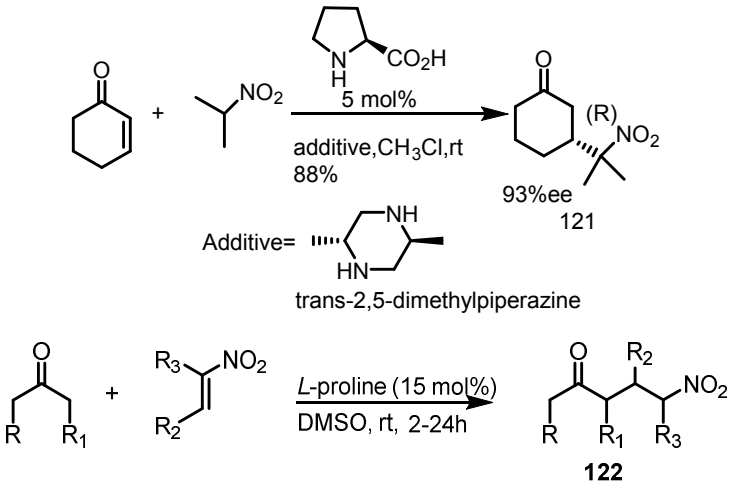
R=	Yield%	dr	%ee
p-$NO_2C_6H_5$	92	20:1	>99
C_6H_5	83	9:1	93
p-$MeOC_6H_5$	88	3:1	61

The first three component organocatalytic direct Mannich reaction reported by List in 2000 involved acetone as a ketone of choice, the later reports involved use of hydroxy acetone as a ketone reactant.[58]The results obtained were similar in both the cases where a *syn* isomer was predominantly formed with higher enantioiselectivities (>99%, **Table 1**).The direct organocatalytic Mannich reaction holds an important place in the field of organic synthetic

chemistry from the point of view that if offers relatively simple operational technique for the synthesis of optically active nirogeneous compounds with higher chemo, regio- and enantioselectivities. Needless to say that it has served as foundation stone for exploration of many more organocatalytic approaches for synthesis of optically active compounds.

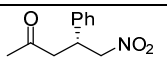
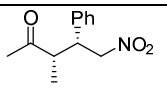
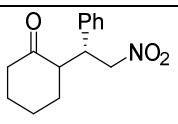
1.2.3.3. Proline Catalyzed Michael Addition

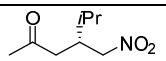
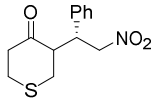
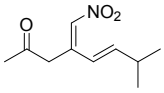
The conjugate addition of carbon and heteroatom nucleophiles to nitroalkanes serves as an important tool in C-C or carbon heteroatom bond formation. With the discovery of asymmetric catalysis, stereoselective and enantioselective Michael addition lead to the synthesis of enantio enriched compounds of biological and pharmaceutical importance. The earlier asymmetric catalytic methods employed in Michael addition reaction were limited to transition metal catalysis or enzymatic catalysis but with the discovery of organocatalysis in late 1990's asymmetric organocatalysis was also employed in enantioselective Michael addition.[59]



Scheme 28: Proline Catalyzed Michael addition.

Table 2: Proline Catalyzed Michael addition

Entry	Product (122)	Yield	dr (*syn:anti*)	ee (%)
1		97	-	7
2		85	3:1	10
3		95	20:1	23

4		87	n.d	n.d
5		92	20:1	n.d
6		85	n.d	n.d

After the first report of Michael addition using *L*-proline as a catalyst **(Table 2)** provided the desired products in excellent yields, several attempts were made to improve the diastereoselectivity and enantioselectivity by changing the solvent and equivalents of *L*-proline.[60] With further scientific exploration modified proline derivatives were synthesized and employed in organocatalytic Michael addition. The results obtained were comparable and in some cases better than the *L*-proline variants.[60]

1.2.3.4: Dihydroxyacetone in Proline catalyzed Aldol Reaction

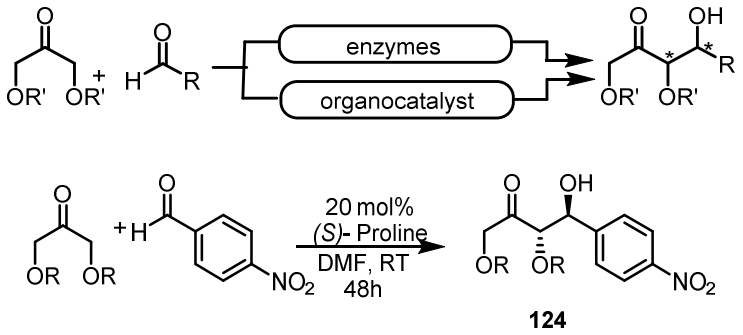
1.2.3.4.1. Introduction:

Since the discovery of proline as catalyst in organocatalyzed aldol reaction, the proline catalyzed aldol has been implemented in synthesizing numerous synthetically important intermediates. The initial reports of intermolecular proline catalyzed reaction employed the use of acetone as the donor substrate. With further exploration different variants of acetone such as hydroxy acetone and dihydroxy acetone were also employed in the reaction.

Aldol reactions involving enzyme as catalyst have served as an important tool in the synthesis of carbohydrates. These reactions typically involve DHAP (dihydroxy acetone phosphate) as the donor reactant wherein two consecutive stereocentres are generated in a single step. These reactions are important from the point of view of stereoselectivities exhibited in the aldol products. The complete stereocontrol achieved in these reaction with the use of appropriate aldolase enzyme in the generation of stereocentres provides an efficient route to synthesis of stereochemically diverse and complex carbohydrates and aza sugars.[61] Several attempts were made to mimick this route using lithium and boron enolate chemistries[62]but further exploring of catalytic highly stereoselective methods remain elusory.[63]

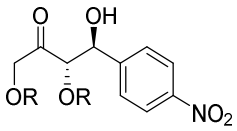
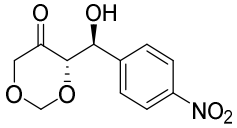
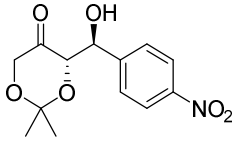
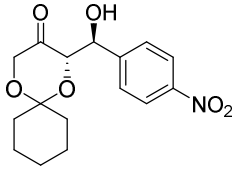
With the introduction of organocatalysis as an alternative method to metal catalysis and enzyme catalysis for asymmetric synthesis, proline was employed as catalyst of choice for many organic transformations such as aldol reaction, Mannich reaction and Michael reaction.

These reactions catalyzed by proline involved enamine based chemistries and mimicked the aldolase enzyme chemistry wherein direct coupling of aldehydes and ketones occurred and did not require preformed enolates to furnish desired products. The results obtained were fascinating in terms of enantioselectivities and diastereoselectivities and products obtained exhibited ee as high as >90%.



Scheme 29: Proline catalyzed Aldol Reaction of Dihydroxyacetone

Table 5: Dihydroxy acetone derivatives in *L*-Proline catalyzed Aldol reaction

Entry	R	Product	% Yield[a]	*anti/syn*[b]	%ee
1	H		trace	-	-
2	Bn				
3	TIPS				
4	-CH_2-		89	2:1	92
5			91	15:1	94[c]
6	-$C(CH_3)_2$-		89	2:1	60
7			90	6:1	93
8			96	16:1	95[c,d]
9	-$C(C_5H_{10})$-		85	5:1	59
10			62	5:1	67

1.2.3.4.2. Organocatalytic Asymmetric Synthesis of Carbohydrates:

In order to mimic the enzymatic route to carbohydrates using DHAP (dihydroxy acetone phosphate) as the donor reactant a C_3 synthon equivalent to dihydroxy acetone phosphate was first employed in the synthesis of carbohydrates and other structurally similar motifs by Enders and co-workers in 2002.[63a, 63b]This synthon bears a protected dioxanone moiety which acts as donor in the proline catalyzed aldol reaction. This protected dioxanone moiety holds a special place in proline catalysis since it can be easily prepared on multigram scale using inexpensive staring materials and is stable to weakly acidic or basic conditions.[64]Also the dioxanone has easily functionalizable carbonyl group which can either be stereoselectively reduced to alcohol or can be converted into amino group. The 1,3-protected hydroxy groups can be easily converted to free alcohol through acid hydrolysis.

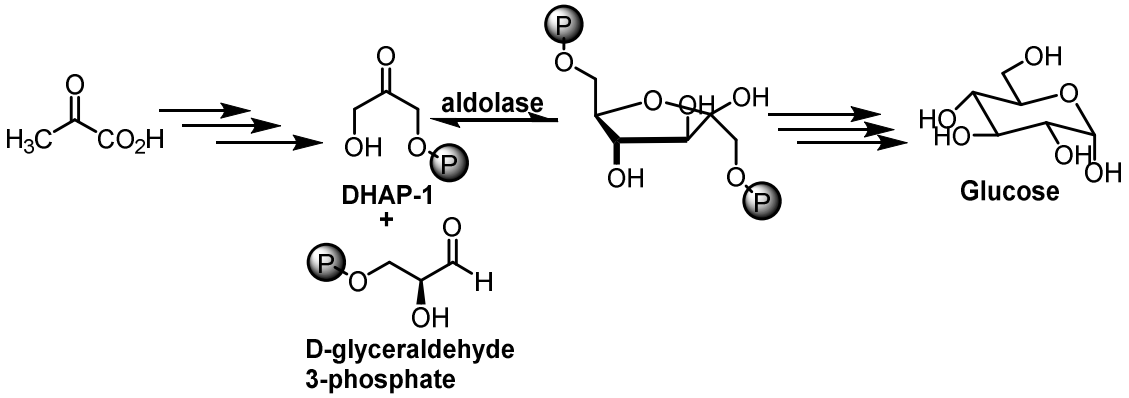
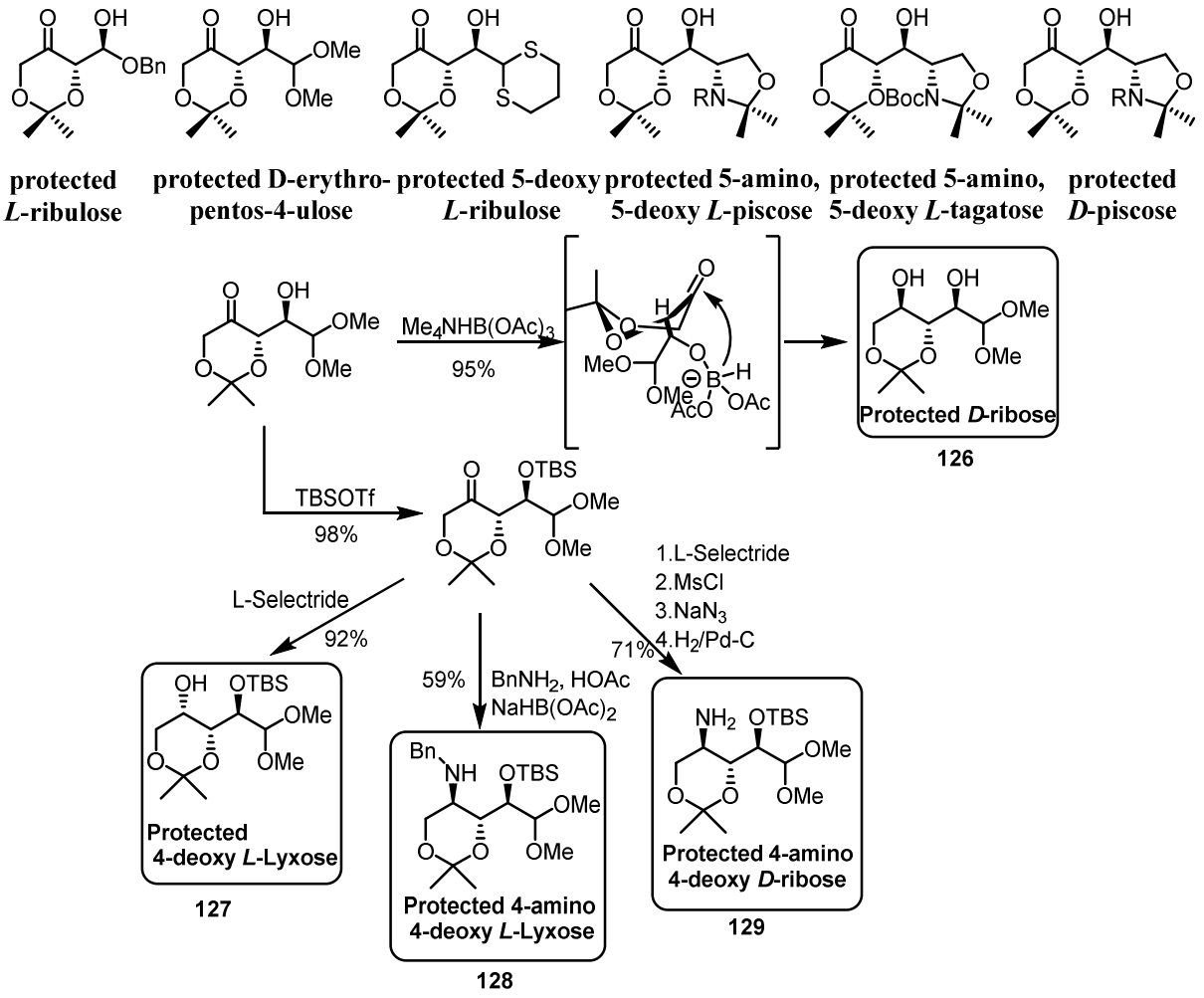


Figure 11: Aldolase catalyzed carbohydrate synthesis



Scheme 30: Carbohydrate Synthesis: Proline-Catalyzed Aldol Reaction of Dioxanone and Various C_2- and C_3-Aldehydes.

The importance of protected 1,3-dioxan-5-one as a C_3 synthon was first demonstrated in the synthesis of various aldoses and ketoses in 1999 using *RAMP/SAMP* hydrazone method by Enders and co-workers.[65]The method involved formation of hydrazone derivative of protected 1,3- dioxan-5-one, enolization of hydrazone and its subsequent addition to an aldehyde. The deoxy and dideoxy sugars formed exhibited excellent diastereo- and enantioselectivity and the method offered a highly efficient and flexible route to a variety of deoxy and dideoxy sugars **(Table 6)**.[66]The desired stereochemistry in deoxy and dideoxy sugars was achieved using the appropriate auxiliary (*RAMP* or *SAMP*).

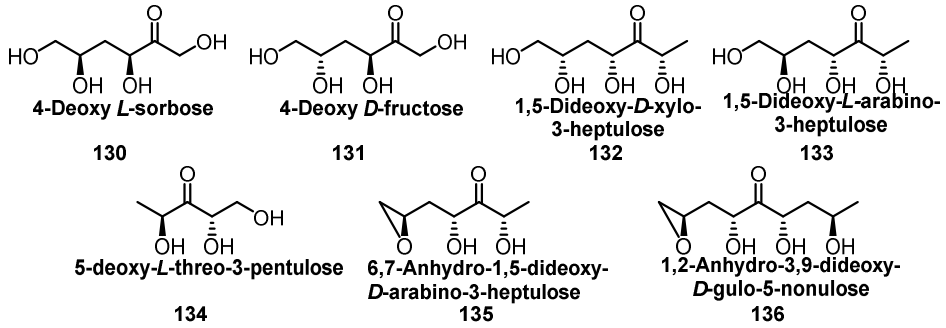
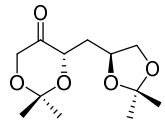
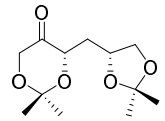
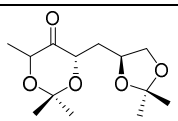
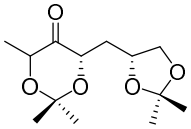
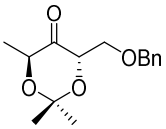
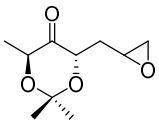
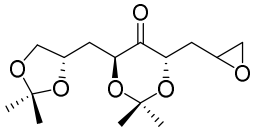


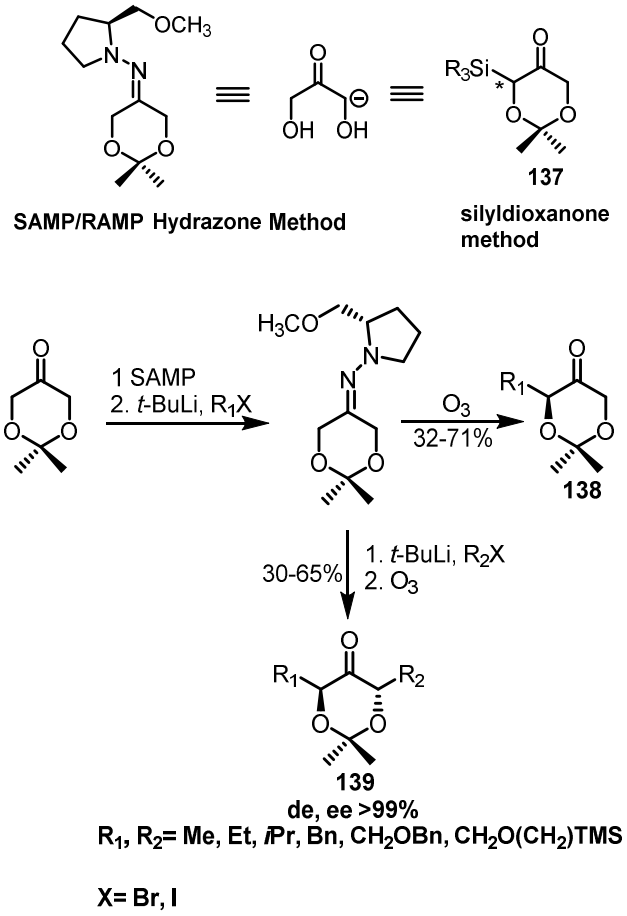
Figure 12: Deoxy and Dideoxy sugars

Table 6: Yields and de, ee values of Protected Deoxysugars

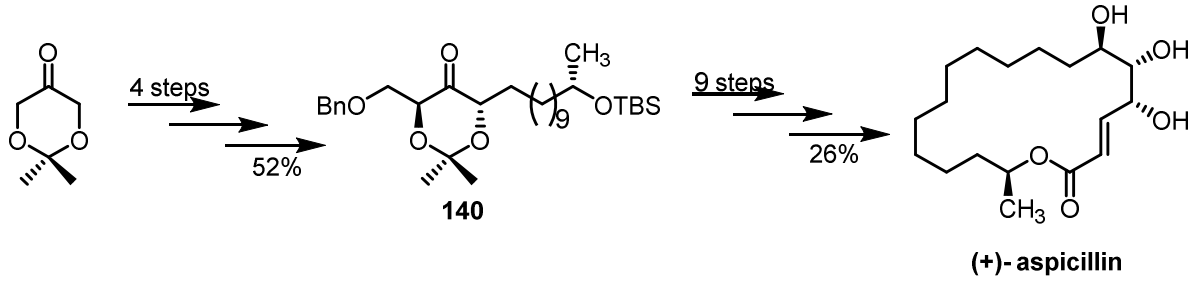
compound	Yields (%)	de (%)	ee (%)
	59	89	≥98
	61	97	≥98
	38	98	≥98
	43	81	≥98
	62	98	≥98
	51	98	≥98
	30	91	≥98

The *RAMP/SAMP* hydrazone method was further elaborated to the formation of corresponding aza enolates of chiral hydrazones and their consequent *α*-electrophilic substitution to furnish desired products in highly diastereoselective manner. In another

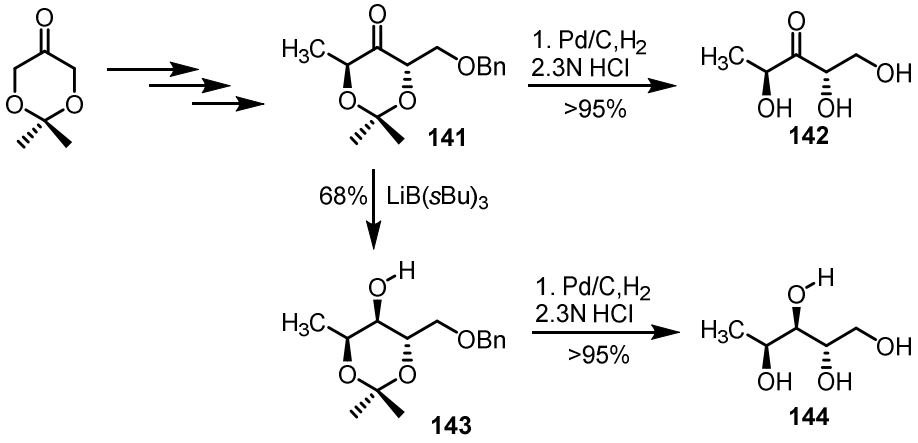
analogous procedure silyldioxanones derived from chiral hydrazones were employed as donor reactants.[67]The silyldioxanone method was employed where the *RAMP/SAMP* hydrazone method failed to provide the desired results. Both these methods were extensively explored for the synthesis of various synthetically and pharmaceutically important intermediates.



Scheme 31: *RAMP/SAMP* hydrazone Method



Scheme 32: Synthesis of (+) aspicillin



Scheme 33: Synthesis of polyhydroxy compounds

1.2.3.5. Proline Catalyzed Asymmetric α-Oxidation, α-Aminoxylation and α-Amination of Carbonyl Compounds

The widely explored chemistry of carbonyl compounds has led to the synthesis of optically active heteroatom-functionalized α carbonyl compounds which are important precursors for many natural and non-natural compounds possessing a nitrogen or oxygen moiety attached to a stereogenic center.

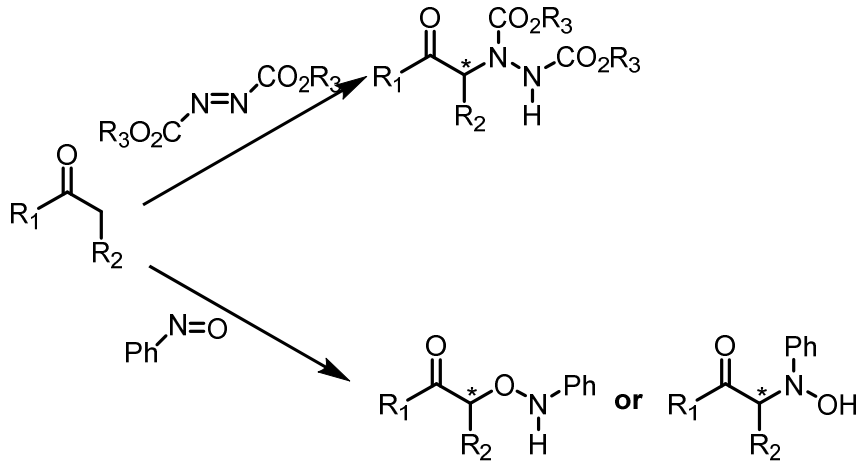
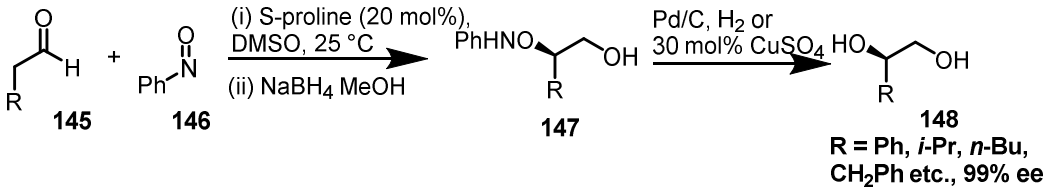


Figure 13: α- Asymmetric direct functionalization of carbonyl with oxygen and nitrogen electrophiles.

Due to the synthetic utility of *α*-functionalized carbonyl compounds having a nitrogen or oxygen moiety, numerous methods have been reported for the synthesis of same.[68,69,70] Although numerous indirect methods have been reported for the synthesis of *α*-functionalized

carbonyl compounds, no direct asymmetric catalytic method is known for the synthesis of same. The recent discovery of enamine catalysis involving proline as catalyst has paved the way for designing of organocatalytic method for the synthesis of α-functionalized carbonyl compounds.

1.2.3.5.1. Proline-catalyzed α-aminoxylation



Scheme 34: Synthesis of 1,2-diols

When an aldehyde **145** without substitution at α-position was reacted with nitrosobenzene **146** in presence of L-proline in DMSO at ambient temperature, aminoxylation of the aldehyde takes place at the α-position. Aldehyde can be reduced *in situ* with sodium borohydride and the aminoxyl moiety undergoes hydrogenolysis with Pd/C, H_2 or $CuSO_4$ to give the corresponding diols **148** in very high enantioselectivities **(Scheme 34)**

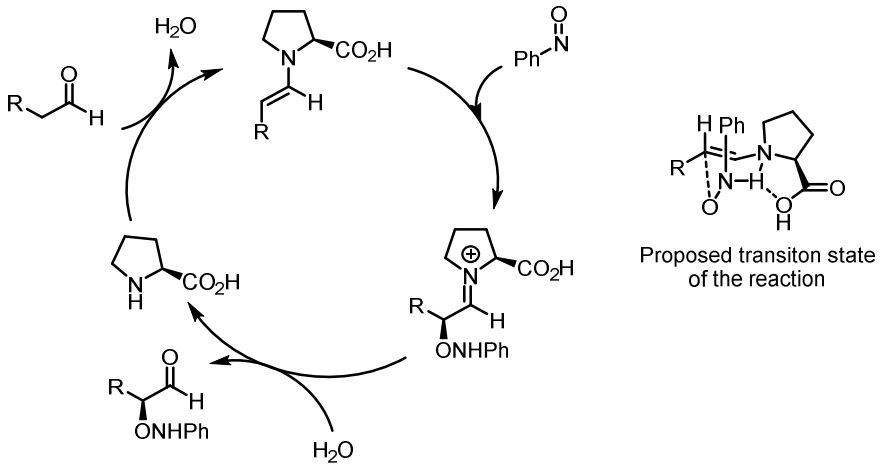
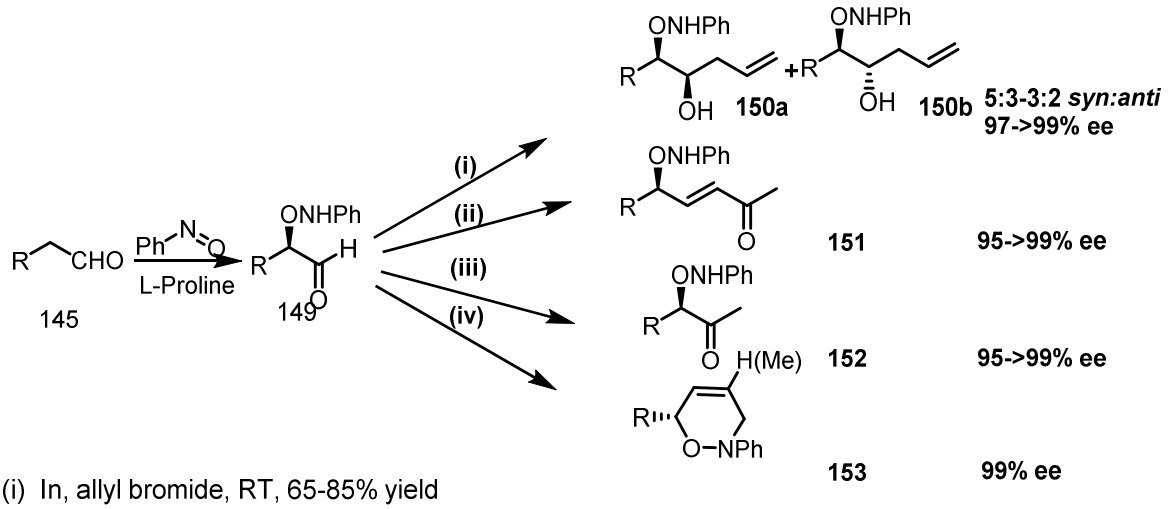


Figure 14: Proposed mechanism of the α-aminoxylation reaction

The formation of α-aminoxylated aldehydes takes place through the formation of enamine intermediate where the *Si* face of α-enamine formed from the aldehyde and L-proline approaches the less hindered oxygen atom of nitrosobenzene to provide a chiral α-aminoxyaldehyde with *R* configuration **(Figure 14)**. Since both the enantiomers of proline are commercially available it is possible to synthesize all the possible enantiomers of α-aminoxylated aldehyde.

The α-aminoxylated aldehyde was isolated into its more stable form of more stable alcohol **147** by reduction of α-aminoxylated aldehyde by $NaBH_4$. In an alternative method the α-aminoxylated aldehydes lead to various synthetic intermediates such as substituted homoallylic alcohols[71] **(150)**, allylic alcohols[72] **(151)** and methyl ketones[73] **(152).** The α-aminoxylation reaction was also useful in the synthesis of 1,3-diols and 1,3-amino alcohols employing an iterative approach.[74a] In a more complex example, dihydro-1,2-oxazines were obtained from the aminoxylated aldehydes in a one-pot fashion by *N*-alkylation followed by an intramolecular Wittig-type reaction[74b] **(153).**

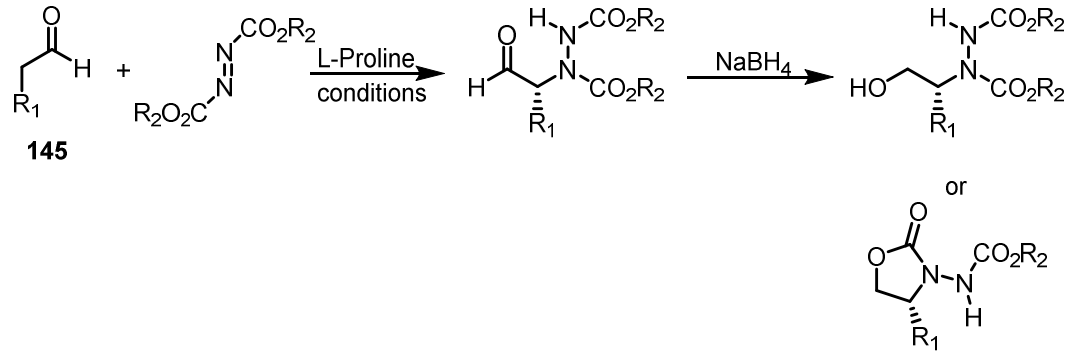


(i) In, allyl bromide, RT, 65-85% yield
(ii) diethyl (2-oxopropyl)phosphonate, Cs_2CO_3, rt, 52-81% yield
(iii) CH_2N_2, $MgCl_2$, Et_2O, rt, 40-60% yield
(iv) $H_2C{=}C(H/Me)\overset{+}{P}Ph_3\bar{B}r$, NaH (2 equiv), 0^oC, 39-82% yield

Scheme 35: Transformation of α-aminoxylated aldehydes to other synthetically useful intermediates.

1.2.3.5.2. Proline-catalyzed α-amination

Optically active α-amino acids, α-amino aldehydes, and α-amino alcohols serve as important intermediates in the synthesis of various nitrogenous compounds. This has triggered the development of various asymmetric direct and indirect methods to synthesize enantiomerically pure α-amino acids, α-amino aldehydes, and α-amino alcohols.The emergence of proline based enamine catalysis has served as a direct method to obtain optically active α-amino acids, α-amino aldehydes, and α-amino alcohols. In 2002 both List[75] and Jørgensen[76]had independently reported the use of proline as a catalyst in the α-amination of aldehydes.



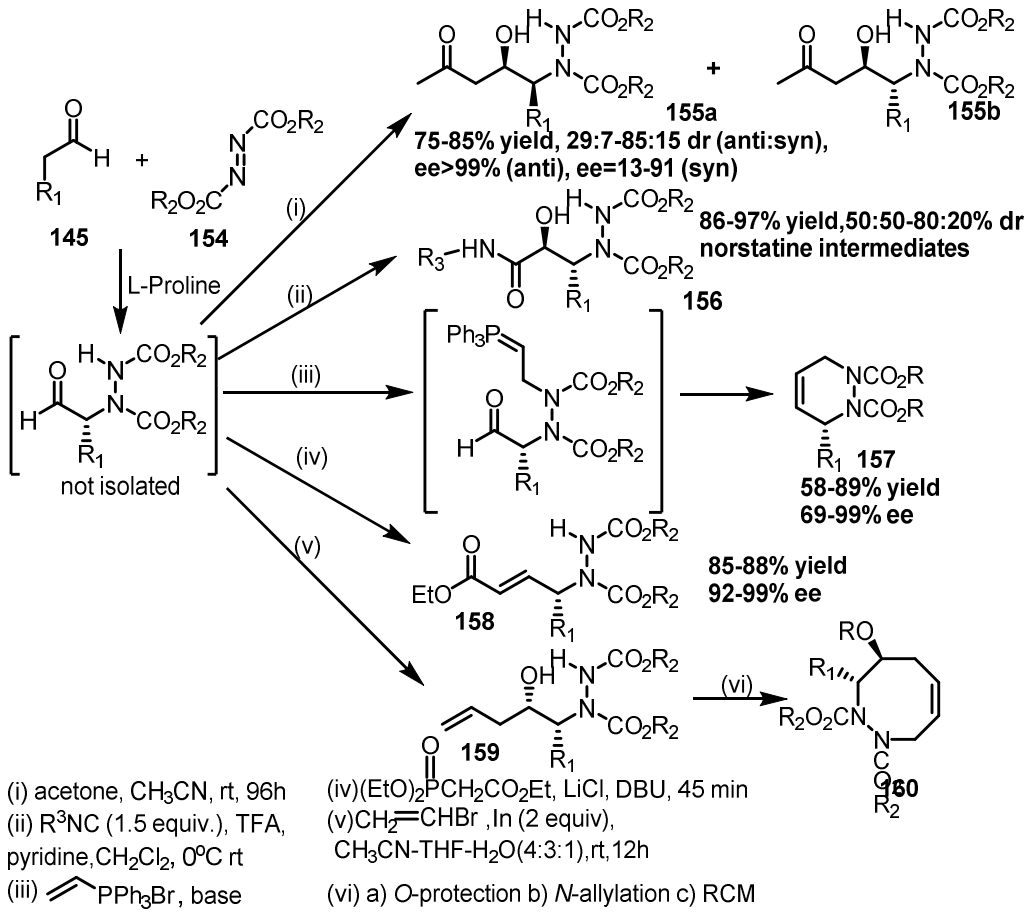
145

Scheme 36: Asymmetric direct α-functionalization of carbonyl with nitrogen electrophiles.

Table 7: Proline catalyzed α-amination of unbranched aldehydes.

R_1	R_2	Conditions	Yields (%)	*ee*(%)
Me, Et, ^{i}Pr, ^{t}Bu, Allyl,Bn	Et,Bn	10 mol%, CH_2Cl_2, rt	57-92	89-95
Me, ^{i}Pr, ^{n}Pr, ^{n}Bu, Bn	Bn	10 mol%, CH_3CN, 0 ^{o}C to rt, 3h	93-99	>95

The α-amination of unbranched aldehydes was carried out by using various azodicarboxylates and the reaction proceeded in an enantioselective and effective manner under L-proline catalysis. As the α-aminated products are very chemically and configurationally unstable due to the presence of an acidic α-H, they were isolated in the form of α-hydrazino alcohol[75,76,77] or subjected to base promoted cyclization to form *N*-aminooxazolidinones.[75,76,78]



Scheme 37: Transformation of α-hydrazinoaldehydes to more complex products or intermediates.[71-74]

1.2.3.5.3: Mechanistic Aspects of Proline catalyzed α-aminoxylation and α-amination of aldehydes:

Proline catalysis operates through the dual activation of both the aldehyde and the electrophile. It is generally believed that the approach of the electrophile was controlled by hydrogen bonding with the carboxyl group of the catalyst. After the discovery of proline as a catalyst for α-aminoxylation and α-amination of aldehydes Jørgensen developed a new silyl-protected diarylprolinol catalyst **162** that could not participate in hydrogen bonding. The results obtained using the diarylprolinol catalyst[78b]were similar as in case of proline catalyzed reaction except the fact that when both the proline and diaryl prolinol catalysts with same absolute configuration were employed in the reaction, they afforded products with opposite stereoselectivity.[78b]This was explained by two transition model as illustrated in the **Figure 16.**

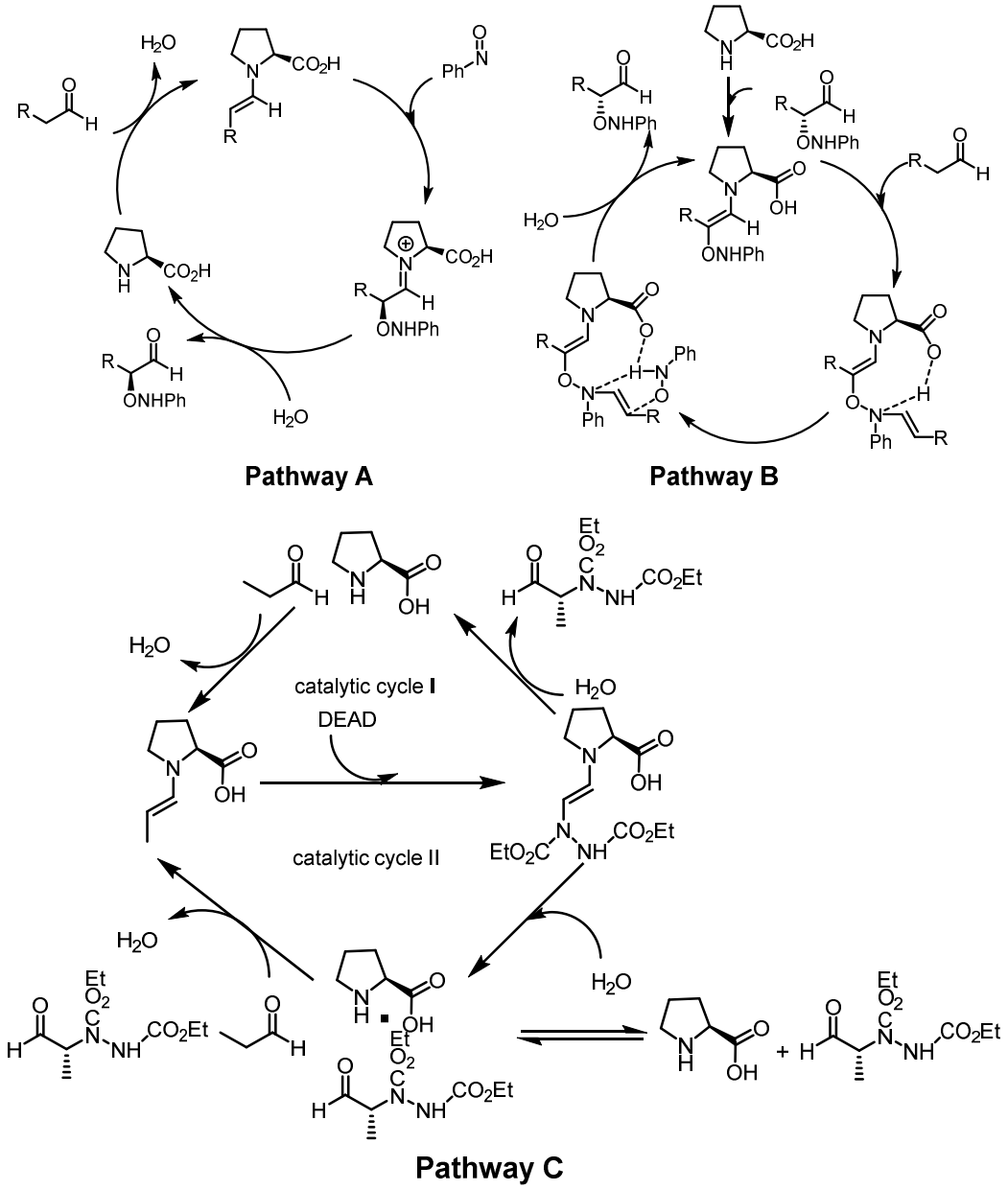


Figure 15. Catalytic cycles of proline-catalyzed amination of aldehydes as proposed by Blackmond *et al.*

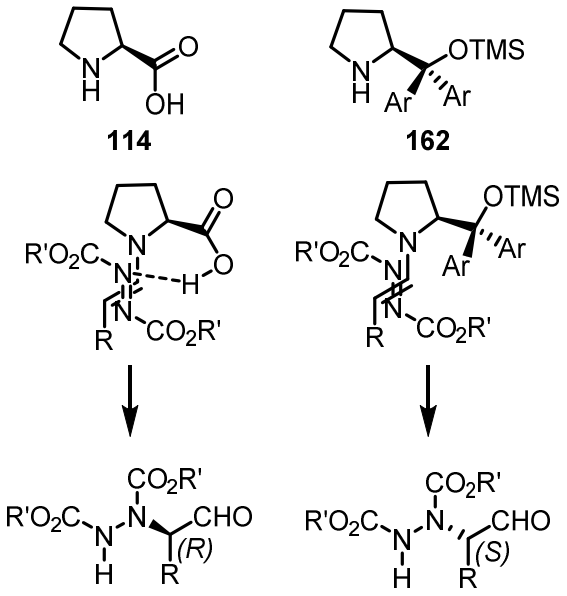


Figure 16: Models to explain the opposite enantioselectivity of amination of aldehydes catalyzed by **114** and **162**

The stereoslectivities observed in the case of these catalysts can be attributed to the the geometry of the enamine and from steric bias of the two enamine faces by the large substituent on the pyrrolidine ring of the catalyst. The origin of the stereoselectivity was further investigated by DFT calculations.[79]

Although the model illustrated in **Figure 16** can reasonably explain the enantioselectivities observed in proline catalyzed α-aminoxylation and α-amination of aldehydes, it cannot account for the autoinductive behavior and asymmetric amplification observed upon detailed kinetic analysis by Blackmond *et al*.[80]This unusual reaction kinetics is observed only in the case of α-aminoxylation and α-amination of aldehydes and not in aldol reaction. The hypothesis that suggests the rate enhancement is due to solubilisation of catalyst can be ruled out on the basis of studies performed on catalyst which are completely soluble in organic solvents where these catalysts exhibited the similar reaction kinetics as in case of proline.

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CHAPTER-2

Synthetic Studies Towards Naturally Occuring 6-Substituted 5,6-dihydro-α-pyrones

Section A:- Polyacylated-6-Heptenyl-5,6-Dihydro-2H-Pyran-2-Ones

Section B: - Synthetic studies towards temporary silicon tethered ring closing directed synthesis of Synparvolide B

Section C: - Synthetic studies towards temporary silicon tethered ring closing directed synthesis of Pectinolide C.

Section D: - Synthetic studies towards (-) Cleistenolide employing Proline catalyzed aldol

Section E: Synthetic studies towards (+) Crassalactone A employing Proline catalyzed aldol

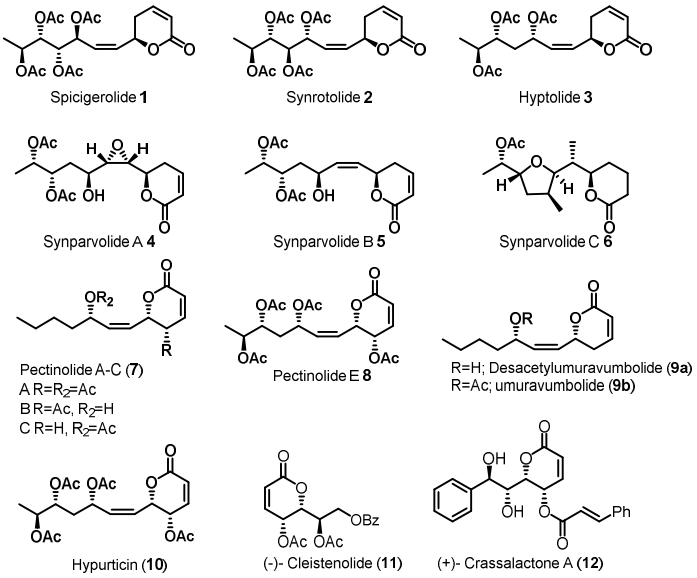
Chapter 2- Section A:- Polyacylated-6-Heptenyl-5,6-Dihydro-2H-Pyran-2-Ones

2.1 Introduction

2.1.1: Introduction to Naturally Occurring 6-Substituted 5,6-dihydro-α-pyrones

6-Substituted 5,6-dihydro-α-pyrone class of naturally occurring compounds have aroused a great deal of interest amongst organic chemist over recent years. These naturally compounds have found a wide variety of applications in medicinal and pharmaceutical chemistry. They are known to exhibit a wide array of biological properties such as antitumor, antifungal, antimicrobial, anti-inflammatory, antistress, antibiotic, antituberculosis, antiparasitic, antiviral.[1] 5,6-Dihydro-*2 H*-pyran-2-ones are also known to induce colony stimulating factor in bone marrow stromal cells. All these wide range of properties make these heterocyclic compounds which also may be considered as *α,β*-unsaturated *δ*-lactones an attractive target for exploration in synthetic and biological chemistry.

In addition, 5,6-dihydro-*2 H*-pyran-2-ones as chemical intermediates have widely been applied to the synthesis of numerous organic compounds including heterocycles.



Herein we cite a few examples of naturally occurring polyacylated-6-heptenyl-5, 6-dihydro-2 *H*-pyran-2-ones: Spicigerolide **(1)** was isolated from *Hyptis spicigera*,

and has been traditionally used in Mexican medicine to treat gastrointestinal disturbances, skin infections, wounds and insects bites.[2,] Synrotolide **(2)** was isolated by Rivett *et al.* from *Syncolostemon rotundifolius*, collected near Margate, Natal. The naturally occurring lactone has been known to possess cytotoxic activity against PANC 1 cell line.[3] Hyptolide **(3),** (-)-deacetylumuravumbolide (**9a**), (+)-umuravumbolide (**9b**) and hypurticin (**10**) naturally occurring polyacylated-6-heptenyl-5,6-dihydro-2*H* -pyran-2-ones were isolated from *Tetradenia, Hyptis* specie which belong to Lamiaceae family. These lactones have been known to possess a wide array of pharmacological properties.[4] Pectinolides A-C (**7**) display convincing antimicrobial and cytotoxic activity.[5] Synparvolides A-C (**4, 5, 6**) obtained from *S. parviflorus*, have been widely used as an aperitive to treat loss of appetite in both adults and children by the Zulu people of Natal.[6]

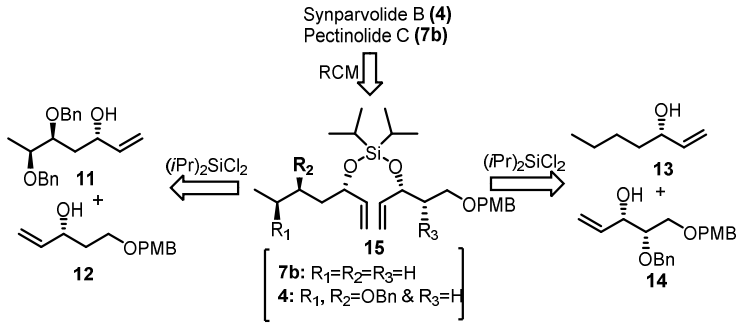
(-) Cleistenolide **11** has been found highly active against bacterial strains of *S. aureus* and *Bacillus anthracis* and certain fungi like *Candida albicans*. Cleistodienediol **(12)** displayed the most promising activity against Plasmodium falciparum (3D7, Dd2), with IC_{50} 0.2 μM and MDAMB-231cell line with IC_{50} 0.03 μM.[7]

One of the crassalactones, crassalactone A **(13)** was investigated for its biological activity. Various bio-assays carried on crassalactone A **(13)** revealed that, it exhibited excellent cytotoxic activity against a variety of cancer cell lines such as murine lymphocytic leukemia (P-388; ED_{50} 0.18 mg/ml), human nasopharyngeal carcinoma (KB; 1.7 mg/ml), human colon cancer (Col-2; 1.9 mg/ml), human breast cancer (BCA-1; 0.92 mg/ml), human lung cancer (Lu-1; 1.9 mg/ml), and rat glioma (ASK; 1.6 mg/ml).[8]

2.1.2: Synthetic strategies towards synthesis of 6-Substituted 5, 6-dihydro-*α*-pyrones

Synthesis of 6-substituted 5, 6-dihydro-*α*-pyrones mainly involves strategies involving ring-closing metathesis to construct the lactone ring and partial hydrogenation of triple bond to generate olefinic bond in the side chain.[9]

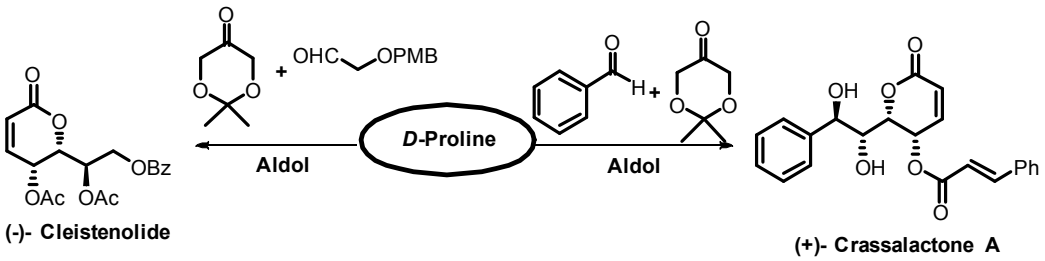
2.1.3. Synthetic Plan



Scheme 1: Retrosynthetic analysis of Synparvolide B **(4)** and Pectinolide C **(7b)**.

In sections B and C we unmask a highly flexible and convergent approach towards the synthesis of Synparvolide B **(4)** and Pectinolide C **(7b)**. All the members of the Lamiaceae family can be synthesized applying this convergent strategy. The general strategy as depicted in **Scheme 1** involves construction of Z-olefin in the side chain employing TST-RCM of bissiloxane intermediate **15. T**he bissiloxane intermediate can be generated through one pot coupling of appropriate allylic alcohols using dialkyl dichlorosilane.

In sections D and E we describe a general synthetic approach towards synthesis of (-) Cleistenolide and (+) Crassalactone A employing proline catalyzed aldol and stereoselective reduction as a key step (**Scheme 2).**



Scheme 2: General Synthetic Approach towards synthesis of (-) Cleistenolide and (+) Crassalactone A.

2.1.4. References:

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Chapter 2- Section B: - Synthetic studies towards temporary silicon tethered ring closing directed synthesis of Synparvolide B

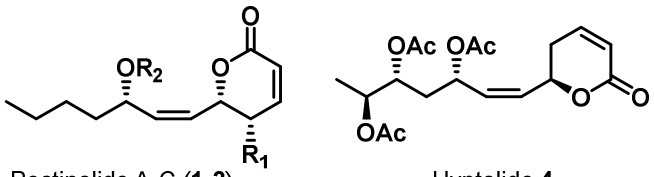
Chapter 2- Section C: Synthetic studies towards temporary silicon tethered ring closing directed synthesis of Pectinolide C.

2.3 Section C

Synthetic studies towards temporary silicon tethered ring closing directed synthesis of Pectinolide C.

2.3.1. Introduction

Pectinolides A-C **(1-3)**, antimicrobial and cytotoxic 5, 6-dihydro-*α*-pyrones, have been isolated from the $CHCl_3$ extracts of the Mexican medicinal plant *Hyptis pectinata*, belonging to the Lamiaceae family. The Lamiaceae family has been known to be a rich source of 5, 6-dihydro-*α*-pyrones (**Figure 1)**.



Pectinolide A-C (**1-3**)
A R_1=R_2=Ac, **1**
B R_1=Ac, R_2=H, **2**
C R_1=H, R_2=Ac, **3**

Hyptolide **4**

Figure 1: Pectinolides A-C (1-3) and Hyptolide 4 from *Hyptis pectinata.*

Hyptis pectinata **(***L*) Poit. (Lamiaceae) is a popular herb in Mexico known for its effectiveness as medicine and as a culinary element in the regional cuisine of the southeastern region of Mexico. The *Hyptis pectinata* **(***L*) Poit. plant provides with numerous biologically active compounds including pectinolides A-C **(1-3),** hyptolide **(4)**, essential oils (thymol), ursolic acid and monoterpenes.[2] Different parts of the plants have been employed in various medicinal formulations. The whole plant is boiled, and the water drunk as an anti-asthmatic or to treat tuberculosis. Smoke from this plant is used as an insect repellant. The whole plant is grounded and brewed as a tea for diarrhea while the decoction used as an aphrodisiac and also used to treat lining cold. The stem and leaves are used for making decoction which is drunk to alleviate liver problems. The decoction obtained from the bark is used to treat menstrual problems and diarrhea. The steeped leaves are used as an emollient. The extract obtained from boiling of leaves and brewed tea is valuable in treating of persistent sores, used as blood cleanser and treating thrush.

The biological assay from the extract of aerials parts of the plant demonstrated antimicrobial activity against Gram-positive bacteria. The initial $CHCl_3$ extract of *H.pectinata* leaves

exhibited inhibitory activity against several microorganisms. Along with anti-microbial activity the extract also exhibited cytotoxic activity (**ED_{50}>2.2 μg/ml**) when tested in the in vitro P-388 murine lymphocytic leukemia assay system. This anti-microbial and cytotoxic activity was attributed to the presence of pectinolides A-C **(1-3).** Further testing of these anti-microbial compounds for cytotoxicity in several tumor cell lines was performed and it demonstrated significant activities. Pectinolide A **(1-3)** displayed antimicrobial activity against *Staphylococcus aureus* and *Bacillus subtilis* in the concentration range of 6.25 – 12.5 μg/ml. Pectinolides B and C **(2 and 3 resp.)** were found to be highly active with an MIC of 12.5 – 25 μg/ml against *B. subtilis* and a value of 100 μg/ml against *S. aureus*. Pectinolides A-C **(1-3)** exhibited significant cytotoxic activity (**ED_{50}<4 μg/ml**) against a variety of tumor cell lines.[1]

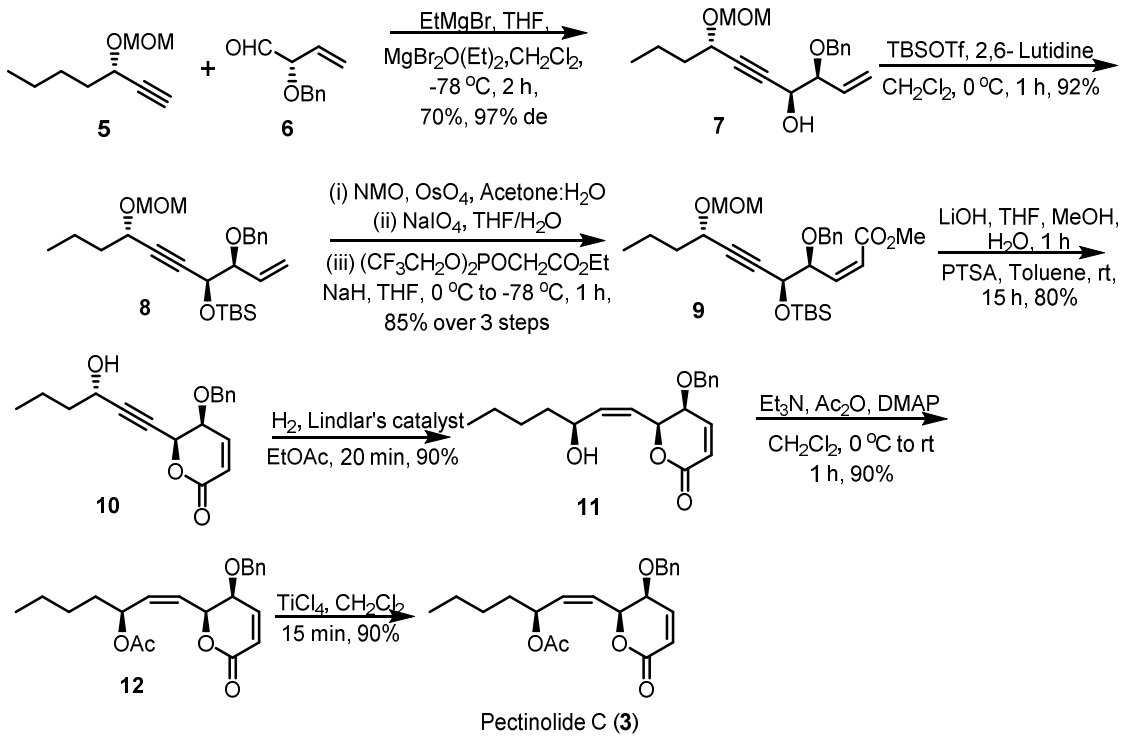
The structures of pectinolides A-C **(1-3)** was analysed and confirmed by Pereda-Miranda and coworkers based on various spectral, chiroptical and chemical evidences.[1] The compound was identified as *6S-[(3S*-acetyloxy)-*1Z*-heptenyl)-*5S*-(acetyloxy)-5,6-dihydro-*2H*-pyran-2-one as in case of pectinolide A **(1)** while pectinolides B **(2)** and C **(3)** were identified as its monodeacetylated forms which was supported by comparison of their spectral data and chemical correlation with the prototype compound (pectinolide A**, 1**).

2.3.2: Review of Literature

Till date only one synthesis of pectinolide C has been reported.[3]

Sabitha *et al*.(2013)[3]

The synthesis of pectinolide C by Sabitha *et al*. describes a convergent approach involving coupling of fragments **5** and **6.** The two were brought together to provide the key intermediate **7** through an in situ metalated alkyne **5** with aldehyde **6** in the presence of $MgBr_2.Et_2O$. The intermediate **7** through further synthetic transformations and subsequent Still-Gennari olefination furnished the desired intermediate **11**, which was eventually converted to target compound **3** .



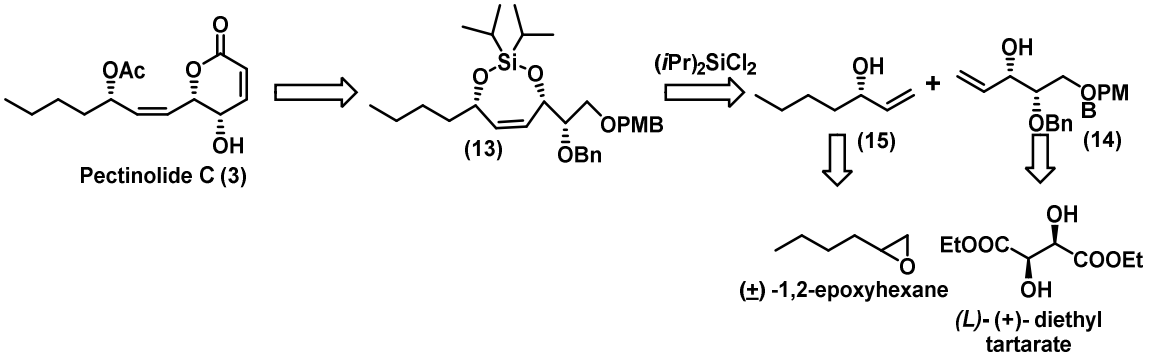
Scheme 1: Synthesis of pectinolide C by Sabitha *et al*.

2.3.3. PRESENT WORK

Objective

Numerous approaches have been developed for the synthesis of polyacylated-6-heptenyl-5,6-dihydro-2*H*-pyran-2-ones with immense success. With the advancement in well established strategies for the synthesis of *α, β*-unsaturated δ–lactones,[2] it aroused our interest in the synthesis of pectinolide C.

We considered devising a new synthetic approach developed by us, exploring temporary silicon tethered ring closing metathesis (TST-RCM) and Still-Gennari for the construction of Z-olefins. The general synthetic analysis is illustrated in **Scheme 2**.



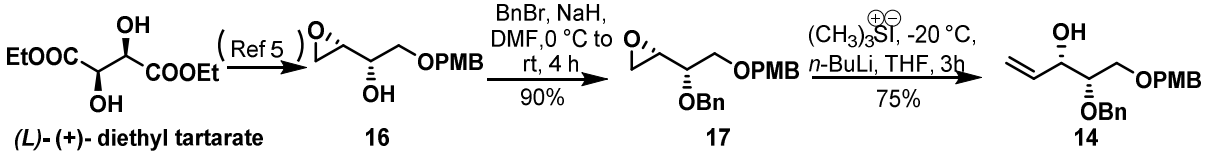
Scheme 2: Retro-synthetic analysis of pectinolide C **(3)**

Our synthesis was directed towards the construction of core intermediate bis-siloxane **13** through TST-RCM. The intermediate **13** would be obtained through coupling of allylic alcohols **14** and **15** which in turn could be obtained from (±) -1,2-epoxyhexane and *(L)*- (+)-diethyl tartarate respectively.

2.3.4. Results and Discussion

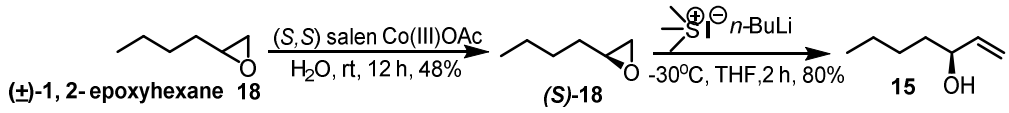
Synthesis of fragment 14

The synthesis of fragment **14** is summarized in **scheme 3**. The introduction of benzyl group on the secondary alcohol moiety of the known epoxy alcohol **16**,[4] derived from diethyl *L*-tartrate according to literature reported procedure afforded **16** in 90% yield,[5] which was further exposed to Corey–Chaykovsky's protocol[6] to produce the one carbon homologated allylic alcohol fragment **14** in 75% yield.



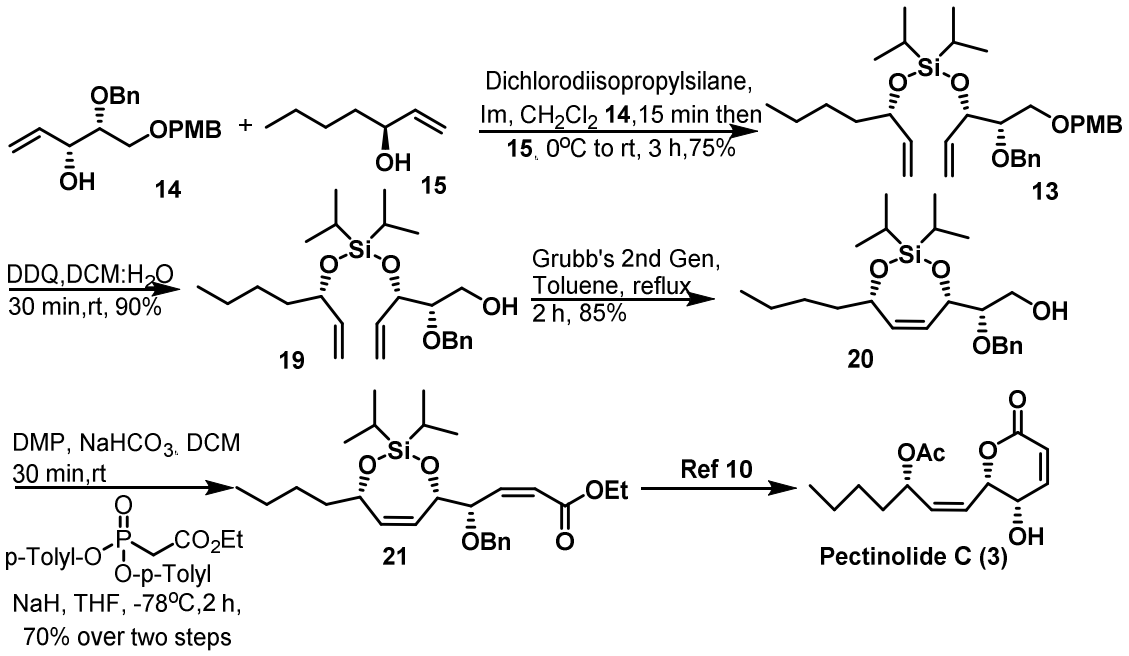
Scheme 3: Synthesis of fragment **14**

The fragment **15** was easily obtained from HKR of (±) – 1, 2- epoxyhexane[7] with *(S, S)* Salen Co(III)OAc catalyst and subsequent homologation with trimethylsulfonium ylide in 85% yield **(Scheme 4).**



Scheme 4: Synthesis of fragment **15**

The construction of the mixed *bis*-alkoxy silane **13** was achieved from the allylic alcohol **14** through the treatment with 1.1 eq of diisopropyldichlorosilane to afford the *mono*-alkoxychlorosilane, followed by the addition of the secondary allylic alcohol **15**.[8] The formation of the bis alkoxy silane **13** was confirmed by ^{1}H NMR and ^{13}C NMR spectral data (δ= 6.86 , 5.94, 5.76, 5.29. ppm for allylic protons and 0.92 to 1.06 ppm for Si-C-H). After installing the bis alkoxy silane group in **15**, we aimed at synthesizing the desired cyclic silyl ether **20**. For this purpose we tried to perform RCM on **13**, but to our dismay there was only partial consumption of starting material **13**. In order to maximize the yield of cyclic silyl ether **20** we first cleaved PMB group by DDQ that provided the primary alcohol **19** in 90% yield (in ^{13}C NMR spectra peak corresponding to δ= 159 ppm disappears). The subsequent RCM of **19** proceeded smoothly to furnish **20** in 85% yields . The formation of the cyclic silyl ether **20** was confirmed by ^{1}H NMR and ^{13}C NMR (δ= 5.77 and 5.35 for C=C-H). Next we turned our attention to the introduction of the pyranone portion of the natural product Pectinolide C (**2**). The alcohol **28** was oxidized to the aldehyde using Dess Martin periodinane in DCM. Olefination of resultant aldehyde with ethyl 2-(bis(*p*-tolyoxylphosphoryl) acetate under Still-Gennari condition[9] gave the corresponding unsaturated ester **21**. The stereoselectivity for this olefination step was >20:1 in favor of the *Z* isomer. which was confirmed by ^{1}H and ^{13}C NMR (δ 6.89 ppm for C=C-H, *J*=8.9 Hz). The conversion of ester **21** to Pectinolide C is already known in the literature.[10]



Scheme 5: Formal synthesis of pectinolide C (**3**)

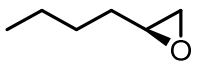
2.3.5. Conclusion

In summary the formal synthesis of pectinolide C has been accomplished using TST-RCM as a key step for the synthesis of key intermediate **21**.[10] The highly convergent strategy consists of synthesis of ester **21,** from allylic alcohol **14** and **15** as the starting materials. The noteworthy feature for this strategy is use of temporary silicon tethered ring closing metathesis (TST-RCM) to establish the side *Z*-olefin. Further application of this methodology to the synthesis of other structurally relevant biologically active compounds for the studies of structure activity relationship is currently underway in our laboratory.

2.3.6. Experimental Section

General information: All reactions were carried out under argon or nitrogen in oven-dried glassware using standard gas-light syringes, cannulas and septa. Solvents and reagents were purified and dried by standard methods prior to use. Optical rotations were measured at room temperature. IR spectra were recorded on an FT-IR instrument. ^{1}H NMR spectra were recorded on 200 MHz, 300 MHz and 500 MHz and are reported in parts per million (δ) downfield relative to $CDCl_3$ as internal standard and ^{13}C NMR spectra were recorded at 50 MHz, 75 MHz and 125 MHz and assigned in parts per million (δ) relative to $CDCl_3$. Column chromatography was performed on silica gel (100-200 and 230-400 mesh) using a mixture of petroleum ether and ethyl acetate as the eluent.

(*S*)-1, 2-epoxyhexane (*S*-18)



The racemic 1, 2-epoxyhexane **18** was resolved to chiral epoxide *S*-**18** in high enantiomeric excess (>99% *ee*) by the HKR method following a literature procedure.[7]

Yield: 9.6 g, 48%,

[α] $^{25}_{D}$: -16.5 (*c*=1.0, pentane); Lit.[11] **[α] $^{24}_{D}$** -18.7 (*c*=0.93, pentane).

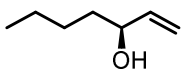
IR ($CHCl_3$, cm^{-1}): ν_{max} 2989, 2925, 2870.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.71-2.67 (m, 1H), 2.57-2.52 (m, 1H), 2.28-2.25 (m, 1H), 1.34-1.10 (m, 6H), 0.78-0.71 (t, *J*=6.13 Hz, 3H) ;

^{13}C NMR (50 MHz, $CDCl_3$): δ = 51.9, 46.6, 31.9, 27.8, 22.2, 13.6,

MS-ESI [M + Na^+]$^+$: m/z 123.07

(*S*)-Hept-1-en-3-ol (15)[10]:



To a suspension of trimethylsulfonium iodide (5.44 g, 26.5 mmol) in dry THF (10 mL) at −20 ^{o}C was added *n*-BuLi (16.68 mL, 1.6 M solution in hexane, 26.5 mmol) dropwise over 20 min and stirred for 30 min. Then the epoxide ***(S)*-18** (0.5 g, 4.37 mmol) in dry THF (5 mL) was added to the above reaction mixture and slowly allowed to warm to 0 °C over 1 h. The reaction mixture was then stirred at ambient temperature for 2 h. After consumption of the starting material the reaction mixture was quenched with H_2O (10 mL) and extracted with

EtOAc (4 × 10 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated. The column chromatography of crude product using pet ether:ethyl acetate (70:30) gave 1**5** (0.45 g, 80%) as a colorless liquid.

[α] $^{25}_{D}$ = +9.5 (*c* 1.4, pentane); Lit[10,11,12] **[α] $^{25}_{D}$ =** + 9.0 (*c* 1.0, $CHCl_3$)

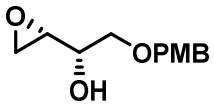
IR ($CHCl_3$, cm^{-1}): ν_{max} 3485, 1613, 1586;

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.88-5.71 (m, 1H), 5.19-4.99 (m, 1H), 4.08-3.96 (m, 1H), 2.34 (s, 1H), 1.48-1.22 (m, 6H), 0.88-0.81 (m, 3 H) ppm

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 141.3, 114.2, 73.0, 36.6, 27.4, 22.5, 13.8 ppm

MS-ESI [M + Na]$^+$: m/z 137.09

(*R*)-4-(4-Methoxybenzyloxy) butane-1, 2-diol (16):



Compound **16** was prepared from *L*-(+)-diethyl tartrate following reported literature procedure.[5] (Yield 83%; colorless liquid).

[α] $^{25}_{D}$= - 1.03 (*c* 1.0, $CHCl_3$); Lit.[5] **[α] $^{25}_{D}$** - 2.6 (*c* 1.4, $CHCl_3$)

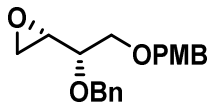
IR ($CHCl_3$) cm^{-1}: ν_{max} =3384, 2934, 1613, 1514, 1249

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.27-7.20 (m, 2 H), 6.90-6.84 (m, 2H), 4.44 (s, 2H), 3.93-3.82 (m, 1H), 3.79 (s, 3H), 3.69-342 (m, 4H), 1.89-1.62 (m, 2H) ppm

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 159.3, 129.8, 129.4, 113.8, 72.9, 71.3, 67.8, 66.5, 55.23, 32.7. ppm

MS-ESI [M + Na]$^+$:m/z 249.1

(*R*)-2-(2-(4-Methoxybenzyloxy) ethyl) oxirane (17):



Compound **17** was prepared following the reported literature procedure.

Yield: 90%; colourless liquid.

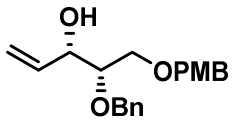
[α] $^{25}_{D}$: +13.82 (*c* 1.0 $CHCl_3$);

IR ($CHCl_3$, cm^{-1}): ν_{max} =2997, 2924, 2860, 1613, 1513

^{1}H NMR ($CDCl_3$, 200 MHz,): δ = 7.29-7.24 (m,2H), 6.91-6.85 (m, 2H), 4.47 (s, 2H), 3.81 (s, 3H), 3.63-3.57 (m, 2H), 3.11-3.02 (m, 1H), 2.81-2.76 (m, 1H), 2.54-2.50 (m, 1H), 1.99-1.71 (m, 2H)

^{13}C NMR ($CDCl_3$, 50 MHz,): δ = 158.7, 128.8, 128.5, 112.3, 73.3, 67.5, 55.5, 50.1, 47.3, 33.8. **MS-ESI [M + Na]$^+$:** m/z 231.099

(*R*)-5-(4-Methoxybenzyloxy) pent-1-en-3-ol (14):



Compound **14** was prepared following the procedure as described for **15** (Yield 75%; colorless liquid).

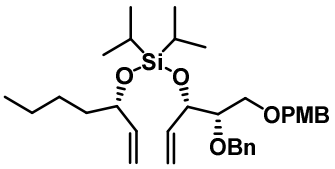
[α] $^{25}_D$= -10.0 (*c* 1.4, $CHCl_3$); Lit.[10] **[α] $^{19}_D$** – 9.2 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3414, 1613, 1586

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.31-7.24 (m, 2H), 6.93-6.86 (m, 2H), 5.97-5.80 (m, 1H), 5.33-5.08 (m, 2H), 4.46 (s, 2H), 3.82 (s, 3H), 3.76-3.57 (m, 2H), 2.99 (s. 1H), 1.94-1.79 (m, 2H) **^{13}C NMR (50 MHz, $CDCl_3$):** δ = 159.1, 140.5, 129.9, 129.2, 114.2, 113.7, 72.8, 71.7, 67.8, 55.1, 36.1.

MS-ESI [M + Na$^+$]$^+$: m/z 245.11.

(*4S, 5S, 9S*)-4-(benzyloxy)-7, 7-diisopropyl-1-(4-methoxyphenyl)-5, 9-divinyl-2,6,8-trioxa-7-silatridecane (13)



Dichlorodiisopropylsilane (0. 094 ml, 0.53 mmol) was added to imidazole (0.11 g, 1.59 mmol) in DCM (0.30 ml) at 0 ºC. The solution was stirred for 5 minutes, then the fragment **14** (0.150 g, 0.456 mmol) in DCM 0.2 ml) was added dropwise over 1 h period at 0 ºC. After the mixture was stirred for 15 minutes at 0 ºC, a solution of the fragment **15** (0.052 g, 0.453 mmol) in DCM (0.035 mL) was added at 0 ºC. The reaction mixture was warmed to the room temperature and stirred for 3 h. The reaction mixture was filtered and washed with hexane, then concentrated in vacuo to afford the crude oil, which was purified by flash chromatography on silica gel (pet ether:ethyl acetate = 95:5) to afford 0.170 g (75%) of bis-alkoxysilane **5** as a colorless oil.

[α] $^{25}_D$ = +62 (*c* 2, $CHCl_3$)

IR (neat, cm^{-1}): ν_{max} 2927, 2865,1613, 1513, 1463, 1363, 1301, 1248, 1095, 1036, 921, 821, 696

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.39–7.22 (m, 7H), 6.86 (d, J = 8.49 Hz, 2H), 5.94 (ddd,J = 6.42, 5.47, 5.09 Hz, 1H), 5.76 (ddd, J = 6.6, 6.42, 3.9 Hz, 1H), 5.29 (td,J = 17.37, 1.70 Hz, 1H), 5.16–4.97 (m, 3H), 4.79 (d, J = 11.8 Hz, 2H), 4.68 (d,J = 11.8 Hz, 2H), 4.57–4.51 (m, 1H), 4.45 (q, J = 14.1 Hz, 2H), 4.25 (q, J = 12.0 Hz,2H), 3.8 (s, 3H), 3.76–3.70 (m, 1H), 3.51–3.44 (m, 1H), 1.59–1.51 (m, 3H), 1.32–1.21 (m, 3H), 0.92–1.06 (m, 14H), 0.87 (t, J = 6.79 Hz, 3H);

^{13}C NMR ($CDCl_3$,100 MHz): δ = 159.0, 141.3, 139.0, 136.7, 130.7, 127.6, 127.4, 115.2, 113.9, 113.6, 81.5,73.6, 73.5, 72.9, 72.7, 71.8, 70.6, 55.2, 37.7, 26.8, 22.8, 17.4, 14.1, 12.7, 12.7;

MS-ESI $[M + Na]^+$: m/z 577.5

(*2S,3S*)-2-(Benzyloxy)-3-((S)-hept-1-en-3-yloxy) diisopropylsilyloxy) pent-4-en-1-ol (19)

To a stirring solution of PMB ether **13** (0.150 g, 0.27 mmol) in DCM/H_2O (0.8:0.1) was added DDQ (0.075 g, 0.324 mmol). The resulting mixture was stirred for 10 min at r.t. The mixture was poured into saturated aqueous $NaHCO_3$ and further diluted with DCM. The layers were separated and the aqueous layer was extracted with DCM (3 x 15mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The solvents were removed under reduced pressure to give the crude product mixture as yellow oil. Silica gel column chromatography of the crude product using pet ether:ethyl acetate (80:20) as eluent gave **16** (0.110 g, 90%).

[α] $^{25}_D$ = +43 (*c* 1, $CHCl_3$);

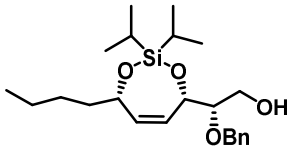
IR (neat, cm^{-1}): ν_{max} 3465, 2925, 2866, 1498, 1463,1347, 1301, 1247, 1092, 917, 878, 694;

^{1}H NMR ($CDCl_3$, 200 MHz): δ=7.42 - 7.28 (m, 5 H), 6.16 - 5.66 (m, 2 H), 5.44 - 5.17 (m, 4 H), 5.17 - 4.91 (m, 1 H), 4.78 - 4.51 (m, 2 H), 4.35 - 4.20 (m, 1 H), 4.20 - 4.00 (m, 1 H), 3.82 - 3.53 (m, 3 H), 2.27 (br. s., 1 H), 1.56 - 1.37 (m, 2 H),), 1.29 - 1.23 (m, 4 H), 1.09 - 1.00 (m, 14 H), 0.95 - 0.81 (m, 4 H) ppm

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 141.1, 138.3, 136.7, 128.4, 127.7, 115.8, 114.1, 81.6, 74.0, 72.6, 72.4, 61.4,37.8, 26.8, 22.7, 17.3, 14.07, 12.7 ppm

MS-ESI $[M + Na]^+$: m/z 457.5

(*S*)-2-(Benzyloxy)-2-((*4S,7S*)-7-butyl-2,2-diisopropyl-4,7-dihydro-1,3,2-dioxasilepin-4-l)ethanol (20):



A solution of 0.100 g (0.23 mmol) **4** in 18 mL toluene was degassed (for 5 minutes using argon), then 20 mg (10 mol%, 23 μmol) Grubbs second-generation catalyst were added and the solution was degassed again. It was refluxed for 2 h, before the solvent was removed in vacuo and the residue was purified by flash chromatography (pet ether:ethyl acetate = 90:10) to give cyclized product **20** as colourless oil **.**

Yield: 0.084 g, 90%

[α] $^{25}_{D}$ = +73 (*c* 0.9, $CHCl_3$);

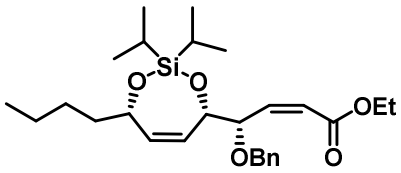
IR (neat, cm^{-1}): ν_{max} 3443,3030, 2934, 2866, 1495, 1462, 1357, 1249, 1208, 1097, 885, 736, 697 cm1;

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.23 - 7.30 (m, 5 H), 5.77 (m, 1 H), 5.35 (m, 1 H), 4.78 (s, 4 H), 4.48 (s, 2 H), 4.27 (br. s., 2 H), 3.81 (m, 2 H), 3.52 - 3.73 (m, 1H), 1.42 (s, 2 H), 1.45 (s, 2 H), 1.32 (d, *J*=7.0 Hz, 14 H), 0.90 - 0.94 (m, 4 H)

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 129.8, 129.4, 128.5, 127.8, 113.9, 113.8, , 73.2, 71.1, 71.1, 61.9, 55.3, 31.9, 29.7, 29.3, 29.2, 26.4, 22.7, 22.5, 17.3, 14.1, 12.7

MS-ESI [M + Na]$^+$: m/z 429.5

(*S,Z*)-Methyl 4-(benzyloxy)-4-((*4S,7S*)-7-butyl-2,2-diisopropyl-4,7-dihydro-1,3,2-oxasilepin-4-yl)but-2-enoate (21)



Dess–Martin periodinane (0.125 g, 0.03 mmol) was added to a solution of compound **12**(0.100g, 0.25 mmol) and pyridine (0.04 ml, 0.312 mmol) in DCM (1.0 ml) at 0 ^{o}C. The reaction was stirred at rt for 30 min, before being quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. The organic layer was washed with satd. NaCl solution and dried over Na_2SO_4 and concentrated to afford an aldehyde that was used immediately in the next step without further purification. To a solution of $(PhO)_2P(O)CH_2COOEt$ (0.093 g, 0.267 mmol) in THF (1.3 mL) at 0°C. After 5 min NaH

(60% dispersion, 0.011 g, 0.267 mmol) was added, and the resulting solution was cooled to −78°C. The aldehyde (0.090 g, 0.222 mmol) dissolved in 1.1mL of THF was then added drop wise. After 2 h at −78°C, saturated NH_4Cl (2.5 mL) was added and the reaction mixture was extracted with Et_2O (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography using pet ether:ethyl acetate (85:15) as eluent to give **13**.

[α] $^{25}_D$= +97 (*c* 0.7, $CHCl_3$)

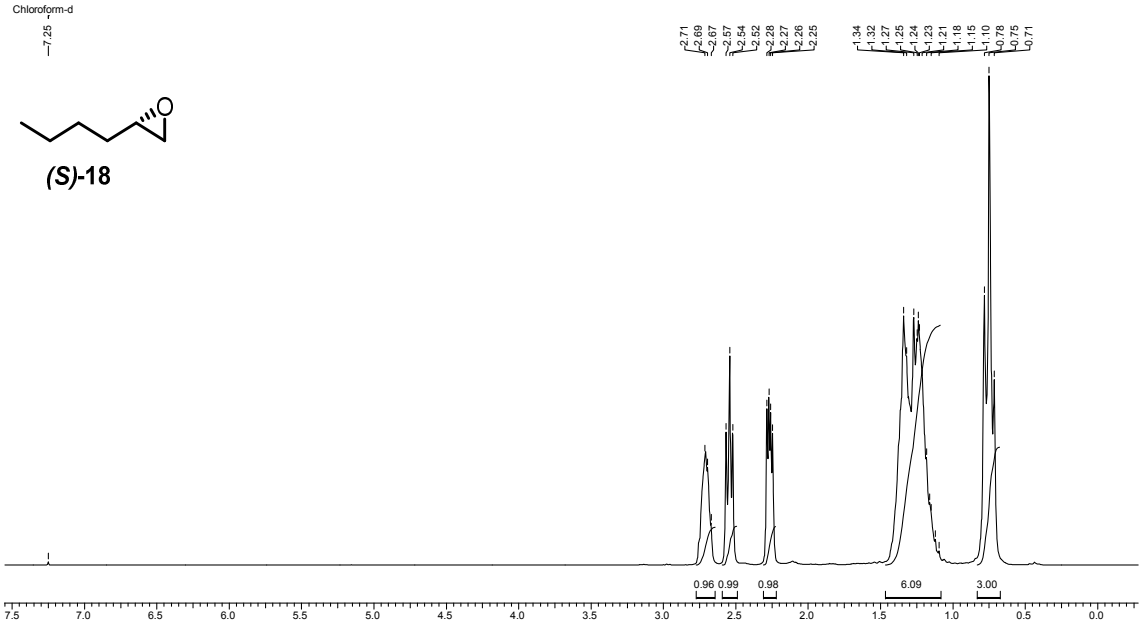
IR (neat, cm^{-1}): ν_{max} 2934, 2843, 1735, 1453, 1470, 1300, 1210, 1044, 762

^{1}H NMR (500MHz ,$CDCl_3$): δ = 7.36 (m, 3 H), 7.25 (m, 3 H), 6.89 (d, *J* = 8.2 Hz, 1 H), 4.78 (s, 2 H), 4.48 (s, 2 H), 4.32 - 4.27 (q, 3 H), 3.81 (s, 2 H), 3.75 -3.61 (m, 1 H), 3.71 - 3.60 (m, 2 H), 2.37-2.27 (m, 1 H), 2.12 - 1.89 (m, 1 H), 1.51 (s, 6 H), 1.31 (br. s., 12 H), 1.26 (br. s., 4 H), 1.05-1.02 (m 4 H), 0.91 - 0.86 (m, 4 H)

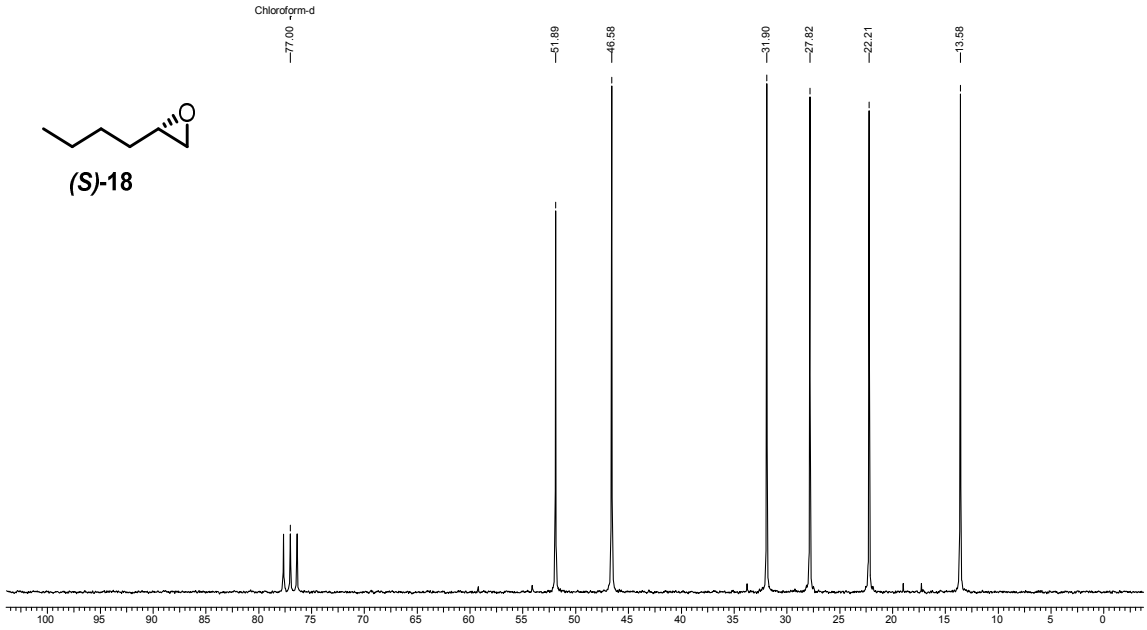
^{13}C NMR (125 MHz ,$CDCl_3$): δ = 169.7, 129.9, 129.5, 128.5, 127.8, 113.9, 113.8, 76.8, 73.2, 71.1, 71.1, 61.9, 55.3, 31.9, 29.7, 29.4, 26.4, 22.7, 17.3, 14.1

MS-ESI [M + Na]$^+$: m/z 497.25

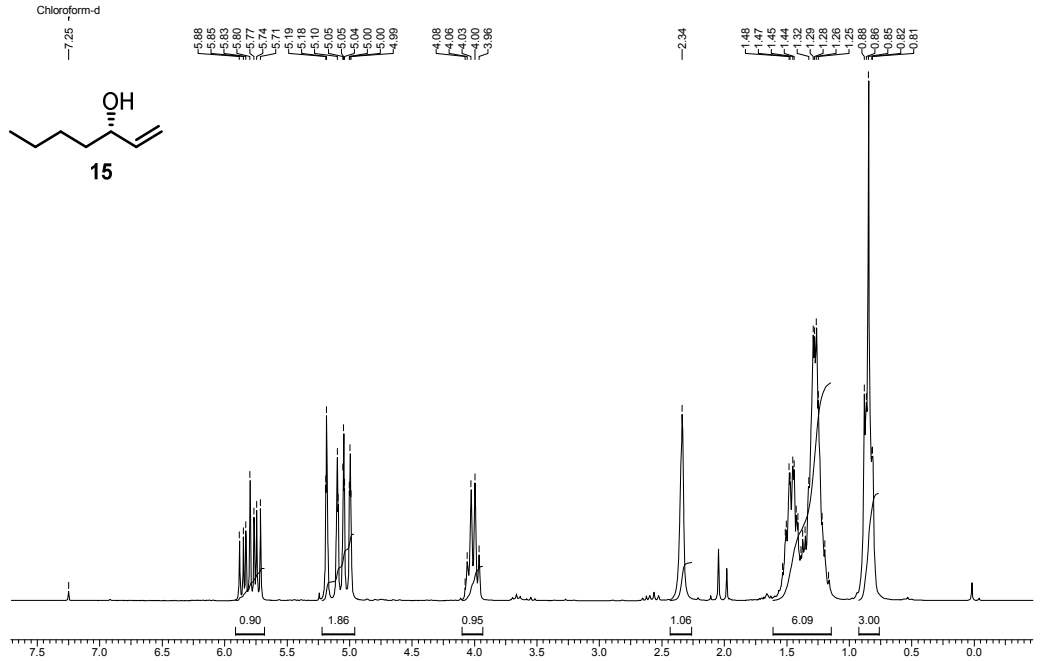
2.3.7. Spectra

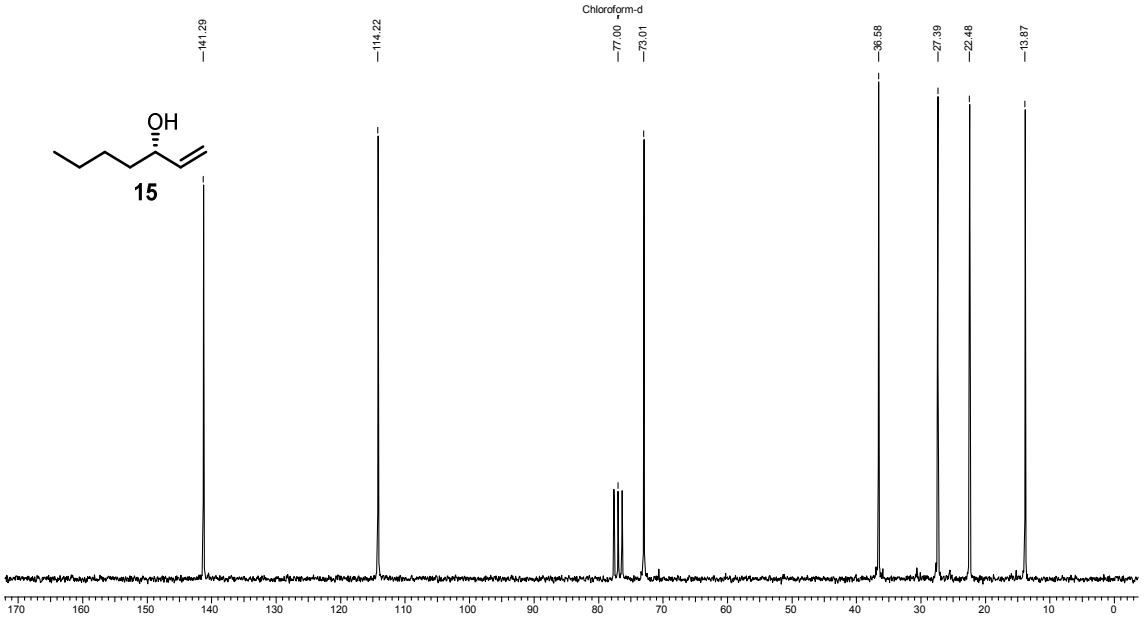

Chloroform-d
7.25
2.71
2.69
2.67
2.57
2.54
2.52
2.28
2.27
2.26
2.25
1.34
1.32
1.27
1.25
1.24
1.23
1.21
1.18
1.15
1.10
0.78
0.75
0.71
0.96
0.99
0.98
6.09
3.00

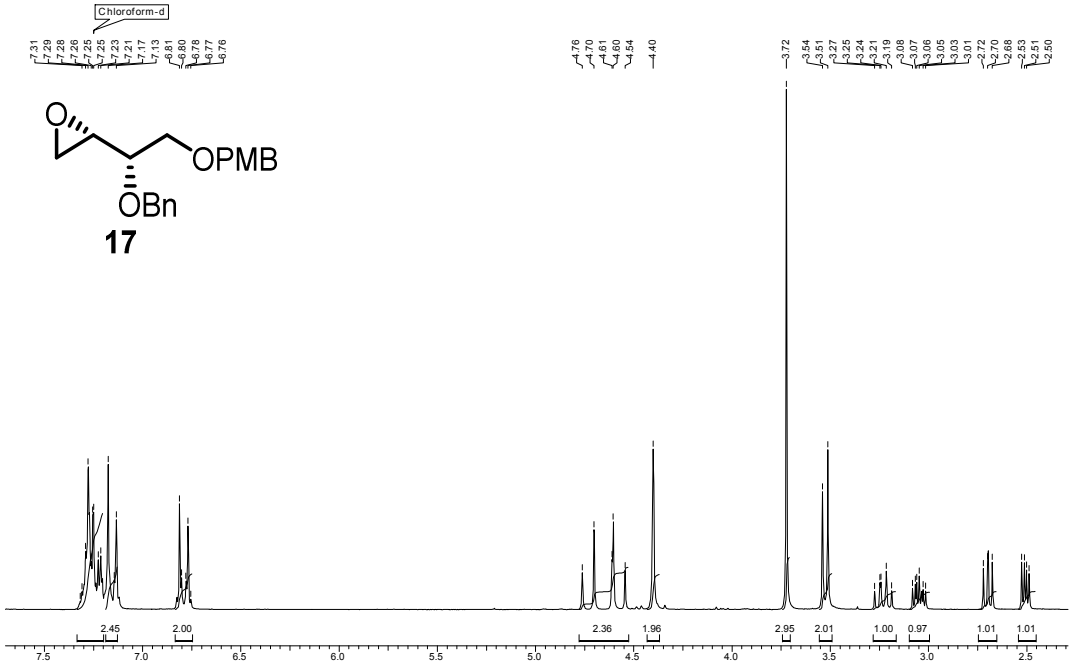
(S)-18

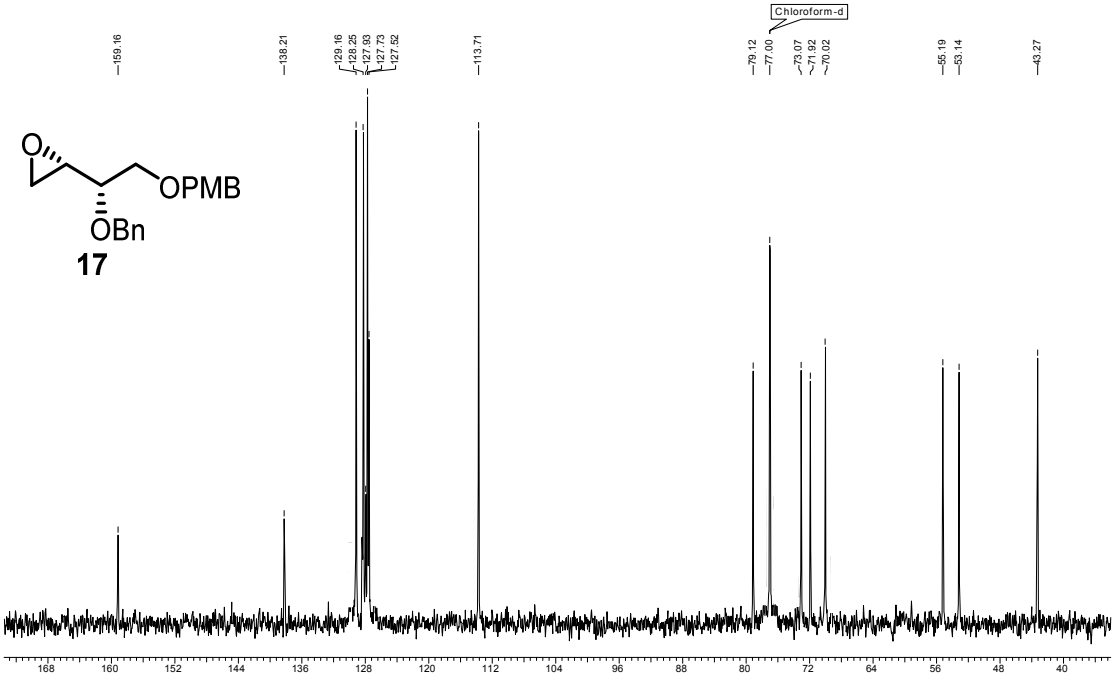

Chloroform-d
77.00
51.89
46.58
31.90
27.82
22.21
13.58

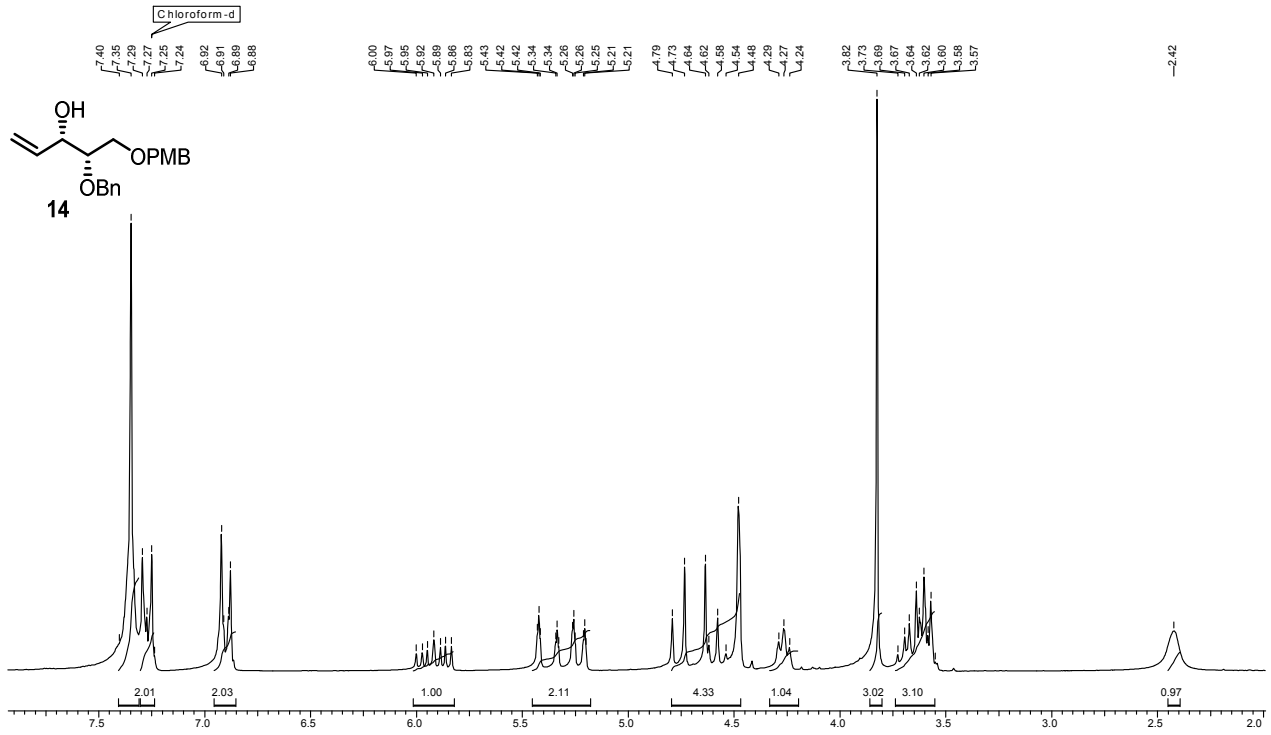
(S)-18

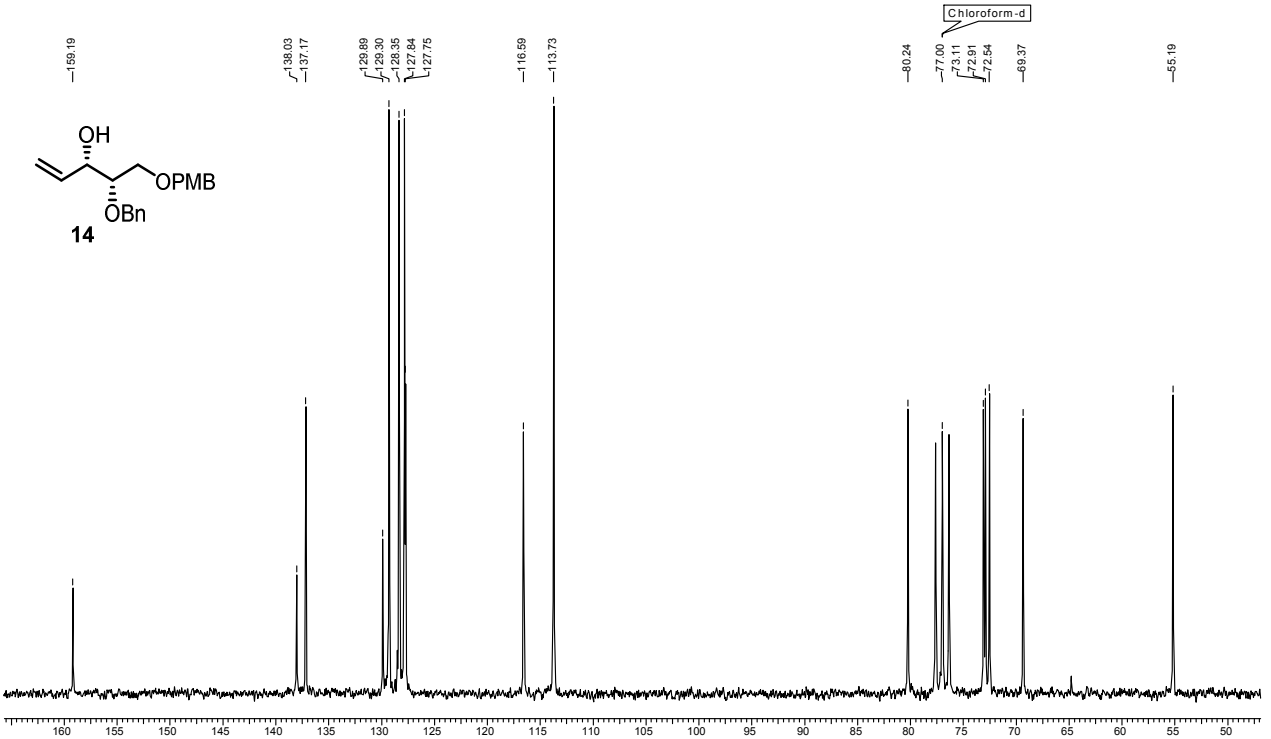

Chloroform-d
7.25
5.88
5.85
5.83
5.80
5.77
5.74
5.71
5.19
5.18
5.10
5.05
5.05
5.04
5.00
5.00
4.99
4.08
4.06
4.03
4.00
3.96
2.34
1.48
1.47
1.45
1.44
1.32
1.29
1.28
1.26
1.25
0.88
0.86
0.85
0.82
0.81
OH
15
0.90
1.86
0.95
1.06
6.09
3.00

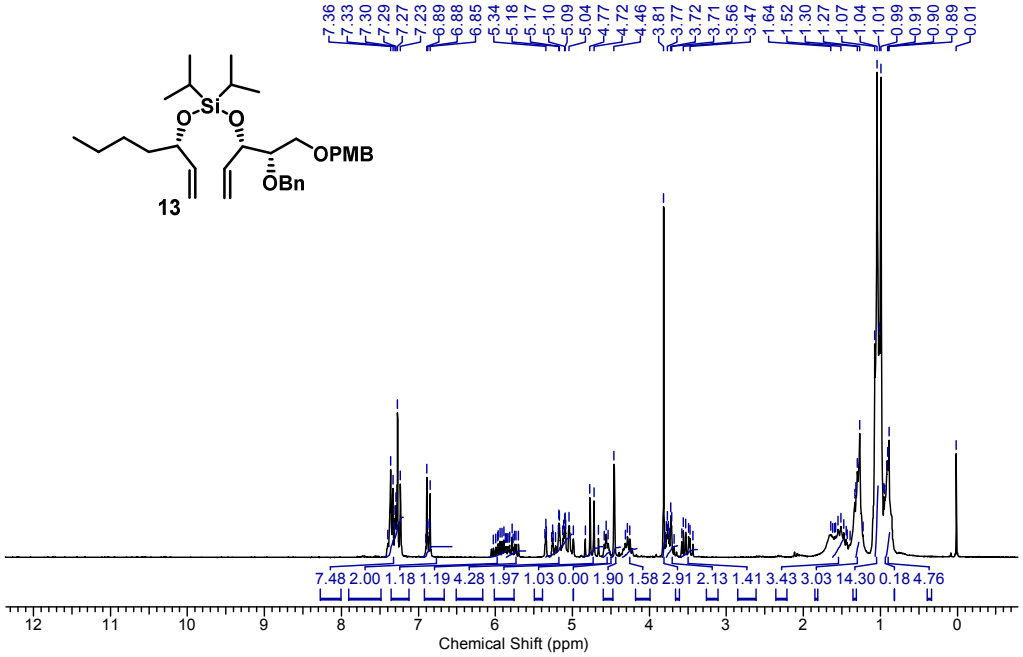

Chloroform-d
141.29
114.22
77.00
73.01
36.58
27.39
22.48
13.87
OH
15

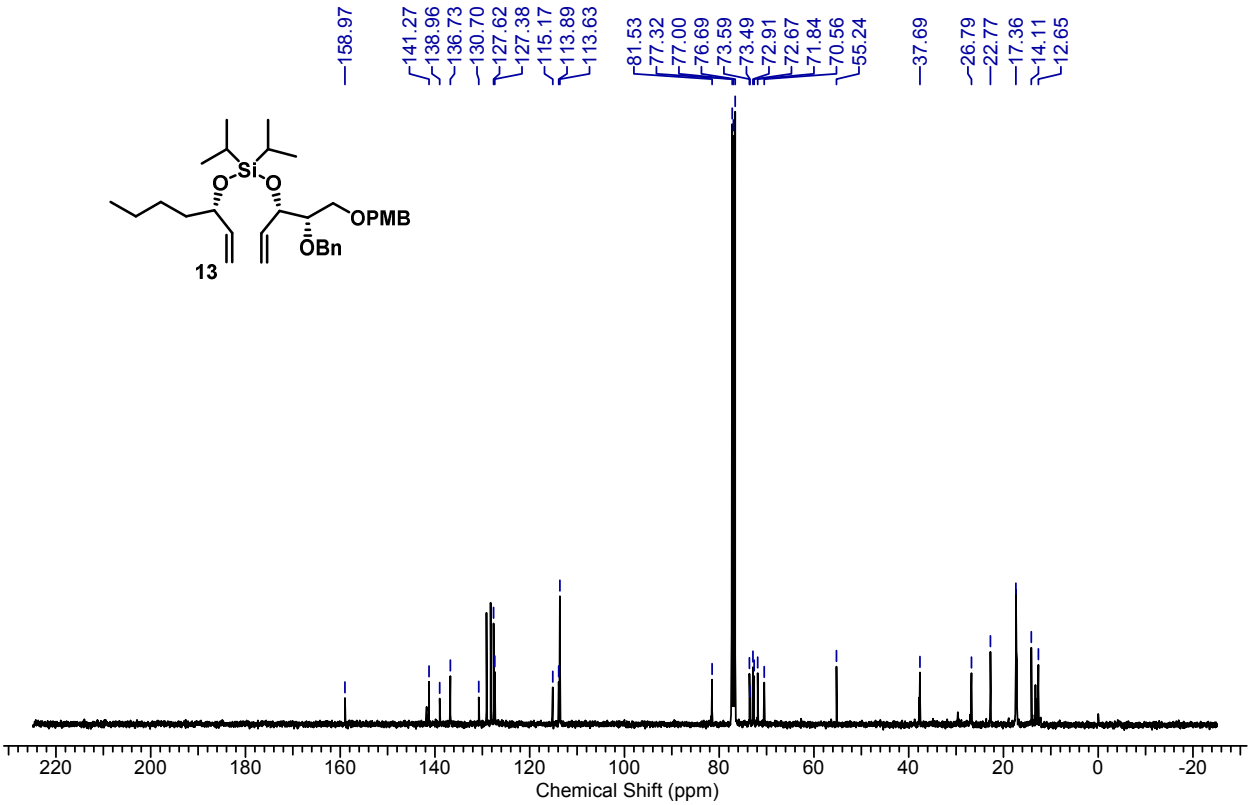

Chloroform-d
7.31
7.29
7.28
7.26
7.25
7.25
7.23
7.21
7.17
7.13
6.81
6.80
6.78
6.77
6.76
4.76
4.70
4.61
4.60
4.54
4.40
3.72
3.54
3.51
3.27
3.25
3.24
3.21
3.19
3.08
3.07
3.06
3.05
3.03
3.01
2.72
2.70
2.68
2.53
2.51
2.50
O
OPMB
OBn
17
2.45
2.00
2.36
1.96
2.95
2.01
1.00
0.97
1.01
1.01
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5

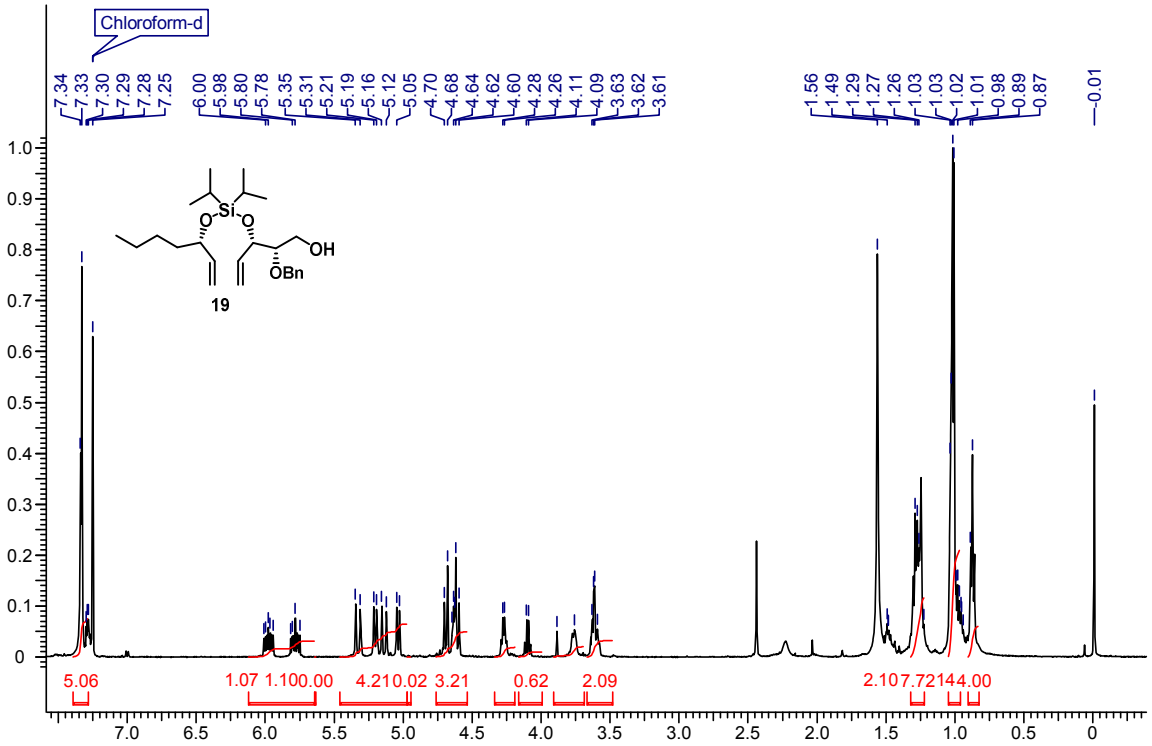

Chloroform-d
159.16
138.21
129.16
128.25
127.93
127.73
127.52
113.71
79.12
77.00
73.07
71.92
70.02
55.19
53.14
43.27
O
OPMB
OBn
17
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40

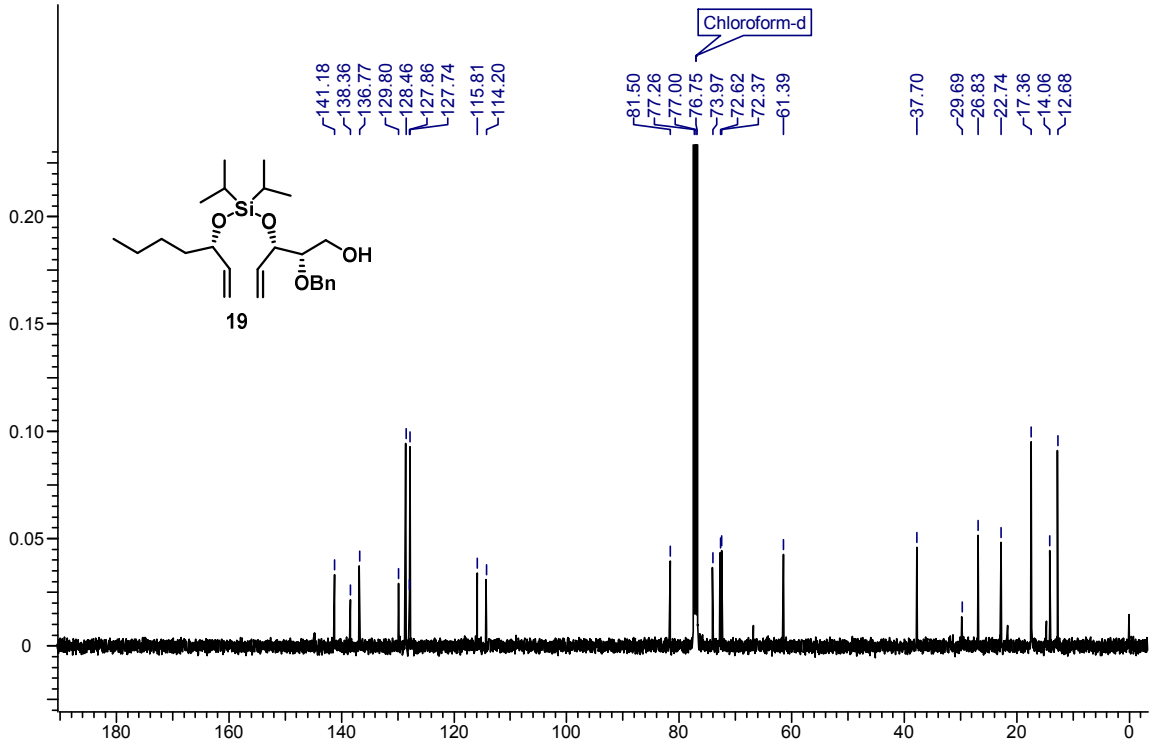

Chloroform-d
OH
OPMB
OBn
14

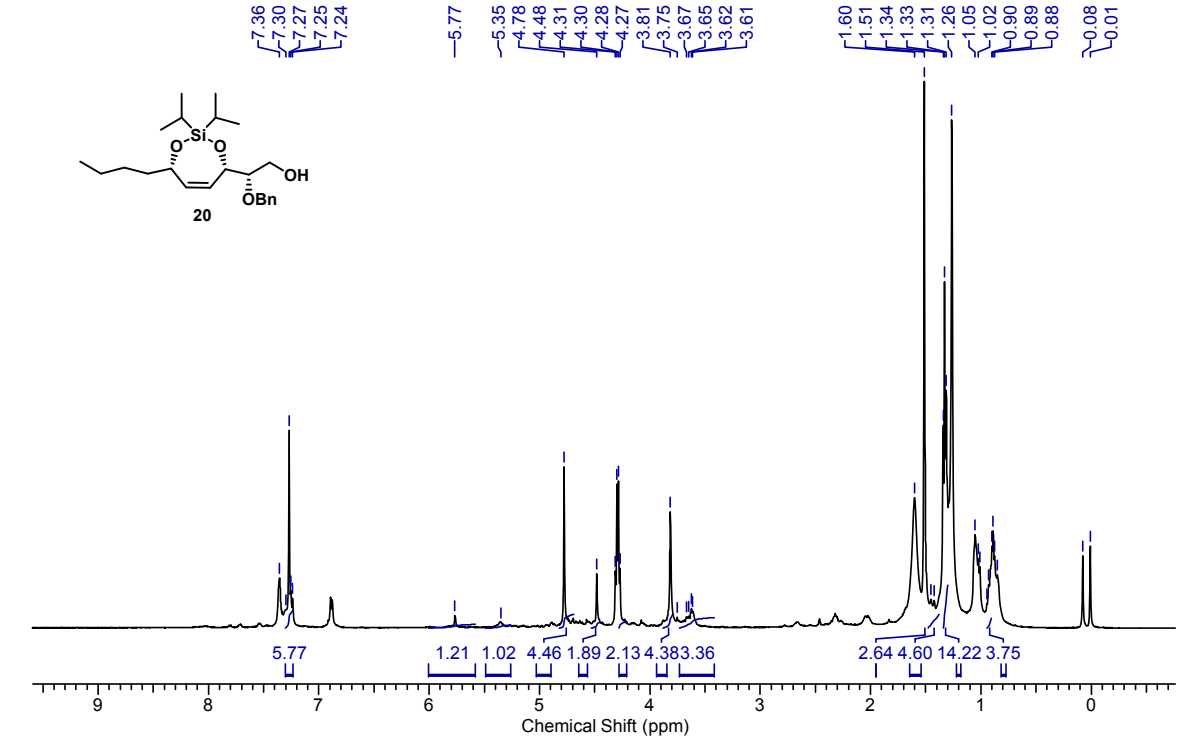

Chloroform-d
OH
OPMB
OBn
14

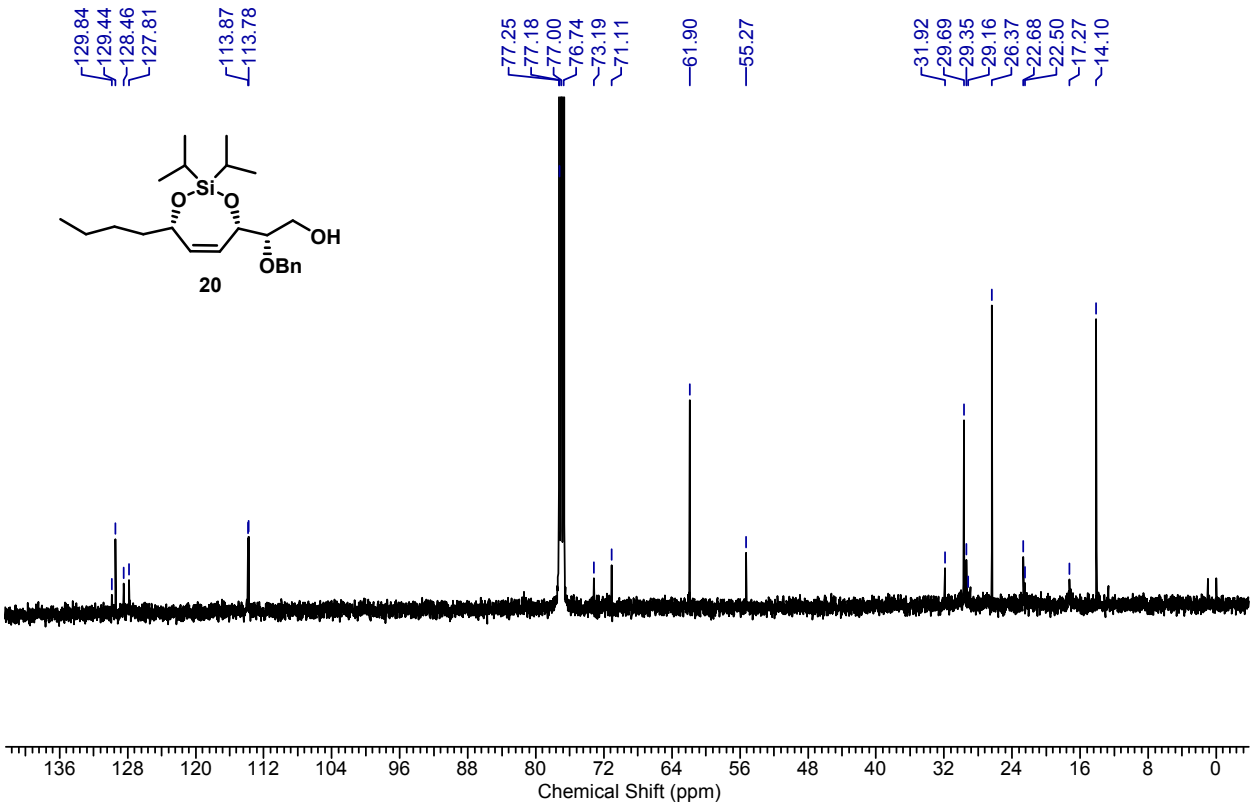

7.36 7.33 7.30 7.29 7.27 7.23 6.89 6.88 6.85 5.34 5.18 5.17 5.10 5.09 5.04 4.77 4.72 4.46 3.81 3.77 3.72 3.71 3.56 3.47 1.64 1.52 1.30 1.27 1.07 1.04 1.01 0.99 0.91 0.90 0.89 0.01
7.48 2.00 1.18 1.19 4.28 1.97 1.03 0.00 1.90 1.58 2.91 2.13 1.41 3.43 3.03 14.30 0.18 4.76
Chemical Shift (ppm)
OPMB
OBn
13

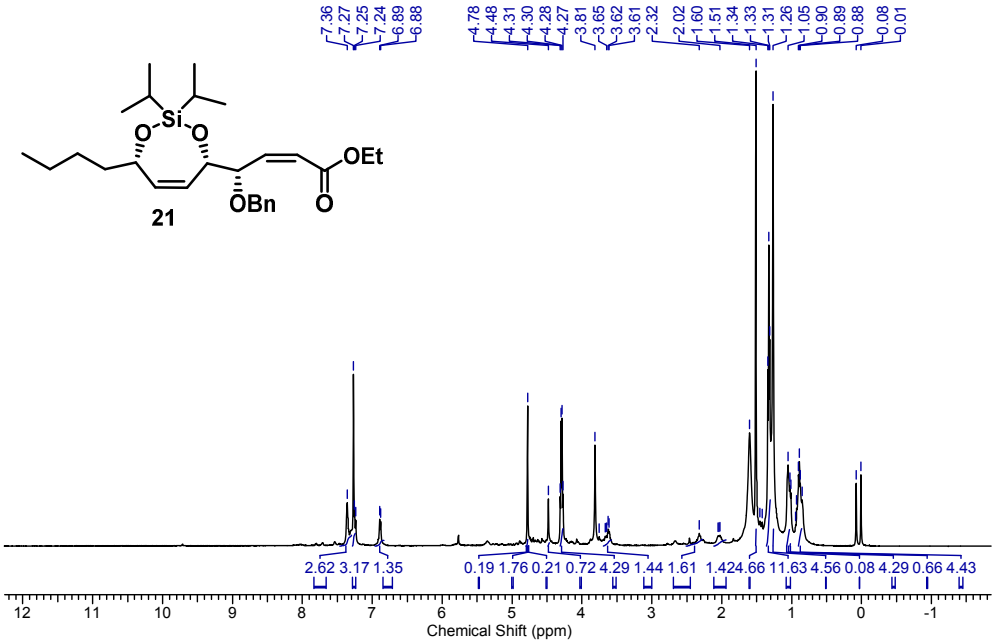

158.97 141.27 138.96 136.73 130.70 127.62 127.38 115.17 113.89 113.63 81.53 77.32 77.00 76.69 73.59 73.49 72.91 72.67 71.84 70.56 55.24 37.69 26.79 22.77 17.36 14.11 12.65
Chemical Shift (ppm)
OPMB
OBn
13

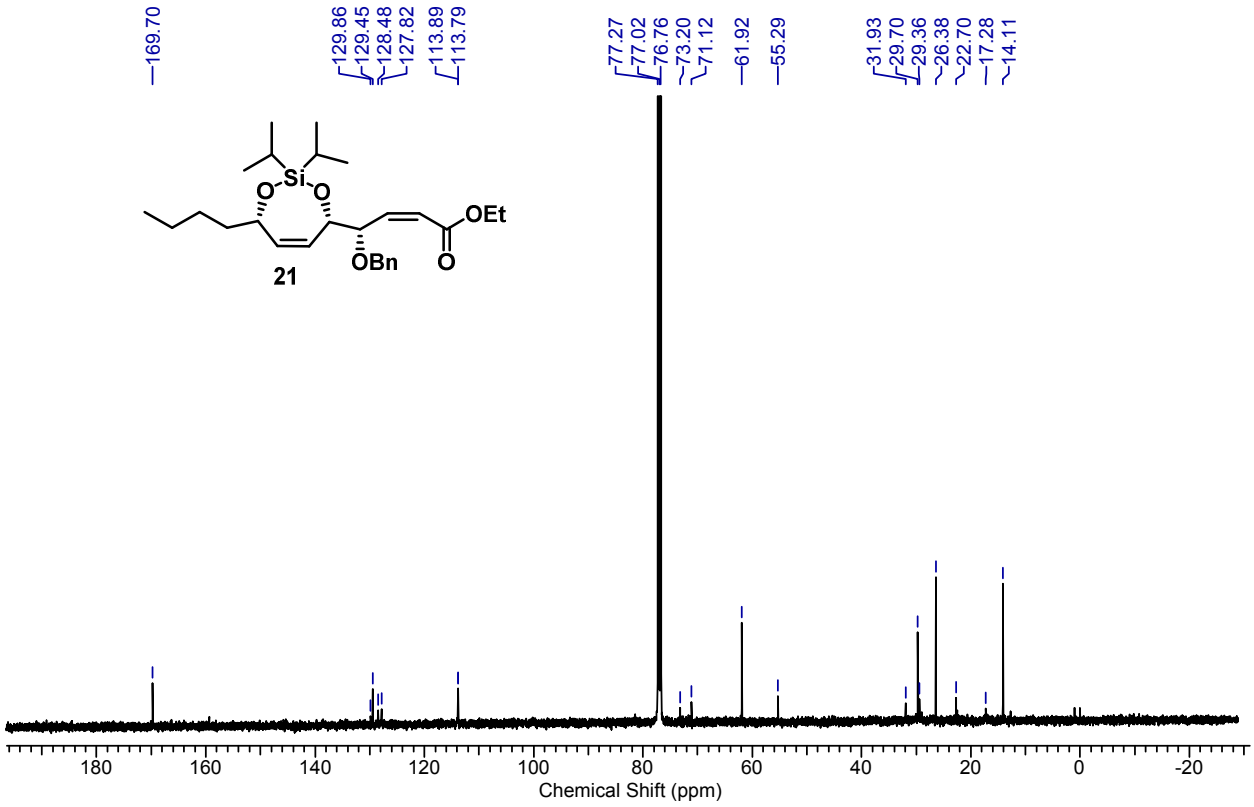

Chloroform-d
7.34 7.33 7.30 7.29 7.28 7.25
6.00 5.98 5.80 5.78 5.35 5.31 5.21 5.19 5.16 5.12 5.05
4.70 4.68 4.64 4.62 4.60 4.28 4.26 4.11 4.09 3.63 3.62 3.61
1.56 1.49 1.29 1.27 1.26 1.03 1.03 1.02 1.01 0.98 0.89 0.87
-0.01
OH
OBn
19
5.06 1.07 1.10 0.00 4.21 0.02 3.21 0.62 2.09 2.10 7.72 14.00


Chloroform-d
141.18 138.36 136.77 129.80 128.46 127.86 127.74 115.81 114.20
81.50 77.26 77.00 76.75 73.97 72.62 72.37 61.39
37.70 29.69 26.83 22.74 17.36 14.06 12.68
OH
OBn
19


7.36
7.30
7.27
7.25
7.24
5.77
5.35
4.78
4.48
4.31
4.30
4.28
4.27
3.81
3.75
3.67
3.65
3.62
3.61
1.60
1.51
1.34
1.33
1.31
1.26
1.05
1.02
0.90
0.89
0.88
0.08
0.01
Si
O
O
OH
OBn
20
5.77
1.21
1.02
4.46
1.89
2.13
4.38
3.36
2.64
4.60
14.22
3.75
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


129.84
129.44
128.46
127.81
113.87
113.78
77.25
77.18
77.00
76.74
73.19
71.11
61.90
55.27
31.92
29.69
29.35
29.16
26.37
22.68
22.50
17.27
14.10
Si
O
O
OH
OBn
20
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)


7.36
7.27
7.25
7.24
6.89
6.88
4.78
4.48
4.31
4.30
4.28
4.27
3.81
3.65
3.62
3.61
2.32
2.02
1.60
1.51
1.34
1.33
1.31
1.26
1.05
0.90
0.89
0.88
0.08
0.01
Si
O
O
OEt
OBn
O
21
2.62 3.17 1.35
0.19 1.76 0.21 0.72 4.29 1.44 1.61 1.42 4.66 11.63 4.56 0.08 4.29 0.66 4.43
12 11 10 9 8 7 6 5 4 3 2 1 0 -1
Chemical Shift (ppm)


169.70
129.86
129.45
128.48
127.82
113.89
113.79
77.27
77.02
76.76
73.20
71.12
61.92
55.29
31.93
29.70
29.36
26.38
22.70
17.28
14.11
Si
O
O
OEt
OBn
O
21
180 160 140 120 100 80 60 40 20 0 -20
Chemical Shift (ppm)

2.3.8. References

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Chapter 2-Section D - Synthetic studies towards (-) Cleistenolide employing Proline catalyzed aldol

2.4 Section D
Synthetic studies towards (-) Cleistenolide employing Proline catalyzed aldol reaction

2.4.1. Introduction

(-) Cleistenolide **1** and other metabolites (**2-17**, **Figure 1**) have been isolated from Annonaceae species *Cleistochlamys kirkii* Oliver which is indigenous to eastern and southern African countries including Malawi, Zambia, Mozambique, Zimbabwe, and Tanzania.[1, 2] The extract of this plant has been used as traditional medicine in Mozambique in the treatment of wound infections, rheumatism, and tuberculosis.[3]

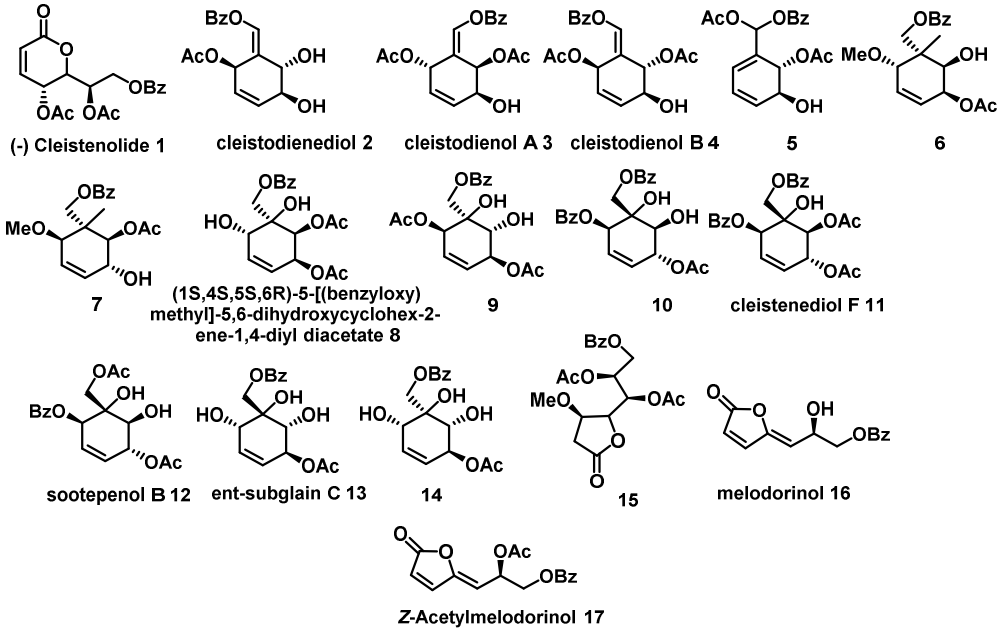


Figure 1: (-) Cleistenolide **1** and other metabolites from *Cleistochlamys kirkii*

The plant species are known to provide wide variety of compounds possessing varied biological properties. The family Annonaceae also provides compounds such as butenolides, a class of unsaturated lactones possessing a five-membered, four-carbon heterocyclic core.[4] The *Cleistochlamys kirkii* belongs to family Annonaceae which serves as a rich source of polyoxygenated cyclohexenes.[5] The polyoxygenated cyclohexenes [4,5] have been known to possess a diverse range of biological properties such as antiproliferative,[6] antimalarial,[7] larval antifeedant[6a], plant root growth inhibitory[8], and cytotoxic[9] activities. A few members of the family Annonaceae, are also known to contain

analogues with an additional alicyclic three-carbon skeleton, and therefore termed heptenolides.[4,10,11]According to the reports the heptenolides are known to exhibit antimicrobial[4], cytotoxic [10,11], anti-inflammatory [12], and mosquito-larvae growth inhibitory activities.[13] Due to the availability of such biologically active compounds *Cleistochlamys kirkii* has been a subject of various biological studies in search of new compounds which can act as antimalarial and anticancer agents and also prove useful in overcoming drug resistance in drug resistant bacteria.[14] The metabolites isolated from *Cleistochlamys kirkii* were subjected to various biological assays for their activity against Plasmodium falciparum (3D7, Dd2), human embryonic kidney cells (HEK-293), and human triple-negative breastcancer cells (MDA-MB-231) and luciferase mRNA translational inhibition. The results obtained from biological assays were astonishing in terms of the antibacterial and cytotoxic activity. It was found that some of the compounds isolated were active against Plasmodium falciparum (3D7, Dd2), with IC_{50}values of 0.2-40 μM, and against

HEK293 mammalian cells (IC_{50}=2.7-3.6 μM).The crude isolate was found to be inactive even at 100 μg/mL against the MDA-MB-231triple-negative breast cancer cell line, the individual compounds obtained were found to exhibit cytotoxic activity with IC_{50} values ranging from 0.03-8.2 μM.[15]

(-) Cleistenolide **1** has been found highly active against bacterial strains of *S. aureus* and *Bacillus anthracis* and certain fungi like *Candida albicans*. Cleistodienediol **2** displayed the most promising activity against Plasmodium falciparum (3D7, Dd2), with IC_{50} 0.2 μM and MDAMB-231cell line with IC_{50} 0.03 μM.[15]

2.4.2. Review of Literature

Till date nine syntheses have been reported in the literature for the synthesis of (-) Cleistenolide **1.** All the reports describe the chiral pool approach for achieving the desired stereocentres in target molecule and utilising ring closing metathesis as a tool for construction of lactone ring.[16-24]

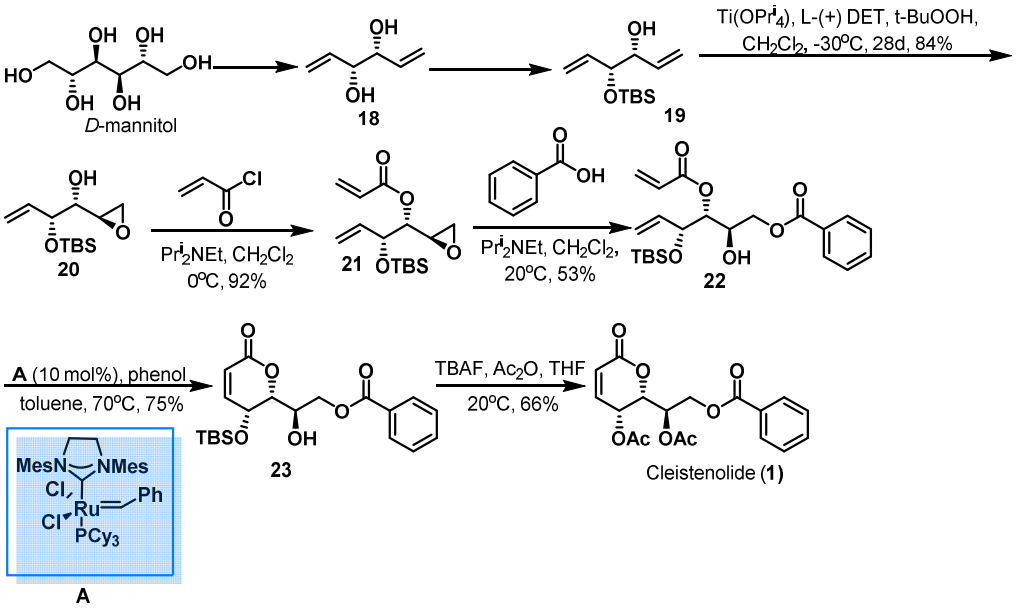
Schmidt *et al.* (2010) [16]

The first synthesis of (-) Cleistenolide **1** was reported by Schmidt and co-workers using *D*-mannitol derived (*R, R*)-1,5-hexadiene-3,4-diol **18** as starting material **(Scheme 1)**. The authors carried out protecting group directed Sharpless epoxidation of compound **19.**

Initially one of the hydroxyl group of (*R,R*)-1,5-hexadiene-3,4-diol **18** was selectively converted to its corresponding TBS ether using TBSCl as silylating agent. The TBS ether **19** was subjected to standard Sharpless epoxidation conditions to furnish epoxide **20.** The epoxy alcohol **20** was transformed to its corresponding acrylate **21** using acroyl chloride and DIPEA. The acrylate **21** was then subjected to selective epoxide opening with benzoic acid to provide benzoate **22**.

Further, the diene **22** underwent RCM when treated with catalyst **A** to afford lactone **23.** The synthesis was finally accomplished by one-pot removal of TBS group and subsequent acylation using TBAF, acetic anhydride in THF. The synthesis was accomplished in six steps

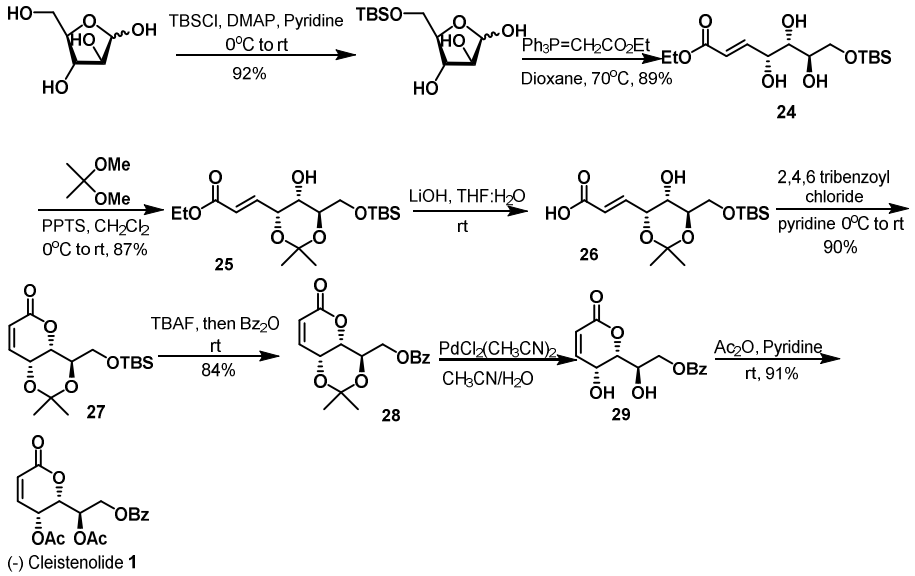
and 18% overall yield from (*R, R*)-hexa-1,5-diene-3,4-diol (**Scheme 1)**.



Scheme 1: Synthesis of (-)-Cleistenolide **(1)** by Schmidt *et al.*

Linhardt *et al.* (2010)[17]

In 2010 Linhardt and co-workers synthesized (-)-Cleistenolide **(1)** using *D*-arabinose as starting material. The key intermediate *α,β*-unsaturated ester **24** was synthesized from D-arabinose using a know procedure.[24]

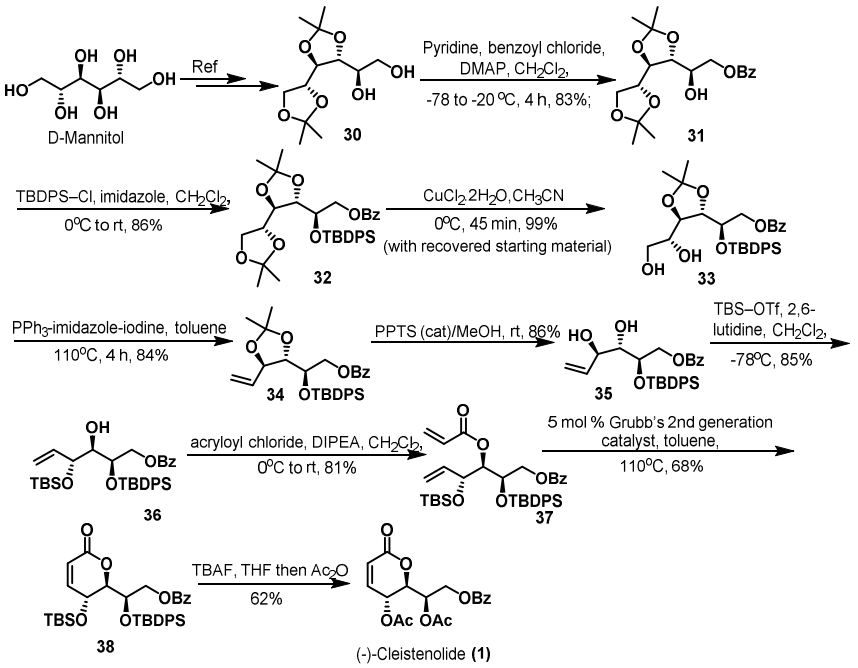


Scheme 2: Synthesis of (-)-Cleistenolide **(1)** by Linhardt *et al.*

Further, the triol **24** on further synthetic manipulation furnished **26.** The acid **26** on Yamaguchi reaction[25] and further synthetic transformation provided benzoate **28.** The target compound **1** was finally synthesized from the benzoate precursor **28 (Scheme 2)**. The stereoselective total synthesis of (-)-cleistenolide (1) was accomplished in eight steps and 49% overall yield from *D*-arabinose.

Meshram *et al.* (2011)[18]

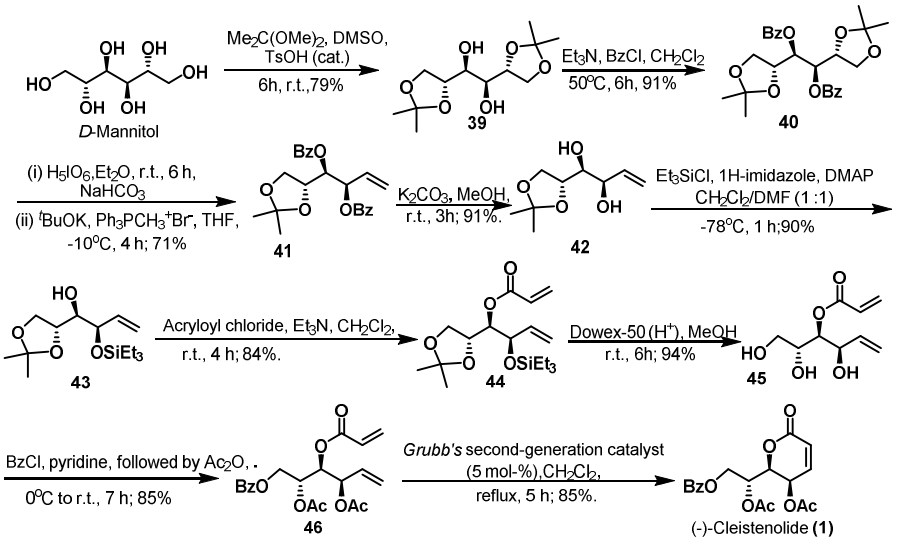
A third synthesis of (-)-Cleistenolide **(1)** was reported by Meshram and co-workers from *D*-mannitol. *D*-Mannitol was first converted to diol **30** according to literature reported procedure.[26] The diol through series of routine synthetic procedures provided allylic alcohol **35.** The diol **35** was used as precursor for the synthesis of advanced intermediate **37** which on further synthetic manipulation furnished target molecule **1** (**Scheme 3).** The synthesis of (-)-Cleistenolide **(1)** was accomplished by single step removal of silyl ether in **38** and subsequent diacetate formation.



Scheme 3: Synthesis of (-)-Cleistenolide **(1)** by Meshram *et al.*

Venkateswarlu *et al.* (2011)[19]

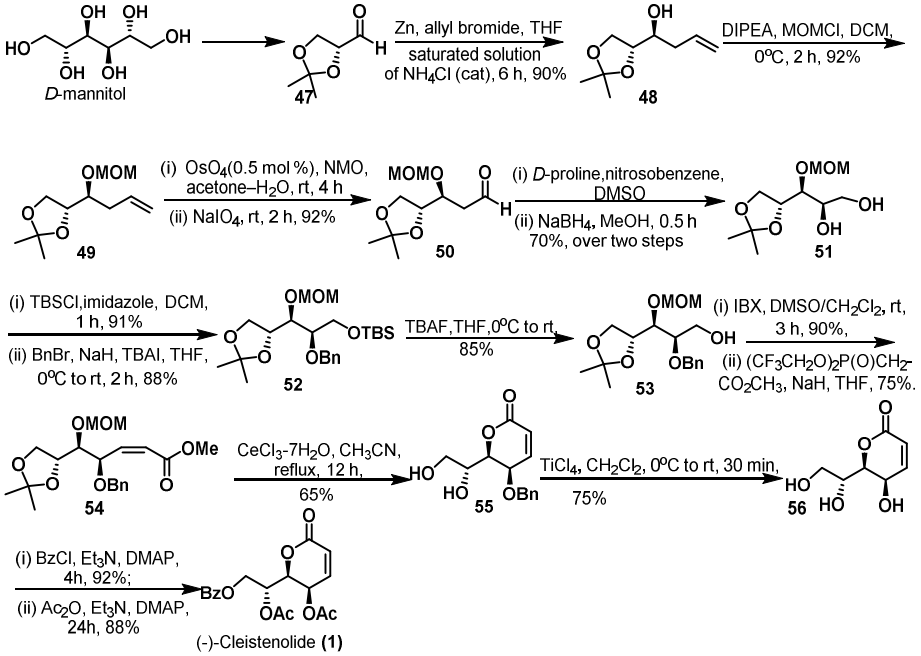
Venkateswarlu and co-workers utilised chiron approach for the synthesis (-)-Cleistenolide **(1).** The authors employed *D*-mannitol as starting material for achieving desired stereocentres in (-)-Cleistenolide **(1) (Scheme 4).** *D*-Mannitol was first converted to diol **42**. The diol **42** through desired synthetic sequence afforded acrylate ester **44.** The intermediate **44** on subsequent reactions furnished the desired compound **1 (Scheme 4).**



Scheme 4: Synthesis of (-)-Cleistenolide **(1)** by Venkateswarlu *et al.*

Yadav *et al.* (2011) [20]

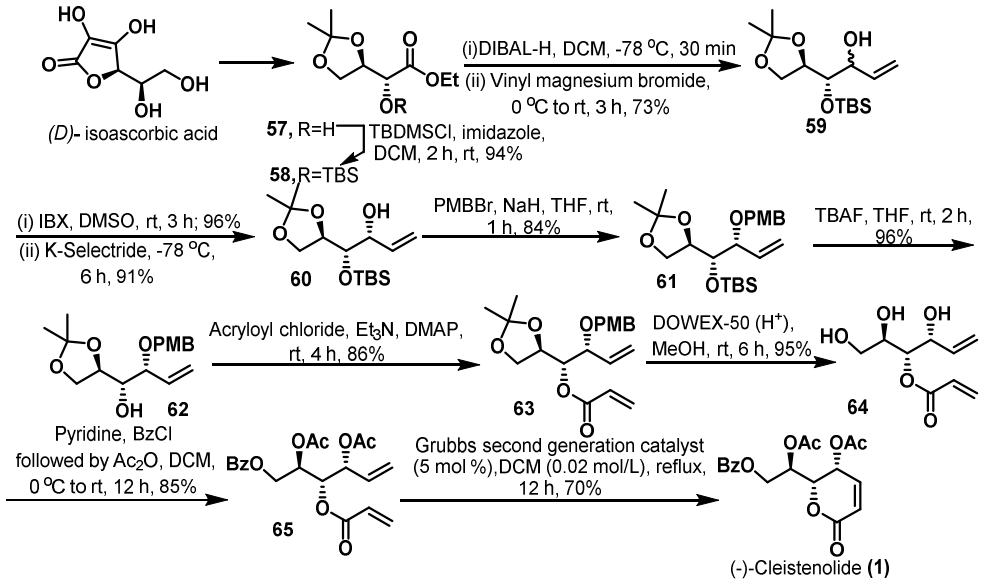
Another synthesis of (-)-Cleistenolide **(1)** was reported by Yadav and co-workers where they employed *D*-mannitol as a source of chirality. *(R)*-Glyceraldehyde 1, 2-acetonide **47** was synthesized from *D*-mannitol using a literature reported procedure.[27] The usual synthetic sequence using **47** as starting provided ester **54.** The ester **54** on cyclization and deprotection -protection furnished Cleistenolide **1 (Scheme 5).**



Scheme 5: Synthesis of (-)-Cleistenolide **(1)** by Yadav *et al.*

Venkateswarlu *et al.* (2011)[21]

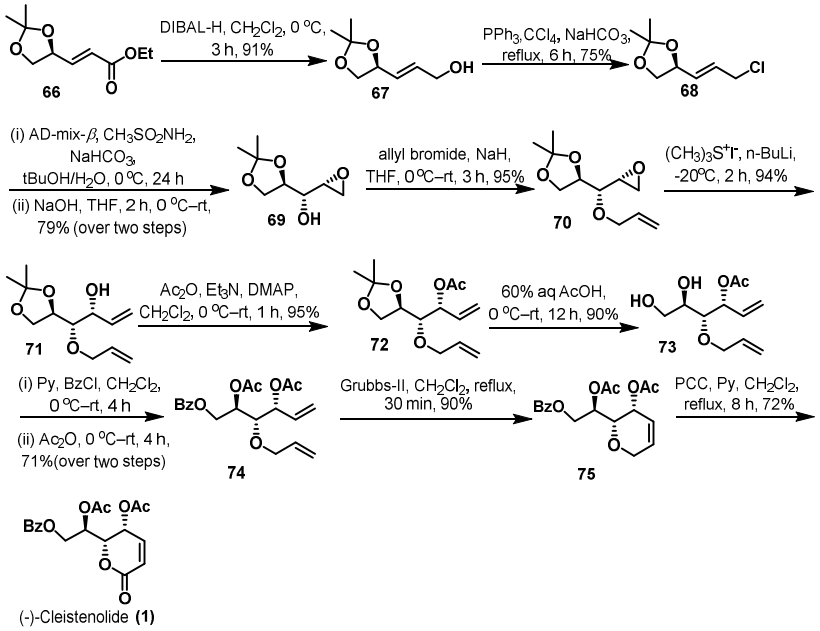
Venkateswarlu and co-workers reported another synthesis of (-)-Cleistenolide **(1)** exploiting existing chirality in *D*-isoascorbic acid for achieving desired stereocentres in target compound **1.** *D*-isoascorbic acid was first converted to *α*-hydroxy ester **57** by a literature procedure.[31] The α-hydroxy ester **57** was then subjected to series of routine transformation to furnish **62.** The alcohol **62** on acrylate formation and ring closing metathesis using Grubbs second generation catalyst furnished compound **1** in 18% overall yield **(Scheme 6)**.



Scheme 6: Synthesis of (-)-Cleistenolide **(1)** by Venkateswarlu *et al*.

Madhusudana Rao *et al.* (2012)[22]

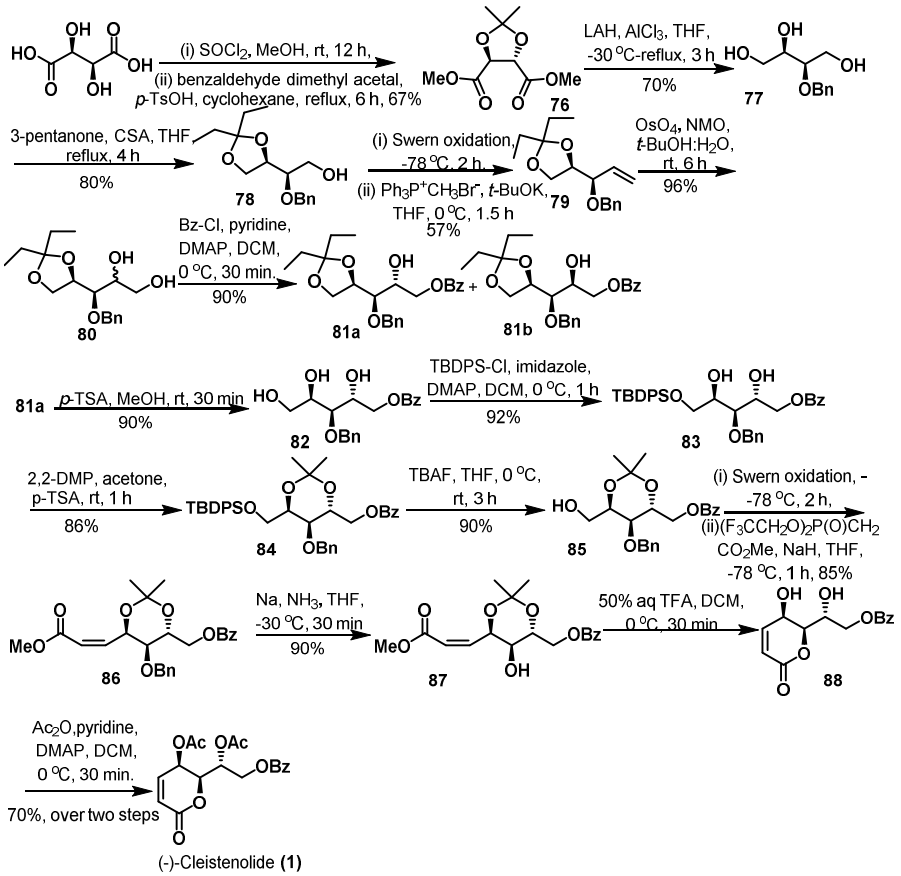
In 2012 Madhusudana Rao and co-workers reported a novel strategy for the synthesis of (-)-cleistenolide **(1)** using *D*-mannitol as the starting material. The authors commenced the synthesis with conversion of *(R)*-glyceraldehyde 1, 2-acetonide **47**, which was derived from *D*-mannitol, to ester **66.** The ester served as starting material for synthesis of epoxy alcohol **70**. The epoxide **70** underwent regioselective ring opening to produce allylic alcohol **71.** The allylic alocohol **71** on further synthetic manipulation and employing RCM as key step provided the target molecule **1** (**Scheme 7)**.



Scheme 7: Synthesis of (-)-Cleistenolide **(1)** by Madhusudana Rao *et al*.

Narsaiah *et al.* (2013)[23]

In 2013 Narsaiah and co-workers synthesized (-)-Cleistenolide **(1)** from *D*-tartaric acid (**Scheme 8)**. The tartaric acid was first converted into it dimethyl ester in presence of $SOCl_2$/MeOH.

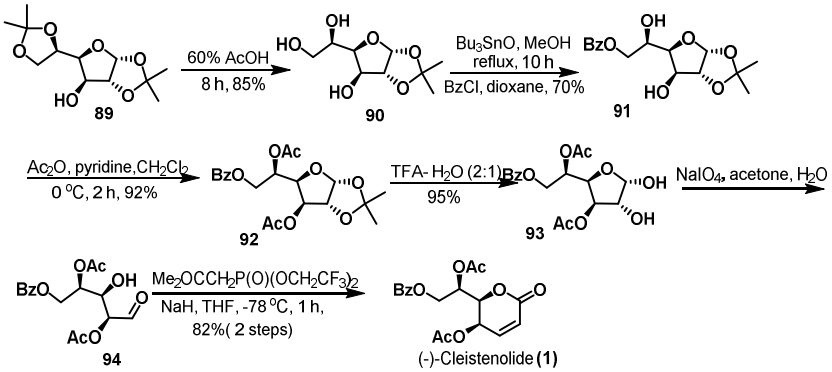


Scheme 8: Synthesis of (-)-Cleistenolide **(1)** by Narsaiah *et al*.

The ester **76** was subsequently converted to alcohol **85.** The alcohol **85** on further reactions furnished *α,β*-unsaturated ester **86**. The ester **86** on successive manipulations afforded the target compound **1.** The target compound **1** was synthesized in 13 steps with overall yield 7.92%.

Yadav *et al.* (2016)[24]

In 2016 Yadav and co-workers used commercially available *D*-glucose diacetonide **89** for the synthesis of (-)-Cleistenolide **(1).** The synthesis of target compound **1** was accomplished using selective benzoylation and Still-Gennari olefination as key steps in 6 steps and 42.5% overall yield **(Scheme 9)**.



Scheme 9: Synthesis of (-)-Cleistenolide **(1)** by Yadav *et al*.

2.4.3. PRESENT WORK

Objective

In our endeavor to explore organocatalytic methods to synthesize natural products, our group has worked towards applying proline catalyzed transformations for the same.[32] Our group has previously reported synthesis of various naturally occurring polyols and amino alcohols which describe proline catalyzed α-aminoxylation and α-amination as synthetic tools to generate asymmetric centre from prochiral starting materials.[32] Inspired by success of proline

catalyzed α-aminoxylation and α-amination in the synthesis of naturally occurring compounds, we intended to apply proline catalyzed aldol reaction of dioxanone **96** with various aldehydes with the same objective as mentioned above. To illustrate the practical application of this strategy we attempted at the synthesis of naturally occurring (-)-Cleistenolide using proline catalyzed aldol reaction (**Figure 2**).

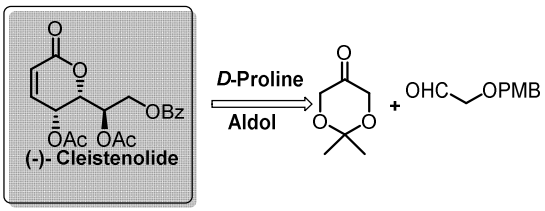
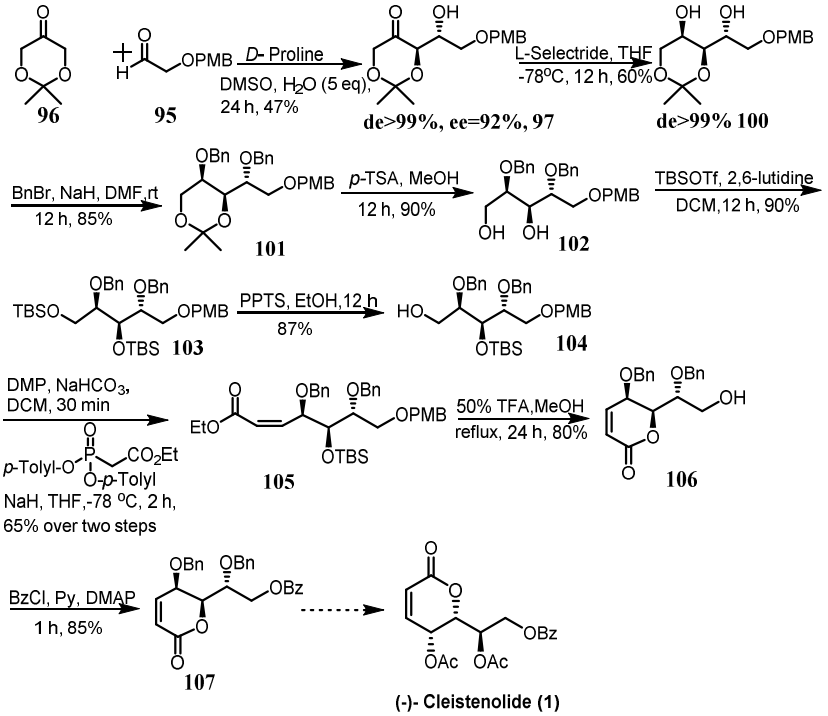


Figure 2: Synthetic Scheme for (-)-Cleistenolide.

2.4.4. Results and Discussion

Our attempt towards the synthesis of (-)-Cleistenolide describes organocatalytic approach for the synthesis of key intermediate **107.** For this purpose proline catalyzed aldol[33] was performed using dioxanone **96** and aldehyde **95** to provide **97** in 92% ee. The presence of *β*-hydroxy ketone 97 was confirmed by ^{1}H and ^{13}C NMR spectroscopy(^{13}C, C=O: δ= 208.1 ppm). With **97** in hand we subjected the *β*-hydroxy ketone to stereoselective reduction using L-selectride as reducing agent. To our delight the desired dihydroxy compound **100** was obtained in excellent diastereoselectivity. The disappearance of carbonyl signal in ^{13}C NMR confirmed reduction of keto group in **97** . As we were successful in obtaining the intermediate **100** with all the desired stereocentres, we now aimed at synthesizing the key intermediate **105.** With this objective in mind, we subjected **100** to benzylation using BnBr/NaH to furnish dibenzyl ether **101** in 85% yield which gave rise to ^{1}H NMR signals in the range δ=7.12 - 7.27 ppm and δ= 4.51-4.69 ppm (m, 4

H, for O-CH_2-Ph) . The dibenzyl ether **101** was then treated with *p*-TSA/ MeOH to yield diol **102** which was subjected to silyl ether formation without further purification using TBSOTf/ 2, 6-lutidine to furnish silyl ether **103.** The presence of bis silyl ether **103** was confirmed by 13C NMR spectroscopy (δ= 18.2, -4.6, -4.7, -5.4, -5.4 ppm for Si-C) The silyl ether **103** was regioselectively cleaved to primary alcohol **104** using PPTS/ EtOH. The primary alcohol **104** was obtained in 87% yield and confirmed by ^{1}H spectroscopy (0.79 - 0.92 for Si-C-CH_3 and-0.06 - 0.10 ppm for Si-C-CH_3). Having this alcohol in hand we subjected it to Dess Martin periodinane oxidation to give corresponding aldehyde which was further converted to *α, β*-unsaturated ester **105** using Ando's protocol. The structure of **105** was confirmed by ^{1}H and ^{13}C spectroscopy. The *α, β*-unsaturated ester **105** was then subjected to acid catalyzed silyl ether cleavage and concomitant lactonization employing 50%TFA/MeOH to furnish lactone **106.** The free alcohol in **106** was then benzoylated using BzCl and pyridine using catalytic amount of DMAP to give benzoate **107** (**Scheme 10**). The benzoate compound **107** gave ^{1}H NMR signals at δ= 7.95 - 8.06 ppm (H-CCO), 6.69 and 6.74 ppm (H-CC-H, pyrone ring) which confirms the formation of advanced precursor **107**. This can be easily converted to target molecule **1** by debenzylation and subsequent diacetylation of the free hydroxy group.



Scheme 10: Synthesis of (-)- Cleistenolide

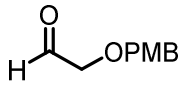
2.4.5. Conclusion.

We have successfully applied proline catalyzed aldol reaction of dioxanone **96** with aldehyde **95** and subsequent stereoselective reduction strategy for generation of desired stereocentres in order to synthesize the precursor **107** which can be further converted to (-)- Cleistenolide. The strategy offers a flexible approach to synthesize unnatural isomers of (-)- Cleistenolide without using chiral pool starting materials.

2.4.6. Experimental

General Information: All reactions were carried out under argon or nitrogen in oven-dried glassware using standard gas-light syringes, cannulas and septa. Solvents and reagents were purified and dried by standard methods prior to use. Optical rotations were measured at room temperature. IR spectra were recorded on an FT-IR instrument. ^{1}H NMR spectra were recorded on 200 MHz, 400 MHz and 500 MHz and are reported in parts per million (δ) downfield relative to $CDCl_3$ as internal standard and ^{13}C NMR spectra were recorded at 50 MHz, 100 MHz and 125 MHz and assigned in parts per million (δ) relative to $CDCl_3$. Column chromatography was performed on silica gel (100-200 and 230-400 mesh) using a mixture of petroleum ether and ethyl acetate as the eluent.

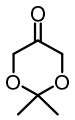
2-((4-Methoxybenzyl)oxy)acetaldehyde (**95**)



Aldehyde **95** was synthesized from 1,4-butenediol using literature reported procedure.[35]

IR (neat, cm^{-1}): ν_{max} 814, 1033, 1094, 1250, 1513, 1610, 2901, 3285, 3439

2,2-Dimethyl-1,3-dioxan-5-one (**96**)

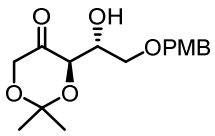


Dioxanone **96** was synthesized from tris hydrochloride using literature reported procedure.[34]

IR (neat, cm^{-1}): ν_{max} 3426

^{1}H NMR (200 MHz): δ= 4.46(d, J= 13.0Hz 2 H,), 4.14(d, J= 13.0Hz, 2 H,), 3.94(s, 2 H), 3.78 (s, l H), 1.43 (s, 3 H), 1.32 (s, 3 H)

(*R*)-4-((*R*)-1-Hydroxy-2-((4-methoxybenzyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxan-5-one (97)



A solution of aldehyde **95** (4g, 0.022 mol) in DMSO (20 ml) was added to a round-bottomed flask containing *D*-proline (0.75g, 0.066mol, 30 mol %), dioxanone **96** (14g,

0.11 mol) and water (0.11 mol, 45 mL) and 35 mL DMSO (2.5 ml/ mmol). Next, the mixture was vigorously stirred for 24 h at room temperature. The reaction was quenched by addition of satd. NH_4Cl followed by extraction with EtOAc (25ml). The aqueous-phase was back-extracted with EtOAc (3X25 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The pure β-hydroxy ketone **97** was isolated by column chromatography (50% pet ether: 50% EtOAc).

Yield: 3.23 g (47%)

[α] $^{25}_{D}$: +150 (*c* 1, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200MHz): δ= 7.48 - 7.05 (m, 2H), 7.03 - 6.82 (m, 2 H), 4.53 (s, 2H), 4.44 (dd, *J* = 1.4, 6.2 Hz, 1 H), 4.37 - 4.21 (m, 1 H), 4.21 - 4.11 (m, 1H), 4.11 - 3.93 (m, 1 H), 3.84 (s, 3H), 3.65 (d, *J* = 4.7 Hz, 2 H), 3.15 - 2.61 (m, 1 H), 1.52 - 1.44 (m, 6 H)

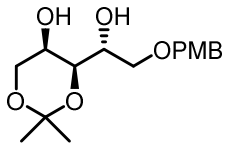
^{13}C NMR ($CDCl_3$, 50 MHz): δ = 208.1, 159.2, 129.5, 129.4, 113.8, 100.1, 98.4, 73.1, 66.8, 55.3, 23.5

IR (neat, cm^{-1}): ν_{max} 3500-3200, 2985-2980, 1740, 1110.

MS-ESI [M + Na]$^+$:m/z 333.18

(4R,5R)-4-((R)-1-Hydroxy-2-((4-methoxybenzyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxan-5-ol

(100)



To a solution of **97** (3.0 g, 9.7 mmoL) in dried THF (140 mL) was cooled to -78 ^{0}C followed by addition of L-selectride (29 mL, 29.1 mmoL, 1M in THF) and the solution was stirred at

-78 ^{0}C for 12 h. After 12 h, the reaction was quenched with satd. NH_4Cl (25 ml) followed by addition of H_2O_2 (30%, 11 ml) and NaOH (10%, 20ml) at 0 ^{0}C and stirred at rt for another 30 min followed by extraction with 50 ml of EtOAc. The organic layer was separated and back extracted with 3X30 mL of EtOAc. The combined organic layers were washed with brine (50 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. Diol **100** was purified by column chromatography (100% EtOAc to 2% MeOH:98% EtOAc).

Yield: 1.93 g (60%)

[α] $^{25}_{D}$: - 15 (*c* 0.8, MeOH)

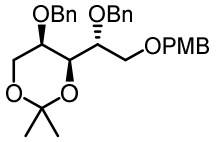
IR (neat, cm^{-1}): ν_{max} 3505, 2989, 2930, 1380, 1120, 850

^{1}H NMR (CDCl$_3$, 200MHz) δ = 7.31 (d, *J* = 2.1 Hz, 2 H), 6.92 (d, *J* = 8.6 Hz, 2 H), 4.65 - 4.38 (m, 2 H), 4.22 - 4.10 (m, 1 H), 4.07 - 4.01 (m, 1 H), 3.98 (dd, *J* = 3.3, 4.8 Hz, 1 H), 3.94 - 3.88 (m, 1H), 3.85 (s, 3 H), 3.81 - 3.44 (m, 3 H), 2.85 (d, *J* = 10.0 Hz, 1 H), 2.67 (d, *J* = 5.4 Hz, 1 H), 1.54 - 1.36 (m, 6 H) ppm

^{13}C NMR (CDCl$_3$, 50MHz): δ = 159.1, 133.0, 129.5, 128.6, 113.8, 107.9, 77.6, 76.4, 67.6, 64.9, 55.2, 29.1, 23.9 ppm

MS-ESI [M + Na]$^{+}$: m/z 335.12

(*4R*,*5R*)-5-(Benzyloxy)-4-((*R*)-1-(benzyloxy)-2-((4-methoxybenzyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxane (101)



A solution of **100** (1.6 g, 5.2 mmoL) in dry DMF (10 mL) was added to as a suspension of NaH (0.375 g, 15.6 mmoL) in dry DMF (5 ml) at 0 ^{0}C . The suspension was stirred at rt for 30 min after which benzyl bromide (1.9 mL, 15.6 mmoL) along with catalytic amount of TBAI (1.04 mmoL, 0.380 g) were added. The turbid mixture was vigorously stirred at rt for 12 h upon which the diol showed completion by TLC analysis. The reaction was quenched with satd. NH_4Cl (5 ml) followed by extraction with EtOAc (15ml). The aqueous-phase was back-extracted with EtOAc (3X15 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The pure dibenzyl ether **101** was isolated by column chromatography (75% pet ether: 25% EtOAc)as yellow oil.

Yield: 2.52 g (85%)

[α] $^{25}_{D}$: -10 (*c* 0.75, $CHCl_3$)

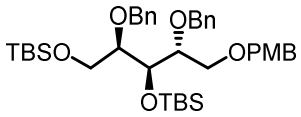
IR ($CHCl_3$, cm^{-1}): ν_{max} 3010, 2900, 1085

^{1}H NMR (200MHz, CDCl$_3$): δ = 7.12 - 7.27 (m, 12 H), 6.55 - 6.87 (m, 2 H), 4.51 - 4.69 (m, 4 H), 4.22 - 4.48 (m, 2 H), 3.77 - 4.06 (m, 3 H), 3.68 - 3.76 (m, 2 H), 3.36 - 3.68 ppm (m, 2 H) ppm

^{13}C NMR: (CDCl$_3$, 50MHz):δ = 159.1, 138.6, 138.5, 130.7, 129.2, 128.5, 128.2, 127.7, 127.7, 127.5, 127.4, 126.9, 113.6, 98.6, 73.0, 72.1, 71.0, 70.0, 69.5, 68.0, 65.3, 61.7, 55.2, 29.1, 18.9

MS-ESI [M + Na]$^+$:m/z 512.25

(*5R*,*6R*)-6-(Benzyloxy)-5-((*R*)-1-(benzyloxy)-2-((4-methoxybenzyl)oxy)ethyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane (103)



A solution of dibenzyl ether **101** (2.0 g, 4.1 mmoL) and PPTS (0.20 g, 0.82 mmol) in MeOH (20 mL) stirred at rt until TLC showed complete consumption of dibenzyl ether **101** (12 h). After completion of reaction, reaction was quenched with pinch of $NaHCO_3$ and mixture was concentrated in vaccum. The solid was then dissolved in 20 ml EtOAc and washed with 5 mL of brine and organic layer was dried over anhydrous $NaSO_4$, filtered and concentrated in vacuum. The crude diol was subjected to further reaction without further purification. This crude diol (1.60 g) was then dissolved in dry DCM (8.8 mL) followed by addition of 2,6- lutidine (1.8 mL,15.9 mmoL) and TBSOTf (2.4 mL, 10.6 mmoL). The solution was stirred at rt for 12 h. After completion of reaction, the reaction was quenched with satd. NH_4Cl (2 ml) followed by extraction with 5 mL DCM. The organic layer was separated and back extracted with 3X5 mL of DCM. The combined organic layers were washed with brine (50 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. Ether **103** was then purified by column chromatography (90% pet ether: 10% EtOAc).

Yield: 3.54 g (80%, over two steps)

[α] $^{25}_D$: -5 (*c* 0.6, $CHCl_3$)

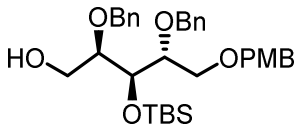
IR (neat, cm^{-1}): ν_{max} 1400, 1340, 1050, 900, 815, 734, 700.

^{1}H NMR ($CDCl_3$, 400MHz): δ = 7.24 - 7.38 (m, 12 H), 6.88 (d, *J*=8.6 Hz, 2 H), 4.71 - 4.75 (m, 1 H), 4.59 - 4.71 (m, 2 H), 4.40 - 4.53 (m, 1 H), 4.06 (dd, *J*=4.5, 3.1 Hz, 1 H), 3.83 (s, 3 H), 3.72 - 3.82 (m, 2H), 3.61 - 3.68 (m, 1 H), 3.55 (d, *J*=4.9 Hz, 1 H), 0.90 (d, *J*=6.1 Hz, 18 H), 0.01 - 0.08 (m, 12 H)

^{13}C NMR ($CDCl_3$, 101MHz):): δ = 159.0, 139.1, 130.7, 129.1, 128.1, 128.1, 127.6, 127.5, 127.2, 127.1, 113.7, 81.9, 80.3, 73.1, 72.9, 72.9, 72.5, 71.0, 63.2, 55.2, 26.0, 25.9, 18.2, -4.6, -4.7, -5.4, -5.4

MS-ESI [M + Na]$^+$:m/z 704.11

(2R,3S,4R)-2,4-Bis(benzyloxy)-3-((tert-butyldimethylsilyl)oxy)-5-((4-methoxy benzyl)oxy)pentan-1-ol (104).



A solution of **103** (3.0 g, 5.2 mmoL) and PPTS (0.5 g, 1.04 mmoL) in EtOH (52 ml) was stirred at rt for overnight. After completion of reaction, reaction was quenched with pinch of $NaHCO_3$ and mixture was concentrated in vaccum. The solid was then dissolved in 25 ml EtOAc and washed with 10 mL of brine and organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The crude alcohol was then purified by column chromatography (80% pet ether: 20% EtOAc) to give **104**.

Yield: 2.2 g (87%)

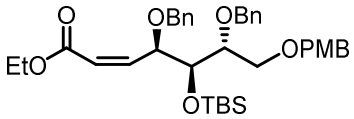
[α] $^{25}_{D}$: -17 (*c* 0.7, $CHCl_3$)

IR (neat, cm^{-1}): ν_{max} 3398, 1450, 1200, 1050,810, 750

^{1}H NMR (CDCl$_3$, 200MHz):δ = 7.13 - 7.43 (m, 12 H), 6.60 - 7.08 (m, 2H), 4.62 (s, 2 H), 4.71 (s, 1 H), 4.45 (d, *J*=4.3 Hz, 1 H), 4.09 (dd, *J*=5.6, 2.4 Hz, 1 H), 3.78 - 3.87 (m, 4 H), 3.61 - 3.78 (m, 4 H), 3.31 - 3.61 (m, 1 H), 0.79 - 0.92 (m, 9 H), -0.06 - 0.10 ppm (m, 6 H)

MS-ESI [M +Na]$^+$:m/z 589.63

Ethyl (4R,5S,6R,Z)-4,6-bis(benzyloxy)-5-((tert-butyldimethylsilyl)oxy)-7-((4-methoxybenzyl)oxy)hept-2-enoate (105)



To a solution of alcohol **104** (0.5 g. 0.88 mmoL) in dry DCM (2. 2 mL) was added Dess martin periodinane (0.311 g, 0.73 mmoL). After completion of reaction (30 min), reaction was quenched with satd. $NaHCO_3$, followed by extraction with DCM (5ml). The aqueous-phase was back-extracted with DCM (3X5 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The aldehyde was directly used for next reaction without further purification.

To a suspension of NaH in dry THF (0.5 mL) was added a solution of ethyl 2-(bis(*p*-tolyloxy)phosphoryl)acetate (0.25 g, 0.71 mmoL) in dry THF (1.0 mL). The mixture was stirred at rt for 30 min and then cooled to -78 ^oC. The crude aldehyde was then added to this cooled mixture at -78 ^oC and stirred at -78 ^oC for 2 h. Upon completion of reaction,

saturated NH_4Cl (1 mL) was added and the product was extracted into EtOAc (3X5 mL). The EtOAc extracts were dried over Na_2SO_4 and evaporated. The crude ester was purified by column chromatography (80% pet ether: 20% EtOAc) to give **105.**

Yield: colourless liquid, 0.3 g (65%, over two steps)

[α] $^{25}_{D}$: +15 (*c* 0.65, $CHCl_3$)

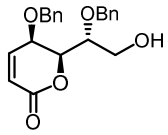
IR (neat, cm^{-1}): ν_{max} 2920, 2850, 1720, 1650, 1150, 870, 675

^{1}H NMR($CDCl_3$, 200MHz): δ = 7.29 (d, *J*=3.3 Hz, 13 H), 6.86 (d, *J*=8.6 Hz, 2 H), 6.40 (d, *J*=9.3 Hz, 1 H), 4.93 (dd, *J*=9.8, 4.6 Hz, 2 H), 4.59 - 4.74 (m, 2 H), 4.31 - 4.58 (m, 4 H), 3.97 (br. s., 2 H), 3.81 (s, 2 H), 3.69 (s, 2H), 3.62 (d, *J*=7.6 Hz, 1 H), 1.27 (br. s., 3 H), 0.88 (s, 9 H), -0.04 - 0.04 (m, 6 H) ppm

^{13}C NMR($CDCl_3$, 50MHz): δ = 165.7, 159.0, 146.2, 138.9, 138.5, 130.7, 129.2, 128.9, 128.6, 128.1, 127.8, 127.3, 127.2, 123.0, 113.6, 79.5, 77.6, 76.4, 75.5, 75.0, 72.8, 72.4, 71.3, 70.3, 60.1, 55.2, 26.0, 18.2, 14.2, -4.3, -4.7 ppm.

MS-ESI [M + Na]$^+$:m/z 657.45

(*5R*,*6S*)-5-(Benzyloxy)-6-((*R*)-1-(benzyloxy)-2-hydroxyethyl)-5,6-dihydro-2H-pyran-2-one (106).



Ester **106** (0.2 g. 0.32 mmoL)was dissolved in a solution of 50%TFA (0.12 mL, 1.6 mmoL) in MeOH (0.25 ml) and the solution was refluxed for 24 h. After completion of reaction, reaction was quenched with pinch of $NaHCO_3$ and mixture was concentrated in vaccum. The solid was then dissolved in 10 ml EtOAc and washed with 2 mL of brine and organic layer was dried over anhydrous $NaSO_4$, filtered and concentrated in vacuum. The crude alcohol was then purified by column chromatography (50% pet ether: 50% EtOAc) to give **106.**

Yield: colurless thick liquid, 0.090 g (80%)

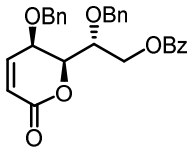
[α] $^{25}_{D}$:+55 (*c* 0.2, $CHCl_3$)

IR ($CHCl_3$, cm-1): ν_{max} 3400, 1735, 1600, 1500, 1071

^{1}H NMR: ^{1}H NMR (CHLOROFORM-d ,200MHz): δ = 7.22 - 7.45 (m, 12 H), 5.02 (s, 1 H), 4.45 - 4.78 (m, 4 H), 4.18 (br. s., 1 H), 3.74 - 3.91 (m, 2H), 3.66 (s, 2 H), 3.41 - 3.63 (m, 3 H), 3.36 (s, 2 H), 2.99 (d, *J*=5.6 Hz, 1 H), 2.48 - 2.83 ppm (m, 2 H)

MS-ESI [M + Na]$^+$: m/z 377.25

(*R*)-2-(Benzyloxy)-2-((2*S*,3*R*)-3-(benzyloxy)-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl benzoate (107)



To a solution of **106** (0.050 g, 0.14 mmoL) in dry DCM (0.4 mL) was added Et_3N (0.02 mL, 0.28 mmoL), benzoic anhydride (0.047 g, 0.21 mmoL) and cat. amount of DMAP. This solution was stirred at rt for 1 h. After completion of reaction, the reaction was quenched with satd. $NaHCO_3$. followed by extraction with DCM (2ml). The aqueous-phase was back-extracted with DCM (2X5 mL). The combined organic layers were washed with brine (5 mL) and dried over anhydrous $NaSO_4$, filtered and concentrated in vacuum. The crude benzoate ester was purified by column chromatography (75% pet ether: 25% EtOAc) to give **107.**

Yield: colourless solid, 0.055g (85%)

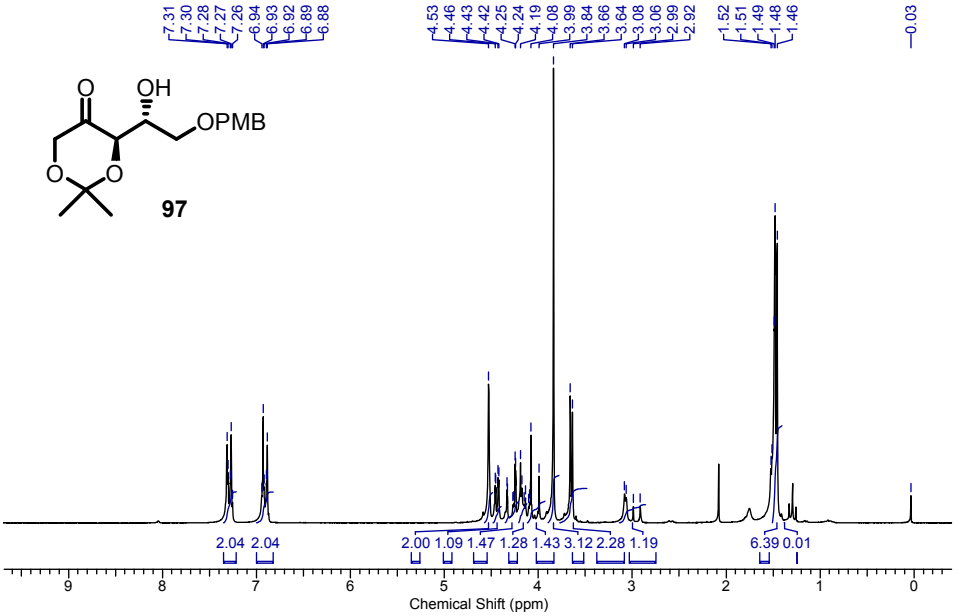
[α] $^{25}_{D}$: +40 **(***c* 0.15, $CHCl_3$**)**

IR ($CHCl_3$, cm^{-1}):ν_{max} 2939, 2855, 1710, 1515, 1413, 1208, 1138, 1064

^{1}H NMR ($CDCl_3$, 200MHz): δ = 7.95 - 8.06 (m, 2 H), 7.54 - 7.67 (m, 1 H), 7.35 - 7.48 (m, 2 H), 7.31 (s, 10 H), 6.69 (d, *J*=3.0 Hz, 1 H), 6.74 (d, *J*=3.2 Hz, 1 H), 5.99 (dd, *J*=10.0, 1.4 Hz, 1 H), 4.55 - 4.78 (m, 6 H), 4.37 - 4.55 (m, 2 H), 3.88 - 4.10 ppm (m, 2 H)

MS-ESI [M + Na^+]$^+$:m/z 481.65

2.4.7. Spectra of selected compounds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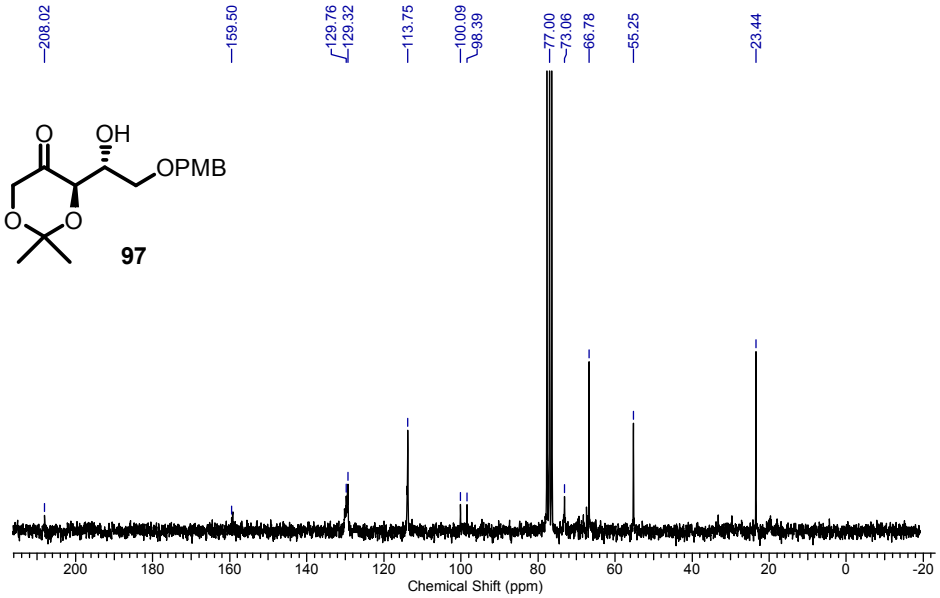
4.42
4.25
4.24
4.19
4.08
3.99
3.84
3.66
3.64
3.08
3.06
2.99
2.92
1.52
1.51
1.49
1.48
1.46
0.03
O
OH
OPMB
O
O
97
2.04 2.04
2.00 1.09 1.47 1.28 1.43 3.12 2.28 1.19
6.39 0.01
9 8 7 6 5 4 3 2 1 0
Chemical Shift (ppm)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113.75
100.09
98.39
77.00
73.06
66.78
55.25
23.44
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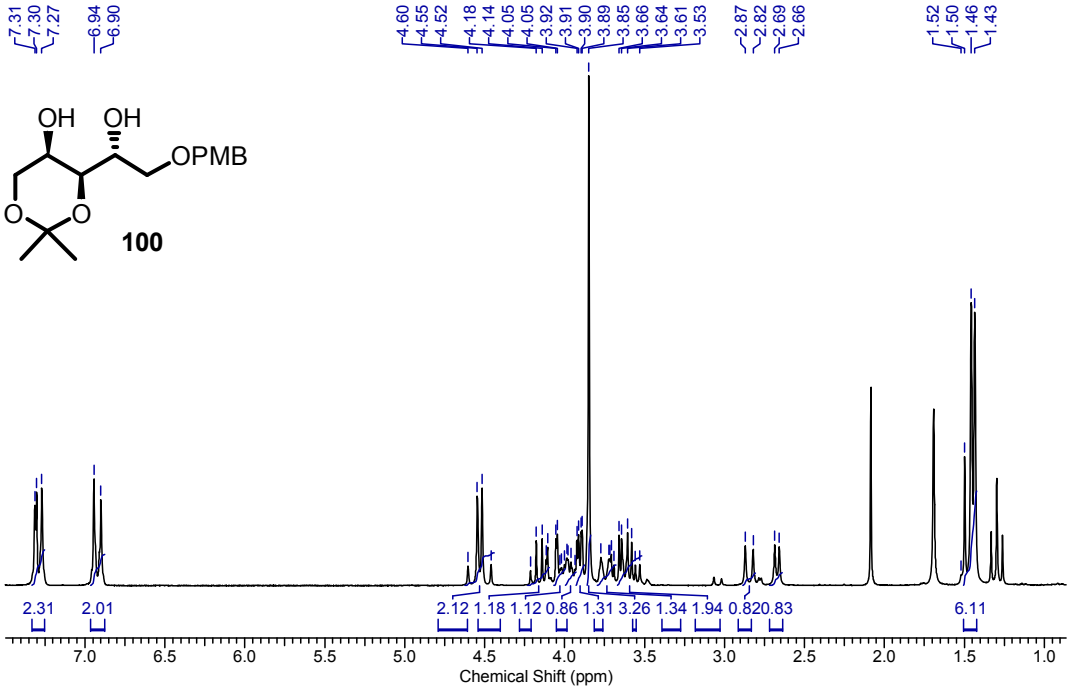
OH
OPMB
O
O
97
200 180 160 140 120 100 80 60 40 20 0 -20
Chemical Shift (ppm)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4.05
4.05
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3.89
3.85
3.66
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1.50
1.46
1.43
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O
O
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2.01
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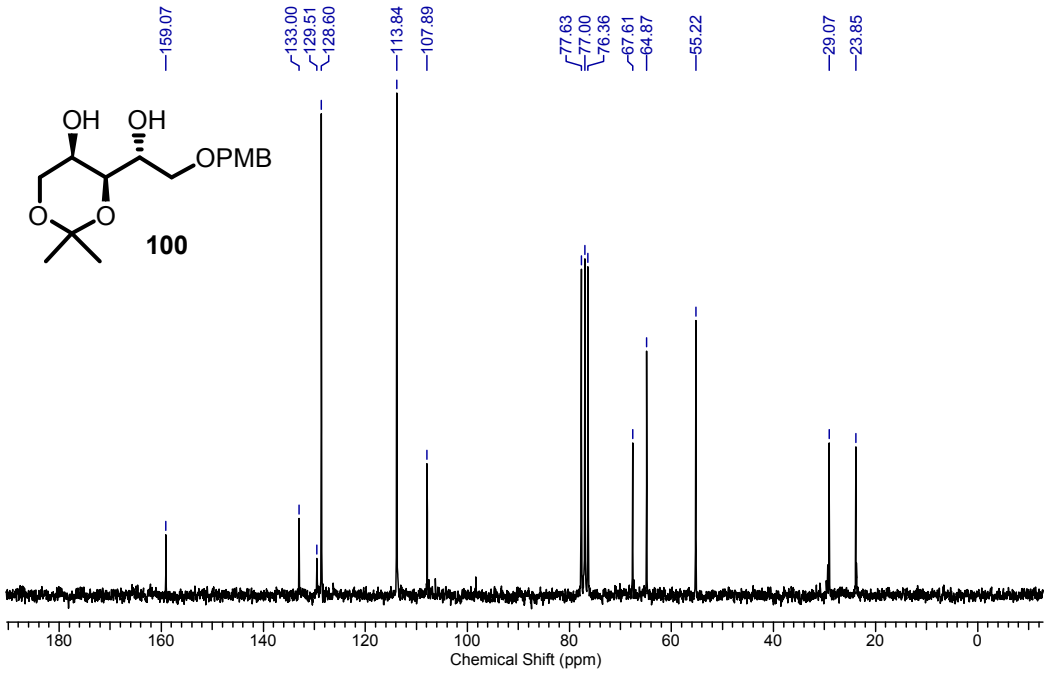
0.82
0.83
6.11
Chemical Shift (ppm)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29.07
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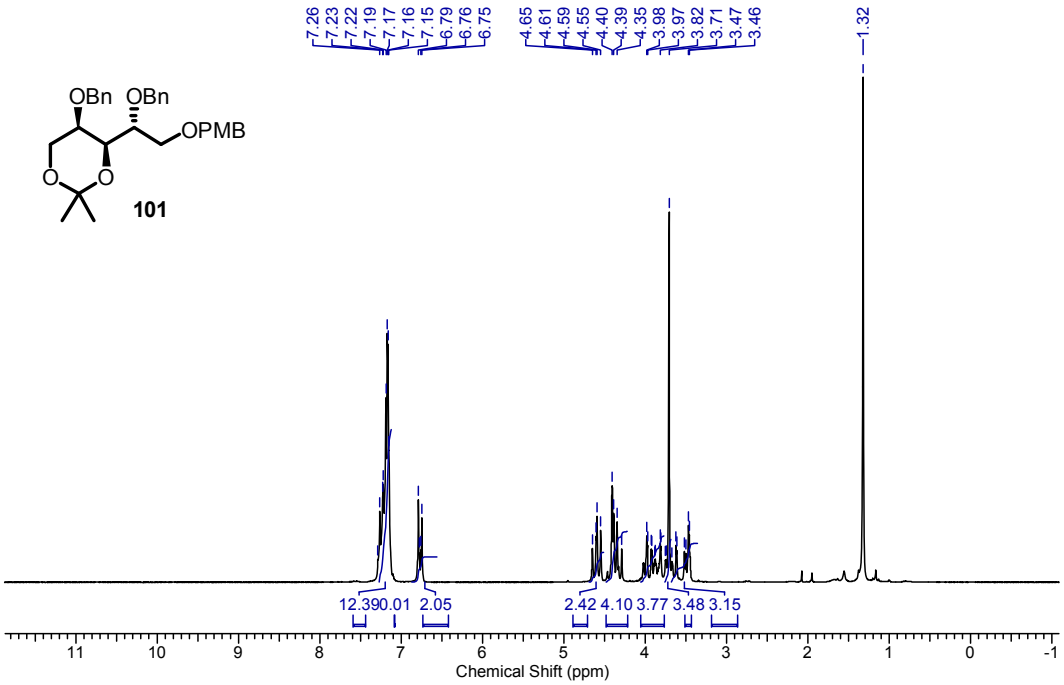
OH
OPMB
O
O
100
Chemical Shift (ppm)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7.15
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6.76
6.75
4.65
4.61
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4.55
4.40
4.39
4.35
3.98
3.97
3.82
3.71
3.47
3.46
1.32
OBn
OBn
OPMB
O
O
101
12.39
0.01
2.05
2.42
4.10
3.77
3.48
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11
10
9
8
7
6
5
4
3
2
1
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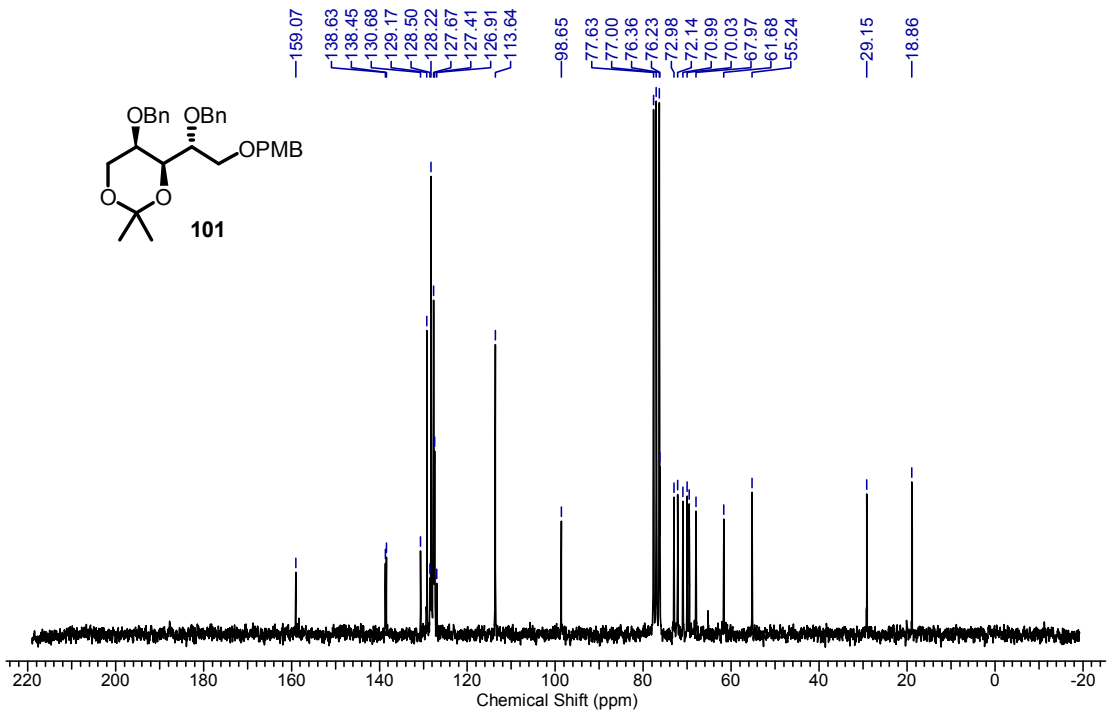
Chemical Shift (ppm)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113.64
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18.86
OBn
OBn
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200
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160
140
120
100
80
60
40
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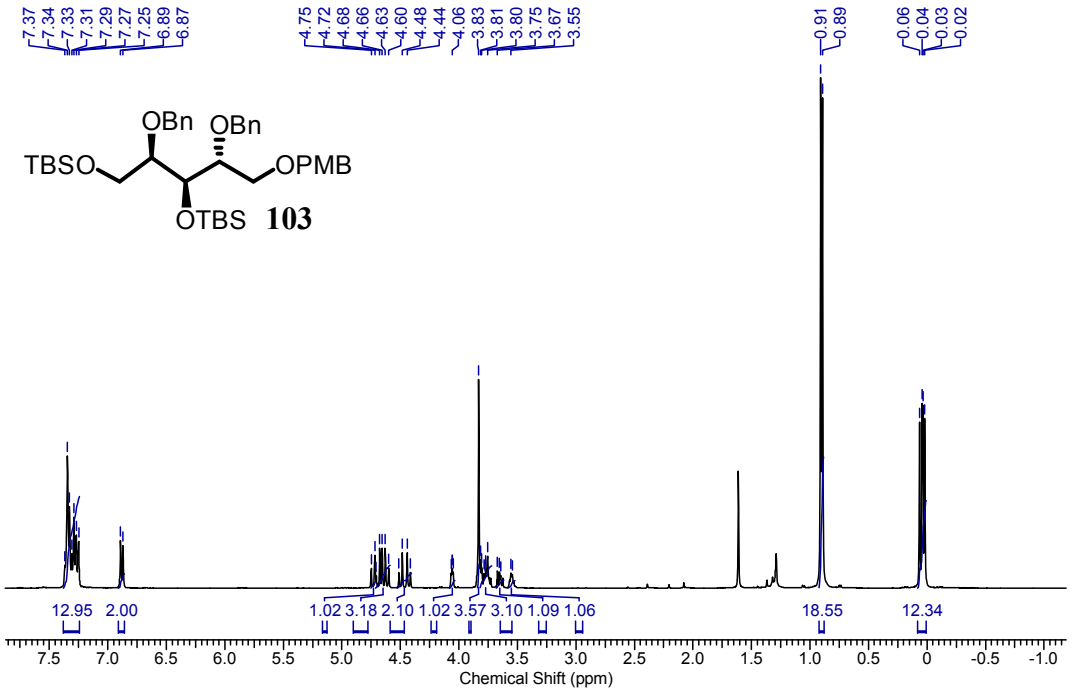
Chemical Shift (ppm)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4.63
4.60
4.48
4.44
4.06
3.83
3.81
3.80
3.75
3.67
3.55
0.91
0.89
0.06
0.04
0.03
0.02
OBn
OBn
TBSO
OPMB
OTBS
103
12.95
2.00
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1.02
3.57
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1.06
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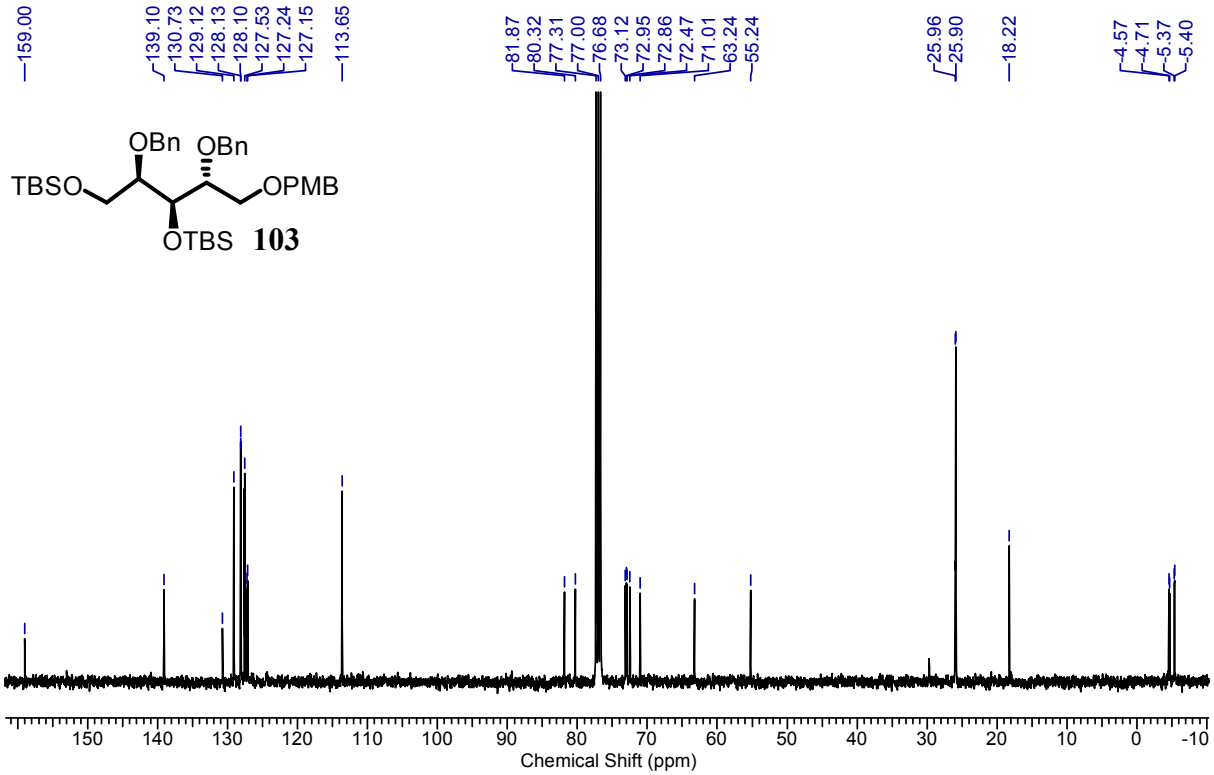
12.34
Chemical Shift (ppm)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76.68
73.12
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72.86
72.47
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55.24
25.96
25.90
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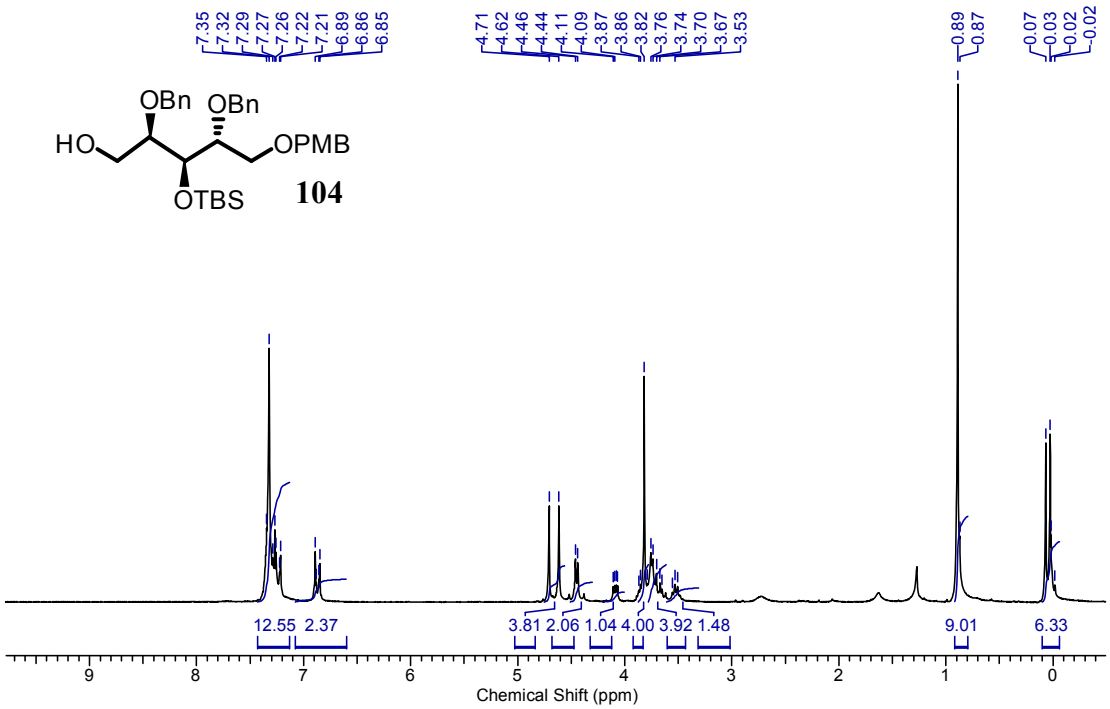
OBn
OBn
TBSO
OPMB
OTBS
103
Chemical Shift (ppm)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4.46
4.44
4.11
4.09
3.87
3.86
3.82
3.76
3.74
3.70
3.67
3.53
0.89
0.87
0.07
0.03
0.02
0.02
OBn
OBn
HO
OPMB
OTBS
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3.81
2.06
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4.00
3.92
1.48
9.01
6.33
9
8
7
6
5
4
3
2
1
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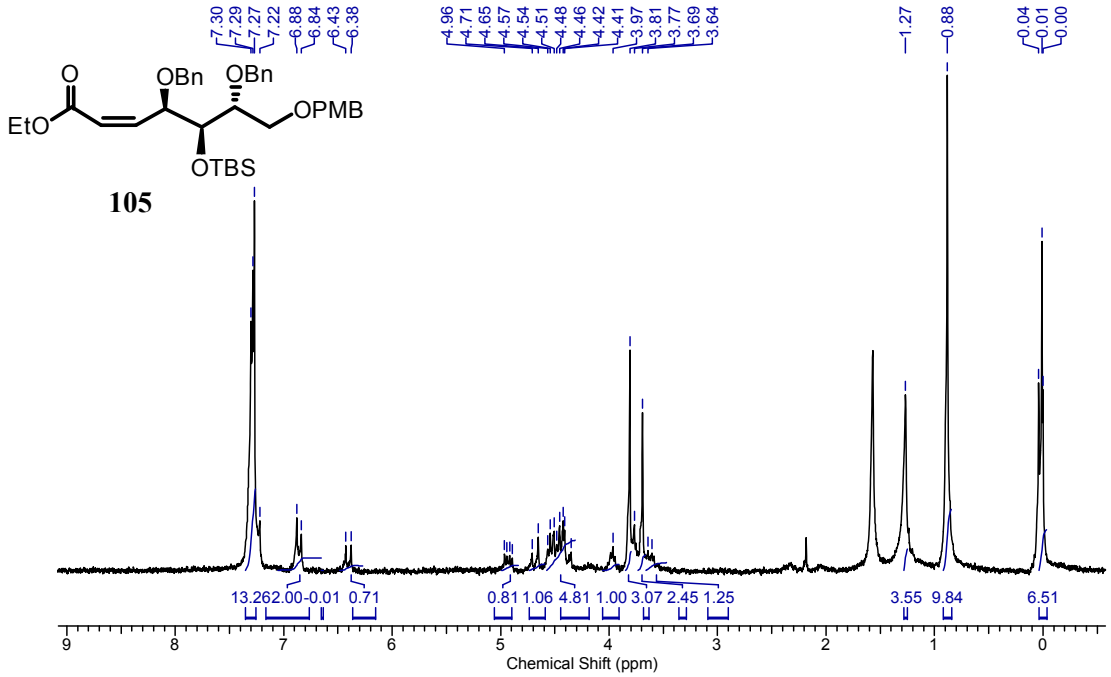
Chemical Shift (ppm)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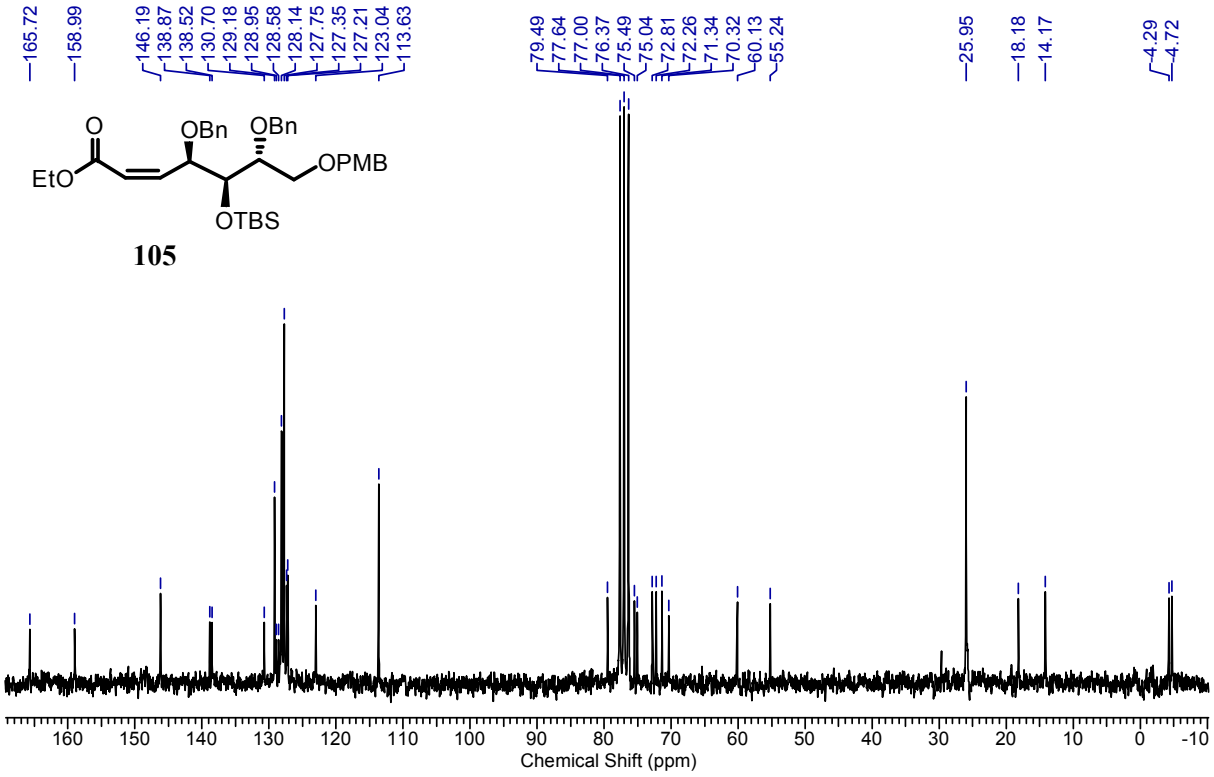
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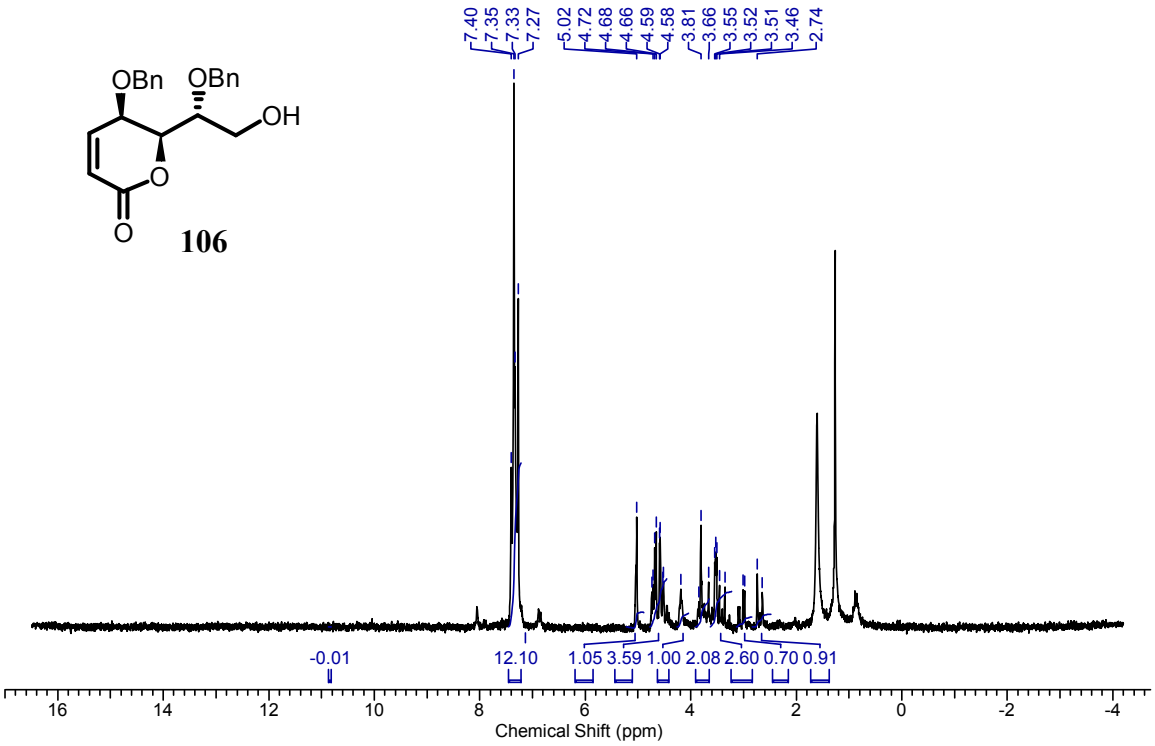
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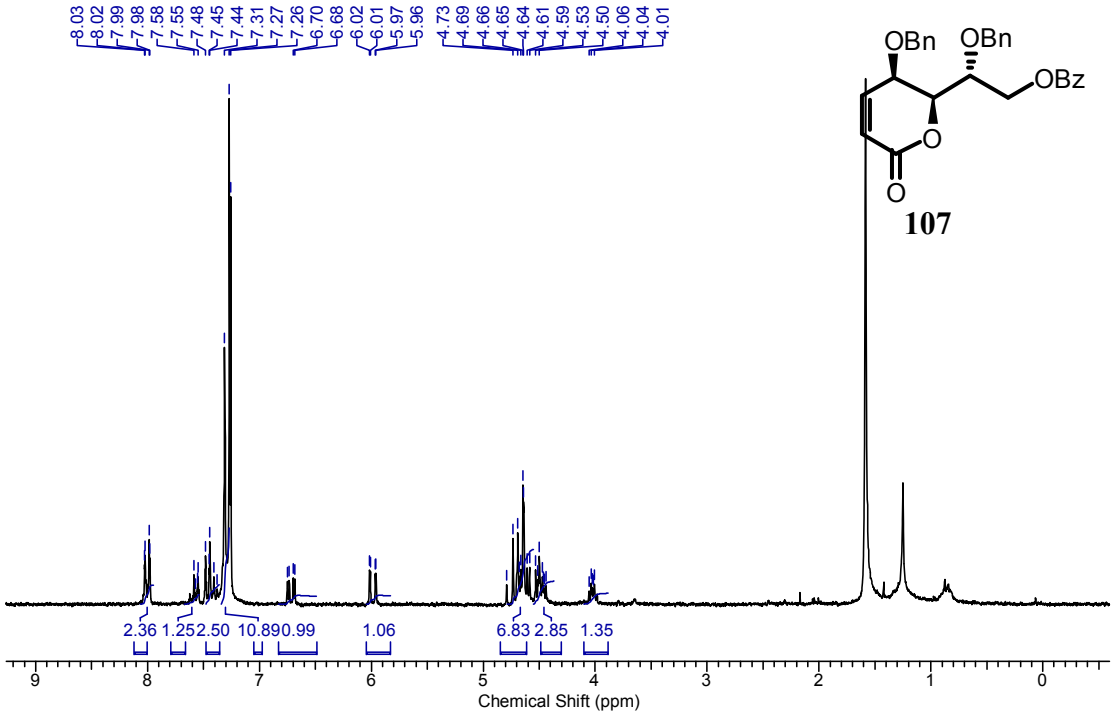
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Chemical Shift (ppm)

2.4.8. References

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Chapter 2- Section E: Synthetic studies towards (+) Crassalactone A employing Proline catalyzed aldol reaction

2.5 Section E

Synthetic Synthetic studies towards (+) Crassalactone A employing Proline catalyzed aldol reaction

2.5.1. Introduction

Crassalactones A-D **(1-4, Figure 1)** has been isolated from a cytotoxic ethyl acetate-soluble extract of the leaves and twigs of *Polyalthia crassa* in 2006 by Tuchinda and co-workers. [1] The *Polyalthia* genus is indegeneous to Asia where different species of *Polyalthia* have been known to possess various medicinal properties. The *Polyalthia* genus is known for being a rich source of various compounds of pharmacological and commercial importance like diterpenes, triterpenes, benzopyrans, 2 -substituted furans, various types of alkaloids, azaanthrazene alkaloid, kalasinamide, 2-substituted furans, and carboxamides. Initial studies on *Polyalthia* genus revealed only azaanthrazene alkaloid, 2-substituted furans, and carboxamides.[2] Different metabolites isolated from various *Polyalthia* species are effective as medicines for various ailments. The extract obtained by brewing of the roots of *P. evecta* and *P. debilis* are used as a galactagogue and as a remedy for abdominal pain.[3]Another species of *Polyalthia, Polyalthia bullata* is used in Malaysia as an aphrodisiac.[4] The *Polyalthia* genus constituents have been known to be active as cytotoxic,[5]antimicrobial,[6] antimalarial,[7] and anti-HIV[8] agents.

Further studies carried out by Tuchinda and co-worker on *Polyalthia* genus, they were able to isolate styryl lactones crassalactones A-D **(1-4),** howiinol A **(5)**, and tricinnamate **(6).** These components possessed the same biological properties as the other components isolated from earlier mentioned *Polyalthia* species.

Amongst these crassalactones A-D **(1-4)** were isolated from the ethyl acetate extract of leaves and twigs of *Polyalthia crassa.*[1] One of the crassalactones, crassalactone A **(1)** was investigated for its biological activity. Various bio-assays carried on crassalactone A **(1)** revealed that, it exhibited excellent cytotoxic activity against a variety of cancer cell lines such as murine lymphocytic leukemia (P-388; ED_{50} 0.18 mg/ml), human nasopharyngeal carcinoma (KB; 1.7 mg/ml), human colon cancer

(Col-2; 1.9 mg/ml), human breast cancer (BCA-1; 0.92 mg/ml), human lung cancer (Lu-1; 1.9 mg/ml), and rat glioma (ASK; 1.6 mg/ml).

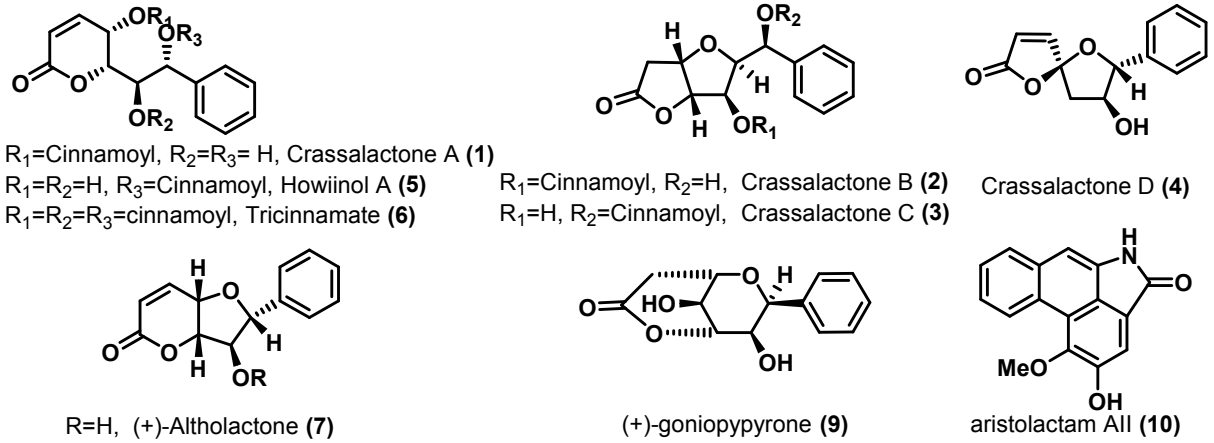


Figure 1: Structures of some styryl-containing lactones

The structures of crassalactones A-D **(1-4)** were analyzed on the basis of modified compounds obtained from crassalactones A-D **(1-4)** by subjecting them to various spectroscopic techniques. In case of crassalactone A **(1),** the data obtained from NMR analysis of **1** was comparable to earlier isolated howiinol A **(5).**[9] The EIMS analysis and elemental analysis revealed that the crassalactone A **(1)** had molecular weight of 344 with molecular formula $C_{22}H_{20}O_6$. Besides, By subjecting to various stereochemical analyses like HMBC, COSY and single crystal X-ray diffraction analysis followed by comparison with stereochemical data of natural (+)-howiinol A (**5**), the stereochemistry of crassalactone A **(1)** was established as 5*S*, 6*R*,7*R*, and 8*R*.

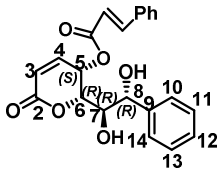


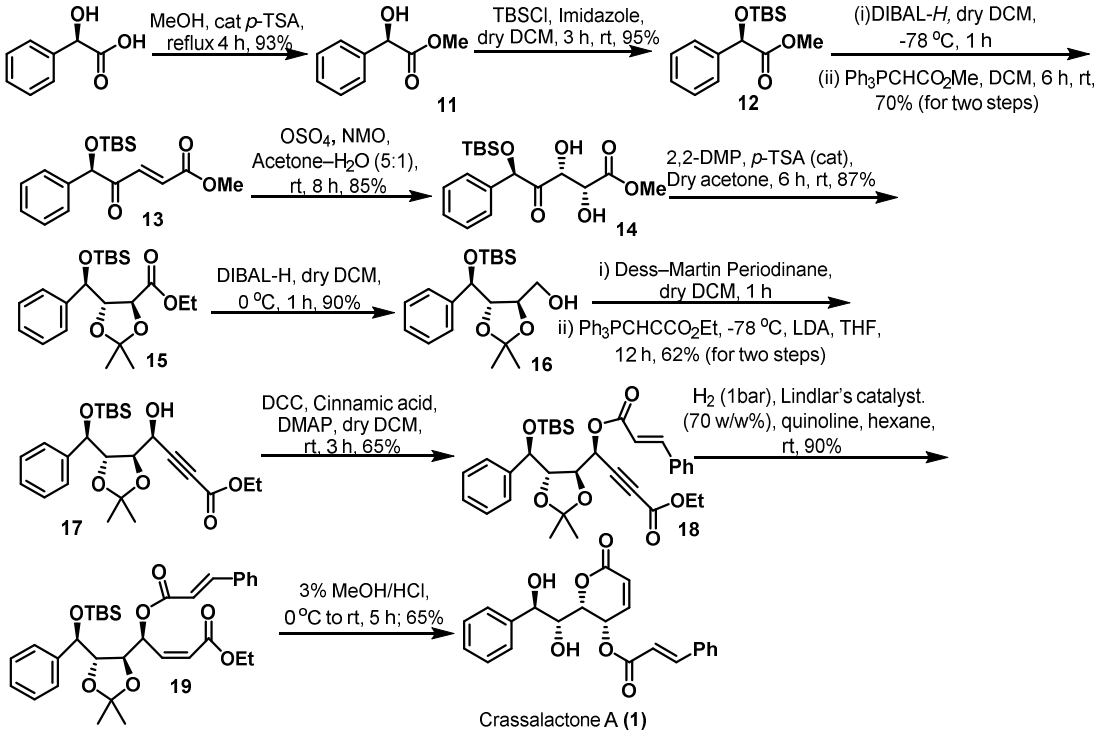
Figure 2: Stereochemistry of crassalactone A **(1)**

2.5.2. Review of Literature

Till date three syntheses of crassalactone A **(1)** have been reported. All the three syntheses highlight the use of chiral starting materials to achieve the desired stereochemistry in the target compound **1.**[10-12]

Venkateswarlu et al. (2010)[10]

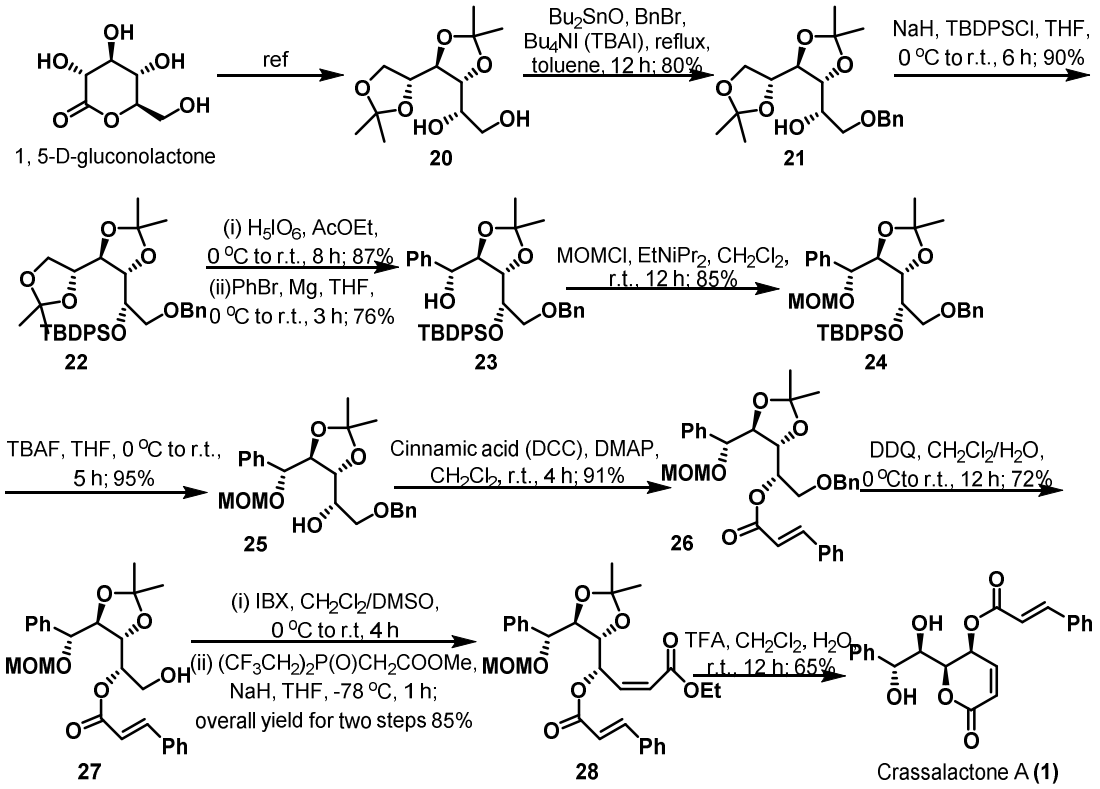
In 2010 *Venkateswarlu et al* reported the first synthesis of crassalactone A **(1)** using *(R)* - mandelic acid as the starting material (**Scheme 1)**. *(R)* - Mandelic acid was converted first to its methyl ester **11** followed by protection of free hydroxy in **11** as its TBS ether **12.** The ester group in **12** was partially reduced to corresponding aldehydes in presence of DIBAL-*H* followed by formation of *α,β*- unsaturated ester **13** by Wittig olefination and formation of diol 14 by oxidation of double bond by OsO_4. The diol **14** was protected as its dimethyl acetal **14** using 2, 2-DMP/*p*-TSA. The ester **15** was reduced to alcohol **16** followed by Dess Martin periodinane oxidation and consequent propargylation using ethyl propiolate / LDA. The free hydroxy ester **17** was converted to cinnamate **18** using DCC coupling procedure.[13]The triple bond in dienyne **18** was partially hydrogenated using Lindlar's catalyst to diene diester **19.** The *α,β*-unsaturated ester **19** underwent one pot cleavage of both acetal and TBS group followed by lactonization to furnish target compound **1.** The authors were able to complete synthesis of target compound **1** in 10 steps with an overall yield of 11% from *(R)*-Mandelic acid.



Scheme 1: Synthesis of crassalactone A **(1)** *by Venkateswarlu et al.*

***Yadav et al.* (2013)[11]**

In 2013 Yadav and co-workers reported another synthesis of crassalactone A **(1)** employing 1, 5-*D*-gluconolactone as starting material **(Scheme 2)**. Commercially available 1, 5-*D*-gluconolactone was first transformed to diacetonide **20** using a literature known procedure. This diacetonide **20** underwent regioselective monobenzoylation using Bu_2SnO/BnBr to furnish benzyl ether **21.** The monobenzyl ether **21** was then converted to its *t*-butyl diphenyl silyl ether **22** using TBDPSCl and NaH.



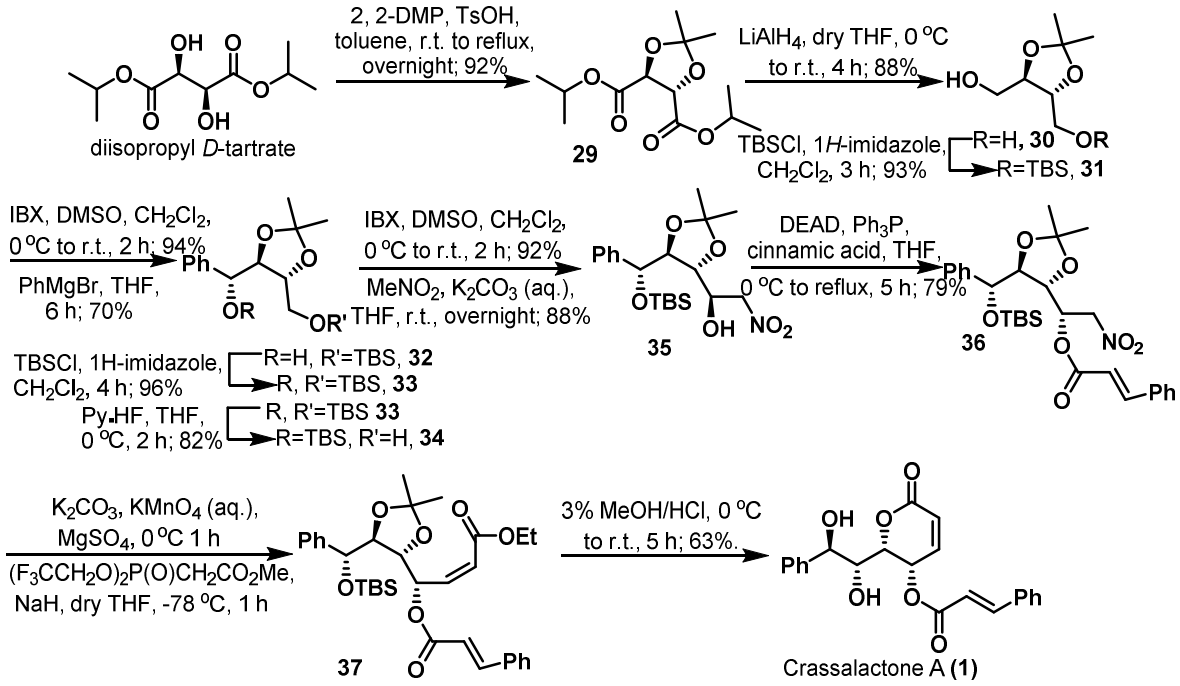
Scheme 2: Synthesis of crassalactone A **(1)** *by Yadav et al.*

The ether **22** was then subjected to single step hydrolysis of terminal acetonide and oxidative cleavage by periodic acid. The resultant aldehyde was subjected to phenyl Grignard to afford alcohol **23.** The alcohol **23** was then protected as its methoxymethyl ether **24**. Following this transformation, TBDPS group was removed using TBAF affording alcohol **25** followed by formation of cinnamate ester **26** using DCC coupling. The cinnamte ester **26** underwent debenzylation using DDQ to provide alcohol **27.** The alcohol **27** was subjected to IBX oxidation which was followed by Stille-Gennari olefination[14] to provide *α,β*- unsaturated ester **28.** The ester when subjected to acid hydrolysis using TFA furnished the target compound **1.**

The synthesis of target compound **1** was accomplished in 12 steps and 8.09% overall yield starting from 1, 5-*D*-gluconolactone.

***Das et al.* (2015)[12]**

Das and co-workers reported another synthesis of crassalactone A **(1)** employing (-)-diisopropyl *D*-tartrate as the starting material (**Scheme 3)**. The synthesis commenced with protection of free hydroxy as its dimethyl acetal to furnish **29**. The acetal **29** was completely reduced to diol **30** using LAH reduction. The diol **30** was regioselectively protected as its TBS ether **31** using TBSCl/1*H*-imidazole. The mono TBS ether **31** was oxidised to corresponding aldehyde using IBX which was followed by addition of phenyl Grignard to the aldehydes to provide alcohol **32.** The alcohol **32** was protected as its TBS ether to afford compound **33.** The diTBS compound **33** was subjected to regioselective cleavage of primary TBS group to provide alcohol **34.** The alcohol **34** upon oxidation with IBX followed by reaction of resultant aldehydes with $MeNO_2$ furnished nitro-alcohol **35.**



Scheme 3: Synthesis of crassalactone A **(1)** *by Das et al.*

The alcohol **35** underwent formation of cinnamate ester **36** under *Mitsunobu* conditions using cinnamic acid. The nitro alkane moiety in **36** underwent oxidation in presence of $KMnO_4$, which was followed by Wittig olefination with

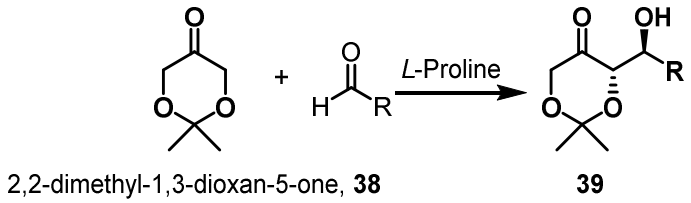
$(F_3CCH_2O)_2P(O)CH_2COOMe$ to afford the precursor **37.** The precursor **37** provided the target compound **1** when subjected to acid hydrolysis employing 3% HCl/MeOH, which involved concomitant removal of acid labile groups followed by in situ lactonization. The authors were able to achieve the target compound **1** in 12 steps and 10.68% overall yield.

2.5.3: PRESENT WORK

Objective

Based on literature survey as mentioned in preceding section, we considered developing a new synthetic route to the advance precursor to target crassalactone A **(1).** Our approach uses proline catalyzed aldol[15] to generate two asymmetric centres simultaneously. Our effort towards the synthesis of advanced intermediate **48** required for **1** is described below and involves proline catalyzed aldol ,stereoselective reduction of *β*-hydroxy ketone, chelation controlled vinylation as key steps.

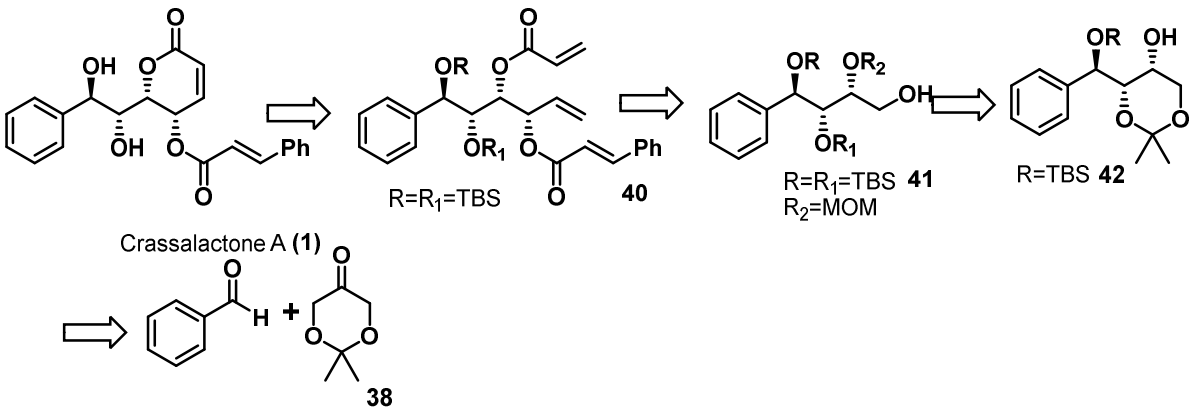
The proline catalyzed aldol involves the reaction of 2, 2-dimethyl-1, 3-dioxan-5-one[16] **38** and aldehyde in presence of proline to furnish *β*-hydroxy ketone **39** which serves as an important intermediate in the synthesis of biologically active products. The *β*-hydroxy ketone **39** serves as surrogate to various optically active polyhydroxylated or amino compounds which can be transformed to various synthetically useful intermediate.[17]



Scheme 4: General Scheme for Proline catalyzed aldol reaction.

Our retrosynthetic analysis for the synthesis of crassalactone A **(1)** relies on synthesizing the tetrahydroxy surrogate **40** which on further transformation would provide the target compound **1**.

The tetrahydroxy **40** can in turn be obtained from alcohol **41** by first oxidation of **41,** followed by vinylation and further protection of free hydroxy as cinnamate ester**.** The alcohol **41** can be derived from alcohol **42** which in turn can be obtained from proline catalyzed aldol reaction of benzaldehye and dioxanone **38 (Scheme 5).**



Scheme 5: Retrosynthetic analysis of crassalactone A **(1)**

2.5.4: Results and Discussion

Our synthesis commenced with the aldol reaction of commercially available benzaldehyde and 2, 2-dimethyl-1, 3-dioxan-5-one **38** in presence of *D*-proline as a catalyst of choice. For synthesis of desire *β*-hydroxy ketone **39a** we went through the literature in order to find the most suitable catalyst- solvent combination to achieve the desired results. It was found that proline in presence of DMSO+5eq of H_2O was the most suitable combination for the synthesis of *β*-hydroxy ketone[18] **39a.**

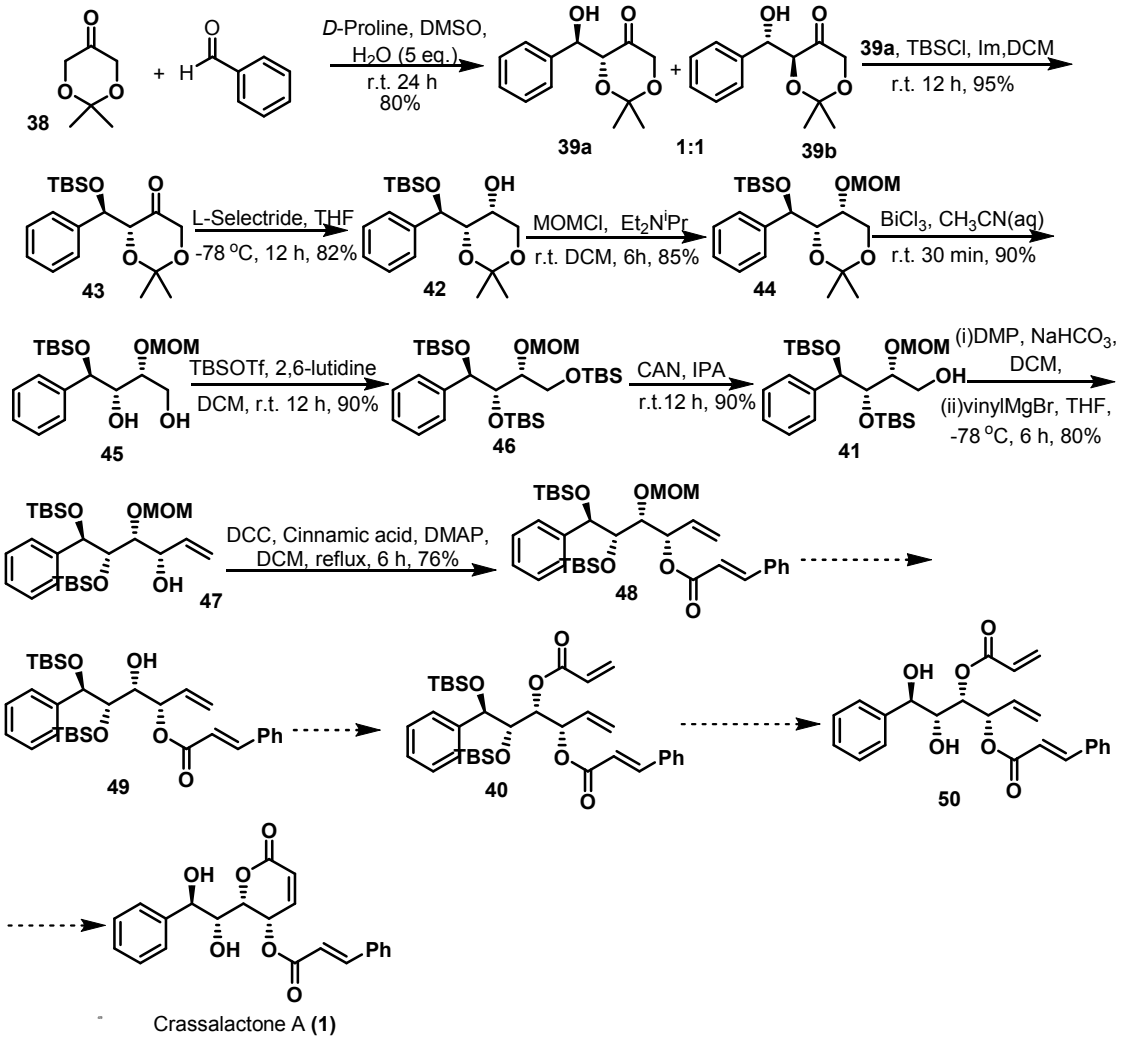
Following the literature reported procedure[18] **39a** benzaldehyde and **38** was reacted using *D*-proline as the catalyst to give a mixture of diastereomers **39a** (***anti***) and **39b** (***syn***) in the ratio (1:1). The diastereoselectivity was determined on the basis of isolated yields of individual isomer as the diastereomers were separable by column chromatography. The desired isomer **39a** (***anti***) was confirmed by ^{1}H NMR and ^{13}C spectroscopy along with optical rotation value [δ=4.91, 4.34, 4.36, 4.29 - 4.18, 4.13, 4.13 ppm for various O-C-H, **[α] $^{25}_{D}$** = +101 (c=1, CH_3Cl), δ= 210.9 ppm for C=O]. With sufficient amount of **39a** in our hands we proceeded for the steroselective reduction of *β*-hydroxy ketone using L-selectride. To our delight the reaction proceeded smoothly but a mixture of diasteromers (1:1) was obtained instead of a single isomer. The formation of mixture may be attributed to the planar nature of benzene ring, which in turn generates a planar transition state which can lead to diastereomeric mixture. To overcome this problem the hydroxy group in **39a** was protected as its TBS ether **43** which was confirmed by ^{1}H NMR and ^{13}C spectroscopy [δ= 1.09-0.67ppm for *t*-butyl-Si and 0.29- -0.16 for $(CH)_3Si$-]. Now this TBS

protected *β*-hydroxy ketone **43** was subjected to L-selectride reduction[19] at -78 ^{o}C. To our delight we were able to isolate **42** as a single diastereomer in 90% yield. The product was confirmed by ^{13}C spectral data which does not show presence of carbonyl carbon (δ= 76.07, 74.7, 66.0, 63.0 ppm for H-C-O).

As we were able to generate three stereocentres with desired stereochemistry, now the focus was on generation of the fourth and final stereocentre. Having **42** in our hand, it was subjected to methoxy methyl protection using MOMCl to furnish methoxy methyl ether **44** in 85% yield which was confirmed by ^{1}H NMR and ^{13}C spectroscopy (δ= 98.0 and 55.6 for -CH_2-O-CH_3 group)**.** The methoxy methyl ether **44** then underwent acetal cleavage in presence of $BiCl_3$·H_2O. The diol **45** was then carried forward for TBS protection without further purification. Initially we attempted to synthesize diTBS ether **46** using TBSCl and imidazole, but the starting material **45** did not show complete consumption even after prolonging reaction to 48 h or using excess of TBSCl. As a result, the diol **45** was then protected using TBSOTf and 2, 6-lutidine to afford triTBS ether **46** in 90% yield. The ^{1}H NMR and ^{13}C spectroscopic analysis confirmed the presence of **46** (δ= -4.5, -4.8, -4.9, -5.0, -5.3, -5.4 ppm for *t*-butyl-Si and $(CH)_3$Si-). The triTBS **46** was converted to alcohol **41** by regioselective cleavage of primary TBS ether using CAN in IPA. The alcohol now shows presence of two 2^{o} silyl ether as confirmed by ^{1}H NMR and ^{13}C spectroscopic data (δ= -4.4, -4.5, -4.7,-4.9 ppm for 2^{o} silyl ether). The alcohol **41** was then oxidised to aldehyde using Dess Martin periodinane followed by vinylation of resultant aldehyde at -78 ^{o}C. Initially we tried to achieve the vinyaltion of aldehyde using 1.5 eq of vinyl magnesium bromide. But to our disappointment the reaction did not proceed as desired and the starting aldehyde remained fully unconsumed even after prolonging the reaction time to 12-24 h. So to circumvent this situation we decided to use excess of vinyl magnesium bromide. After several trials, an excess of vinyl magnesium bromide (5.5 eq.) provided the desired product as a single diastereomer **47** in 80% yield. Thus the fourth stereocentre was fixed using chelation controlled stereoselective vinylation.

The allylic alcohol **47** was then subjected to cinnamate ester formation using standard procedure (1.2 eq cinnamic acid, 1.5 eq DCC and 10 mol% DMAP)[13], but were unsuccessful in obtaining the cinnamate ester **48.** In order to obtain ester **48** in desired quantity, the procedure was modified by employing a large excess of reagents (5 eq

cinnamic acid, 5.5 eq DCC and 20 mol% DMAP) and refluxing the reaction mixture for 6 h.



Scheme 6: Synthesis of compound **48**, an advanced precursor for crassalactone A (1).

As a result of this modification we were able to synthesize cinnamte ester **48** in 80% yield. The ^{1}H and ^{13}C NMR spectroscopic analysis confirmed the presence of **48** (δ= 165.7 ppm for -C=O, δ = 7.90 - 7.62, 7.53, 7.43 - 7.27 ppm for aromatic -C-H, δ= 6.60 - 6.32 ppm for *trans*-C=C-H).

2.5.5: Conclusion

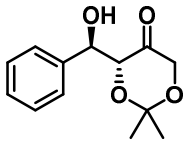
We have successfully synthesized the desired tetrahydroxy motiff **48** by employing proline catalyzed aldol, stereoselective reduction of *β*-hydroxy ketone and chelation controlled vinylation. All the stereocentres have been generated with excellent stereoselectivities. All the intermediates starting from *β*-hydroxy ketone **39a** to

cinnamte ester **48** have been formed in moderate to excellent yields. As shown in **Scheme 6** compound **48** can be used as an advanced intermediate to synthesize target compound crassalactone A **(1)** by converting it to acrylate and eventually the ring construction by ring closing metathesis. Further work is in progress in this direction.

2.5.6: Experimental

General Information: All reactions were carried out under argon or nitrogen in oven-dried glassware using standard gas-light syringes, cannulas and septa. Solvents and reagents were purified and dried by standard methods prior to use. Optical rotations were measured at room temperature. IR spectra were recorded on an FT-IR instrument. ^{1}H NMR spectra were recorded on 200 MHz, 400 MHz and 500 MHz and are reported in parts per million (δ) downfield relative to $CDCl_3$ as internal standard and ^{13}C NMR spectra were recorded at 50 MHz, 100 MHz and 125 MHz and assigned in parts per million (δ) relative to $CDCl_3$. Column chromatography was performed on silica gel (100-200 and 230-400 mesh) using a mixture of petroleum ether and ethyl acetate as the eluent.

***(R)*-4-(*(R)*-Hydroxy (phenyl) methyl)-2, 2-dimethyl-1,3-dioxan-5-one (39a)**



39a was synthesized using benzaldehyde (2.0 g, 0.0188 mol), dioxanone **38** (12.2 g, 0.0941 mol), D-proline (0.630 g, 0.00564 mol), H_2O (1.7 ml, 0.0941 mol) and DMSO (47 ml) following the same procedure as **98** (***chapter 2, section D***). The reaction led to a mixture of two diastereomers **39a** and **39b** in 1:1 ratio**.** The desired compound **39a** was separated from **39b** by column chromatography.

Yield: 1.78 g (40% for **39a**)

[α] $^{25}_{D}$ = +101 (*c* 1, CH_3Cl)

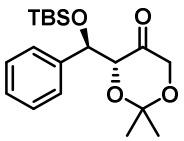
IR (neat, cm^{-1}): ν_{max} 3550-3280, 3030, 2257, 1748, 1375, 1110, 923

^{1}H-NMR ($CDCl_3$, 400 MHz): δ= 7.43 - 7.29 (m, 5 H), 4.91 (d, *J* = 7.8 Hz, 1 H), 4.34 (s, 1 H), 4.36 (s, 1 H), 4.29 - 4.18 (m, 1H), 4.13 (d, *J* = 6.9 Hz, 1 H), 4.08 - 3.98 (m, 1 H), 1.37 (s, 3 H), 1.26 (s, 3 H) ppm

^{13}C-NMR ($CDCl_3$, 50 MHz): δ = 210.9, 139.3, 128.0, 127.1, 101.1, 72.7, 66.8, 66.7, 23.6, 23.2 ppm

MS-ESI [M + Na^{+}]$^{+}$:m/z 259

(*R*)-4-((*R*)-((tert-Butyldimethylsilyl) oxy) (phenyl) methyl)-2, 2-dimethyl-1, 3-dioxan-5-one (43)



To a solution of **39a** (1.5 g, 0.0063 mol) in DCM (15 ml) and *1H*-imidazole (0.64 g, 0.0095 mol) was added *t*-butyl dimethyl silyl chloride (1.14 g, 0.0075 mol) at 0 ^{0}C .The reaction mixture was stirred for 1 h at r.t. After completion of reaction, the reaction was quenched with 10 ml of satd. NH_4Cl solution at 0 ^{o}C. The solution was then diluted with 15 ml of DCM. The organic layer was separated and the aqueous layer was again extracted with 15 ml of DCM. The organic layer was then washed with 15 ml of brine and dried over sodium sulphate. The organic layer was concentrated in vacuo and purified by column chromatography (2% EtOAc: 98% pet ether) to furnish **43** as colourless oil.

Yield: 1.89 g (85%)

[α] $^{25}_D$ =+50 (*c* 1, CH_3Cl)

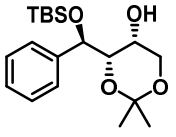
IR (neat, cm^{-1}): ν_{max} 2890, 2278, 1720, 1450, 1220

^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 7.50 - 7.27 (m, 5 H), 4.90 - 4.63 (m, 3 H), 4.63 - 4.34 (m, 1 H), 4.09 (td, *J* = 5.0, 6.5 Hz, 1 H), 4.00 - 3.77 (m, 1 H), 3.76 - 3.57 (m, 1 H), 3.47 - 3.19 (m, 6 H), 2.92 (d, *J* = 5.3 Hz, 1 H), 1.09 - 0.67 (m, 9 H), 0.29 - -0.16 (m, 6 H) ppm

^{13}C-NMR ($CDCl_3$, 50 MHz): δ = 209.0, 140.9, 128.0, 127.5, 126.7, 98.9, 77.6, 76.4, 76.1, 74.7, 66.0, 63.0, 29.4, 25.7, 18.4, 18.2, -4.9, -5.2 ppm

MS-ESI $[M + Na^+]^+$: m/z 373

(4*S*, 5*R*)-4-((*R*)-((tert-Butyldimethylsilyl) oxy)(phenyl)methyl)-2,2-dimethyl-1,3-dioxan-5-ol (42)



The compound was prepared using the same procedure as compound **101**(***chapter 2, section C***) using **43**(1.6 g, 0.0045 mmol), L-selectride (6.8 ml, 0.0068 mmol, 1.0 M in THF) and dry THF (22.5 ml).

Yield: 1.32 g (82%)

[α] $^{25}_{D}$=-60 (*c* 1, $CHCl_3$)

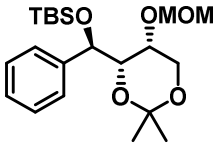
IR (neat, cm^{-1}): ν_{max} 3430, 2900, 2810, 1460, 1100, 881, 825, 690.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.28 - 7.21 (m, 3 H), 6.90 - 6.85 (m, 2 H), 4.48 - 4.38 (m, 2 H), 4.38 - 4.30 (m, 2 H), 4.18 (dd, *J* = 1.4, 16.0 Hz, 1 H), 3.91 - 3.83 (m, 1 H), 3.82 - 3.80 (m, 2 H), 3.69 (dd, *J* = 7.8, 9.2 Hz, 1 H), 3.48 (dd, *J* = 5.7, 9.4 Hz, 1H), 1.44 (d, *J* = 5.0 Hz, 6 H), 0.88 - 0.86 (m, 9 H), 0.12 - 0.06 (m, 6 H) ppm

^{13}C-NMR ($CDCl_3$, 50 MHz): δ = 140.9, 128.0, 127.5, 127.2, 126.7, 98.9, 76.04, 74.7, 66.0, 63.0, 29.7, 29.4, 25.7, 18.4, 18.2, -4.9, -5.2 ppm

MS-ESI [M + Na$^+$]$^+$: m/z 375

***t*er- Butyl (*(R)*-((4*S*, 5*R*)-5-(methoxymethoxy)-2,2-dimethyl-1,3-dioxan-4-yl) (phenyl) methoxy) dimethylsilane (44)**



To a solution of **42** (1.0 g, 0.0028 mol) in dry DCM (7.1 ml) was added Et_2N^iPr (0.72 ml, 0.0042 mol) and MOMCl (0.25 ml, 0.0034 mol) at 0 ^oC at r.t for 6 h. After completion of reaction, the reaction was quenched with 5 ml of satd. NH_4Cl solution at 0 ^oC. The solution was then diluted with 10 ml of DCM. The organic layer was separated and the aqueous layer was again extracted with 10 ml of DCM. The organic layer was washed with 10 ml of brine and dried over sodium sulphate. The organic layer was concentrated in vacuo and purified by column chromatography (10% EtOAc: 90% pet ether) to furnish **44** as colourless oil.

Yield: 0.86 g (85%)

[α] $^{25}_{D}$=-25 (c=1,$CHCl_3$)

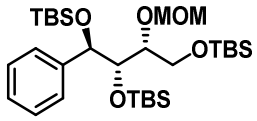
IR (neat, cm^{-1}):ν_{max} 2800, 1480, 1240, 1130, 1080, 860, 750**.**

^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 7.43 - 7.06 (m, 5 H), 4.89 (s, 2 H), 4.74 (d, *J* = 9.0 Hz, 1 H), 4.17 (d, *J* = 2.0 Hz, 1 H), 4.03 (d, *J* = 1.6 Hz, 1 H), 3.87 (dd, *J* = 1.6, 8.9 Hz, 1 H), 3.73 (d, *J* = 1.8 Hz, 1 H), 3.51 (s, 3H), 1.28 (s, 3 H), 1.17 (s, 3 H), 0.84 (s, 9 H), 0.00 (s, 3 H), -0.42 (s, 3 H) ppm

^{13}C-NMR ($CDCl_3$, 50 MHz): δ = 142.5, 127.7, 127.6, 127.4, 98.6, 98.0, 72.6, 71.6, 64.6, 55.6, 28.9, 25.8, 18.5, 18.0, -4.3, -5.1 ppm

MS-ESI [M + Na$^+$]$^+$:m/z 419

(5*R*, 6*S*, 7*R*)-6-((*tert*-Butyldimethylsilyl) oxy)-7-(methoxymethoxy)-2, 2, 3, 3, 10, 10, 11, 11-octamethy l-5-phenyl-4, 9-dioxa-3, 10-disiladodecane (46)



To a solution of **44** (0.750 g, 0.0019 mol) in wet CH_3CN (18.9 ml) was added $BiCl_3$ (0.0062 g, 0.00019) at 0 ^oC and the solution was stirred at r.t for 30 min. After 30 min the reaction was quenched with solid $NaHCO_3$ and filtered over celite. The filtrate was concentrated in vaccum and the crude diol **45** was subjected directly to next reaction without further purification. This crude diol (0.700 g, 0.002 mol) was dissolved in dry DCM (5 ml) and cooled to 0 ^oC. To this cold solution was then added 2, 6-lutidine (1.4 ml, 0.006 mol) and TBSOTf (1.1 ml, 0.005 mol). The solution was then stirred at r.t for 12 h. After completion of reaction, the reaction was quenched with 5 ml of satd. NH_4Cl solution at 0 ^oC. The solution was then diluted with 10 ml of DCM. The organic layer was separated and the aqueous layer was again extracted with 10 ml of DCM. The organic layer was washed with 10 ml of brine and dried over sodium sulphate. The organic layer was concentrated in vacuo and purified by column chromatography (2% EtOAc: 98% pet ether) to furnish **46** as colourless oil.

Yield: 1.15 g (81% over two steps)

[α] $^{25}_D$=+1.0 (*c* 1, $CHCl_3$)

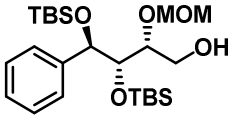
IR (neat, cm^{-1}): ν_{max} 1400, 1340, 1050, 900, 815, 734

^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 7.47 - 6.94 (m, 5 H), 4.93 - 4.48 (m, 3H), 4.18 - 3.93 (m, 1 H), 3.85 - 3.73 (m, 1 H), 3.64 (d, *J* = 5.8 Hz, 2 H), 3.36 (s, 3 H), 1.02 - 0.71 (m, 27 H), 0.10 - -0.05 (m, 12H), -0.39 (s, 3 H), -0.32 (s, 3 H)

^{13}C-NMR ($CDCl_3$, 50 MHz): 142.6, 128.5, 127.6, 127.4, 97.5, 80.0, 75.9, 62.8, 55.2, 26.1, 25.9, 18.3, 18.2, 18.1, -4.5, -4.8, -4.9, -5.0, -5.3, -5.4

MS-ESI $[M + Na^+]^+$: m/z 584

(2*R*, 3*S*, 4*R*)-3, 4-bis ((*tert*-Butyldimethylsilyl)oxy)-2-(methoxymethoxy)-4-phenylbutan-1-ol (41)



A solution of 46 (1.0 g, 0.0017 mol) and CAN (0.093 g, 0.00017 mol) in isopropanol (17 ml) was stirred at r.t for 12 h. After completion of reaction, the reaction was quenched with satd. $NaHCO_3$ and diluted with ethyl acetate (10 ml). The aqueous layer was separated and extracted with 2X10ml of ethyl acetate. The combined organic layer was then washed with 15 ml of brine, separated and dried over sodium sulphate. The solution was then concentrated in vacuum and the crude product was purified by column chromatography (10% EtOAc: 90% pet ether) to furnish **41** as colourless oil.

Yield: 0.72 g (90%)

$[\alpha]_D^{25}$=+27.0 (*c* 1, $CHCl_3$)

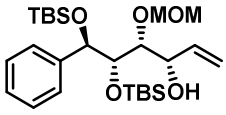
IR (neat, cm^{-1}): ν_{max} 3447, 2940, 1481, 1275, 906, 776

^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 7.39 - 7.07 (m, 5 H), 4.88 - 4.47 (m, 1 H), 3.98 - 3.72 (m, 1H), 3.72 - 3.48 (m, 1 H), 3.48 - 3.20 (m, 2 H), 0.94 - 0.54 (m, 18 H), 0.08 - -0.19 (m, 6 H), -0.33 (s, 3 H), -0.56 (s, 3 H) ppm

^{13}C-NMR ($CDCl_3$, 50 MHz): δ = 142.2, 141.8, 138.5, 137.5, 127.9, 127.8, 127.5, 116.6, 115.9, 98.4, 97.4, 83.9, 80.4, 76.4, 75.7, 72.5, 71.8, 55.8, 26.0, 25.9, 18.2, 18.1, -4.4, -4.5, -4.7, -4.9, -5.2 ppm

MS-ESI $[M + Na]^+$: m/z 470

(3*S*, 4*R*, 5*S*, 6*R*)-5, 6-Bis((*tert*-butyldimethylsilyl)oxy)-4-(methoxymethoxy)-6-phenylhex-1-en-3-ol (47)



To a solution of **41** (0.50 g, 0.001 mol), in dry DCM (2.7 ml) was added pyridine (0.25 ml, 0.003 mol). The solution was cooled to 0 ^oC followed by addition of Dess Martin periodinane(1.27 g, 0.003 mol) and the reaction mixture was stirred at r.t. After completion of reaction (30 min), the reaction was quenched with satd. $NaHCO_3$ and diluted with DCM (10 ml). The aqueous layer was separated and extracted with

2X5ml of DCM. The combined organic layer was then washed with 10 ml of brine, separated and dried over sodium sulphate. The solution was then concentrated in vacuum and the crude aldehyde was subjected to next step without further purification. The crude aldehyde (0.45 g, 0096 mol) was dissolved in dry THF (9.6 ml) and cool to -78 ^{o}C. To this cold solution was added vinyl magnesium bromide (5.3 ml, 0.0053 mol, 1.0 M in THF). The solution was stirred at -78 ^{o}C until complete consumption of aldehyde (6 h). After completion of reaction, the reaction was quenched with 5 ml of satd. NH_4Cl solution at 0 ^{o}C. The solution was then diluted with 10 ml of ethyl acetate. The organic layer was separated and the aqueous layer was again extracted with 2X10 ml of ethyl acetate. The organic layer was washed with 15 ml of brine and dried over sodium sulphate. The organic layer was concentrated in vacuum and the crude product was purified by column chromatography (5% EtOAc: 95% pet ether) to furnish **47** as amorphous solid.

Yield: 0.42 g (80% over two steps)

$[\alpha]_D^{25}$= -15 (*c* 0.7, CH_3Cl)

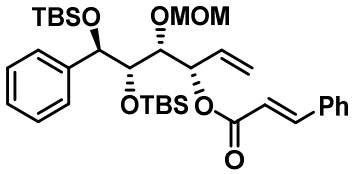
IR (neat, cm^{-1}): ν_{max} 3070, 2900, 2855, 1400, 1100, 930 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz) : δ = 7.49 - 7.02 (m, 5 H), 6.02 - 5.52 (m, 1 H), 5.42 - 4.89 (m, 2 H), 4.89 - 4.39 (m, 3 H), 4.27 - 4.04 (m, 1 H), 3.95 (ddd, *J* = 4.6, 6.5, 17.9 Hz, 1 H), 3.83 - 3.47 (m, 2 H), 3.36 (d, *J* = 6.9 Hz, 3 H), 0.92 - 0.67 (m, 18 H), 0.17 - -0.16 (m, 6 H), -0.19 (d, *J* = 2.8 Hz, 3 H), -0.31 (s, 1 H), -0.42 (s, 1 H) ppm

^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 138.5, 138.0, 137.7, 128.8, 128.7, 128.1, 128.0, 116.7, 115.5, 97.5, 97.3, 94.1, 84.2, 83.9, 78.3, 78.1, 77.3, 76.7, 76.4, 72.5, 71.4, 56.2, 56.1, 29.7, 25.9, 25.8, 18.1, -4.6, -5.0 ppm

MS-ESI [M + Na$^+$]$^+$: m/z 519

(3*S*, 4*R*, 5*S*, 6*R*)-5, 6-Bis ((*tert*-butyldimethylsilyl) oxy)-4-(methoxymethoxy)-6-phenylhex-1- en-3-yl cinnamate (49)



To a solution of DCC (0.57 g, 0.0027 mol) in dry DCM (3 ml) was added trans-cinnamic acid (0.37 g, 0.0025 mol) at r.t and the homogeneous solution was stirred for 15 min. To this mixture was added a solution of **41** (0. 25 g, 0.0005 mol) in dry DCM

(2 ml) dropwise at r.t. and DMAP (0.012 g, 0.0001 mol). The mixture was refluxed for 6 h until TLC showed complete consumption of alcohol **41.** After completion of reaction, the reaction was quenched with satd. $NaHCO_3$ (10 ml) and diluted with DCM (10 ml). The aqueous layer was separated and extracted with 2X5ml of DCM. The combined organic layer was then washed with 10 ml of brine, separated and dried over sodium sulphate. The organic layer was concentrated in vacuum and the crude product was purified by column chromatography (2% EtOAc: 98% pet ether) to furnish **47** as colourless liquid.

Yield: 0.24 g (76%)

$[\alpha]^{25}_{D}$ =-21 (*c* 0.4, CH_3Cl)

IR (neat, cm^{-1}):ν_{max} 2940, 1650, 1200, 1100, 767

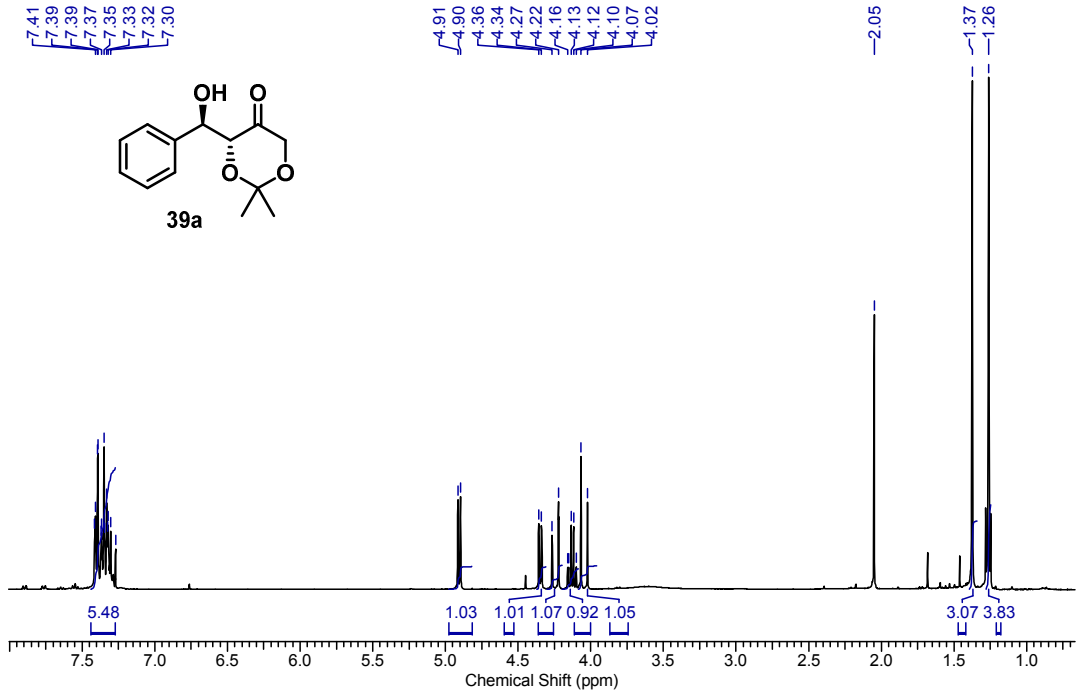
^{1}H-NMR ($CDCl_3$, 200 MHz: δ = 7.90 - 7.62 (m, 1 H), 7.53 (dd, *J* = 1.8, 4.0 Hz, 2 H), 7.43 - 7.27 (m, 8 H), 6.60 - 6.32 (m, 1 H), 6.08 - 5.78 (m, 1 H), 5.54 - 5.18 (m, 2 H), 5.08 (d, *J* = 17.3 Hz, 1 H), 4.85 - 4.53 (m, 3 H), 4.09 - 3.71 (m, 2 H), 3.43 (s, 2 H), 0.92 - 0.80 (m, 18 H), 0.10 - 0.01 (m, 6 H), -0.14 - -0.39 (m, 6 H) ppm

^{13}C-NMR ($CDCl_3$, 50 MHz: δ = 165.7, 144.8, 141.8, 134.5, 133.0, 130.2, 128.9, 128.0, 127.9, 127.5, 119.7, 118.3, 97.5, 77.6, 76.4, 75.4, 55.6, 29.7, 26.1, 25.9, 18.2, -4.2, -4.5, -4.8, -4.9 ppm

MS-ESI $[M + Na^+]^+$:m/z 649

2.5.7:Selected Spectra

Sr. No.	Contents
1	^{1}H and ^{13}C spectra of compound **39a**
2	^{1}H and ^{13}C spectra of compound **43**
3	^{1}H and ^{13}C spectra of compound **42**
4	^{1}H and ^{13}C spectra of compound **44**
5	^{1}H and ^{13}C spectra of compound **46**
6	^{1}H and ^{13}C spectra of compound **41**
7	^{1}H and ^{13}C spectra of compound **47**
8.	^{1}H and ^{13}C spectra of compound **48**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7.39
7.39
7.37
7.35
7.33
7.32
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4.90
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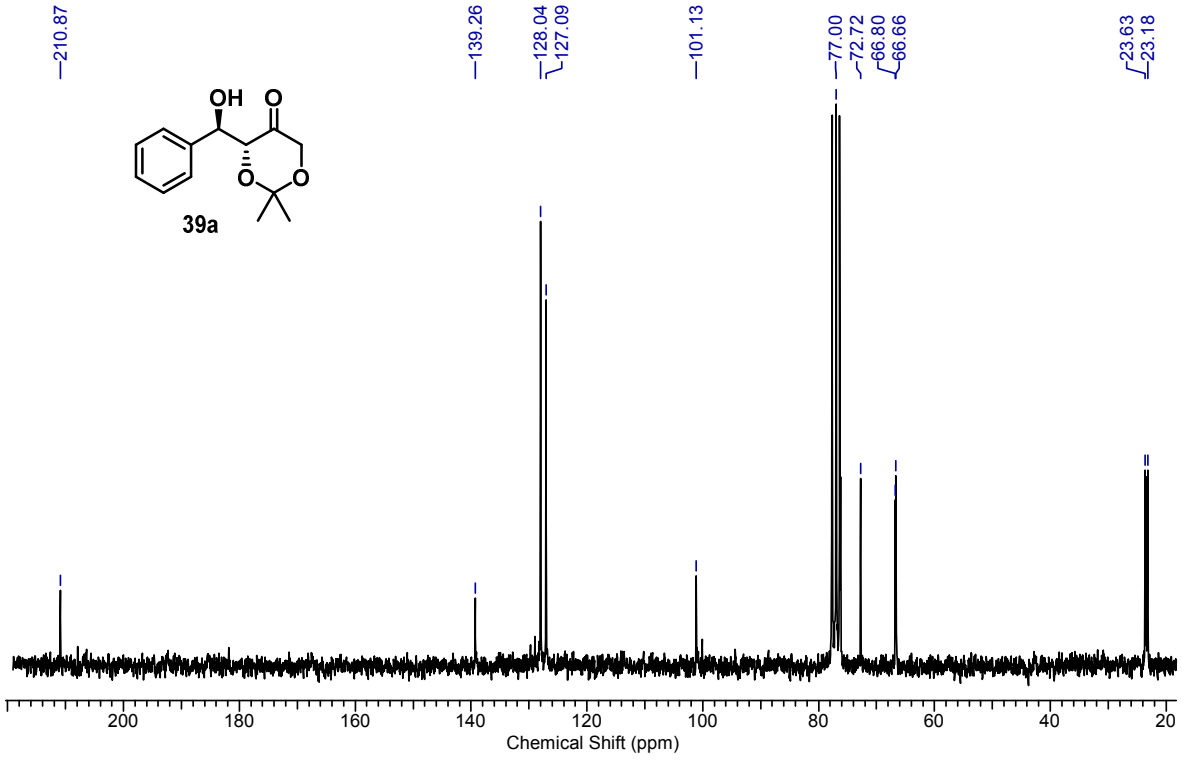
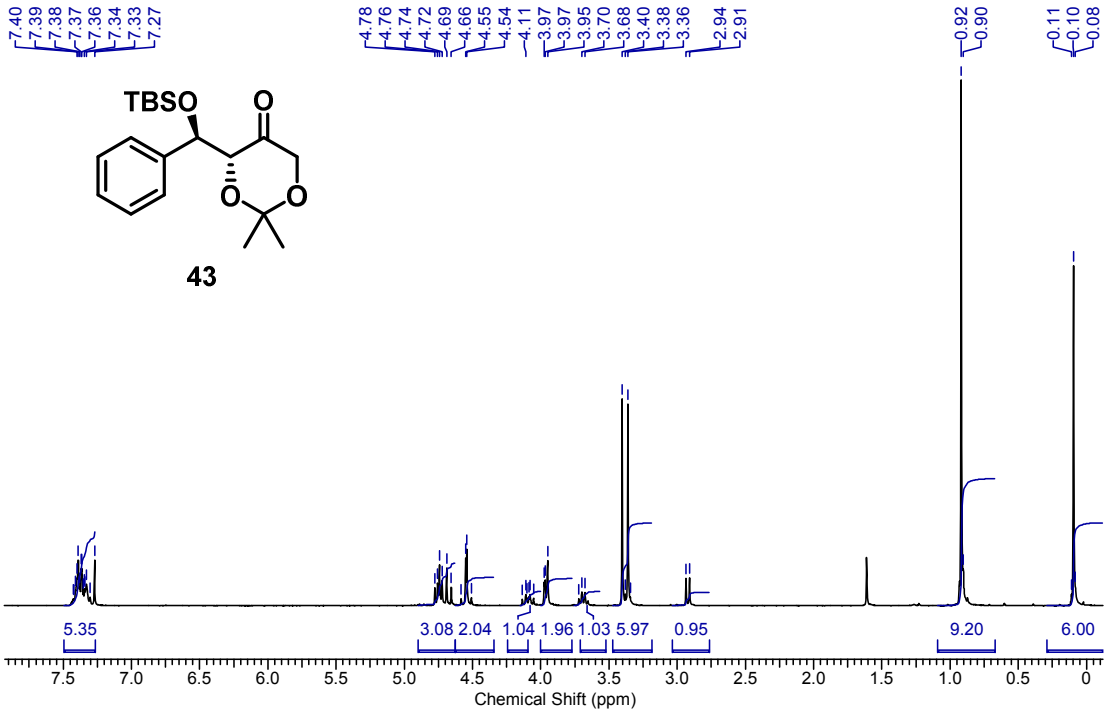
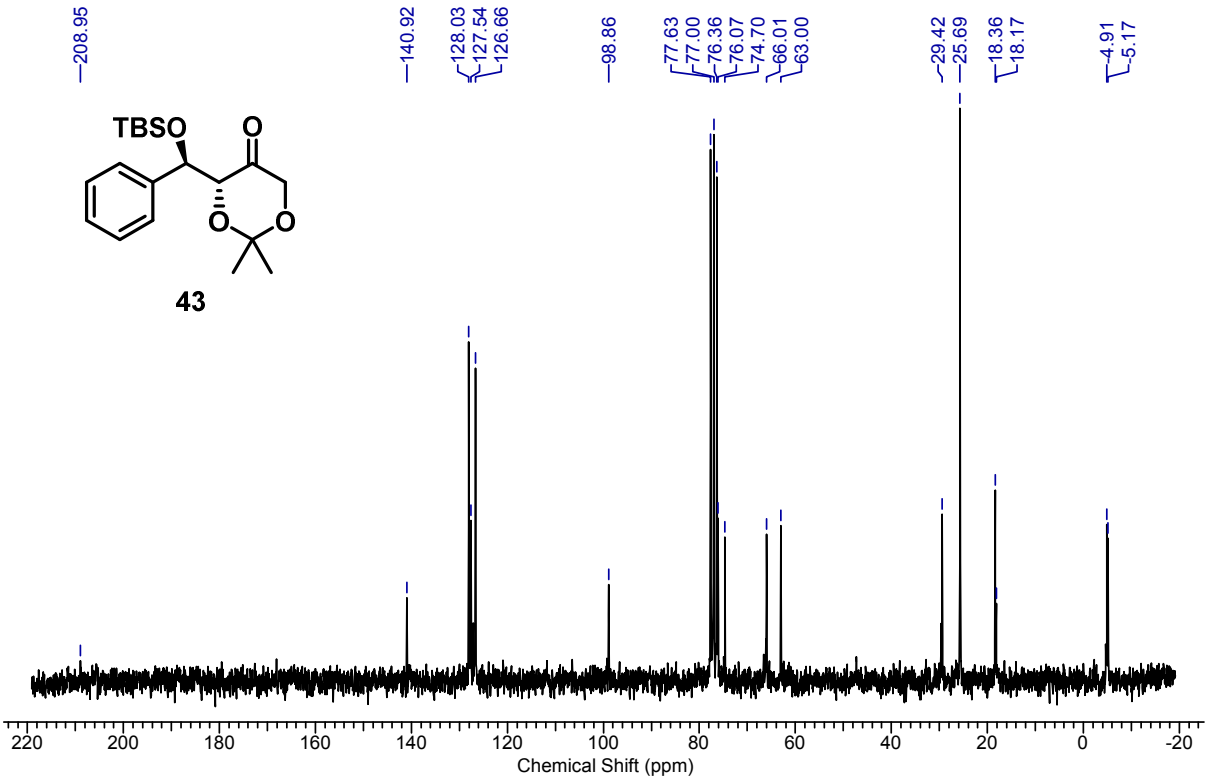
4.27
4.22
4.16
4.13
4.12
4.10
4.07
4.02
2.05
1.37
1.26
OH
O
O
O
39a
5.48
1.03
1.01
1.07
0.92
1.05
3.07
3.83
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)


210.87
139.26
128.04
127.09
101.13
77.00
72.72
66.80
66.66
23.63
23.18
OH
O
O
O
39a
200
180
160
140
120
100
80
60
40
20
Chemical Shift (ppm)


7.40
7.39
7.38
7.37
7.36
7.34
7.33
7.27
4.78
4.76
4.74
4.72
4.69
4.66
4.55
4.54
4.11
3.97
3.97
3.95
3.70
3.68
3.40
3.38
3.36
2.94
2.91
0.92
0.90
0.11
0.10
0.08
TBSO
O
O
O
43
5.35
3.08
2.04
1.04
1.96
1.03
5.97
0.95
9.20
6.00
Chemical Shift (ppm)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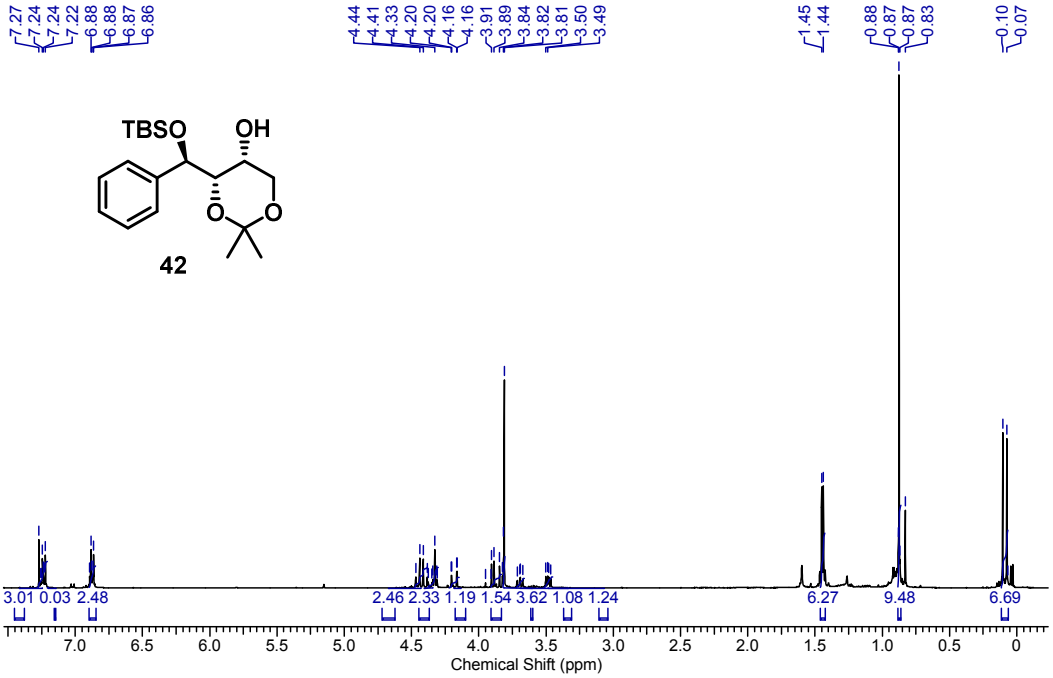
127.54
126.66
98.86
77.63
77.00
76.36
76.07
74.70
66.01
63.00
29.42
25.69
18.36
18.17
4.91
5.17
TBSO
O
O
O
43
Chemical Shift (ppm)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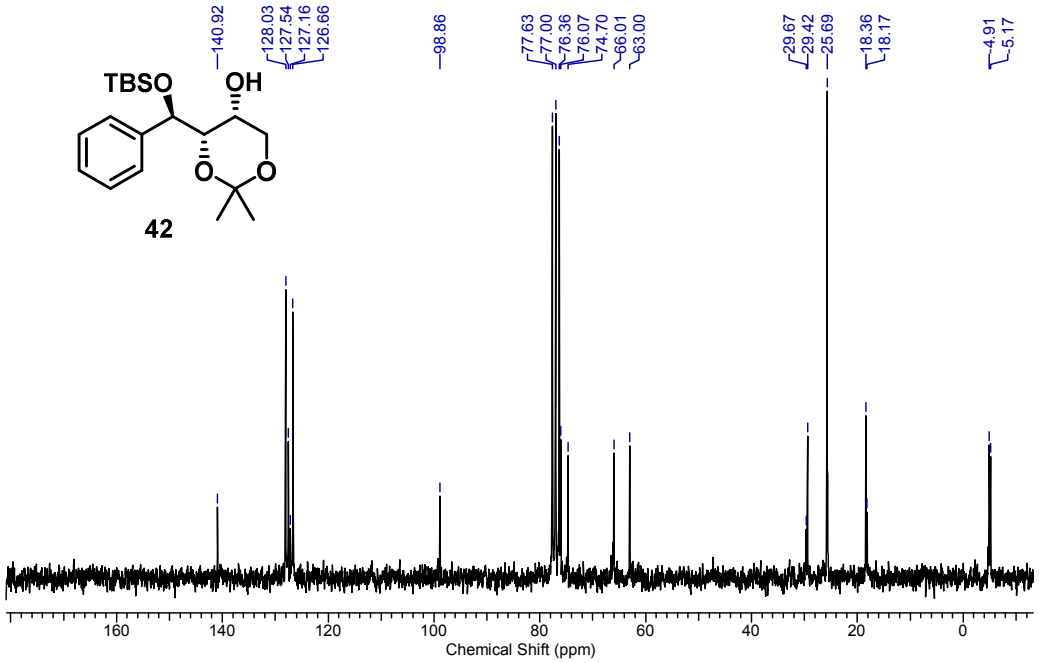
7.24
7.24
7.22
6.88
6.88
6.87
6.86
4.44
4.41
4.33
4.20
4.20
4.16
4.16
3.91
3.89
3.84
3.82
3.81
3.50
3.49
1.45
1.44
0.88
0.87
0.87
0.83
0.10
0.07
TBSO
OH
42
3.01 0.03 2.48
2.46 2.33 1.19 1.54 3.62 1.08 1.24
6.27
9.48
6.69
Chemical Shift (ppm)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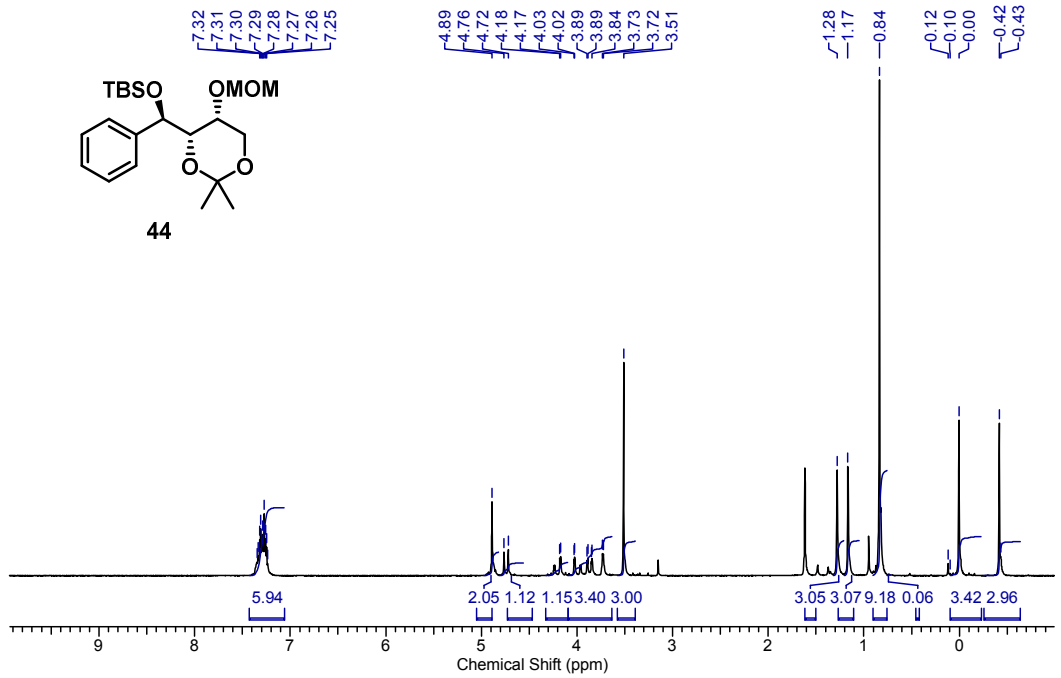
126.66
98.86
77.63
77.00
76.36
76.07
74.70
66.01
63.00
29.67
29.42
25.69
18.36
18.17
4.91
5.17
TBSO
OH
42
Chemical Shift (ppm)


TBSO
OMOM
44
7.32
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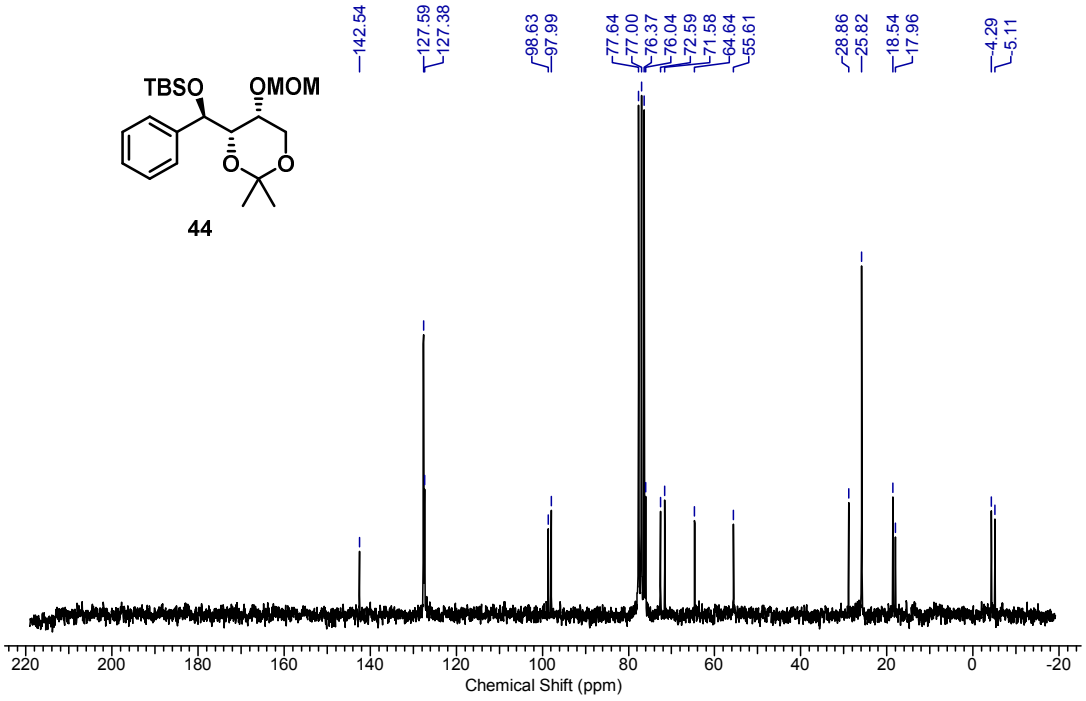
7.30
7.29
7.28
7.27
7.26
7.25
4.89
4.76
4.72
4.18
4.17
4.03
4.02
3.89
3.89
3.84
3.73
3.72
3.51
1.28
1.17
0.84
0.12
0.10
0.00
-0.42
-0.43
5.94
2.05
1.12
1.15
3.40
3.00
3.05
3.07
9.18
0.06
3.42
2.96
Chemical Shift (ppm)


TBSO
OMOM
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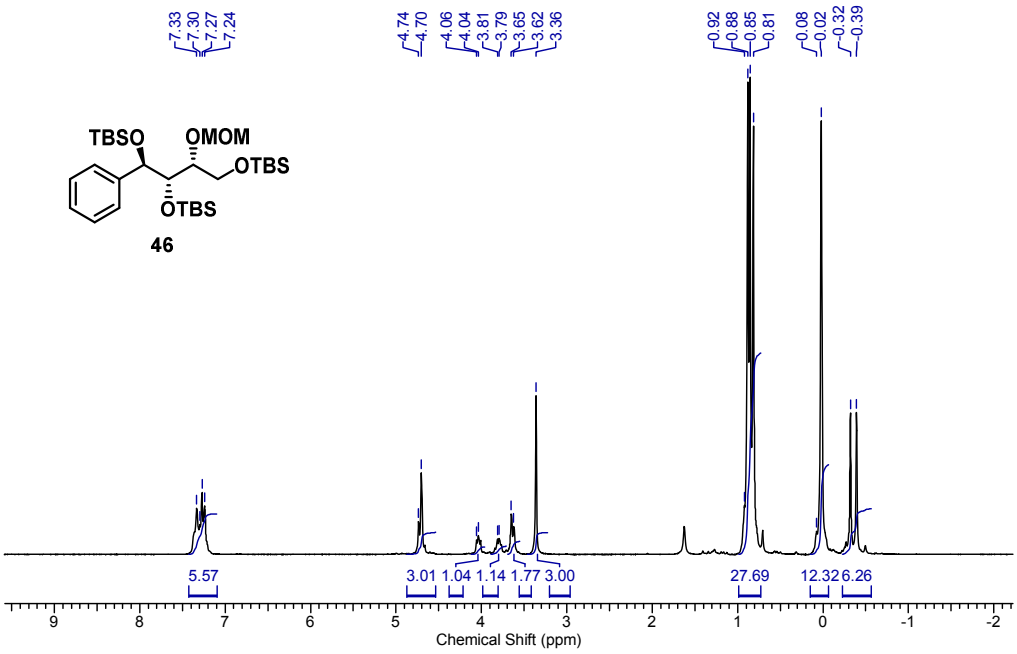
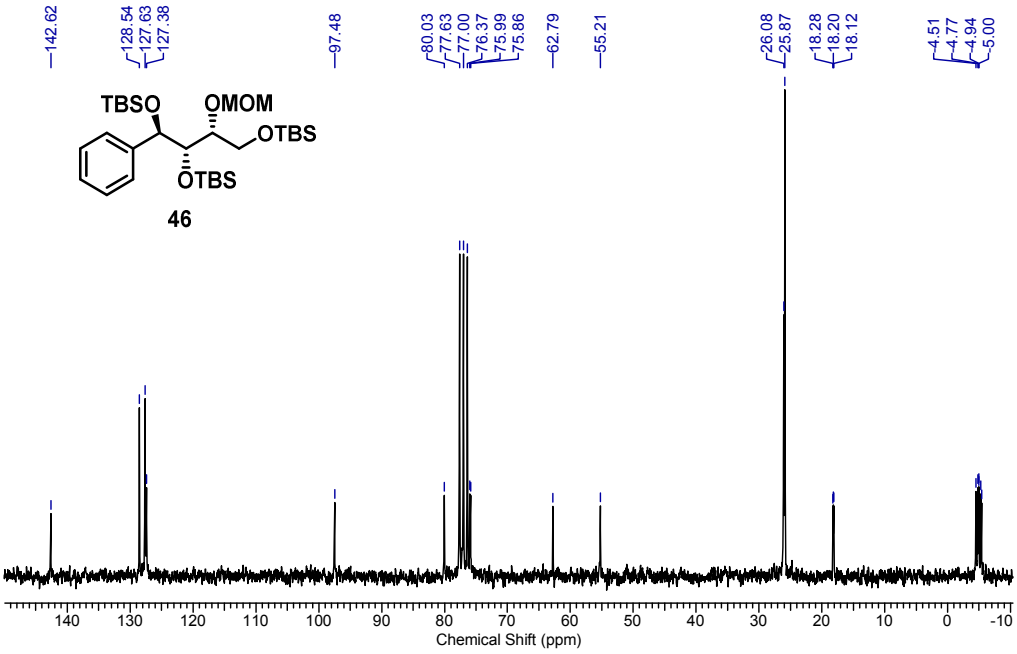
142.54
127.59
127.38
98.63
97.99
77.64
77.00
76.37
76.04
72.59
71.58
64.64
55.61
28.86
25.82
18.54
17.96
-4.29
-5.11
Chemical Shift (ppm)


7.33
7.30
7.27
7.24
4.74
4.70
4.06
4.04
3.81
3.79
3.65
3.62
3.36
0.92
0.88
0.85
0.81
0.08
0.02
-0.32
-0.39
TBSO
OMOM
OTBS
OTBS
46
5.57
3.01
1.04
1.14
1.77
3.00
27.69
12.32
6.26
Chemical Shift (ppm)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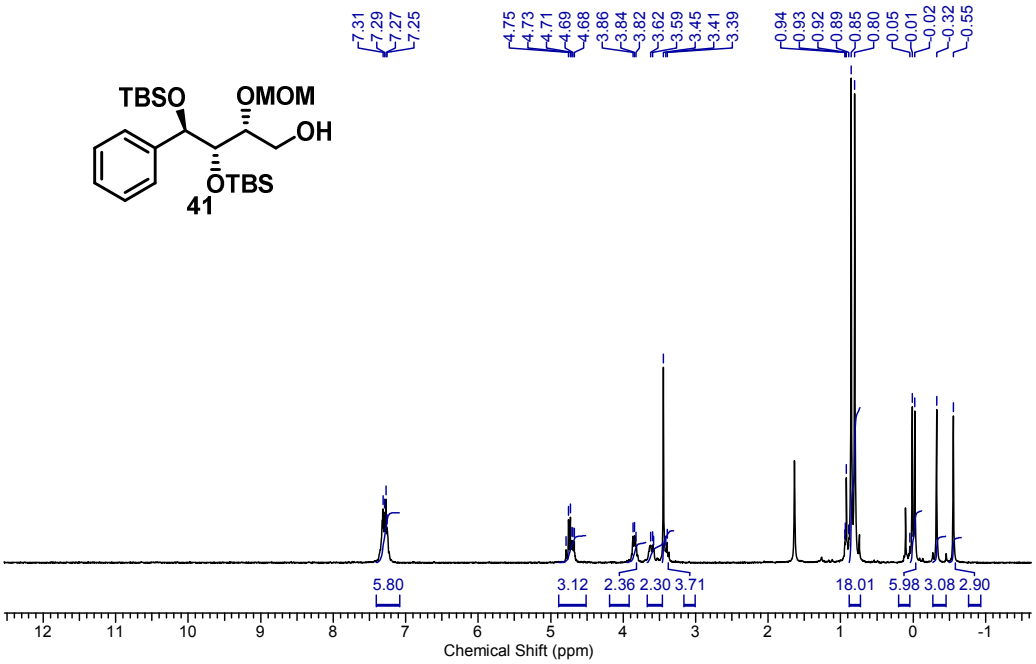
128.54
127.63
127.38
97.48
80.03
77.63
77.00
76.37
75.99
75.86
62.79
55.21
26.08
25.87
18.28
18.20
18.12
4.51
4.77
4.94
5.00
TBSO
OMOM
OTBS
OTBS
46
Chemical Shift (ppm)


TBSO
OMOM
OH
OTBS
41
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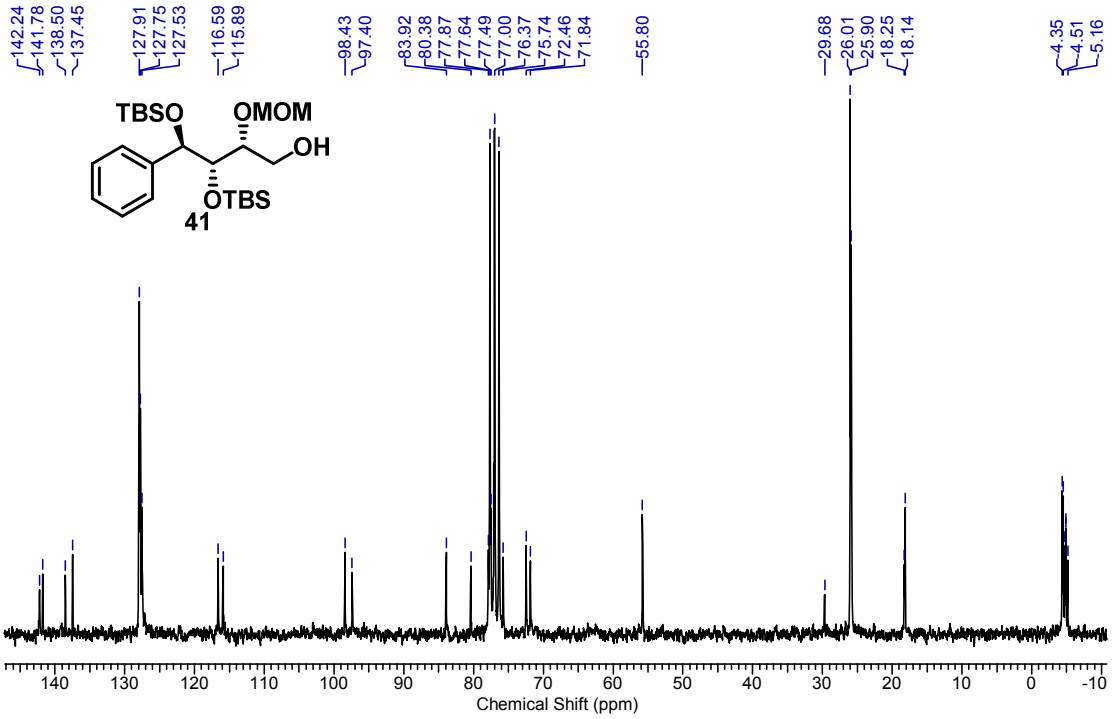
7.29
7.27
7.25
4.75
4.73
4.71
4.69
4.68
3.86
3.84
3.82
3.62
3.59
3.45
3.41
3.39
0.94
0.93
0.92
0.89
0.85
0.80
0.05
0.01
-0.02
-0.32
-0.55
5.80
3.12
2.36
2.30
3.71
18.01
5.98
3.08
2.90
Chemical Shift (ppm)


TBSO
OMOM
OH
OTBS
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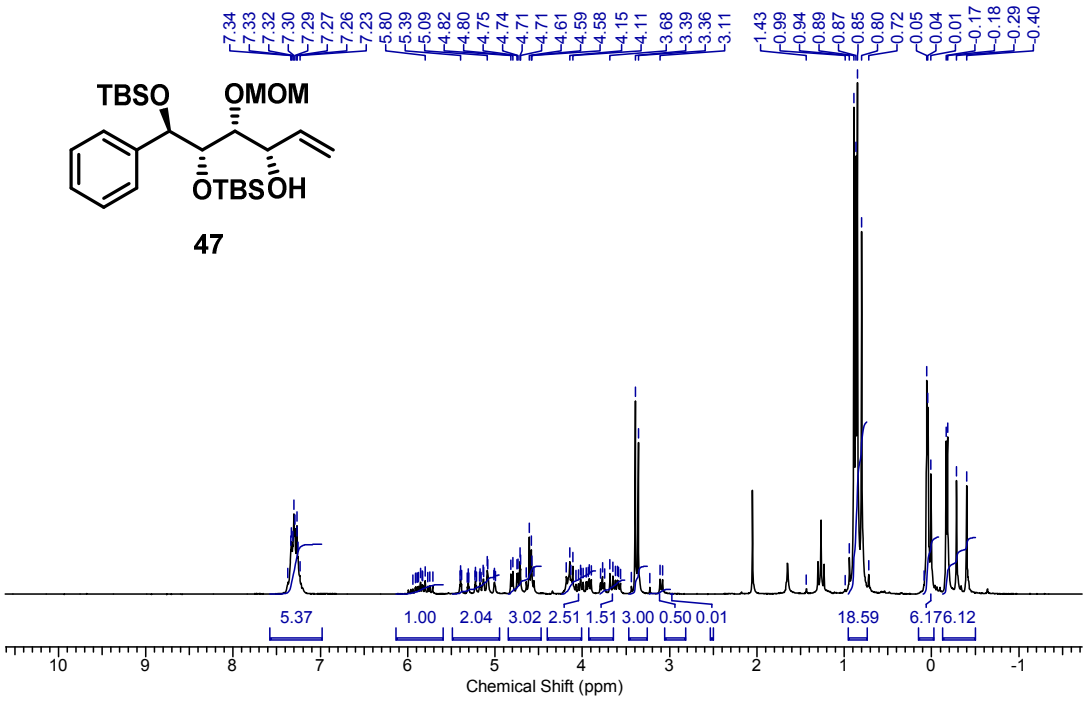
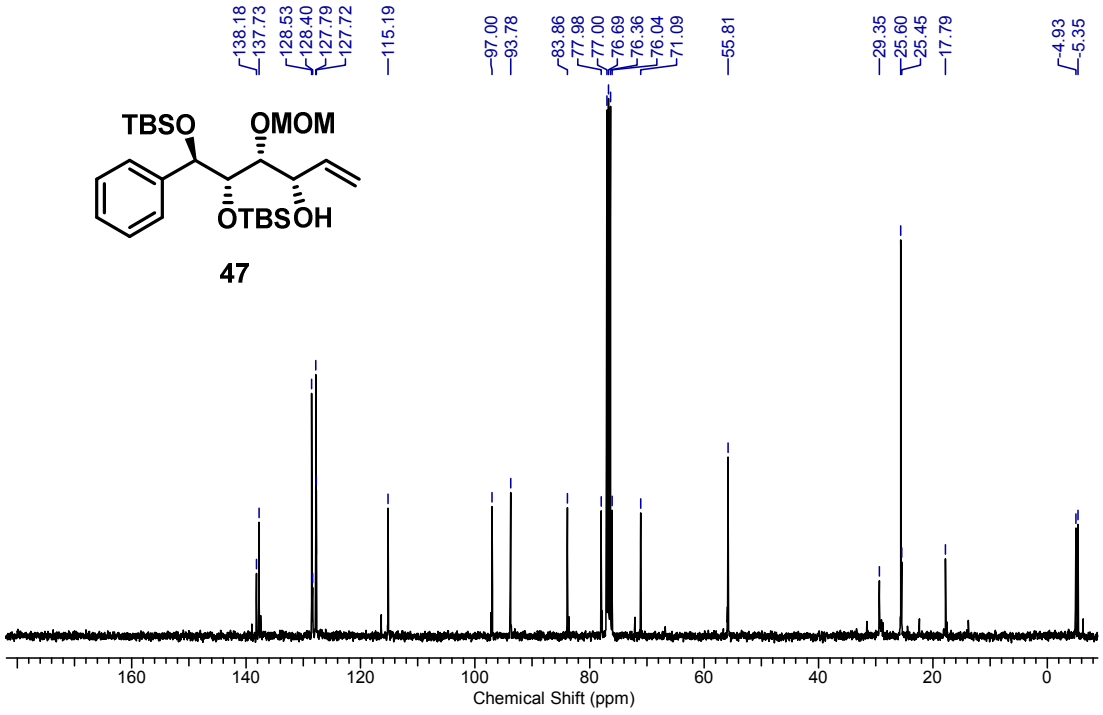
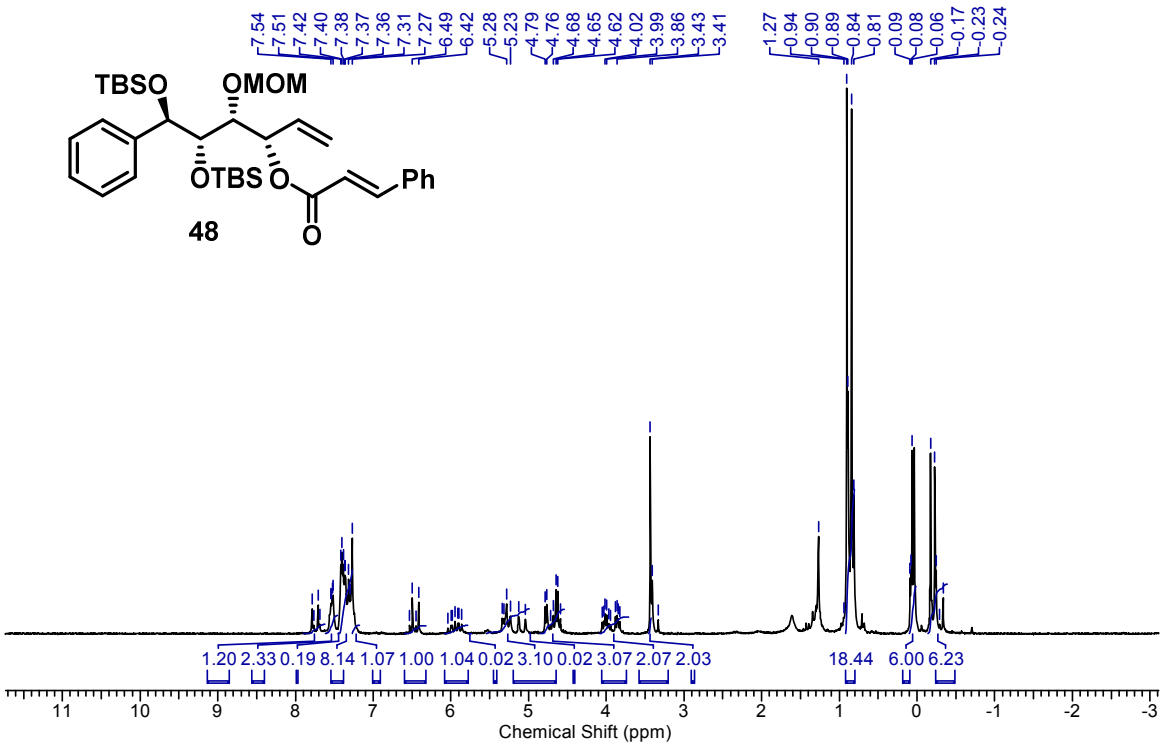
142.24
141.78
138.50
137.45
127.91
127.75
127.53
116.59
115.89
98.43
97.40
83.92
80.38
77.87
77.64
77.49
77.00
76.37
75.74
72.46
71.84
55.80
29.68
26.01
25.90
18.25
18.14
-4.35
-4.51
-5.16
Chemical Shift (ppm)


TBSO
OMOM
OTBSOH
47
7.34
7.33
7.32
7.30
7.29
7.27
7.26
7.23
5.80
5.39
5.09
4.82
4.80
4.75
4.74
4.71
4.71
4.61
4.59
4.58
4.15
4.11
3.68
3.39
3.36
3.11
1.43
0.99
0.94
0.89
0.87
0.85
0.80
0.72
0.05
0.04
0.01
0.17
0.18
0.29
0.40
5.37
1.00
2.04
3.02
2.51
1.51
3.00
0.50
0.01
18.59
6.17
6.12
Chemical Shift (ppm)


TBSO
OMOM
OTBSOH
47
138.18
137.73
128.53
128.40
127.79
127.72
115.19
97.00
93.78
83.86
77.98
77.00
76.69
76.36
76.04
71.09
55.81
29.35
25.60
25.45
17.79
4.93
5.35
Chemical Shift (ppm)


7.54
7.51
7.42
7.40
7.38
7.37
7.36
7.31
7.27
6.49
6.42
5.28
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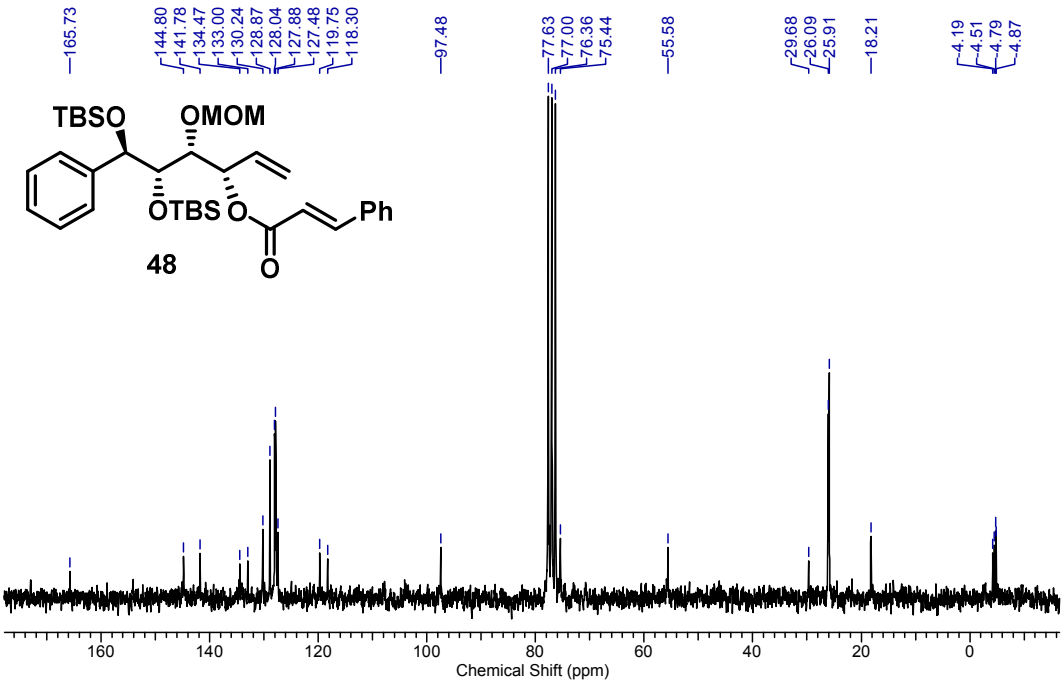
4.79
4.76
4.68
4.65
4.62
4.02
3.99
3.86
3.43
3.41
1.27
0.94
0.90
0.89
0.84
0.81
0.09
0.08
0.06
-0.17
-0.23
-0.24
TBSO
OMOM
OTBS
O
Ph
O
48
1.20 2.33 0.19 8.14 1.07 1.00 1.04 0.02 3.10 0.02 3.07 2.07 2.03
18.44 6.00 6.23
Chemical Shift (ppm)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144.80
141.78
134.47
133.00
130.24
128.87
128.04
127.88
127.48
119.75
118.30
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77.63
77.00
76.36
75.44
55.58
29.68
26.09
25.91
18.21
4.19
4.51
4.79
4.87
TBSO
OMOM
OTBS
O
Ph
O
48
Chemical Shift (ppm)

2.5.8: References

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Med. **1978**, *33*, 243.(b) Guinaudeau, H.; Ramahatra, A.; Leboeuf, M.; Cave, A. *Plant Med*. *Phytother.*, **1978***, 12*, 166; (c) Abu Zarga, M. H.; Shamma, M. *J. Nat. Prod.* **1982**, *45*, 471.(d) Connolly, J. D.; Haque; M. E.; A. A. Kadir, *Phytochemistry*, **1996**, *43*, 295.(e) Kanokmedhakul, S.; Kanokmedhakul,K. Yodbuddee, D.; Phonkerd, N.; *J. Nat.Prod.* **2003**, *66*, 616. (f) Kanokmedhakul, S.; Kanokmedhakul, K.; Lekphrom, R. *J. Nat. Prod.* **2007**, 70, 1536 (g). Lavault, M.; Guinaudeau, H.; Bruneton, J.; Sevenet ,T. Hadi, H. A. *Phytochemistry*, **1990**, *29*, 3845.(h) Hasan, C. M.; Healey, T. M.; Waterman, P. G.; Schwalbe, C. H.; *J. Chem. Soc. Perkin Trans. I*, **1982**, 2807. (i) Hocquemiller, R.; Dubois,G.; Kunesch, N.; Leboeuf, M.; Cave, A. *Tetrahedron Lett.* **1985**, 26, 4937. (j) Jossang, A.; Leboeuf, M.; Cabalion P.; A. Cave, *Planta Med.*, **1983**, *49*, 20. (k) Seetharaman,T. R.; *Fitoterapia,* **1986**, *57*, 198.(l). Wu, Y. C.; Duh, C. Y. Wang, S. K.; Chen K. S.; T. H. Yang, **1990**. *53*, 1327. (m) Li, H. Y.; Sun, N. J.; Kashiwada, Y., Sun, L.; Snider,J. V.; Cosentino. L. M.; Lee, K. H. *J. Nat. Prod.*, **1993**, *56*, 1130 (n) Kijjoa, A.; Pinto, M. M. M.; Pinho, P. M. M.; Tantisewie, B.; Herz, W. *Phytochemistry,* **1990**, *29*, 653 (o). Hasan, C. M.; Hossain, M. A.; Rashid; M. A.; Connolly, J.D.; *Fitoterapia,* **1994**, *65*, 283.

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Thanyachareon, W.; Sophasan, S.; Yoosook, C.; Santisuk, T.; Pezzuto, J. M.; *Planta Med.* **2001**, *67*, 572.

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Chapter 3

Chapter 3: Aryne intermediates in the Synthesis of Phenyl Indolines

3

Aryne intermediates in the Synthesis of Phenyl Indolines

3.1. Introduction

Indoline scaffolds have been tremendously popular as a heterocyclic motif occurring in many naturally occurring compounds and pharmaceutically active compounds. The indoline scaffold has been known to occur in numerous bioactive alkaloids such as vinblastine **(1)**[1], strychnine **(2)**[2], (–)-physostigmine **(3)**[3], ajmaline **(4)**[4], and (+)-aspidospermidine **(5)**[5] (**Figure 1**) and is also the structural component of several important pharmaceutically active compounds, such as angiotensin-converting enzyme (ACE) inhibitor and the antihypertensive drug "pentopril" **(6)**[6] In 2005, indoline derivatives oleracein A–D (**7-10**, **Figure 1**) were isolated from the edible plant *Portulaca oleracea* used in Chinese traditional medicine.[7] The plant is reported to possess many pharmacological properties including antioxidant, anticancer, antidiabetic, hypocholesteremic, neuroprotective, hepatoprotective, nephroprotective, anti-inflammatory, antiulcer, antimicrobial, wound healing, uterine bleeding control and wormicidal and insecticidal activities due to the presence of indoline alkaloids.

Another class of indoline alkaloids communesin alkaloids (**11-15, 16, 17 and 18**)[8] and akuammiline alkaloids (**19-23**)[9] also exhibit interesting biological properties (**Figure 2**).

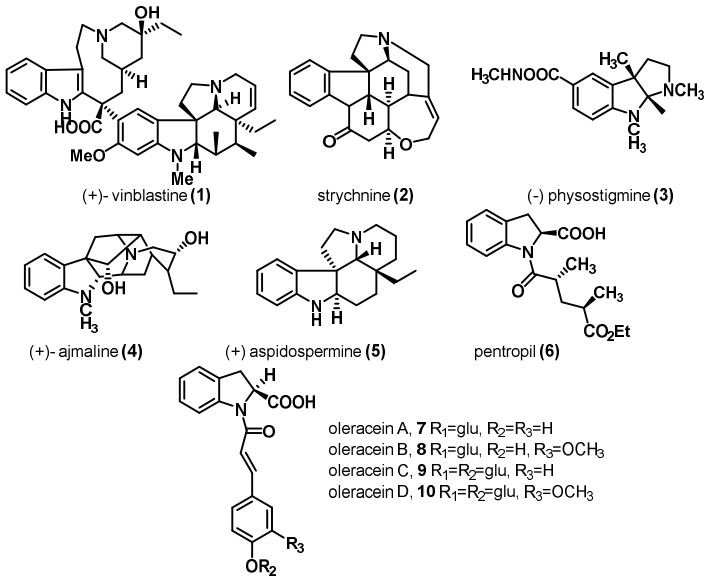


Figure 1: Indoline containing bioactive alkaloid and pharmaceuticals

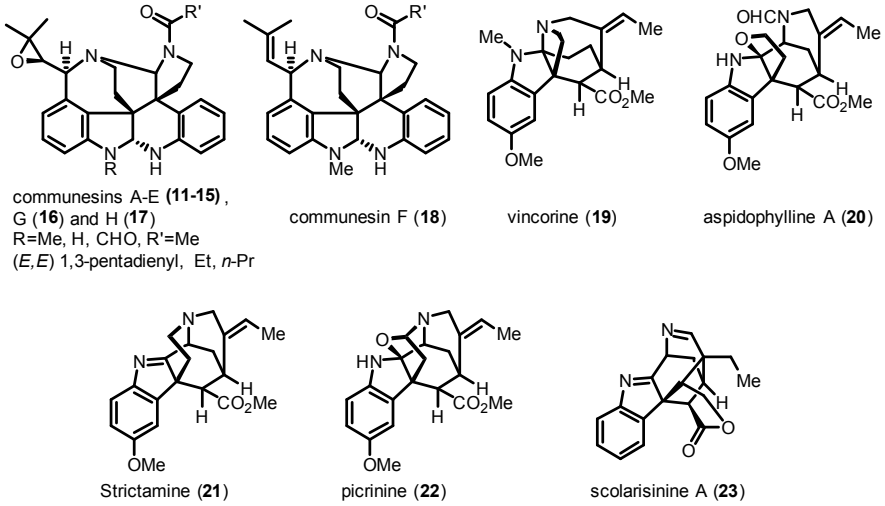


Figure 2: Structures of Communesin Alkaloids (**11-15, 16, 17 and 18**) and Akuammiline Alkaloids (**19-23**)

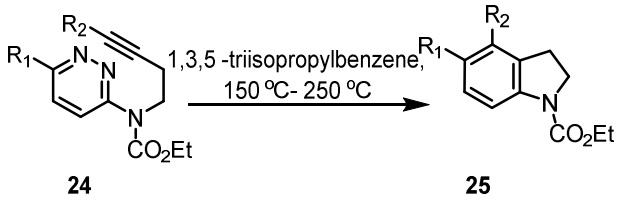
3.2. Review of Literature

3.2.1. Synthesis of 3-substituted indoline scaffolds

Owing to the presence of 3-substituted indoline scaffolds in many naturally occurring compounds and synthetic analogue, 3-substituted indoline scaffolds have become an appealing target for many synthetic chemists. Most approaches involve a similar approach which requires a nucleophilic nitrogen moeity and electrophilic carbon and formation of indoline ring after the attack of nitrogen on electrophilic carbon.[4] Other strategies involve single step indoline formation through cycloaddition[5] and hydrogenation of indoles.[6] Herein we describe few strategies towards the synthesis of 3-substituted indoline scaffolds.

Boger *et al.* (1984)[10]

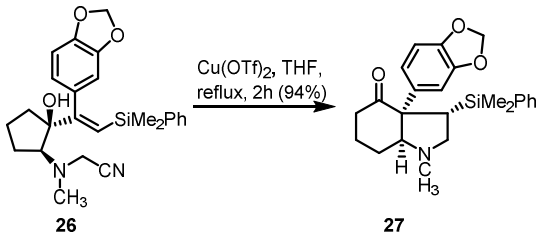
Boger *et al.* synthesized indoline scaffold **25** by employing intramolecular Diels-Alder reaction of 1,2-diazines (**Scheme 1**).



Scheme 1: Synthesis of 1,2-dihydro-*3H*-pyrrolo[3,2-e]

Overman *et al.* (1989)[11]

The authors report tandem aza-Cope rearrangement-Mannich cyclization reaction approach for the synthesis of preparing cis-3a-arylhydroindoles **27** using $Cu(OTf)_2$ as Lewis acid to induce cyclization. The approach has been utilised for the synthesis of *umaryllidaceae* alkaloids as described by the authors **(Scheme 2)**.

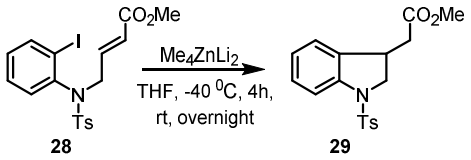


26 27

Scheme 2: Synthesis of cis-3a-arylhydroindoles **27.**

Sakamoto *et al.* (1998)[12]

Sakamoto and co-workers synthesized methyl 2-(1-tosylindolin-3-yl) acetate **29** employing intramolecular Michael addition in presence of lithium tetramethylzincate (**Scheme 3)**.

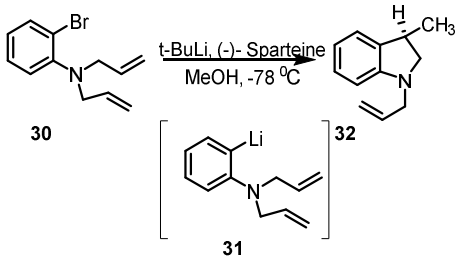


28 29

Scheme 3: Synthesis of methyl 2-(1-tosylindolin-3-yl) acetate **29** by Sakamoto *et al.*

Bailey *et al.* (2000)[13]

Bailey *et al*. employed 2-(*N*,*N*-diallylamino) phenyllithium **31** as the precursor for the synthesis of 3-substituted indoline **32**.The product was obtained by cycloisomerization of olefinic organolithium **31** (**Scheme 4**).

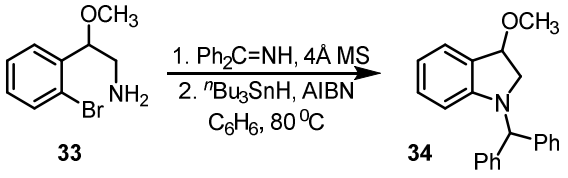


30 32 31

Scheme 4: Synthesis of 3-substituted indoline by Bailey *et al.*

Johnston *et al.* (2001)[14]

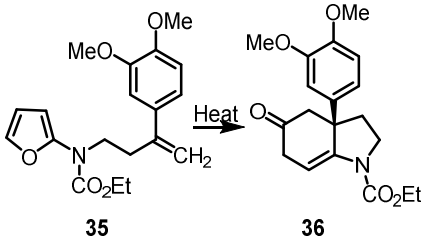
Johnson and co-workers describe a general approach for the synthesis of 3-alkoxy indolines using *o*-bromophenethylamine **33** as starting material. *o*-Bromophenethylamine cyclizes to 3-alkoxy indoline **34** in presence of *n*-Bu_3SnH and a radical initiator (**Scheme 5).**



Scheme 5: Synthesis of 3-alkoxy indolines by Johnston *et al.*

Padwa *et al.* (2001)[15]

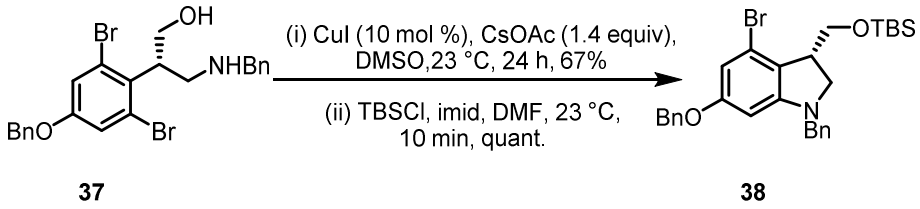
Padwa *et al*. constructed the hexahydroindolinones core **36** by employing a intramolecular Diels-Alder cycloaddition reaction of furanyl carbamates carrying tethered alkenyl groups.



Scheme 6: Synthesis of hexahydroindolinones by Padwa *et al*.

Fukuyama *et al.* (2003)[16]

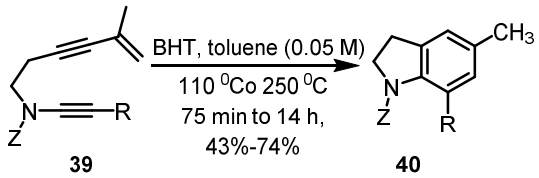
Fukuyama *eta al.* employed CuI iodide mediated C-N bond formation as a crucial step in the synthesis of indoline intermediate **38** which was desirable for synthesis of (+)-duocarmycins A and SA (**Scheme 7)**.



Scheme 7: Synthesis of the Indoline Key Intermediate **38.**

Danheiser *et al.* (2005)[17]

The authors implemented [4+2] cycloaddition of ynamide **39** under reflux conditions to furnish indoline **40 (Scheme 8)**.

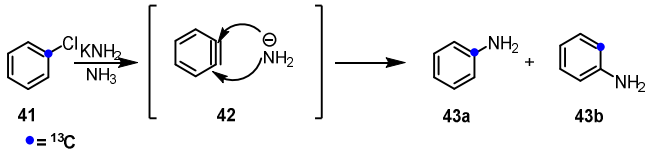


Scheme 8: Synthesis of indolines via intramolecular [4 + 2] cycloaddition of ynamides and conjugated enynes by Danheiser *et al.*

3.2.2. Arynes in Organic Chemistry

3.2.2.1: Introduction to arynes

Benzyne **42** or 1,2-dehydrobenzene is a six membered ring bearing a highly strained alkyne. As a result of this considerable ring strain it exhibits high reactivity and serves as electrophile in many organic reactions. The organic molecules containing such high strained alkyne system are in general called as aryne and show similar reactivity to its prototype. Initial work carried out by Roberts that described reaction of sodamide with ^{13}C labelled chlorobenzene **41** that finally yielded a mixture of labeled isomers, of aniline-1-^{14}C (**43a**) and aniline-2-^{14}C (**43b**) in 43% yield (**Scheme 8)**.[18] It was suspected that the formation of regioisomers was due to the presence of reactive intermediate that was symmetrical in nature.

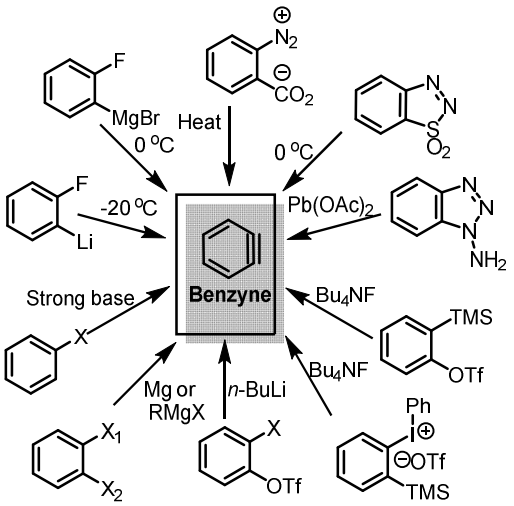


Scheme 8: Initial report of benzyne **42**

3.2.2.2: Generation of arynes and their application in synthesis of *N*-heterocyclic compounds

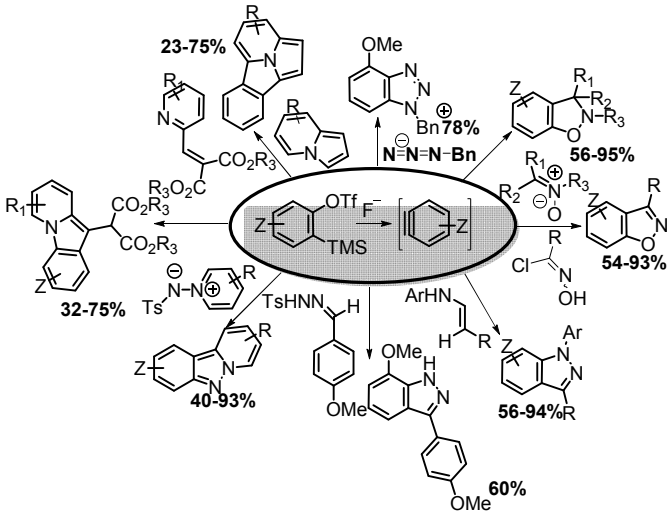
With the initial reports coming from Roberts *et al*[18] for the generation of benzyne using KNH_2 and chlorobenzene, many more groups of chemists have developed several other methods for generation of arynes. With extensive research dedicated in this direction, numerous milder methods have been developed for the same. As a result of this, several

natural product syntheses have been reported by the use of aryne intermediates in the synthesis for the key intermediates.[19]



Scheme 9: Many pathways to benzyne

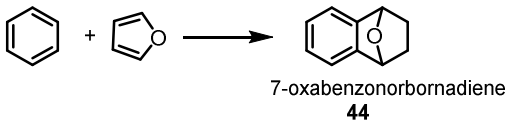
Since the introduction of arynes in synthetic arena[20]and progressive development of milder methods for aryne generation [21], aryne chemistry is complementing the usual methods of C-C and C-X (X= O, N, S) bond formation. Out of the countless methodologies reported for the synthesis of *N*-heterocycles, we majorly focus on the intra- and intermolecular cycloaddition reactions.



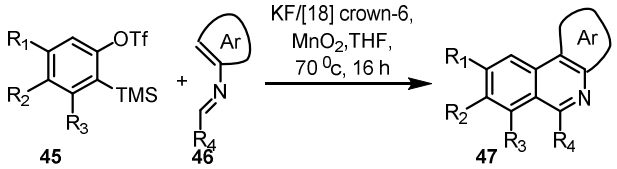
Scheme 10: Use of benzynes for the synthesis of heterocycles

Diels–Alder cycloadditions

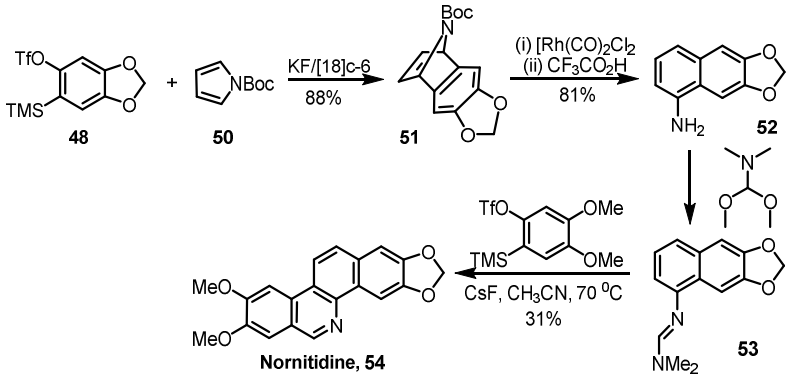
The most pioneer reaction involving aryne in Diels–Alder cycloaddition describes synthesis of 7-oxabenzonorbornadiene **44** in which aryne was added to furan to provide the desired compound **44**.[22] Later on this strategy was further extended to synthesis of polycyclic compounds (**Scheme 11-13)**.[23]



Scheme 11: Synthesis of 7-oxabenzonorbornadiene **44**.



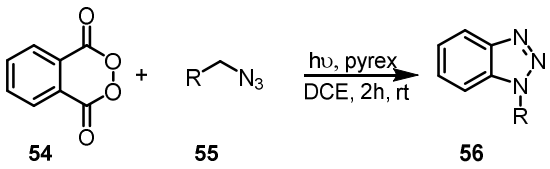
Scheme 12: Synthesis of isoquinolines by aryne aza-Diels-Alder Reaction.



Scheme 13: Two aryne Diels-Alder.

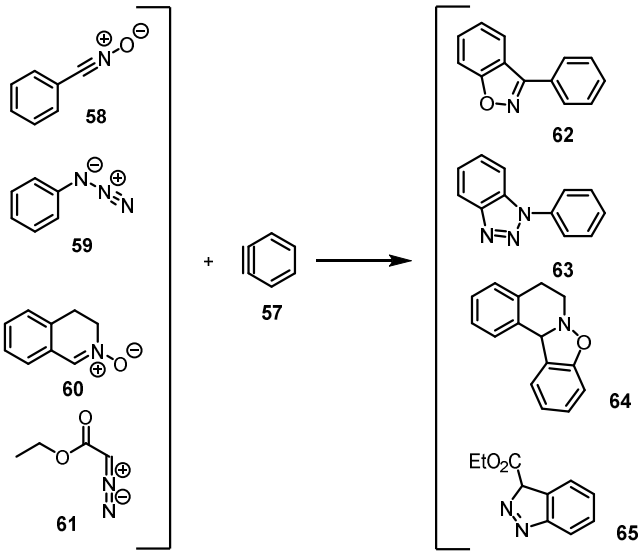
[3+2] Cycloadditions

Shi *et al*[24] employed photolytic method for generation of arynes from phthaloyl peroxides **54** which then reacted with azide **55** to provide benzotriazoles **56 (Scheme 14).**



Scheme 14:Synthesis of Benzotriazoles.

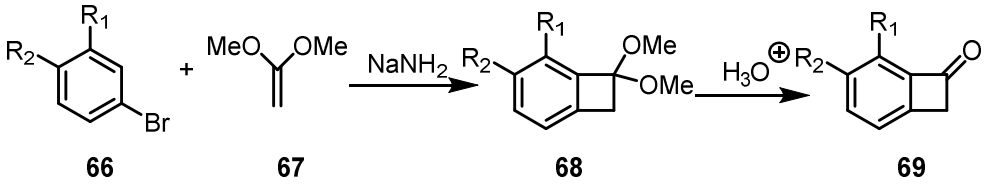
Using 1,3 dipoles like nitrile oxides[25a] **(58)**, azides[25b] **(59)**, nitrones[25c] **(60)** and diazoalkanes[25d] **(61)** several other heterocyclic aromatic compounds **(62-65)** were also synthesized (**Scheme 15)**.



Scheme 15: [3+2] cycloadditions of aryne **57** with 1,3-dipoles.

[2+2] cycloadditions

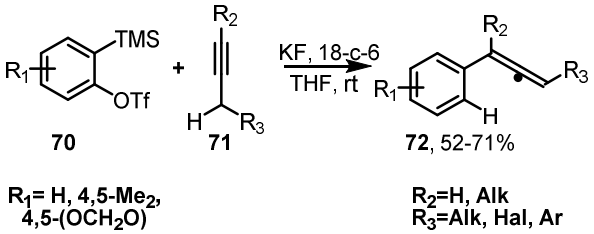
Aryne chemistry was involved in the synthesis of benzocyclobutenes **68** which on acid hydrolysis furnished corresponding ketone **69**. This reaction has been successfully employed to synthesize important intermediates in the synthesis of natural products like taxodione[26], xylopinine[27]and also in steroid synthesis[28].



Scheme 16: Facile access to benzocyclobutenes

Ene reactions of arynes

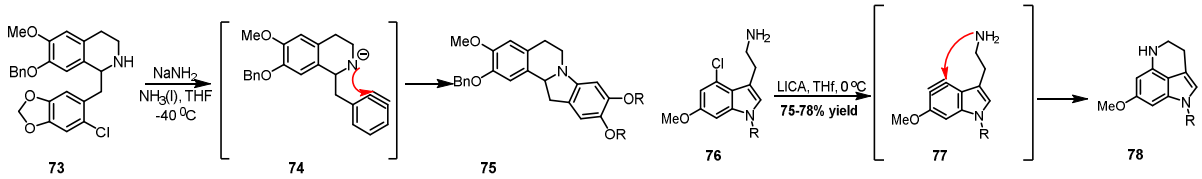
Aryne served as a reactive intermediate in the synthesis of allene **72** when reacted with alkyne **71.** In addition to allene compounds, this reaction also serves as important tool to synthesize various phenanthrene, phenylallene and phenylalkyne derivatives.[29]



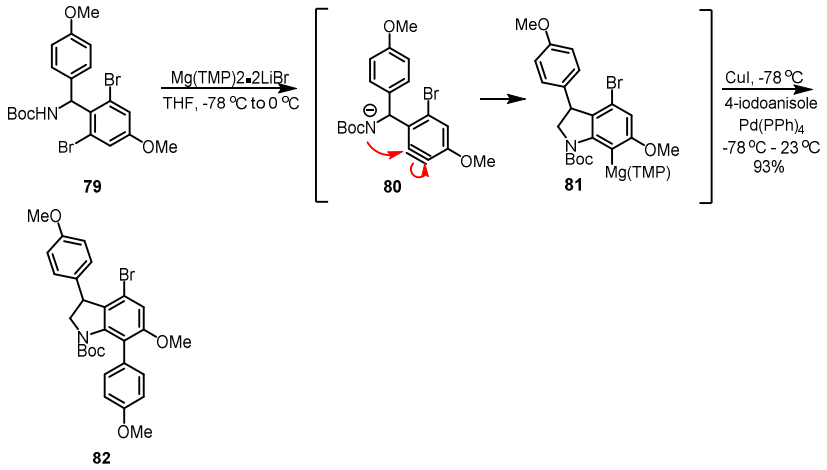
Scheme 17: Ene reaction of arynes with alkynes.

Annulation reactions of arynes

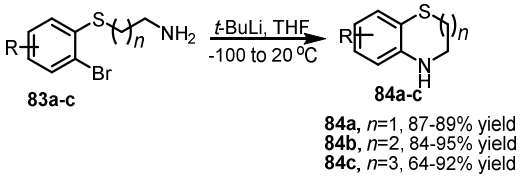
Aryne intermediate has been successfully utilised in the synthesis of 4-, 5- or 6-membered ring systems through annulation process. Various annulation reactions ([2+2], [3+2] and [4+2]) of arynes serve important in several heterocycles like indolinoisioquinolines[30] **(75)**, 4-aminoindoles[31] **(78),** indolines [32]**(82)** , benzothiazines , benzothiazepines, benzothiazocines (**84a-b** resp.),[32] tetrahydroquinoxalines, benzoxazines, benzothiazines and many more (**Schemes 18-22**).[33]



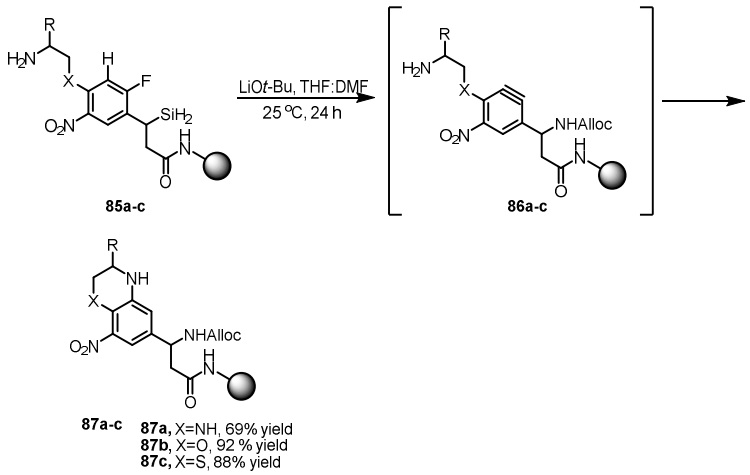
Scheme 18: Synthesis of indolinoisioquinolines **Scheme 19:** Synthesis of aminoindoles



Scheme 20: Synthesis of indolines



Scheme 21: benzothiazines **84a**, benzothiazepines **84b**, benzothiazocines **84c**



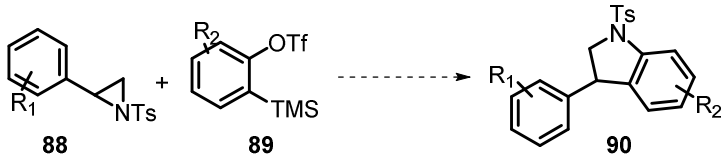
Scheme 22: tetrahydroquinoxalines **87a** , benzoxazines **87b**, benzothiazines **87c.**

3.3: PRESENT WORK

Objective

In our undertaking for the synthesis of heterocycles, we have developed numerous strategies towards synthesis of oxacycles like lactones and cyclic ethers.[34] With tremendous success achieved in this endeavour, we directed our attention towards synthesis of azacycles which are of commercial importance. While surfing through a sea of heterocyclic chemistry based literature, we found that indoline based compounds that are naturally occurring as well as synthetically prepared could be an interesting target. Indolines have been known to be an important moiety occurring in many natural products as well as other synthetic compounds of commercial importance.[1-9] Due to availibilty of limited methods to access indolines, out of which many are transition metal based and multi step synthesis, we aimed our attention for developing a transition metal free and one step approach for the same.

With indolines as our target, we started searching for an ammenable and milder approach for the synthesis of same. With greater delight we discovered that aryne chemistry can be explored for the synthesis of indolines, as previous reports supported our proposed approach. In earlier reports chemist have utilised arynes for the synthesis of numerous *N*-heterocycles.[19]



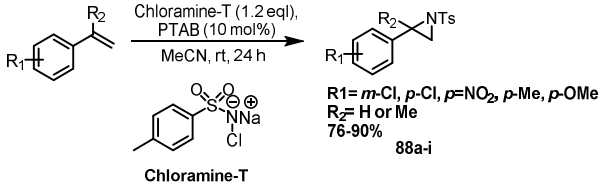
88 89 90

Scheme 23: Proposed strategy for the synthesis of phenyl indolines

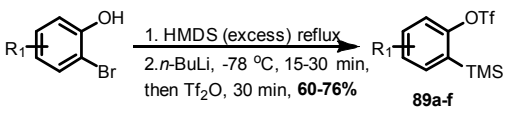
3.4: Results and Discussion

As depicted in scheme **23**, we considered exploring the reaction of aryne derived from **89** with *N*-tosyl phenyl aziridines **88** we envisaged that the use of suitable reagents and optimal reaction condition could lead to the substituted phenyl indoline **90**. Our strategy describes in situ generation of reactive aryne intermediate using excess of CsF, which then reacts with preformed *N*-tosyl phenyl aziridines to furnish indoline. For this purpose we synthesized various 2-(trimethylsilyl) phenyl trifluoromethanesulfonates and *N*-tosyl phenyl aziridines. 2-(trimethylsilyl) phenyl trifluoromethanesulfonates were prepared from appropriate 2-bromo phenols

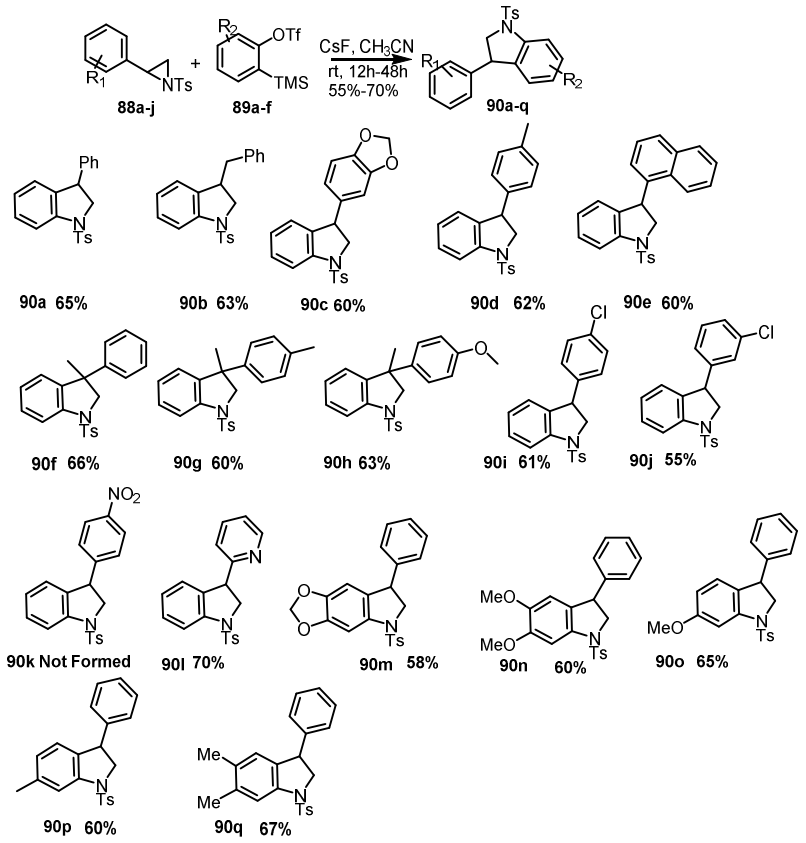
following a known procedure (**Scheme 25**).[35] These 2-(trimethylsilyl) phenyl trifluoromethanesulfonates served as aryne precursor to generate the desirable reactive aryne intermediates in presence of excess of CsF. Also for *N*-tosyl phenyl aziridines, using substituted styrenes as starting materials and reacting them with chloramine-T/PTAB we were able to prepare the required *N*-tosyl phenyl aziridines (**Scheme 24**).[36] Having the two reacting partners in hands we applied our strategy to the synthesis of indolines. For model reaction we employed *N*-tosyl phenyl aziridine (1.0 eq) and 2-(trimethylsilyl) phenyl trifluoromethanesulfonate (1.2 eq) as reacting partners and employed CsF (5 eq) as a fluoride source. The desired product obtained was purified by column chromatography (25%EtOAc:75% Pet ether) and was characterised by ^{1}H and ^{13}C spectroscopy. To our delight we were able to isolate desired products in good to moderate yields (55-70%, **Scheme 24)**. The products were characterised by ^{1}H, ^{13}C NMR and Mass spectroscopy (δ= 3.77, 2.99, 2.40 ppm for -C-H, **90a**). The reaction was successful with a variety of substitution for both 2-(trimethylsilyl) phenyl trifluoromethanesulfonates and *N*-tosyl phenyl aziridines with the exception of *N*-tosyl 4-nitrophenyl aziridine . Also *N*-tosyl pyridyl aziridine provided the desired product. The reasons behind *N*-tosyl 4-nitrophenyl aziridine not providing the desired product cannot be fully explained yet and necessary studies are ongoing in this direction. Besides *N*-tosyl phenyl aziridines, the reaction of *N*-tosyl 1-napthyl aziridines with 2-(trimethylsilyl) phenyl trifluoromethanesulfonates also provided the same result and desired product was obtained in good yields (60%).



Scheme 24: Synthesis of N-Tosyl Aziridines



Scheme 25: Synthesis of Aryl TMS triflates



Scheme 26: Synthesis of 3-aryl indolines

3.5: Conclusion

In summary we have successfully applied single step and transition metal free approach for the synthesis of 3-aryl indolines. The strategy employs easily accessible 2-(trimethylsilyl) phenyl trifluoromethanesulfonates and *N*-tosyl phenyl aziridines as reacting partners using CsF as fluoride source for generation of reactive aryne intermediates. By varying substituents on both the partners, it is possible to synthesize a library of 3-aryl indolines. The strategy can also help to access more complex 3-substituted indoline scaffold required in multi step synthesis. As the reaction conditions are milder and display large functional group tolerance, this method can be used as a general reaction for preparing 3-substituted indolines using appropriate starting materials.

3.6: Experimental

General Information: All reactions were carried out under argon or nitrogen in oven-dried glassware using standard gas-light syringes, cannulas and septa. Solvents and reagents were purified and dried by standard methods prior to use. Optical rotations were measured at room temperature. IR spectra were recorded on an FT-IR instrument. ^{1}H NMR spectra were recorded on 200 MHz, 400 MHz and 500 MHz and are reported in parts per million (δ) downfield relative to $CDCl_3$ as internal standard and ^{13}C NMR spectra were recorded at 50 MHz, 100 MHz and 125 MHz and assigned in parts per million (δ) relative to $CDCl_3$. Column chromatography was performed on silica gel (100-200 and 230-400 mesh) using a mixture of petroleum ether and ethyl acetate as the eluent.

General method of preparation of 88a-i: A mixture of styrene (3 mmol) and the chloramine-T (3.3 mmol) in 15 ml of acetonitrile was added to phenyltrimethylammonium tribromide (0.3 mmol) at room temperature and the resulting mixture stirred for 12 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated and filtered through a short column of silica gel (20-50% EtOAc:80-50% pet ether). The isolated product was confirmed by ^{1}H, ^{13}C NMR and Mass spectroscopy (δ= 3.77, 2.98, 2.38 ppm for azirdine ring protons, **88a**).

Preparation of 88j: The compound was synthesized using (±)- phenyl alanine as starting material following a procedure reported by Craig *et al*.[37]

General procedure for ortho-trialkylsilylaryl triflates 89a-h: A mixture of ortho-bromohydroxyarene (11.6 mmol) and HMDS (excess, 10 eq) in THF (4 ml) was refluxed for 90 minutes. The solvent was evaporated under reduced pressure and the residue was subjected to vacuum to remove excess NH_3 and unreacted HMDS. After ^{1}H NMR confirmation of the quantitative formation of the corresponding silyl ether, the crude product was dissolved in THF (15 ml), the solution was cooled to -100 °C and *n*-BuLi (1.6 M in hexane, 14 ml, 23 mmol) was added drop wise. The mixture was stirred for 20 min while the temperature reached to -80 °C. Then the mixture was again cooled to -100 °C, Tf_2O (4.0 ml, 23 mmol) was added drop wise and stirring was continued for 20 min while the temperature reached to -80 °C. Cold

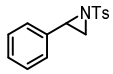
sat. aq. $NaHCO_3$ was added, the phases were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (silica, hexane/EtOAc) afforded silyl triflate ^1H, ^{13}C NMR and Mass spectroscopy (δ= 118.7, -0.6 for S-C-F and -Si-C resp., **89a**).

General method of preparation of 90a-q: To a solution of N-tosyl aziridine **88** (0.100 g) in dry CH_3CN (3 ml/mmol) was added ortho-trialkylsilylaryl triflates **89** (1.2 eq) and CsF (5 eq) and the mixture was stirred under argon for 12-48 h until complete consumption of **88**. The progress of reaction was monitored by TLC. Upon completion of reaction, the reaction was passed through celite to provide clear solution and the celite was washed with EtOAc (3x10 ml) to remove any organic residue. The solution was concentrated under vacuum and the residue was purified by column chromatography (25% to 50% EtOAc: 75% to 50% pet ether) to provide **90**.

Spectral data for selected compounds

Analytical data of *N*- (p-Tolylsulfonyl)-2- aryl aziridines[38]

2-Phenyl-1-tosylaziridine (88a)



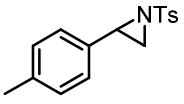
White solid**, Mp:** 90-92^{o}C (lit. mp 88-89^{o}C)[38]

^{1}H NMR (CDCI3, 400 MHz): δ 7.86 (d, , J = 8.3 Hz, 2H), 7.27 (m, 7H) 3.77 (dd, ,J=7.2 Hz, J= 4.5 Hz, 1H), 2.98 (d, J = 7.8 Hz, 1H), 2.43 (s, 3H), 2.38 (d, 1H, J = 4.4 Hz,)

^{13}C NMR (CDCI3, 101 MHz): δ 144.5, 134.9, 129.6, 28.4, 128.1, 27.8, 126.4,40.9, 35.7, 21.4

MS-ESI [M + Na^+]$^+$: m/z 296.11

***N*- (p-Tolylsulfonyl) - 2- (p-methylphenyl) aziridine (88b)**



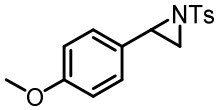
White solid**, Mp:**134-136 ^{o}C; (lit=136-137 ^{o}C)[38]

^{1}H NMR ($CDCl_3$, 500 MHz): δ= 7.86 (d, J = 8.3 Hz, 2H,), 7.31 (d, J = 7.9 Hz, 2H), 7.09 (s, 4H,), 3.73 (dd, *J* = 7.2 Hz, *J*= 4.5 Hz, 1H,), 2.96 (d, *J* = 7.2 Hz, 1H), 2.42 (s, 3H,), 2.36 (d, *J* = 4.5 Hz, 1H), 2.3 (s, 3H,)

^{13}C NMR ($CDCl_3$,125 MHz):δ= 144.4,138.0, 135.1, 132.0, 129.6, 129.1, 127.8, 126.4, 41.0, 35.6, 21.5, 21.0.

MS-ESI [M + Na^+]$^+$: m/z 310.09

***N*- (p-Tolylsulfonyl)-2- (p-methoxyphenyl) aziridine (88c)**



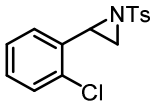
White solid, **Mp:** 85-87 ^{o}C, (lit=87-88 ^{o}C)[38]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.85 (d, J = 8.4 Hz, 2H), 7.33-7.31 (m, 2H), 7.12 (d, J = 8.4 Hz, 2H), 6.82-6.80 (m, 2H), 3.77 (s, 3H), 3.73 (dd, J = 6.8, 4.4 Hz, 1H), 2.95 (d, J = 6.8 Hz, 1H), 2.43 (s, 3H), 2.37 (d, J = 4.4 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 159.8, 144.7, 135.2, 129.9, 128.0, 127.9, 127.1, 114.1, 55.4, 41.1, 35.9, 21.8. 1161.

MS-ESI [M + Na^+]$^+$: m/z 326.38

***N*- (p-Tolylsulfonyl)-2- (p-chlorophenyl)aziridine (88d)**



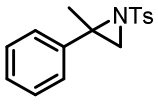
White solid, **Mp:** 115-116 ^{o}C

^{1}H NMR ($CDCl_3$,200MHz): δ = 7.91 (d, *J*=8.3 Hz, 2 H), 7.22 - 7.42 (m, 5 H), 7.15 - 7.22 (m, 2 H), 4.05 (dd, *J*=7.2, 4.4 Hz, 1 H), 3.04 (d, *J*=7.2 Hz, 1 H), 2.46 (s, 3 H), 2.30 ppm (d, *J*=4.3 Hz, 1 H)

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 145.0, 134.7, 133.9, 133.2, 129.9, 129.4, 129.3, 128.2, 127.6, 127.1, 39.1, 35.8, 21.8.

MS-ESI (M + Na^+)$^+$: m/z 330.09

2-Methyl-2-phenyl-1-tosylaziridine (88e)



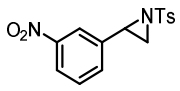
White solid, **Mp:**133-135 ^{o}C

^{1}H NMR (CDCl3, 400 MHz): δ = 7.87 (d, J = 6.8 Hz, 2H), 7.39-7.24 (m, 7H), 2.96 (s, 1H), 2.52 (s, 1H), 2.43 (s, 3H), 2.05 (s, 3H).

^{13}C NMR (CDCl3, 100.6 MHz): δ = 144.1, 141.1, 137.8, 129.7, 128.5, 127.9, 127.6, 126.7, 52.0, 42.0, 21.8, 21.1.

MS-ESI (M + Na^+)$^+$: m/z 310.19

3-Nitro-2-phenyl-1-tosylaziridine (88f)



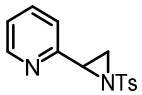
Yellow solid. **Mp:** 118-120 ^{o}C

^{1}H NMR ($CDCl_3$, 200MHz): δ = 8.15 (ddd, *J*=8.0, 2.3, 1.4 Hz, 1H), 8.06 (t, *J*=2.0 Hz, 1 H), 7.84 - 7.94 (m, 2 H), 7.56 - 7.65 (m, 1 H), 7.43 - 7.55 (m, 1 H), 7.38 (d, *J*=8.0 Hz, 2 H), 3.86 (dd, *J*=7.2, 4.3 Hz, 1H), 3.05 (d, *J*=7.1 Hz, 1 H), 2.46 (s, 3 H), 2.41 ppm (d, *J*=4.3 Hz, 1 H)

^{13}C NMR ($CDCl_3$,101MHz): □ = 148.4, 145.2, 137.5, 134.4, 132.8, 129.9, 129.7, 128.0, 123.3, 121.5, 77.3, 76.7, 39.5, 36.4, 21.7 ppm.

MS-ESI [M + Na^+]$^+$: m/z 341.07

3-(1-Tosylaziridin-2-yl) pyridine (88g)



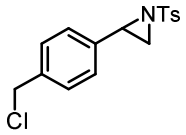
White solid. **Mp:** 122-123 ^{o}C

^{1}H NMR ($CDCl_3$, 200MHz): δ = 8.28 - 8.84 (m, 1 H), 7.77 - 7.97 (m, 2 H), 7.64 (td, *J*=7.7, 1.8 Hz, 1 H), 7.20 - 7.41 (m, 4 H), 3.91 (dd, *J*=7.2, 4.4 Hz, 1 H), 2.98 (d, *J*=7.2 Hz, 1 H), 2.67 (d, *J*=4.4 Hz, 1 H), 2.44 ppm (s, 3 H)

^{13}C NMR ($CDCl_3$, 50MHz): δ = 149.6, 136.8, 129.7, 128.1, 123.3, 121.7, 77.6, 76.4, 41.3, 35.0, 21.6 ppm

MS-ESI [M + Na^+]$^+$: m/z 297.34

2-(4-(Chloromethyl)phenyl)-1-tosylaziridine (88h)



White solid, **Mp:** 102-104 ^{o}C, (lit=101-103 ^{o}C)[38]

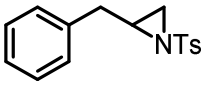
^{1}H NMR ($CDCl_3$, 200MHz): δ = 7.82 - 7.95 (m, 2 H), 7.28 - 7.47 (m, 5 H), 7.15 - 7.28 (m, 2 H), 4.50 - 4.63 (m, 2 H), 4.13 (q, *J*=7.1 Hz, 1 H), 3.45 - 3.86 (m, 1 H), 2.92 - 3.06 (m, 1 H), 2.45 (s, 3 H), 2.34 - 2.41 (m, 1 H)

^{13}C NMR ($CDCl_3$, 100MHz): δ= 138, 129.7, 128.8, 128, 127.9, 126.9, 126.8, 45.7, 40.5,

36.0, 21.6

MS-ESI [M + Na^+]$^+$: m/z 343.21

N-Tosyl-benzylaziridine (88i)



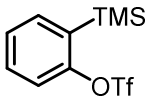
^{1}H NMR ($CDCl_3$, 400 MHz):δ= 7.20 and 7.69 (2d, J = 8.4 Hz, 2 H each) 7.00-7.08, 7.12-7.18 (2m, 5 H), 2.95 (m,1 H), 2.81 (dd, J= 14.4, 5.2 Hz,1 H), 2.71 (d, J=6.8 Hz, 1 H), 2.68 (dd, J=14.4, 7.2 Hz, 1 H), 2.42 (s., 3 H), 2.16 (d, J = 4.4 Hz, 1 H)

^{13}C NMR ($CDCl_3$, 400 MHz):δ= 144.2, 136.9, 134.8, 129.5, 128.6, 128.3, 127.7, 126.4, 41.1, 37.4, 32.7, 21.5,

MS-ESI [M^+ + 1]$^+$: m/z 288

Spectral data for aryl trimethyl sulfonates[35]

2-(Trimethylsilyl)aryl Trifluoromethanesulfonate (89a)



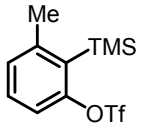
Colorless oil

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.56 (dd, J = 7.5, 2.0 Hz, 1H), 7.46 (m, 1H), 7.36 (m, 2H), 0.40 (s, 9H) ppm

^{13}C NMR ($CDCl_3$,125 MHz): δ 155.3, 136.5, 132.8, 131.5, 127.7, 119.7, 118.7 (q, *J* = 318 Hz, CF3), -0.6 ppm

MS-ESI [M + Na^+]$^+$: 311.09

2-Methyl-6-(trimethylsilyl)phenyl Trifluoromethanesulfonate(89b)



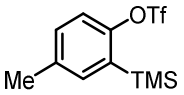
Yellow oil

^{1}H NMR ($CDCl_3$, 200MHz): δ = 7.23 - 7.41 (m, 3 H), 2.40 - 2.46 (m, 3 H), 0.41 - 0.46 ppm (m, 9 H) ppm

^{13}C NMR ($CDCl_3$, 126 MHz,): δ 151.1, 134.8, 134.5, 133.7, 131.4, 127.9, 118.6 (q, *J*C−F = 319.8 Hz), 17.3, 0.1.ppm

MS-ESI [M + Na^+]$^+$: m/z 235.40

4, -Methyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (89c)



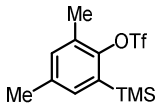
Yellow oil

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.31 (s, 1 H), 7.22 (s, 2 H), 2.38 (s, 3 H), 0.38 (s, 9 H) ppm

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 153.1 (3 d), 137.2, 136.7, 132.2, 131.7, 119.3, 118.5 (q, *J* = 320 Hz, CF3), 20.8 (q), -0.8 (q,) ppm.

MS-ESI (M + Na^+)$^+$: m/z 235.35

2,4-Dimethyl-6-(trimethylsilyl)phenyl trifluoromethanesulfonate (89d)

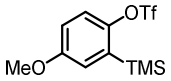


^{1}H NMR ($CDCl_3$, 400 MHz): 7.18 (br. s), 7.10 (br. s, 1 H), 2.35 (s, 3 H), 2.34 (s, 3), δ = 0.39 (s, 9 H)ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 149.1, 137.6, 135.0 (d), 134.3 (d), 134.3, 130.9, 118.7 (q, *J* = 320 Hz, CF3), 20.7 (q), 17.2 (q) 0.1(q, 9H) ppm

MS-ESI [M + Na^+]$^+$: m/z 349.43

4-Methoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (89e)



Yellow liquid.

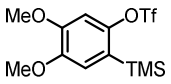
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.25 (d, *J* = 9.1 Hz, 1 H), 7.01 (d, *J* = 3.2 Hz, 1 H), 6.90 (dd, *J* = 9.1, 1 H), 3.82 (s, 3 H), 0.37 (s, 9 H)

^{13}C NMR ($CDCl_3$,100 MHz,): δ = 158.1, 148.3, 134.2, 121.5, 120.8, (2 d), 118.5 (q, *J* =

320 Hz, CF3), 113.7 (d, Ar), 55.6 (q) -0.9 (q) ppm

MS-ESI [M + Na$^+$]$^+$: m/z 351.04

4,5-Dimethoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (88f)

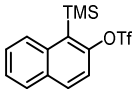


Yellow liquid

^{1}H NMR ($CDCl_3$, 200MHz): δ = 6.40 (d, *J*=1.9 Hz, 1 H), 6.50 (d, *J*=1.9 Hz, 1 H), 3.81 (d, *J*=3.8 Hz, 6 H), 0.34 ppm (s, 9 H)

MS-ESI [M + Na$^+$]$^+$: m/z 381.14

1-(Trimethylsilyl)-2-naphthyl trifluoromethanesulfonate (89g)



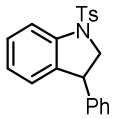
^{1}H NMR ($CDCl_3$, 200MHz): δ = 8.12 - 8.39 (m, 1 H), 7.77 - 8.06 (m, 2 H), 7.51 - 7.70 (m, 2 H), 7.33 - 7.51 (m, 1 H), 0.58 - 0.70 (m, 9 H) ppm

^{13}C NMR ($CDCl_3$, 50MHz): δ = 152.5, 137.5, 132.4, 132.4, 129.3, 129.0, 128.8, 126.6, 126.2, 119.1, 2.2 ppm

MS-ESI [M + Na$^+$]$^+$: m/z 371.16

Spectral data of 3-aryl indolines

3-Phenyl-1-tosylindoline (90a)



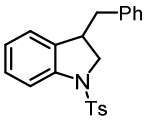
Yellow Solid, **Mp:** 85-87 ^{o}C

^{1}H NMR ($CDCl_3$, 200MHz): δ = 7.88 (d, *J*=8.3 Hz, 2 H), 7.18 - 7.40 (m, 11 H), 3.78 (dd, *J*=4.5 Hz, 1 H), 2.99 (d, *J*=7.2 Hz, 1 H), 2.44 (s, 3 H), 2.40 ppm (d, *J*=4.5 Hz, 1 H)

^{13}C NMR ($CDCl_3$, 50MHz): δ = 144.0, 142.6, 141.8, 134.9, 133.9, 129.7, 128.5, 128.3, 127.9, 127.5, 126.6, 114.7, 41.0, 35.9, 21.6 ppm

MS-ESI [M + Na^+]$^+$: m/z 372.11

3-Benzyl-1-tosylindoline (90b)



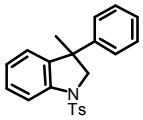
Yellow Solid, **Mp:**105-107 ^{o}C

^{1}H NMR ($CDCl_3$,200MHz): δ = 7.69 (d, *J*=8.2 Hz, 2 H), 7.08 - 7.49 (m, 9 H), 6.84 - 7.08 (m, 2 H), 2.82 - 3.05 (m, 2 H), 2.68 - 2.81 (m, 2 H), 2.43 (s, 3 H), 2.17 (d, *J*=4.4 Hz, 1 H) ppm

^{13}C NMR ($CDCl_3$,50MHz): δ = 145.9, 143.7, 142.0, 137.0, 129.6, 128.7, 128.4, 127.9, 126.5, 115.5, 41.2, 37.5, 32.8, 21.6 ppm

MS-ESI [M + Na^+]$^+$: m/z 389. 43

3-Methyl-3-phenyl-1-tosylindoline (90f)



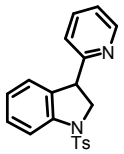
Yellow Solid, **Mp:** 107-109 ^{o}C

^{1}H NMR ($CDCl_3$,400MHz): δ = 7.60 (d, *J*=8.2 Hz, 1 H), 7.49 (d, *J*=7.8 Hz, 2 H), 7.37 - 7.40 (m, 1H), 7.26 - 7.35 (m, 7H), 7.23 - 7.26 (m, 1H), 7.19 - 7.23 (m, 2 H), 6.75 - 6.88 (m, 2 H), 5.29 (s, 1 H), 5.06 (s, 1 H), 4.64 (s, 1 H), 2.45 ppm (s, 3 H)

^{13}C NMR ($CDCl_3$,101MHz): δ = 143.5, 142.4, 141.5, 138.4, 138.1, 135.0, 129.5, 129.4, 129.2, 129.0, 128.7, 128.5, 128.3, 128.2, 128.0, 127.9, 127.8, 127.8, 127.7, 127.4, 126.5, 116.9, 77.3, 76.7, 54.3, 21.5 ppm

MS-ESI [M + Na^+]$^+$: m/z 389.13

3-(Pyridin-2-yl)-1-tosylindoline (90l)



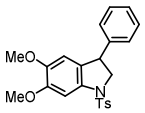
Orange yellow solid, **Mp:**125-127 ^oC

^{1}H NMR ($CDCl_3$, 400MHz): δ = 8.40 - 8.55 (m, 1 H), 7.82 (d, *J*=8.2 Hz, 2 H), 7.59 (td, *J*=7.7, 1.6 Hz, 1 H), 7.29 (s, 3 H), 7.18 - 7.25 (m, 2 H), 7.09 - 7.18 (m, 1H), 3.96 - 4.18 (m, 1 H), 3.86 (dd, *J*=7.1, 4.4 Hz, 1 H), 2.93 (dd, *J*=7.3, 0.9 Hz, 1 H), 2.54 - 2.68 (m, 1 H), 2.38 (s, 3 H) ppm

^{13}C NMR ($CDCl_3$, 101MHz): δ = 154.2, 149.6, 144.7, 136.8, 134.5, 129.7, 129.6, 128.1, 127.0, 126.4, 123.2, 121.7, 77.3, 76.7, 41.3, 35.0, 21.6, 21.5 ppm

MS-ESI [M + Na+]$^+$: m/z 373.17

5,6-Dimethoxy-3-phenyl-1-tosylindoline (90n)



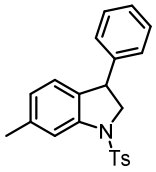
Yellow Solid, **Mp:**112-114 ^oC

^{1}H NMR ($CDCl_3$,200MHz): δ = 7.61 - 7.86 (m, 3 H), 7.42 - 7.60 (m, 3 H), 7.22 - 7.35 (m, 6 H), 7.08 - 7.21 (m, 1 H), 6.87 - 7.08 (m, 1 H), 6.39 - 6.58 (m, 1H), 5.99 (dd, *J*=7.0, 2.2 Hz, 1 H), 5.71 - 5.86 (m, 1 H), 5.45 (d, *J*=3.5 Hz, 1 H), 4.13 - 4.49 (m, 1 H), 3.77 - 4.02 (m, 3H), 3.73 (d, *J*=7.8 Hz, 3 H), 3.58 (s, 1 H), 3.34 - 3.53 (m, 1 H), 3.25 (br. s., 1 H), 2.47 - 2.52 ppm (m, 3 H)

^{13}C NMR ($CDCl_3$,50MHz): δ = 166.2, 162.5, 155.3, 121.8, 115.4, 112.0, 98.1, 97.3, 77.6, 76.4, 63.4, 55.5, 55.4, 52.8, 29.7 ppm

MS-ESI [M + Na^+]$^+$: m/z 432.16

6-methyl-3-phenyl-1-tosylindoline (90p)



Light Yellow solid, **Mp**=102-104 ^{o}C

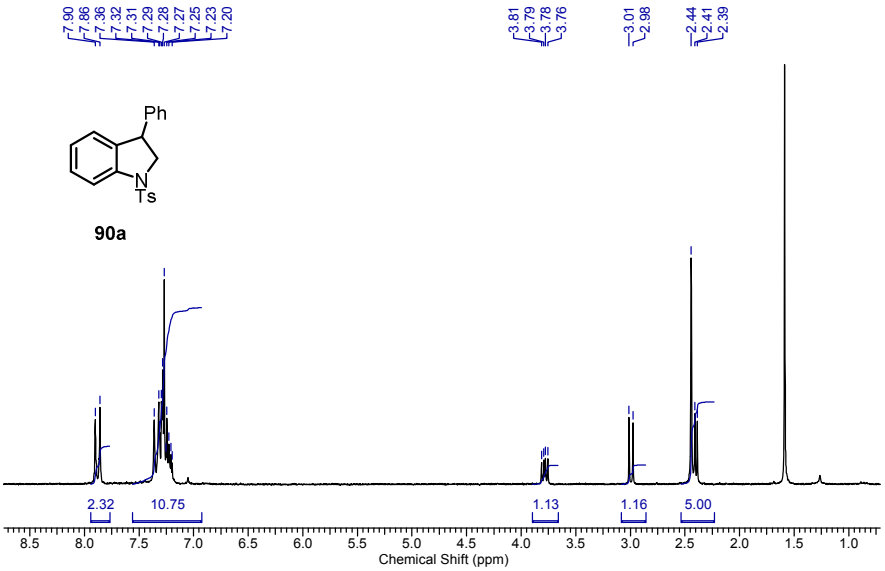
^{1}H NMR ($CDCl_3$, 200 MHz): = δ 7.67 - 7.76 (2 H, m) 7.28 (2 H, d, *J*=5.43 Hz), 7.20 (4 H, dd, *J*=6.57, 3.79 Hz), 7.04 - 7.09 (1 H, m), 7.10 (1 H, s), 2.86 - 3.06 (1 H, m), 2.65 - 2.84 (3 H, m), 2.46 (3 H, s), 2.20 (1 H, d, *J*=4.42 Hz) ppm

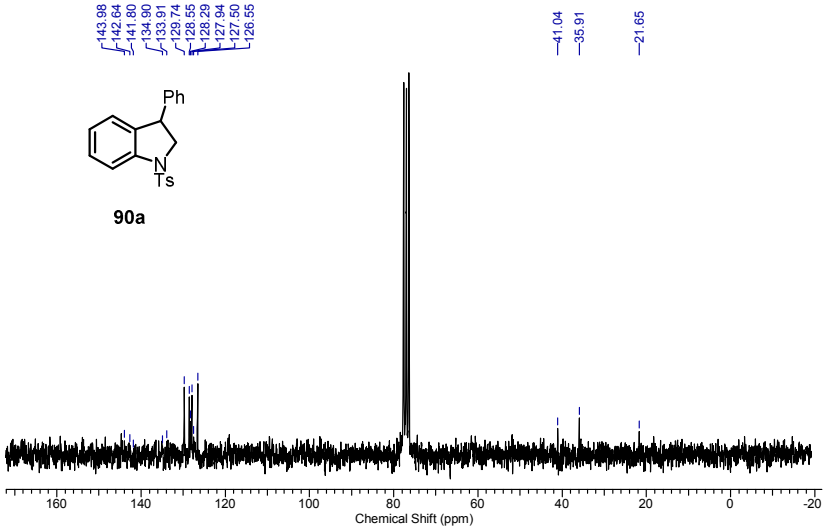
^{13}C NMR ($CDCl_3$, 50 MHz): δ 144.29,136.97, 129.56, 128.69, 128.42 127.84, 126.47, 41.16, 37.47, 32.80, 21.59 ppm

MS-ESI [M + Na^+]$^+$: m/z 386.15

3.7. Selected Spectra

Sr. No.	Contents
1	^{1}H and ^{13}C spectra of compound **90a**
2	^{1}H and ^{13}C spectra of compound **90 b**
3	^{1}H and ^{13}C spectra of compound **90f**
4	^{1}H and ^{13}C spectra of compound **90l**
5	^{1}H and ^{13}C Spectra of compound **90n**


7.90
7.86
7.36
7.32
7.31
7.29
7.28
7.27
7.25
7.23
7.20
3.81
3.79
3.78
3.76
3.01
2.98
2.44
2.41
2.39
Ph
N
Ts
90a
2.32
10.75
1.13
1.16
5.00
Chemical Shift (ppm)


143.98
142.64
141.80
134.90
133.91
129.74
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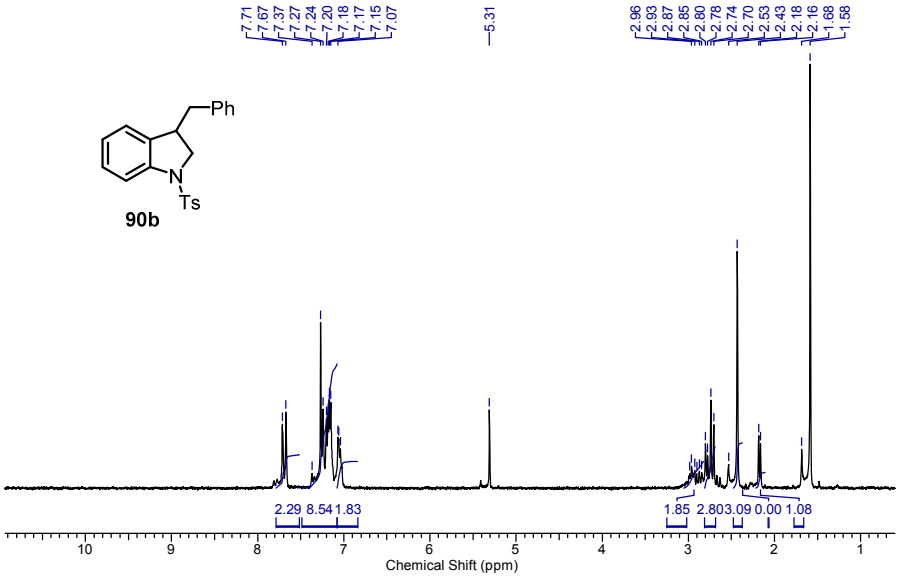
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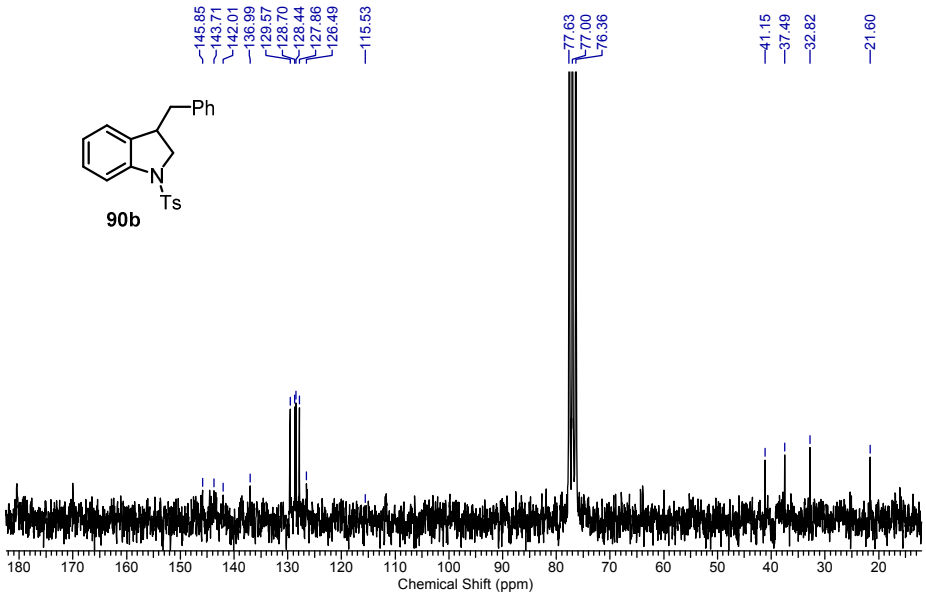
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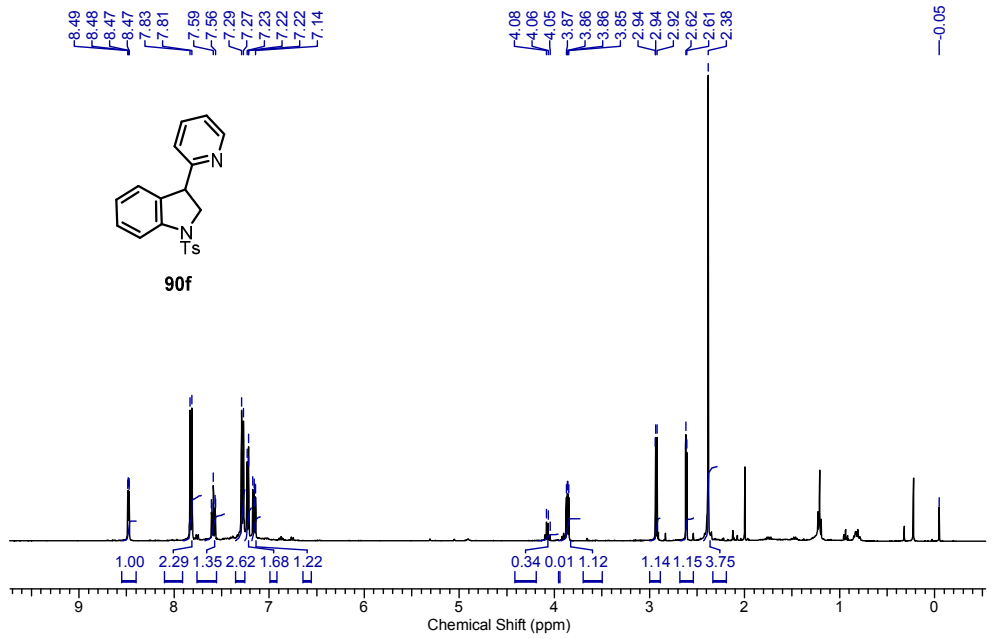
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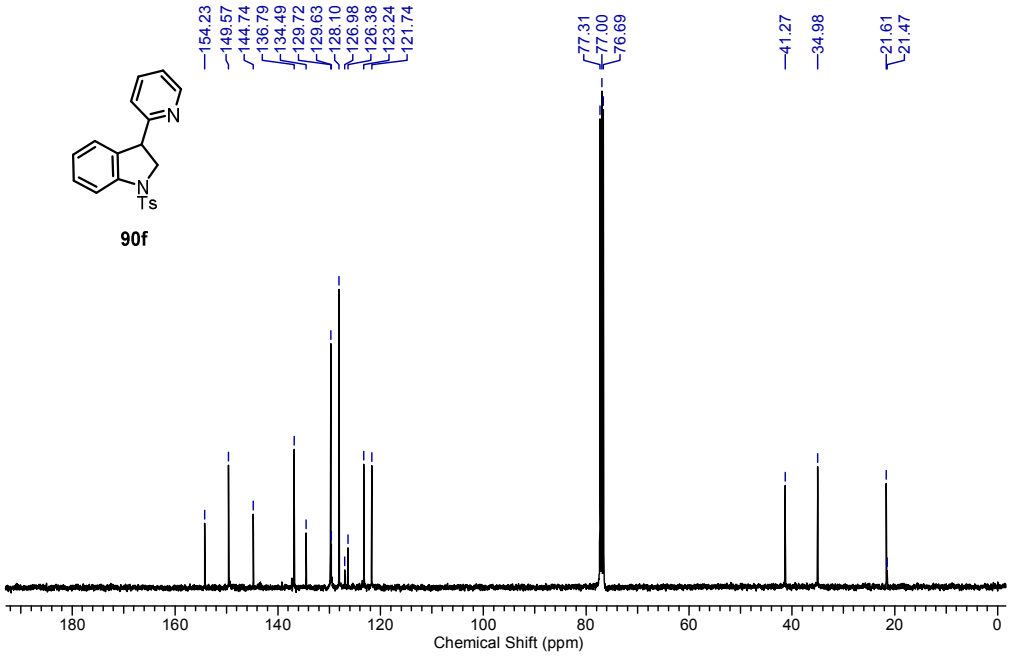
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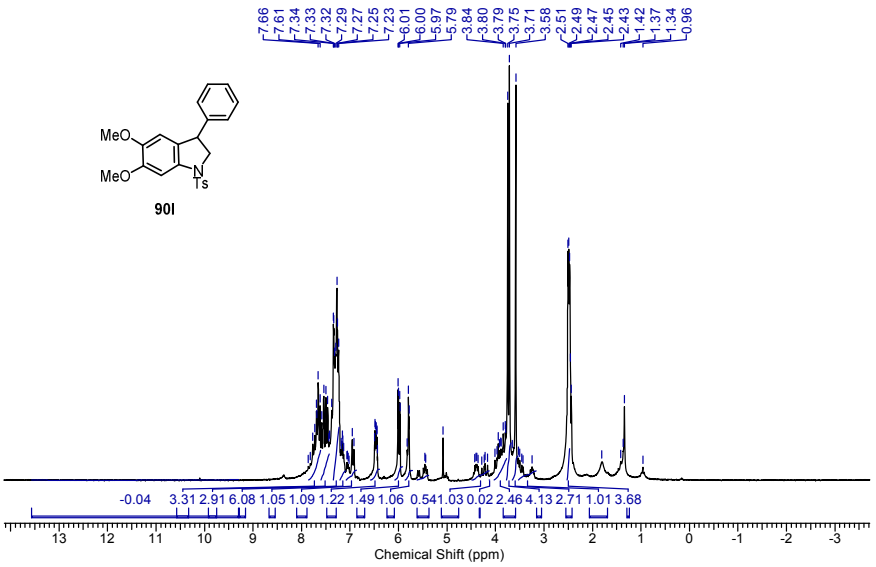
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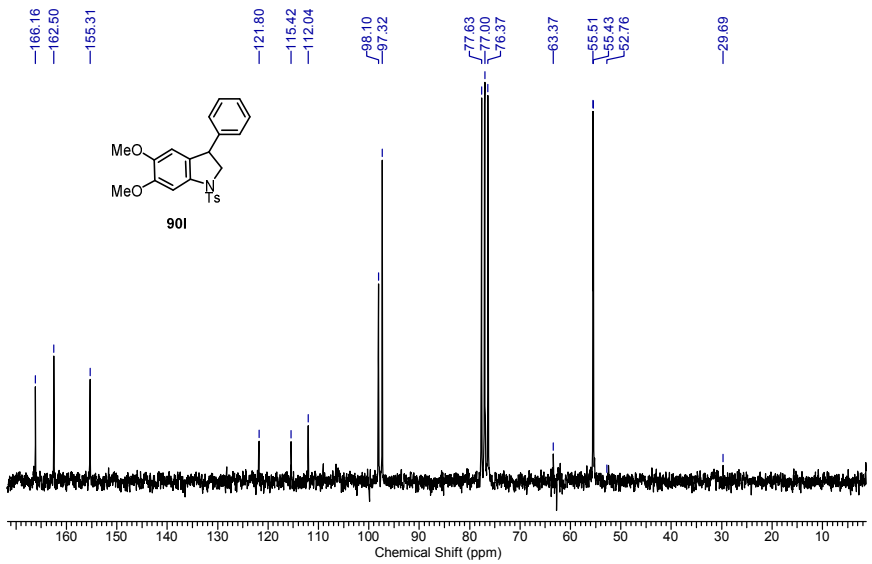
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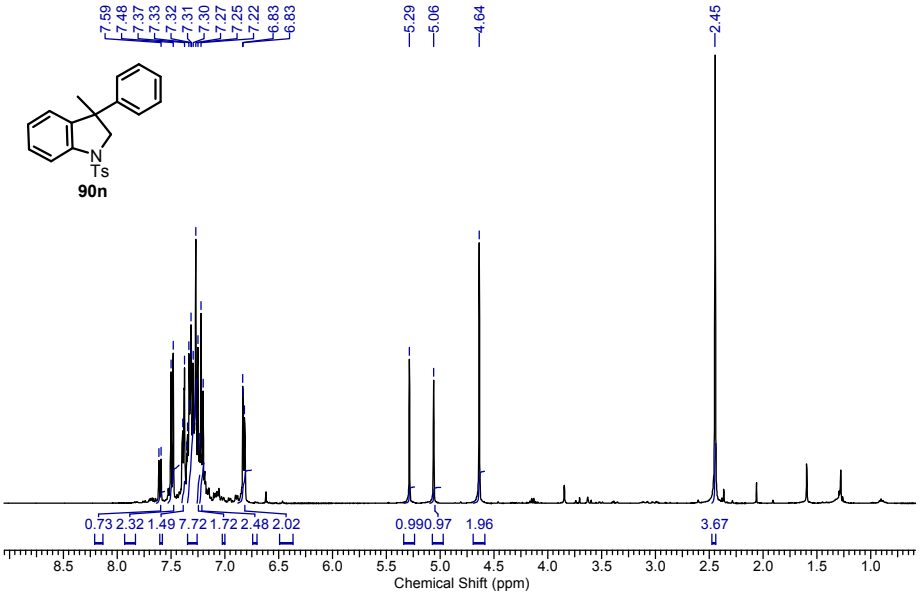
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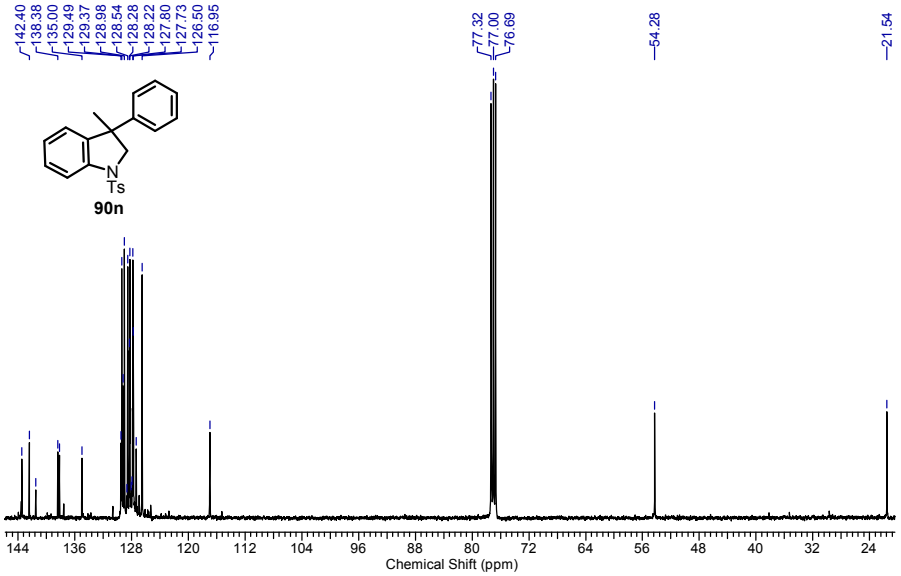
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CHAPTER-4

Pd-SBA-TAT catalyzed C-C Cross Coupling Reactions

4
Pd-SBA-TAT catalyzed C-C Cross Coupling Reactions

4.1. Introduction

C-C bond forming reactions remain the most widely explored area in the field of synthetic organic chemistry. The palladium catalyzed cross coupling reactions form an important class of C-C bond forming reactions. The products obtained lead to important intermediates which have varied applications in the field of pharmaceuticals, natural product synthesis, material chemistry and many more.[1] Although homogeneous palladium catalysts involving the use of phosphine ligands have been dominating the area for quite some time, the field of heterogeneous catalysis in recent times has emerged an important area in the palladium catalyzed carbon-carbon bond forming reactions.[2] The homogeneous palladium catalysis successfully delivers good reactivity and good yields of coupled product however it suffers from the drawback such as separation of products from catalyst and ligand, and also the palladium catalyst is expensive.[2]

Over the past few years researchers have been successful in synthesizing various heterogeneous palladium catalysts. These include palladium complexes anchored to various inorganic or organic supports like Pd/SiO_2,[3] Pd/C,[4] palladium/resin,[5] palladium/MgO,[6] Pd-montmorillonite,[7] Pd/Al_2O_3,[8] palladium incorporated zeolites,[9] SBA-15 supported palladium catalyst,[10] and many others.[11] These catalysts tend to catalyse only one kind of cross coupling reaction most of the times. Hence it becomes necessary to develop a robust and versatile catalyst which can be employed in most of the cross coupling reactions. In recent times ordered mesoporous materials have been utilized as a solid support in the synthesis of heterogeneous catalysts. Among these materials SBA-15 has triggered the interests of various researchers due to its high thermal stability, high surface areas, ease of accessibility and uniform pores size. The SBA-15 has added advantage that it can be suitably modified to develop various catalysts by functionalizing the organic hydroxyl groups and further the covalent bonding with inorganic support prevents the leaching of active site.

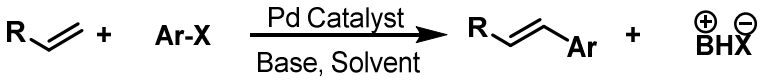
Singh and co-workers developed covalently anchored 2, 4, 6-Triallyloxy-1, 3, 5-triazine (TAT): Pd (II): complex over modified surface of SBA-15 for the hydrogenation of a variety of aromatic nitro and unsaturated compounds to their saturated counterparts.[12,13] The catalyst was found to be highly active for hydrogenation reaction under mild conditions. The

catalyst displayed high TON under low catalytic loading and the hydrogenation reaction was completed in shorter period of time.

4.1.1.1. A brief introduction to Heck, Suzuki, Sonogashira and Hiyama cross coupling reactions

Heck Reaction

The Heck reaction can be described as vinylation or arylation of olefins which involves reaction of aryl halide with acrylates, styrenes and compounds with intramolecular double bonds in presence of catalyst. Later on a different version of reaction was developed where along with aryl halides like aromatic triflates, aroyl chlorides, aryl sulfonyl chlorides, aromatic diazonium salts, aroyl anhydrides, aryl chlorides and arylsilanols were also employed. The reaction was discovered by Heck[14] and Mizoroki[15] independently four decades ago.



Scheme 1: General scheme for Heck reaction

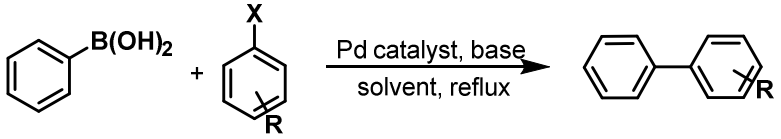
The preferred metal which is employed as catalyst in the reaction is usually palladium due to its property of tolerating a wide variety of functional groups and remarkable reactivity towards formation of C-C bond when appropriately functionalized substrates are involved.[16]

The greater functional group tolerance towards wide variety of substrates makes Heck reaction a versatile and robust tool for C-C bond formation. In addition to intermolecular, intramolecular Heck reaction is also employed for the construction of many compounds with quaternary and/or asymmetric carbon centres. Tremendous efforts have been invested in the development of palladium based methodologies, as a result different palladium catalyst are now available for both homogeneous and heterogeneous palladium catalysis.

Suzuki Reaction

Suzuki-Miayura reaction popularly known as Suzuki cross coupling reaction was discovered in 1979 by Suzuki and Miayura.[17] The reaction essentially involves coupling of aryl or vinyl boronic acid with aryl or vinyl halides and also with different reagents like alkenes,alkynes, amines, pseudohalides, metallorganic compounds etc. catalyzed by palladium (0): compounds. The Suzuki reaction has emerged as a powerful tool for C-C bond formation due

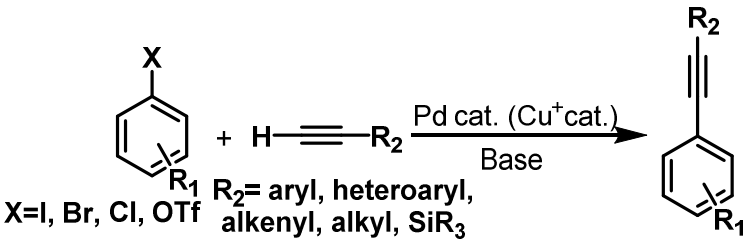
to its ability to provide desired products with excellent yields using readily available organoboron reagents, that are inert to water and related solvents, as well as oxygen, and generally thermally stable and tolerant toward various functional groups. These attractive features have led to extensive research dedicated to development of enhanced methodologies for the synthesis of not only simple coupled products but also complex compounds.[18]



Scheme 2: General scheme for Suzuki reaction

Sonogashira Coupling

The Sonogashira cross coupling reaction was discovered by Sonogashira and co-workers[19a] in 1975 on the basis of Stephans-Castro coupling[19b]. The original Sonogashira reaction is performed using acetylenes and aryl halides in presence of palladium and copper (I):iodide as a co-catalyst in organic solvents, that are environmentally benign and economical.Since its discovery Sonogashira reaction has served as a powerful tool for C-C bond formation over few decades.

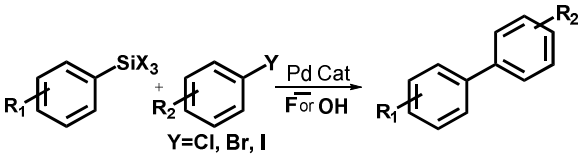


Scheme 3: General scheme for Sonogashira reaction.

Although tremendous research has already been dedicated towards development of improved methodologies, a significant amount of numerous modifications is still being discovered. These modifications include variety of additives,[20] solvents,[21] phase transfer catalysts,[22] copper-free versions,[23] heterogeneous versions,[23] polymer-supported Pd–triazine complex[24] and solid supported Pd catalyst.[25] Besides copper other metal salts like zinc, tin, boron and aluminium have also been reported.[26] In recent times microwave assisted Sonogashira reaction has also been discovered.[27] With numerous efforts devoted towards development of Sonogashira reaction, the reaction has emerged as an efficient tools for synthesis of heterocycles, several natural products and pharmaceuticals.[28]

Hiyama Coupling

Organosilicon compounds hold an important place in synthetic organic chemistry due to their stability, non-toxicity, and natural abundance of silicon. One such reaction which illustrates the significance of organosilicon chemistry is Hiyama coupling. The Hiyama coupling reaction involves synthesis of biaryl compounds using aryl iodides and aryl trialkoxy silanes in presence of palladium catalyst and fluoride source (or hydroxide): and was discovered by Hiyama and co-workers in 1988 (**Scheme 4)**.[29]



Scheme 4: General scheme for Hiyama Coupling

Since the discovery of Hiyama reaction lot of literature have been reported for the same which consists of different organosilicon compounds, different types of palladium catalysts and in some cases fluoride free Hiyama coupling.[30] With continual advancements in the methodologies, the Hiyama coupling has proven to be highly efficient and practical method for C-C bond formation giving access to variety of complex natural products.[31]

4.1.2. Heterogeneous Cataysis in C-C bond forming reactions: Efficient route to palladium catalyst recovery

Although there are numerous methods employed for carbon-carbon bond forming reactions involving homogeneous palladium catalysis, these methods suffer from drawbacks such as wastage of expensive palladium catalyst, contamination of final product with metal or ligand impurities and tedious separation of final product. Since the palladium catalysis is also employed on industrial level, it becomes important to obtain the final products in their purest form free from any aforementioned impurities. Also these products are used for pharmaceutical, cosmetic and food purpose contamination of final product by metal and ligand impurities becomes a major concern. Apart from these disadvantages of homogeneous palladium catalysis, the process also possesses threat to the environment since it is cost ineffective and laborious to get rid of the contamination caused by metal and ligand impurities.

In order to attenuate the undesirable effects of homogeneous palladium catalyst, heterogeneous palladium catalyst was first introduced in 1969 by Holland employing palladium incorporated zeolite for oxidation of methane.[32] Since then innumerable

heterogeneous palladium catalysts involving palladium anchored to various solid supports have been synthesised and reported for different palladium catalyzed reactions.[32] The immobilized catalytic system involving covalently anchored palladium to solid support provides an efficient way of metal transfer in reactions without any appreciable contamination of final product by metal. Besides, the heterogeneous catalyst can be recovered by simple hot filtration and reused without loss of catalytic activity.

4.1.3. 2, 4, 6-Triallyloxy-1, 3, 5-triazine (TAT): Pd (II): Complex over Modified Surface of SBA-15

Since the first report of SBA-15 in 1992 by Beck *et al.,* lot of applications of SBA-15 as mesoporous solid support for anchoring of palladium have been reported for various palladium catalyzed reactions.[33] SBA-15 is a mesoporous solid aluminosilicate material similar to that of zeolite but they have larger pore size as compared to zeolites. Depending on the intercalation process, SBA-15 can be synthesized with pore size ranging from 8nm to 50 nm. Under appropriate reaction conditions the materials with pore size as high as 16Å to 100Å have also been synthesized.[34] These solid materials have surface area 400–1500 m^2/g, this makes them well suited for adsorption, separation, optics and solid support for catalyst. The high internal surface area increases contact between reactants and products and the enhanced pore size facilitates exclusion and inclusion of materials of different size.[35] These interesting features of SBA-15 make the most explored solid support material for heterogeneous catalyst. A lot of heterogeneous catalyst system using SBA-15 has been reported since the first synthesis of mesoporous silicate materials. These include SBA-15 silica-supported potassium catalysts[36], tungstophosphoric acid supported on SBA[37], SBA-15-based polyamidoamine dendrimer tethered Wilkinson's rhodium complex[38], SBA-15 supported palladium catalyst[39,] SBA-15-supported metallocene [40], chromium and copper-modified SiO_2 and SBA-15[41], SBA-15 immobilized Ruthenium carbenes [42], chromium/santa barbara amorphous SBA-15 catalysts [43], Cr/nanosilica catalysts [44], the polydicyclopentadiene (PDCPD)/mesoporous mol. sieve SBA-15 composites [45] TiO_2 supported on SBA-15[46] SBA-15 supported FeW catalysts[47], Gold-ceria SBA-15-supported catalyst[48], Ni/SBA-15 catalyst[49], short-mesochannel SBA-15 supported quinine[50], MnxOy-Na_2WO_4/SiO_2 catalyst[51].

Although numerous mesoporous materials composing of inorganic oxides and inorganic-organic hybrid siliceous material have been explored for SBA-15 supported catalysts there is a lot of room left for exploration of organic framework based mesoporous materials. In 2011 Bhaumik *et al* reported synthesis of purely organic framework based mesoporous materials

applying surfactant template approach.[61] This material synthesized from polymerization of 2, 4, 6-triallyloxy-1, 3, 5-triazine was called MPTAT-1 and was used as support for immobilizing Pd (II): at its surface **(Figure 1)**. The heterogeneous catalyst derived from grafting of Pd (II): on MPTAT-1 was used as catalyst for Mizoroki–Heck, Sonogashira and Suzuki–Miyaura reactions. Since then lot of literature has been reported using polymeric 2, 4, 6-triallyloxy-1, 3, 5-triazine as an organic mesoporous material.[69-73] These materials are important from catalytic point of view as these have strong donor sites for active binding. The oxygen and nitrogen atoms present in these mesoporous materials act as excellent donors with multielectron transfer properties facilitating wide range of oxidation states making them excellent support for heterogeneous catalysts.

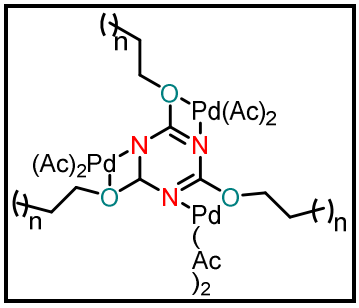


Figure 1: MPTAT-1

The synthesis of SBA-15-TAT-Pd (II): catalyst was carried out by the procedure described by Singh and co-workers.[31] The procedure involves stirring and refluxing a mixture of organofunctionalized SBA-15, 2, 4, 6 -triallyloxy-1, 3, 5-triazine and azobisisobutyronitrile (AIBN): (initiator): in DMF at 100 °C for 24h under nitrogen atmosphere. The solid obtained was filtered and purified by soxhlet extraction using DCM and then vacuum dried. For anchoring of palladium on triazine modified SBA-15, a solution of Pd (OAc):$_2$ and triazine modified SBA-15 in DMSO was stirred and resultant product was purified by washing with THF and soxhlet extraction using DCM. The catalyst was well characterised for its texture, structure of mesoporous channel and other physiochemical properties using analytical techniques such as CP-OES, XRD, N_2 sorption measurement isotherm, TGA & DTA, solid state ^{13}C, ^{29}Si NMR spectroscopy, FT-IR, XPS, DRS UV-Visible, SEM and TEM.[30, 31]

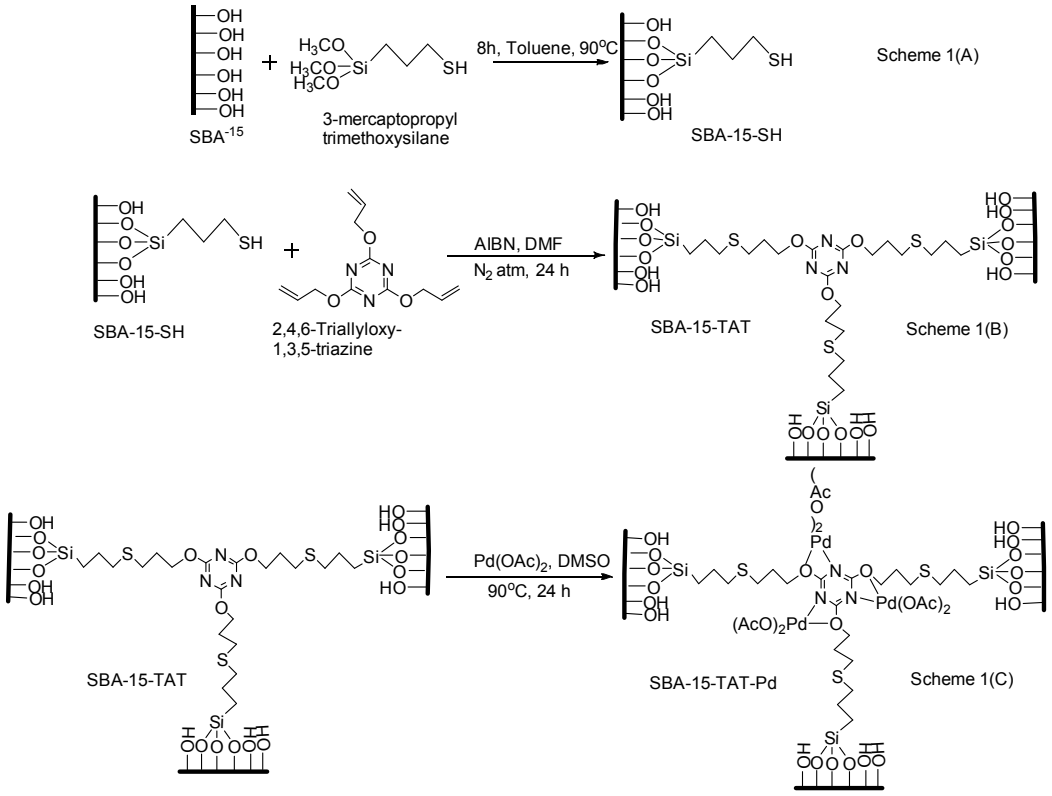


Figure 2: SBA-15-TAT-Pd (II): catalyst

4.2: PRESENT WORK

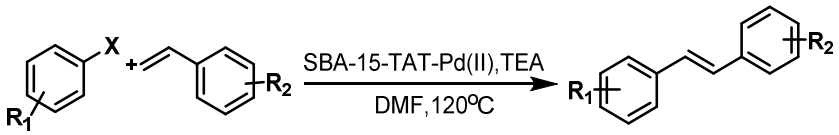
In this section we have investigated covalently anchored 2, 4, 6-triallyloxy-1, 3, 5-triazine Pd(II): complex over modified surface of SBA-15 for various carbon-carbon bond forming reactions such as Heck reaction, Suzuki-Miayura Coupling, Sonogashira Coupling and Hiyama Coupling.

4.3: Results and Discussion

4.3.1. Heck reaction using covalently anchored 2, 4, 6-triallyloxy-1, 3, 5-triazine Pd(II): Complex over modified surface of SBA-15

For the Heck coupling, the model reaction was carried using iodobenzene and ethyl acrylate as a starting materials using DMF as solvent and triethyl amine as base at 120^{o}C **(Scheme 5)**. Under this optimum reaction condition the reaction went smoothly to furnish the desired

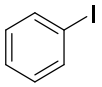
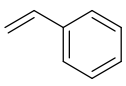
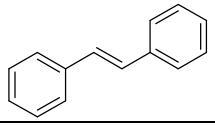
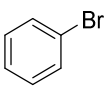
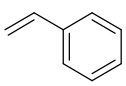
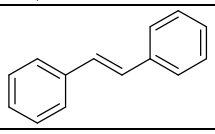
product, ethyl cinnamate in excellent yield. The product obtained was confirmed by ^{1}H, ^{13}C and GC-MS analysis. The signals at δ 7.69 (d, J = 16.0 Hz, 1 H): and 6.44 (d, J = 16.0 Hz, 1 H): confirmed the presence of olefinic bonds adjacent to phenyl ring. It was further confirmed by ^{13}C NMR spectrum showing signals at δ 166.8, 144.4, 134.3, 130.0, 128.7, 127.9, 118.2 and M^{+} peak at 176.1. To examine the scope of catalyst various substituted aryl iodides, acrylates and styrenes were also employed in the reaction under the optimized conditions. In case of aryl iodides the substituents showed negligible effect on the outcome of reactions. The reaction proceeded well with both the electron withdrawing and electron donating groups. Under the same reaction conditions we examined bromo benzene and chloro benzene for the Heck reaction. It was observed that the products were obtained in prolonged reaction time (24 h for bromobenzene and 30 h for chlorobenzene). In case of bromobenzene and chlorobenzene the electron withdrawing substituents produced an accelerating effect on the rate of reaction although the yields were found to be similar in both the cases. While studying the effect of substitution on other coupling partners i.e. styrenes and acrylates it was found that the catalyst works well with both electron withdrawing and electron donating substitutents. Another interesting observation of these studies was that *α*-methyl styrene took longer time for the completion of reaction (**Table 1, entry 1o**). This is probably due to the steric bulk of methyl group.

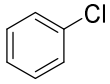
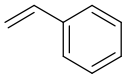
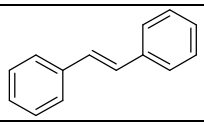
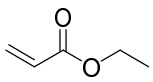
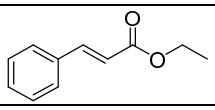
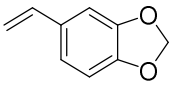
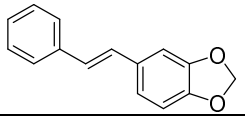
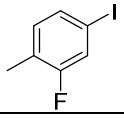
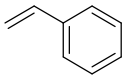
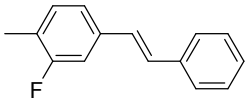
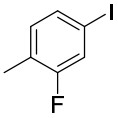
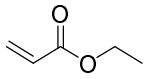
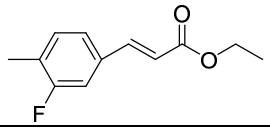
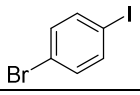
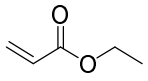
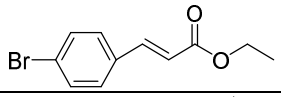
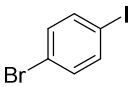
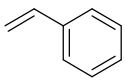
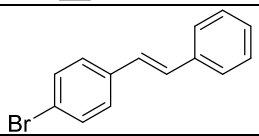
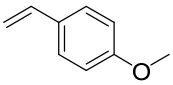
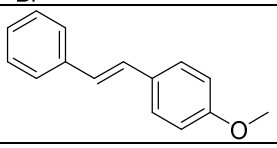
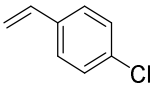
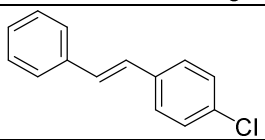
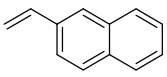
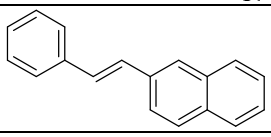
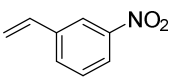
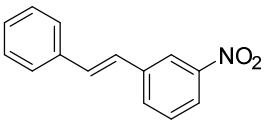
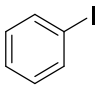
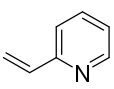
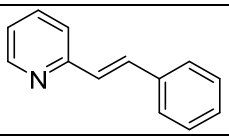
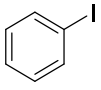
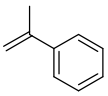
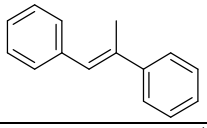
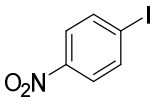


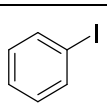
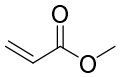
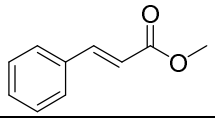
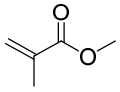
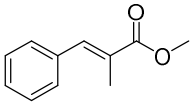
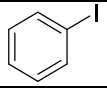
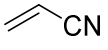
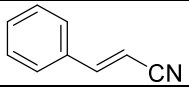
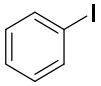
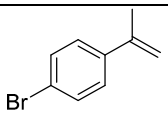
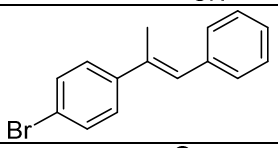
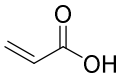
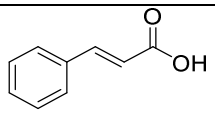
Scheme 5: Reaction Scheme for Heck Reaction

Reaction Conditions: Aryl halide (1 mmol), Alkene (1.15 mmol), TEA (3 mmol), DMF (3.5 mL), with (30 mg): heterogeneous SBA-15-TAT-Pd (II): catalyst.

Table 1: Heck Reaction

Entry	Aryl halide	Olefins	Product	Yield (%):	Time (h):
1a				95	1
1b				92	24

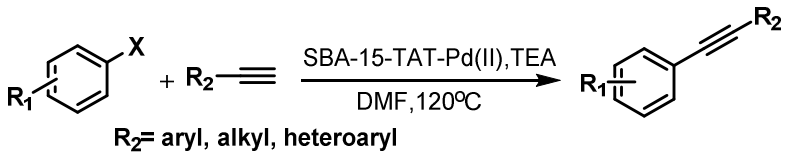
1c				90	30
1d				95	1
1e				90	1
1f				90	1
1g				85	1
1h				85	1
1i				90	1
1j				85	1
1k				90	1
1l				90	1
1m				80	1
1n				75	2
1o				80	1
1p				75	4

1q				80	1
1r				70	1
1s				75	1
1t				75	12
1u				70	1

4.3.2. Sonogashira reaction using covalently anchored 2, 4, 6-triallyloxy-1, 3, 5-triazine Pd(II): Complex over modified surface of SBA-15

We then further investigated the compatibility of SBA-15-TAT-Pd (II): catalyst for Sonogashira reaction. The reaction was optimised using iodobenzene and phenylacetylene as coupling partners **(Scheme 6)**. The analysis of product obtained was carried out by ^{1}H, ^{13}C and GC-MS analysis. The product diphenyl acetylene was confirmed by presence of peaks at δ 7.60-7.67 (m, 4H), 7.38-7.48 (m, 6H): in ^{1}H NMR and δ 131.6, 128.3, 128.2, 123.2, 89.4 in ^{13}C NMR spectra.To study the effect of CuI on Sonogashira reaction, the reaction was carried out both in presence and in absence of CuI. It was found that the CuI was required only when inorganic bases like K_2CO_3 were used for reaction. When triethyl amine was used as a base in reaction the desired product was obtained even in absence of CuI. Based on this observation we proceeded ahead to carry out Sonogashira reaction of various aryl iodides and substituted phenyl acetylenes in presence of NEt_3 as base. As in the case of Heck the SBA-15-TAT-Pd

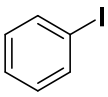
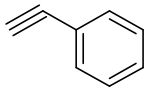
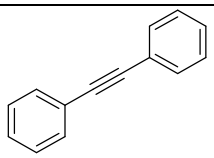
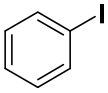
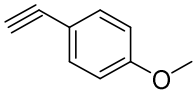
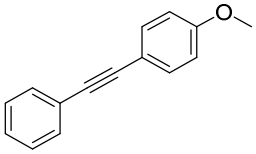
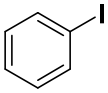
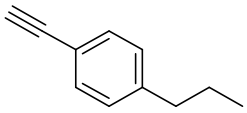
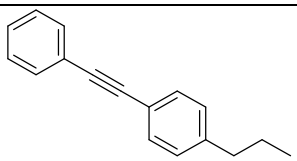
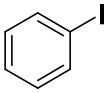
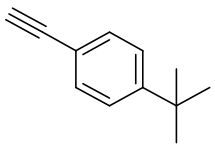
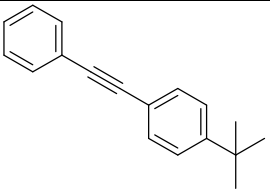
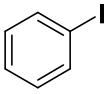
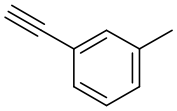
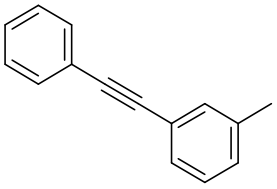
(II): catalyst showed tolerance for wide range of substitutents furnishing desired product in moderate to high yields (**see Table 2**). In case of aliphatic acetylenes the presence of CuI was essential for the progress of reaction.

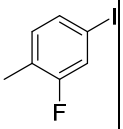
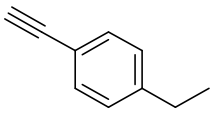
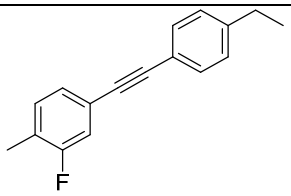


Scheme 6: Reaction Scheme for Sonogashira Reaction

Reaction Conditions: Aryl halide (1 mmol), Alkyne (1.15 mmol), TEA (3 mmol), DMF (3.5 mL), with (30 mg): heterogeneous SBA-15-TAT-Pd (II): catalyst.

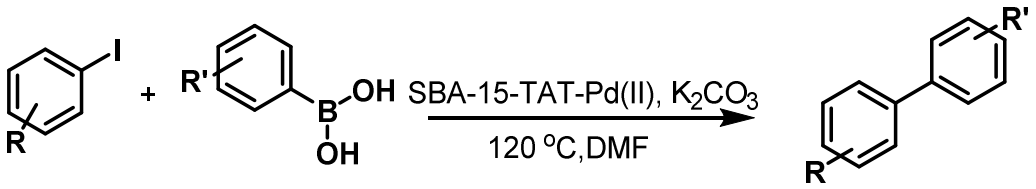
Table 2: Sonogashira coupling

Entry	Aryl halide	Acetelyene	Product	Yield (%):	Time (h):
2a				90	1
2b				85	1
2e				85	1
2f				87	1
2g				90	1

2j				80	1

4.3.3. Suzuki and Hiyama reaction using covalently anchored 2, 4, 6-triallyloxy-1, 3, 5-triazine Pd(II): Complex over modified surface of SBA-15

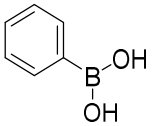
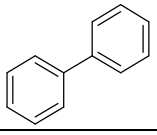
Since we were successful in employing SBA-15-TAT-Pd (II): catalyst in Heck and Sonogashira reaction we now further considered investigating the performance of catalyst in case of Suzuki and Hiyama coupling reactions **(Scheme 7 and Scheme 8)**. The model reaction was performed using iodobenzene and phenyl boronic acid as starting material DMF as solvent and K_2CO_3 as the base. The reaction proceeded smoothly to afford the desired product in excellent yield. In order to extend the substrate scope the reaction was performed with other substituted aryl iodides and phenylboronic acids under the optimised conditions. The results obtained were similar as in case of Heck and Sonogashira coupling reactions.

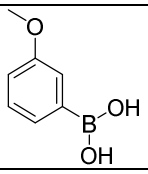
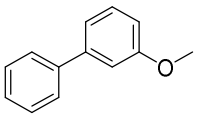
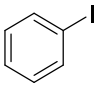
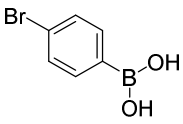
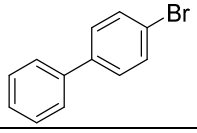
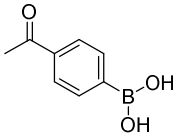
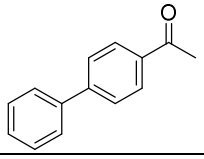
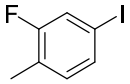
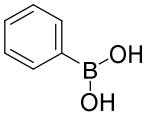
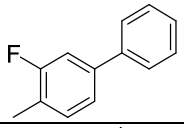
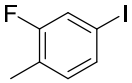
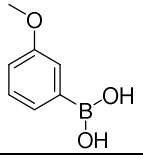
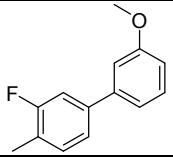
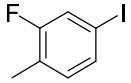
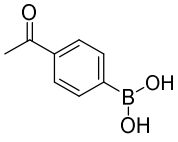
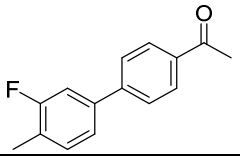
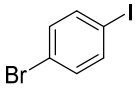
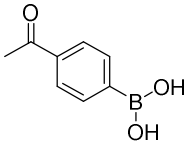
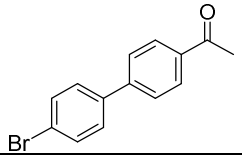
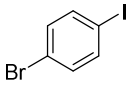
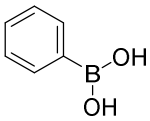
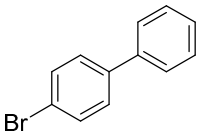
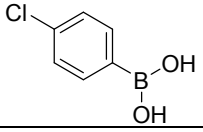
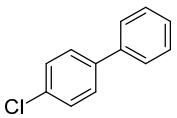
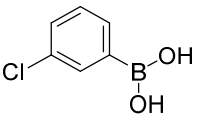
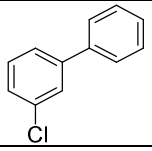
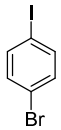
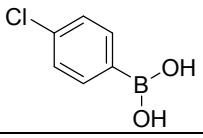
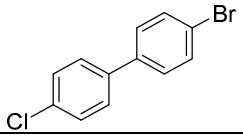
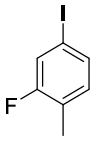
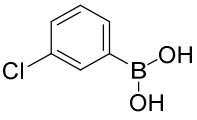
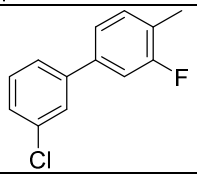


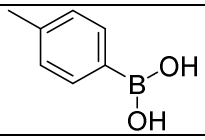
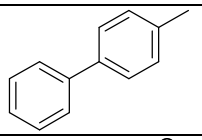
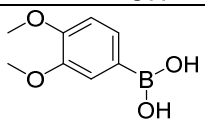
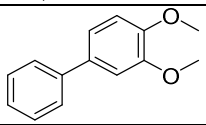
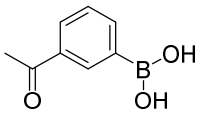
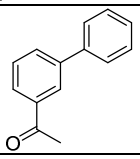
Scheme 7: Reaction Scheme for Suzuki- Miayura Reaction

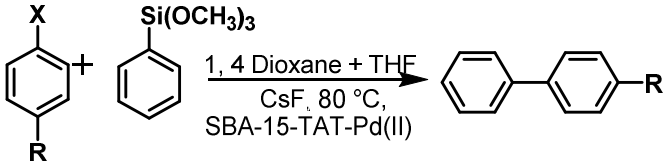
Reaction Conditions: Aryl halide (1 mmol), phenyl boronic acids (1.15 mmol), K_2CO_3 (3 mmol), DMF (3.5 mL), with (30 mg): heterogeneous SBA-15-TAT-Pd (II): catalyst.

Table 3: Suzuki Coupling

Entry	Aryl Iodide	Pheny Boronic Acid	Product	Yield (%):	Time (h):
3a				90	1

3b				90	1
3c				85	1
3d				82	1
3e				80	1
3f				85	1
3g				85	1
3h				85	1
3i				85	1
3j				85	1
3k				90	2
3l				85	1
3m				82	1

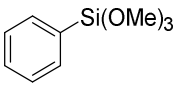
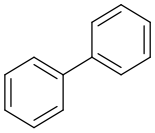
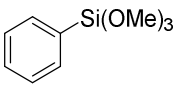
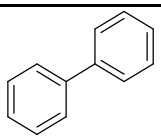
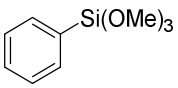
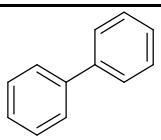
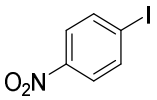
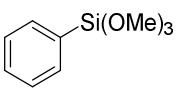
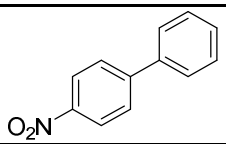
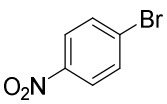
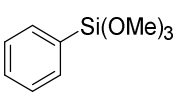
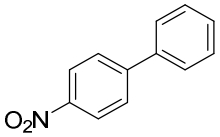
3n				85	1
3o				80	1
3p				87	2

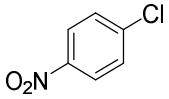
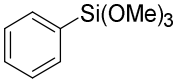
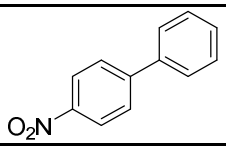
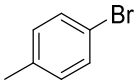
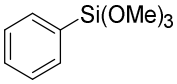
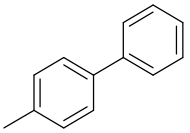
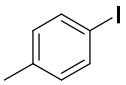
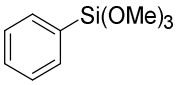
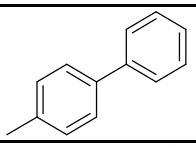
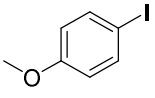
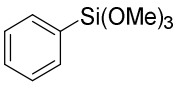
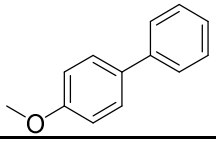


Scheme 8: Reaction Scheme for Hiyama Reaction

Reaction Conditions: Aryl halide (1 mmol), phenyl trimethoxy silane (1.15 mmol), CsF (3 mmol), 1, 4- Dioxane: THF (1:1): (3.5 mL), with (30 mg): heterogeneous SBA-15-TAT-Pd (II): catalyst.

Table 4: Hiyama Coupling

Entry	Aryl Iodide	Phenyl trimethoxy silane	Product	Yield (%):	Time (h):
3a				29	12
3a				83	8
3a				98	3
4a				98	1
4a				99	2

4a				99	1
3i				96	5
3l				94	4
4b				89	5

4.3.4. Recovery of Catalyst

The catalyst was then further screened for its recyclability and reusability. The catalyst was easily recovered through simple vacuum filtration over whatmann filter paper. The catalyst after washing with ethyl acetate and drying in oven was subjected for the use in next reaction. The catalyst showed no loss of activity and can be reused (upto five times).

4.4: Conclusion

In conclusion we have successfully employed covalently anchored 2, 4, 6-triallyloxy-1, 3, 5-triazine Pd(II): Complex over modified surface of SBA-15 for Heck reaction, Suzuki-Miayura Coupling, Sonogashira Coupling and Hiyama Coupling reactions. The products obtained were in good to excellent yields.

4.5: Experimental

General Information: All reactions were carried out under argon or nitrogen in oven-dried glassware using standard gas-light syringes, cannulas and septa. Solvents and reagents were purified and dried by standard methods prior to use. Optical rotations were measured at room temperature. IR spectra were recorded on an FT-IR instrument. ^{1}H NMR spectra were recorded on 200 MHz, 400 MHz and 500 MHz and are reported in parts per million (δ) downfield relative to $CDCl_3$ as internal standard and ^{13}C NMR spectra were recorded at 50 MHz, 100 MHz and 125 MHz and assigned in parts per million (δ) relative to $CDCl_3$. Column chromatography was performed on silica gel (100-200 and 230-400 mesh) using a mixture of petroleum ether and ethyl acetate as the eluent.

General procedure for Heck Reaction: To a solution of aryl iodide (1 mmol): in DMF (3.5mL): was added olefin (1.15 mmol): and SBA-15-TAT-Pd (II): catalyst (0.62 mmol% Pd). The mixture was stirred at 120 °C until TLC showed complete consumption of aryl iodide. After the completion of reaction, the mixture was filtered over whatmann filter paper and washed with ethyl acetate (3X25mL). The organic layer was washed with water (25mL): and consequently brine (25mL). The combined organic layer was dried over sodium sulphate

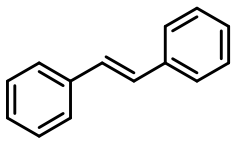
and subjected to concentration under vacuum to get the crude product. The desired product was purified by silica gel chromatography (230-400 mesh): and pet ether: ethyl acetate (0-5%): as an eluent **(Table 1)**.

General procedure for Sonogashira Coupling: To a solution of aryl iodide (1 mmol): in DMF (3.5mL): was added acetylene (1.15 mmol): and SBA-15-TAT-Pd(II): catalyst (0.62 mmol% Pd): The mixture was stirred at 120 °C until TLC showed complete consumption of aryl iodide. After the completion of reaction the mixture was filtered over whatmann filter paper and washed with ethyl acetate (3X25mL). The organic layer was washed with water (25mL): and brine (25mL). The combined organic layer was dried over sodium sulphate and subjected to concentration under vacuum to get the crude product. The desired product was purified by silica gel chromatography (230-400 mesh): and pet ether: ethyl acetate (0-5%): as an eluent **(Table 2)**.

General procedure for Suzuki-Miyaura Coupling: To a solution of aryl iodide (1 mmol): in DMF (3.5mL): was added phenyl boronic acid (1.15 mmol): and SBA-15-TAT-Pd(II): catalyst (0.62 mmol% Pd): The mixture was stirred at 120 °C until TLC showed complete consumption of aryl iodide. After the completion of reaction the mixture was filtered over whatmann filter paper and washed with ethyl acetate (3X25mL). The organic layer was washed with water (25mL): and brine (25mL). The combined organic layer was dried over sodium sulphate and subjected to concentration under vacuum to get the crude product. The desired product was purified by silica gel chromatography (230-400 mesh): and pet ether: ethyl acetate (0-5%): as an eluent **(Table 3)**.

General procedure for Hiyama Coupling: To a solution of aryl iodide (1 mmol): in DMF (3.5mL): was added phenyl trimethoxysilane (1.5 mmol): and SBA-15-TAT-Pd(II): catalyst (0.62 mmol% Pd): The mixture was stirred at 120 °C until TLC showed complete consumption of aryl iodide. After the completion of reaction, the mixture was filtered over whatmann filter paper and washed with ethyl acetate (3X25mL). The organic layer was washed with water (25mL): and brine (25mL). The combined organic layer was dried over sodium sulphate and subjected to concentration under vacuum to get the crude product. The desired product was purified by silica gel chromatography (230-400 mesh): using pet ether: ethyl acetate (0-5%): as an eluent **(Table 4)**.

Spectral data for Heck Coupling



(*E*)-1, 2-Diphenylethene(1a,1b,1c):

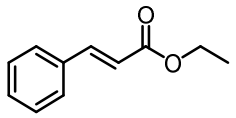
Crystalline white Solid; Mp: 123 °C(lit.,122-124 °C): [52, 53]

^{1}H NMR ($CDCl_3$, 200MHz): δ = 7.57 - 7.50 (m, 4 H), 7.43 - 7.33 (m, 4 H), 7.33 - 7.28 (m, 2 H), 7.13 (s, 2 H) ppm

^{13}C NMR (CDCl3, 50MHz): δ = 137.4, 128.7, 127.6, 126.5

GC-MS (m/z): 180 $[M]^+$

Ethyl cinnamate(1d):



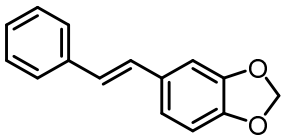
Colourless liquid[52, 53];

^{1}H NMR ($CDCl_3$, 200MHz): δ = 7.69 (d, J = 16.0 Hz, 1 H), 7.56 - 7.47 (m, 2 H), 7.41 - 7.32 (m, 3 H), 6.44 (d, J = 16.0 Hz, 1 H), 4.26 (q, J = 7.1 Hz, 2 H), 1.41 - 1.25 (m, 3 H) ppm

^{13}C NMR ($CDCl_3$, 50MHz): δ = 166.8, 144.4, 134.3, 130.0, 128.7, 127.9, 118.2, 60.3, 14.2;

GC-MS (m/z): 176.1 $[M]^+$

(*E*)-5-Styrylbenzo[d][1,3]dioxole(1e):



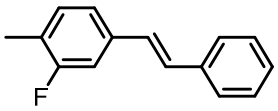
White solid; Mp: 88-89 °C(lit.,88-90 °C): [52, 53]

^{1}H NMR ($CDCl_3$, 500MHz): δ = 7.52 (d, J = 7.3 Hz, 2 H), 7.39 (t, J = 7.6 Hz, 2 H), 7.27 (m, 1 H), 7.12 - 7.05 (m, 2 H), 7.01 - 6.95 (m, 2 H), 6.84 (d, J = 7.9 Hz, 1 H), 6.01 (s, 2 H) ppm

^{13}C NMR ($CDCl_3$, 50MHz): δ = 148.1, 147.3, 137.4, 131.9, 128.6, 128.3, 127.3, 127.0, 126.3, 121.4, 108.4, 105.6, 101.1 ppm.

GC-MS (m/z): 224.2 $[M]^+$

(*E*)-2-Fluoro-1-methyl-4-styrylbenzene(1f):



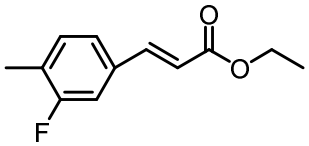
Colourless liquid;

^{1}H NMR ($CDCl_3$, 200MHz): δ = 7.58 - 7.47 (m, 2 H), 7.45 - 7.32 (m, 3 H), 7.25 - 7.14 (m, 3 H), 7.11 - 6.97 (m, 2 H), 2.34 - 2.24 (m, 3 H): ppm

^{13}C NMR ($CDCl_3$,101MHz): δ = 160.3, 137.0, 131.5, 128.9, 128.7, 127.7, 127.5, 126.5, 124.2, 124.1, 122.2, 112.4, 14.4 ppm

GC-MS (m/z): 212 $[M]^+$

Ethyl (*E*)-3-(3-fluoro-4-methylphenyl): acrylate (1g):



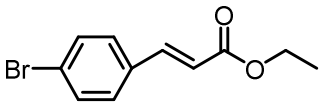
Colourless liquid;

^{1}H NMR ($CDCl_3$, 200MHz): δ = 7.68 (d, J = 16.0 Hz, 1 H), 7.27 (s, 3 H), 6.45 (d, J = 15.9 Hz, 1 H), 4.34 (q, J = 7.1 Hz, 2 H), 2.37 (d, J = 1.9 Hz, 3 H), 1.41 (t, J = 7.1 Hz, 3 H) ppm

^{13}C NMR ($CDCl_3$, 50MHz): δ = 167.4, 164.4, 159.6, 143.9, 134.7, 132.4, 127.9, 124.4, 119.1, 114.5, 61.1, 15.1 ;

GC-MS (m/z): 180 [M]+

Ethyl (*E*)-3-(4-bromophenyl):acrylate(1h):



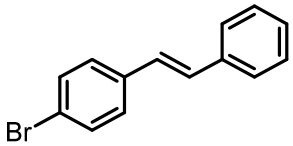
Colourless liquid[54]

^{1}H NMR ($CDCl_3$, 200MHz): δ = 7.60 (d, J = 16.0 Hz, 1 H), 7.55 - 7.45 (m, 2 H), 7.44 - 7.30 (m, 2 H), 6.41 (d, J = 16.0 Hz, 1 H), 4.41 - 4.02 (m, 2 H), 1.35 - 1.24 (m, 3 H) ppm

^{13}C NMR ($CDCl_3$, 50MHz): δ = 166.7, 142.6, 133.3, 132.1, 129.4, 124.4, 118.9, 60.6, 14.3 ppm

GC-MS (m/z): 255.1$[M]^+$

(*E*)-1-Bromo-4-styrylbenzene(1i):



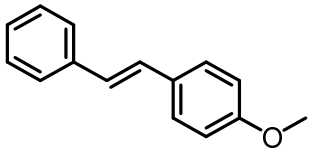
White solid; **Mp::** 126-127 °C(lit.,126-127 °C): [52, 53]

^{1}H NMR ($CDCl_3$, 500MHz): δ = 7.48 (dd, J = 7.8, 13.6 Hz, 4 H), 7.39 - 7.23 (m, 5 H), 7.05 (q, J = 16.2 Hz, 2 H):

^{13}C NMR ($CDCl_3$, 50MHz): δ = 136.9, 136.3, 131.8, 129.4, 128.7, 127.9, 127.4, 126.5, 21.3

GC-MS (m/z): 259.1$[M]^+$

(*E*)-1-Methoxy-4-styrylbenzene (1j):



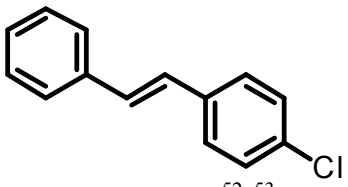
White solid; **Mp::** 135-136 °C(lit.,135-136 °C): [52, 53];

^{1}H NMR ($CDCl_3$, 400MHz): δ = 7.54 - 7.45 (m, 4 H), 7.40 - 7.34 (m, 2 H), 7.28 - 7.22 (m, 1 H), 7.12 - 6.97 (m, 2 H), 6.95 - 6.89 (m, 2 H), 3.85 (s, 3 H): ppm

^{13}C NMR ($CDCl_3$, 50MHz): δ = 159.3, 137.7, 130.2, 128.6, 128.2, 127.7, 127.2, 126.6, 126.2, 113.9, 55.3 ppm

GC-MS (m/z): 210.2$[M]^+$

(*E*)-1-Chloro-4-styrylbenzene(1k):



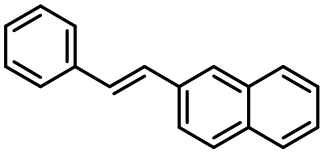
White Solid; **Mp:** 125-127 °C(lit.,125-127 °C): [52, 53];

^{1}H NMR ($CDCl_3$, 400MHz): δ = 7.53 - 7.50 (m, 2 H), 7.45 (d, J = 8.6 Hz, 2 H), 7.40 - 7.32 (m, 4 H), 7.31 - 7.28 (m, 1 H), 7.08 (d, J = 2.9 Hz, 2 H): ppm

^{13}C NMR ($CDCl_3$, 101MHz): δ = 137.0, 135.8, 133.2, 129.3, 128.8, 128.7, 127.9, 127.6, 127.4, 126.5 ppm

GC-MS (m/z): 214.6 $[M]^+$

(*E*)-2-Styrylnaphthalene(1l):



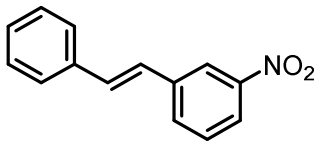
White crystalline Solid; **Mp::** 70-71 °C(lit.,70-71 °C): [52, 53];

^{1}H NMR (CDCl$_3$, 200MHz): δ = 7.81 - 7.69 (m, 4 H), 7.69 - 7.62 (m, 1 H), 7.52 - 7.42 (m, 2 H), 7.27 (s, 4 H), 7.20 - 7.15 (m, 3 H) ppm

^{13}C NMR (CDCl$_3$, 50MHz): δ = 137.4, 134.8, 133.7, 133.0, 129.0, 128.8, 128.7, 128.3, 128.0, 127.7, 126.6, 126.5, 126.3, 125.9, 123.5;

GC-MS (m/z): 230 $[M]^+$

(*E*)-1-Nitro-3-styrylbenzene(1m):



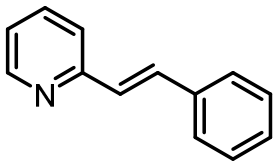
Yellow solid; **Mp::** 109 °C(lit.,109-110 °C): [52, 53];

^{1}H NMR (CDCl$_3$, 200MHz): δ = 8.36 (t, J = 2.0 Hz, 1 H), 8.09 (ddd, J = 1.0, 2.2, 8.1 Hz, 1 H), 7.79 (d, J = 7.8 Hz, 1 H), 7.58 - 7.49 (m, 3 H), 7.48 - 7.26 (m, 4 H), 7.20 (s, 1 H), 7.16 (s, 1 H): ppm

^{13}C NMR (CDCl$_3$,101MHz): δ = 148.7, 139.1, 136.2, 132.2, 131.7, 129.6, 128.9, 128.5, 126.8, 126.1, 122.0, 120.9 ppm

GC-MS (m/z): 533.1 $[M]^+$

(*E*)-2-Styrylpyridine(1n):



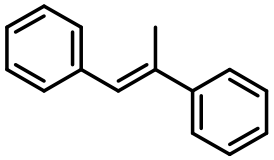
Pale yellow solid; **Mp:** 92 °C(lit.,91.5-93 °C): [52, 53];

^{1}H NMR (CDCl$_3$, 400MHz): δ = 7.11-7.18 (2H, m), 7.25-7.38 (4H, m), 7.56-7.66 (4H, m), 8.59 (1H, d, J = 4.0 Hz) ppm

^{13}C NMR (CDCl$_3$, 101MHz,): δ = 121.9, 122.0, 127.0, 127.8, 128.2, 128.6, 132.6, 136.4, 136.5, 149.5, 155.5 ppm

GC-MS (m/z): 181.1$[M]^+$

(*E*)-Prop-1-ene-1,2-diyldibenzene(1o):



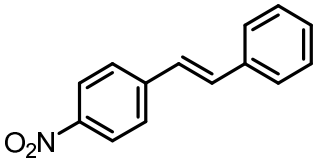
White solid; **Mp:** 81-82 °C(lit.,80-83 °C): [54];

^{1}H NMR ($CDCl_3$, 200MHz): δ = 7.56 - 7.49 (m, 2 H), 7.43 - 7.26 (m, 8 H), 6.83 (d, J = 1.1 Hz, 1 H), 2.28 (d, J = 1.4 Hz, 3 H) ppm

^{13}C NMR ($CDCl_3$, 100MHz): δ = 143.9, 138.3, 137.4, 129.1, 128.3, 128.2, 127.7, 127.2, 126.4, 126.0, 17.5 ppm

GC-MS (m/z): 194.1 $[M]^+$

(*E*)-1-Nitro-4-styrylbenzene(1p):



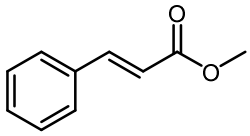
Yellow solid; **Mp:** 159-160 °C(lit.,159-160 °C): [54];

^{1}H NMR ($CDCl_3$, 400MHz): δ = 8.23 (d, J = 8.8 Hz, 2 H), 7.65 (d, J = 8.8 Hz, 2 H), 7.57 (d, J = 7.3 Hz, 2 H), 7.44 - 7.39 (m, 2 H), 7.38 - 7.29 (m, 2 H), 7.21 - 7.12 (m, 1 H) ppm

^{13}C NMR ($CDCl_3$, 50MHz): δ = 146.7, 143.8, 136.1, 133.3, 128.8, 127.0, 126.8, 126.2, 124.1 ppm

GC-MS (m/z): 225.2 $[M]^+$

(*E*)-Methyl cinnamate (1q):



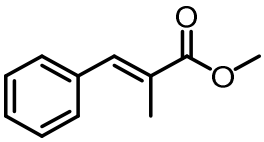
White Solid; **Mp:** 37-38 °C(lit.,37-39 °C): [52, 53] ;

^{1}H NMR ($CDCl_3$, 400MHz): δ = 3.67 (3H, s), 6.34 (1H, d, J = 16.0 Hz), 7.23-7.39 (5H, m), 7.59 (1H, d, J = 16.0 Hz): ppm

^{13}C NMR ($CDCl_3$, 100MHz): δ = 51.1, 117.3, 127.6, 128.4, 129.8, 133.9, 144.3, 166.8 ppm

GC-MS (m/z): 162.18 $[M]^+$

Methyl (E)-2-methyl-3-phenyl acrylate(1r):



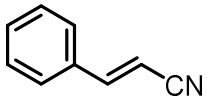
Colourless Liquid[55];

^{1}H NMR ($CDCl_3$, 400MHz): δ = 7.71 (d, J = 1.4 Hz, 1 H), 7.44 - 7.19 (m, 7 H), 3.83 (s, 3 H), 2.14 (d, J = 1.4 Hz, 3 H) ppm

^{13}C NMR ($CDCl_3$, 100MHz): δ = 169.1, 138.9, 135.3,129.6, 129.0, 128.5, 126.3, 52.0, 14.0 ppm

GC-MS (m/z): 176.21 $[M]^+$

(*E*)-Cinnamonitrile(1s):



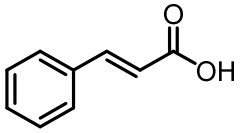
Colourless liquid[56];

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.71-7.66 (m, 3H,), 7.55-7.50 (m, 2 H,), 7.41 (d J=16.8 Hz, 1 H), 6.18 (d, J=16.8 Hz, 1H) ppm

^{13}C NMR ($CDCl_3$, 100MHz): δ = 151.5, 134.4, 132.1, 130.0, 128.3, 119.1, 97.2 ppm

GC-MS (m/z): 129.16 $[M]^+$

Cinnamic acid (1t):



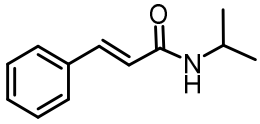
White solid; **Mp:** 132 °C(lit.,130-132 °C) [55];

^{1}H NMR ($CDCl_3$, 200MHz): δ = 7.79 (d, J = 15.9 Hz, 1 H), 7.60 - 7.51 (m, 2 H), 7.44 - 7.37 (m, 3 H), 6.45 (d, J = 16.0 Hz, 1 H) ppm

^{13}C NMR ($CDCl_3$, 101MHz): δ = 171.9, 146.8, 133.7, 130.4, 128.6, 128.0, 116.9 ppm

GC-MS (m/z): 148 $[M]^+$

(*E*)-N-Styrylpropan-2-amine (1u):



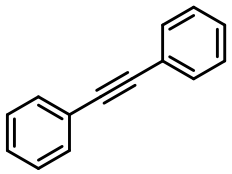
Yellow solid ; **Mp:** 93-95 °C;

^{1}H NMR ($CDCl_3$, 200MHz): δ = 7.60 (d, J = 15.5 Hz, 1 H), 7.52 - 7.44 (m, 2 H), 7.42 - 7.29 (m, 3 H), 6.34 (d, J = 15.7 Hz, 1 H), 5.42 (br. s., 1 H), 4.31 - 4.12 (m, 1 H), 1.25 - 1.19 (m, 6 H) ppm

^{13}C NMR ($CDCl_3$, 100MHz): δ = 164.7, 140.4, 134.6, 129.2, 128.5, 127.4, 120.6, 41.3, 22.5;
GC-MS (m/z): 161.2 $[M]^+$

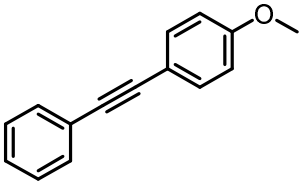
Spectral data for Sonogashira Coupling

1, 2-Diphenylethyne (2a):



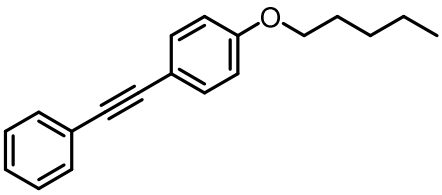
Colorless Crystalline; **Mp:** 68-70 °C (lit., 68-70 °C) [57, 58];
^{1}H NMR ($CDCl_3$, 200MHz): δ= 7.60-7.67 (m, 4H), 7.38-7.48 (m, 6H) ppm
^{13}C NMR ($CDCl_3$, 50 MHz): δ = 131.6, 128.3, 128.2, 123.2, 89.4 ppm
GC-MS (m/z): 228.2 $[M]^+$

1-(p-Methoxylphenyl)-2-phenylacetylene(2b):



White Solid; **Mp:** 88 °C (lit.,88-89 °C) [57, 58];
^{1}H NMR ($CDCl_3$, 200MHz): δ = 7.55–7.46 (m, 4H), 7.35–7.29 (m, 3H), 6.88 (d, J= 8.1 Hz,2H), 3.83 (s, 3H) ppm
^{13}C NMR ($CDCl_3$, 50MHz): δ = 159.6, 133.0, 131.4, 128.3, 127.9,123.5, 115.3, 113.9, 89.3, 88.0, 55.3 ppm
GC-MS (m/z): 208.2 $[M]^+$

1-(Pentyloxy)-4-(phenylethynyl):benzene(2c):



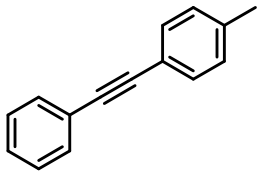
White Solid; **Mp**: 44-46 °C;

^{1}H NMR ($CDCl_3$, 500MHz): δ = 7.43 - 7.56 (m, 4 H), 7.30 - 7.39 (m, 3 H), 6.83 - 6.92 (m, 2 H), 3.98 (t, J=6.7 Hz, 2 H), 1.75 - 1.86 (m, 2 H), 1.38 - 1.48 (m, 4 H), 0.95(t, J=7.2 Hz, 3 H) ppm

^{13}C NMR ($CDCl_3$, 50MHz): δ = 159.0, 132.8, 131.2, 128.0, 127.6, 114.3,89.2, 87.7, 67.8, 28.6, 27.9, 22.2, 13.7 ppm

GC-MS (m/z): 264.3 $[M]^+$

1-Methyl-4-(phenylethynyl):benzene(2d):



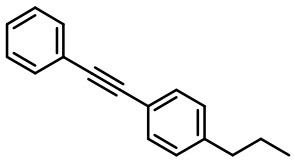
White Solid; **Mp:** 67 °C(lit.,67-69 °C) [57,58] ;

^{1}H NMR ($CDCl_3$, 200MHz): δ= 7.49-7.53 (m, 2H), 7.41-7.44 (m, 2H), 7.32-7.38 (m, 3H), 7.14-7.17(m, 2H), 2.36 (s, 3H): ppm

^{13}C NMR (CDCl3, 50MHz): δ= 138.3, 131.5, 131.4, 129.1, 128.3, 128.1, 123.4, 120.1, 89.5, 88.6, 21.5 ppm

GC-MS (m/z): 192 $[M]^+$

1-(*tert*-Butyl)-4-(phenylethynyl):benzene(2e):



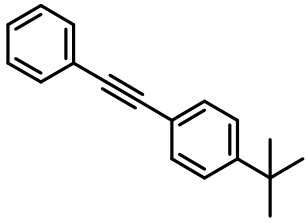
White Solid; **Mp:** 64 °C(lit.,62-63 °C) [57, 58]

^{1}H NMR ($CDCl_3$, 200MHz): δ = 7.75 - 7.69 (m, 2 H), 7.58 - 7.29 (m, 5 H), 7.16 - 7.08 (m, 2 H), 1.36 - 1.23 (m, 9 H) ppm

^{13}C NMR ($CDCl_3$, 101MHz): δ = 151.6, 131.8, 131.6, 128.5, 128.3, 125.4, 123.8, 120.5, 89.8, 88.7,35.0, 31.4;

GC-MS (m/z): 234 $[M]^+$

1-Methyl-3-(phenylethynyl):benzene(2f):



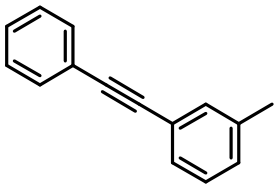
Colourless Liquid[59];

^{1}H NMR ($CDCl_3$, 400MHz): δ = 7.54 (dd, 2 H), 7.42 - 7.31 (m, 5 H), 7.26 - 7.13 (m, 2 H), 2.39 - 2.34 (m, 3 H) ppm

^{13}C NMR ($CDCl_3$, 100MHz): δ = 138.0, 132.2, 131.6, 129.2, 128.7, 128.3, 128.2, 128.2, 123.4, 123.1, 89.6, 89.0, 21.2 ppm

GC-MS (m/z): 234.3 $[M]^+$

(Cyclohexylethynyl): benzene (2g):



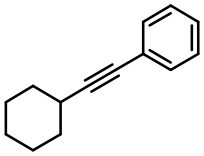
Colourless liquid[59, 60, 61];

^{1}H NMR ($CDCl_3$, 200MHz): δ =7.30-7.36 (m, 2H), 7.16-7.24 (m, 3H), 2.47-2.56 (m, 1H), 1.23-1.82(m, 10 H) ppm

^{13}C NMR ($CDCl_3$, 100MHz): δ = 131.5, 128.1, 127.3, 124.1, 94.5, 80.5, 32.8, 29.8, 26.1, 25.0;

GC-MS (m/z): 184 $[M]^+$

(3-Cyclohexyl1propynyl):benzene(2h):



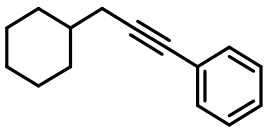
Colourless liquid[59];

^{1}H NMR ($CDCl_3$, 200MHz): δ=7.247.40(5H,m),2.29(2H,d,J=6.7Hz),1.021.88(11H,m)

^{13}C NMR ($CDCl_3$, 100MHz): δ=131.5,128.1,127.4,124.2,89.3,37.5,32.8,27.2,26.3,26,2;

GC-MS(m/z):192.2 $[M]^+$

4-((4-Ethylphenyl):ethynyl)-2-fluoro-1-methylbenzene(2i):



Yellow Solid; **Mp:** 54 °C;

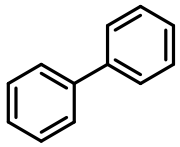
^{1}H NMR ($CDCl_3$, 200MHz): δ = 7.52 - 7.40 (m, 2 H), 7.31 - 7.07 (m, 5 H), 2.68 (q, J = 7.6 Hz, 2 H), 2.30 (d, J = 1.9 Hz, 3 H), 1.28 - 1.23 (m, 3 H) ppm

^{13}C NMR ($CDCl_3$, 101MHz): δ = 162.0, 159.6, 144.8, 131.4, 127.6, 125.4, 120.2, 117.9, 89.7, 87.7, 29.2, 14.9 ppm

GC-MS (m/z): 238.3 $[M]^+$

Spectral data for Suzuki-Miyaura Coupling

1'-**Biphenyl (3a):**



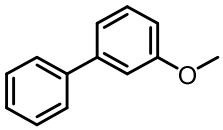
White solid; **Mp:** 70 °C (lit., 69-70 °C) [62, 63, 64];

^{1}H NMR ($CDCl_3$, 200MHz): δ = 7.73 - 7.55 (m, 4 H), 7.49 - 7.33 (m, 6 H) ppm

^{13}C NMR ($CDCl_3$, 50MHz): δ = 127.20, 128.79;

GC-MS (m/z): 154.21 $[M]^+$

3-Methoxy-1,1'biphenyl (3b):



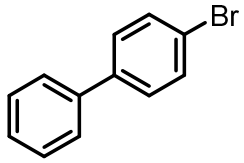
Colourlessliquid[62,63,64];

^{1}H NMR($CDCl_3$, 200MHz): δ = 7.56 - 7.49 (m, 2 H), 7.25 (m, 4 H), 7.16 - 7.05 (m, 2 H), 6.87 - 6.79 (m, 1 H), 3.79 (s, 3 H) ppm

^{13}C NMR ($CDCl_3$, 50MHz): δ = 159.9, 142.7, 141.1, 129.7, 128.7, 127.3, 119.6, 112.9, 112.7, 55.2 ppm

GC-MS (m/z): 184 $[M]^+$

4-Bromo-1,1'-biphenyl(3c,3i):



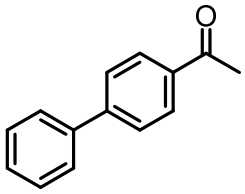
White solid; **Mp:** 91-92 °C(lit., 90-92 °C) [65];

^{1}H NMR ($CDCl_3$, 500MHz): δ = 7.55—7.34 (m, 9 H) ppm

^{13}C NMR ($CDCl_3$, 125MHz): δ = 140.1, 140.0, 131.8, 128.9, 128.7, 127.6, 126.9, 121.5 ppm

GC-MS (m/z): 233.1 $[M]^+$

1-([1,1'-Biphenyl]-4-yl):ethan-1-one(3d):



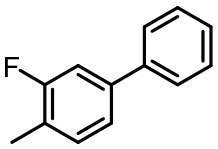
White solid; **Mp:** 121 °C(lit.,121-123 °C) [62,63,64];

^{1}H NMR ($CDCl_3$, 500MHz): δ = 8.03 (d, J = 8.5 Hz, 2 H), 7.70 - 7.61 (m, 4 H), 7.49 - 7.38 (m, 3 H), 2.63 (s, 3 H) ppm

^{13}C NMR ($CDCl_3$, 125MHz): δ = 197.7, 145.8, 139.9, 135.9, 128.9, 128.2, 127.2, 26.6;

GC-MS (m/z): 196.1 $[M]^+$

3-Fluoro-4-methyl-1,1'-biphenyl(3e):



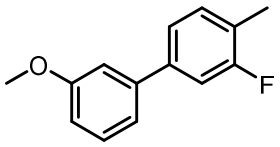
White solid; Mp: 38 °C(lit.,38-39 °C) [65];

^{1}H NMR ($CDCl_3$, 200MHz): δ = 7.63 - 7.53 (m, 2 H), 7.50 - 7.22 (m, 6 H), 2.34 - 2.21 (m, 3 H) ppm

^{13}C NMR ($CDCl_3$, 50MHz): δ = 163., 143.4, 137.7, 137.0, 130.1, 129.6, 126.9, 122.5, 113.7,113.7, 21.0 ppm

GC-MS (m/z): 186$[M]^+$

3-Fluoro-3'-methoxy-4-methyl-1,1'-biphenyl(3f):



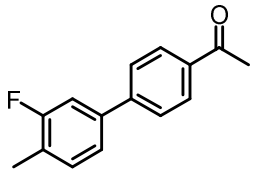
Pale yellow liquid;

^{1}H NMR ($CDCl_3$, 200MHz): δ = 7.38 - 7.27 (m, 1 H), 7.27 - 7.19 (m, 3 H), 7.18 - 7.06 (m, 2 H), 6.89 (ddd, *J* = 0.9, 2.6, 8.1 Hz, 1 H), 3.85 (s, 3 H), 2.30 (d, *J* = 1.8 Hz, 3 H) ppm

^{13}C NMR ($CDCl_3$, 50MHz): δ = 160.0, 159.1, 131.6, 129.8, 122.4, 119.4, 113.8, 113.4, 112.9, 112.7, 55.3, 14.2 ppm

GC-MS (m/z): 216.2 $[M]^+$

1-(3'-Fluoro-4'-methyl-[1,1'-biphenyl]-4-yl):ethan-1-one(3g):



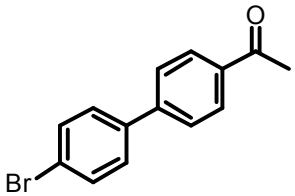
White solid; **Mp:** 93 °C;

^{1}H NMR ($CDCl_3$, 200MHz): δ = 8.07 - 7.97 (m, 2 H), 7.70 - 7.59 (m, 2 H), 7.30 (s, 2 H), 2.63 (s, 3 H), 2.32 (d, J = 1.9 Hz, 3 H) ppm

^{13}C NMR ($CDCl_3$, 101MHz): δ = 197.3, 162.9, 144.1, 139.3, 139.0, 135.7, 131.6, 128.6, 126.6, 124.6, 124.7, 122.2, 113.4, 26.4, 14.0 ppm

GC-MS (m/z): 228.2 $[M]^+$

1-(4'-Bromo-[1,1'-biphenyl]-4-yl):ethan-1-one(3h):



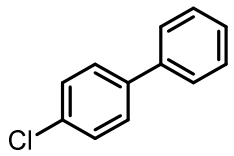
White solid; **Mp:** 131-132 °C(lit.,131-132 °C) [67];

^{1}H NMR ($CDCl_3$, 500MHz): δ = 8.02 (d, J = 8.2 Hz, 2 H), 7.70 - 7.57 (m, 4 H), 7.51 - 7.44 (m, 2 H), 2.67 - 2.60 (m, 3 H) ppm

^{13}C NMR ($CDCl_3$, 125MHz): δ = 197.3, 144.2, 138.5, 135.9, 131.8, 128.7, 126.9, 122.4, 26.4 ppm

GC-MS (m/z): 275.1 $[M]^+$

4-Chloro-1,1'-biphenyl(3j):



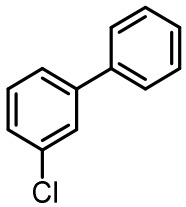
White Solid; **Mp:** 78 °C(lit.,76-78 °C) [66];

^{1}H NMR ($CDCl_3$, 200MHz): δ = 7.61 - 7.54 (m, 3 H), 7.53 - 7.48 (m, 2 H), 7.48 - 7.37 (m, 4 H) ppm

^{13}C NMR ($CDCl_3$, 50MHz): δ 140.0, 139.7, 133.4, 128.9, 128.9, 128.4, 127.6, 127.0;

GC-MS (m/z): 188[M]+

4-Bromo-4'-chloro-1,1'-biphenyl(3k):



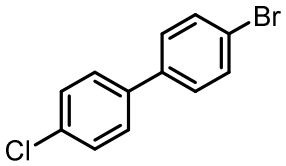
White Solid; **Mp:** 157-158 °C(lit.,157-159 °C) [65];

^{1}H NMR ($CDCl_3$, 200MHz): δ = 7.66 - 7.49 (m, 3 H), 7.49 - 7.38 (m, 5 H) ppm

^{13}C NMR ($CDCl_3$, 50MHz): δ=139,133.2,129.5,130.0,122.0,121.7 ppm

GC-MS (m/z): 266 $[M]^+$

4-Methyl-1,1'-biphenyl(3l):



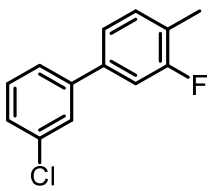
White Solid; **Mp:** 46 °C(lit.,46-48 °C) [66];

^{1}H NMR ($CDCl_3$, 200MHz): δ = 7.71 - 7.52 (m, 2 H), 7.51 - 7.33 (m, 4 H), 7.33 - 7.26 (m, 1 H), 7.26 - 7.17 (m, 2 H), 2.36 (s, 3 H) ppm

^{13}C NMR ($CDCl_3$, 100MHz): δ= 141.1, 138.3, 137.0, 129.5, 128.7, 127.0, 126.9, 21.1 ppm

GC-MS (m/z): 168.23 $[M]^+$

3,4-Dimethoxy-1,1'-biphenyl(3m):



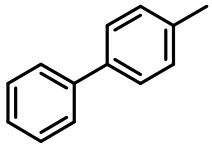
White crystalline solid; Mp: 71 °C(lit.,68-72 °C): [68];

^{1}H NMR ($CDCl_3$, 200MHz): δ = 7.63 - 7.53 (m, 2 H), 7.51 - 7.31 (m, 3 H), 7.23 - 7.10 (m, 2 H), 7.03 - 6.91 (m, 1 H), 3.95 (d, J = 5.1 Hz, 6 H) ppm

^{13}C NMR ($CDCl_3$, 100MHz): δ = 149.1, 148.6, 141.0, 134.2, 128.7, 126.9, 119.4, 111.4, 110.5, 55.97,55.93 ppm

GC-MS (m/z): 214 $[M]^+$

1-([1,1'-Biphenyl]-3-yl):ethan-1-one(3n):



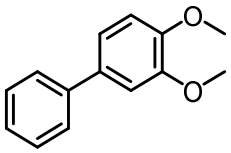
Colourless liquid;

^{1}H NMR ($CDCl_3$, 200MHz): δ = 8.20 (t, J = 1.7 Hz, 1 H), 7.95 (td, J = 1.4, 7.7 Hz, 1 H), 7.81 (td, J = 1.4, 7.8 Hz, 1 H), 7.67 - 7.58 (m, 2 H), 7.56 - 7.35 (m, 4 H), 2.67 (s, 3 H) ppm

^{13}C NMR ($CDCl_3$, 50MHz): δ = 198.1, 141.7, 140.1, 137.6, 131.7, 129.0, 128.9, 127.8, 127.2, 126.9, 26.7 ppm

GC-MS (m/z): 196$[M]^+$

3-Nitro-1,1'-biphenyl(3o):



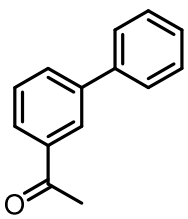
Yellow Solid; **Mp:** 60-61 °C(lit.,60-61 °C) [62, 63, 64];

^{1}H NMR ($CDCl_3$, 200MHz): δ = 8.45 (t, J = 2.0 Hz, 1 H), 8.20 (ddd, J = 1.0, 2.3, 8.2 Hz, 1 H), 7.92 (td, J = 1.4, 7.8 Hz, 1 H), 7.67 - 7.59 (m, 3 H), 7.58 - 7.39 (m, 4 H) ppm

^{13}C NMR ($CDCl_3$, 50MHz): δ = 148.6, 142.7, 138.5, 132.9, 129.6, 129.1, 128.4, 127.0, 121.8 ppm

GC-MS (m/z): 199.2$[M]^+$

N,N-dimethyl-[1,1'-biphenyl]-4-amine(3p):



White Solid; **Mp:** 121 °C(lit.,121-122 °C) [67];

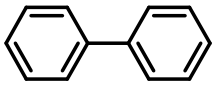
^{1}H NMR ($CDCl_3$, 200MHz): δ = 7.61 - 7.50 (m, 4 H), 7.48 - 7.29 (m, 3 H), 6.85 (d, J = 8.6 Hz, 2 H), 3.01 (s, 6 H) ppm

^{13}C NMR ($CDCl_3$, 101MHz): δ = 149.7, 141.1, 128.6, 127.7, 126.3, 126.0, 113.0, 40.7 ppm

GC-MS (m/z): 197 $[M]^+$

Spectral data for Hiyama Coupling

1'-Biphenyl (3a):



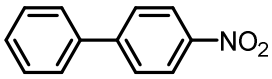
White solid; **Mp:** 70 °C (lit., 69-70 °C) [61, 62, 63];

^{1}H NMR (CDCl3, 200MHz): δ = 7.73 - 7.55 (m, 4 H), 7.49 - 7.33 (m, 6 H) ppm

^{13}C NMR (CDCl3, 50MHz): δ = 127.20, 128.79 ppm

GC-MS (m/z): 154.21 $[M]^+$

4-Nitro-1,1'-biphenyl(4b):



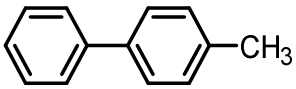
Yellow Solid; ; **Mp:** 114 °C(lit.,114-115 °C) [61, 62, 64];

^{1}H NMR ($CDCl_3$, 200MHz): δ = 7.40-7.44 (m, 3H), 7.54-7.59(m, 2H), 7.65-7.69 (m, 2H), 8.21-8.26 (d, 2 H) ppm

^{13}C NMR ($CDCl_3$, 50MHz): δ =123.09,126.37 126.78 ,127.89, 128.13, 137.77, 146.62 ppm

GC-MS (m/z): 199.2 $[M]^+$

4-Methyl-1, 1'-biphenyl(3l):



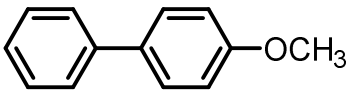
White Solid; **Mp:** 46 °C(lit.,46-48 °C) [66];

^{1}H NMR ($CDCl_3$, 200MHz): δ = 7.71 - 7.52 (m, 2 H), 7.51 - 7.33 (m, 4 H), 7.33 - 7.26 (m, 1 H), 7.26 - 7.17 (m, 2 H), 2.36 (s, 3 H) ppm

^{13}C NMR ($CDCl_3$, 100MHz): δ= 141.1, 138.3, 137.0, 129.5, 128.7, 127.0, 126.9, 21.1 ppm

GC-MS (m/z): 168.23 $[M]^+$

4-Methoxy-1, 1'-biphenyl (4b):



White Solid; **Mp:** 87 °C(lit.,86-88 °C) [66];

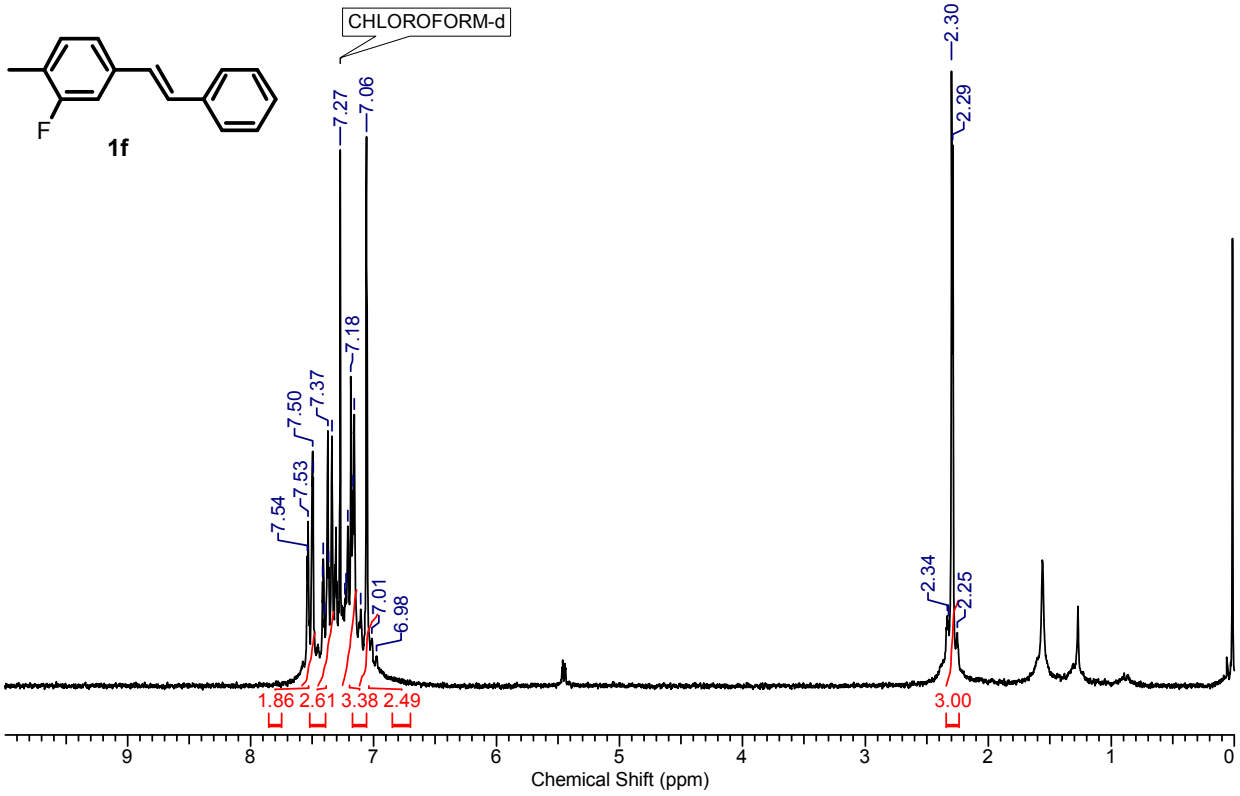
^{1}H NMR ($CDCl_3$, 200MHz): δ = 3.83 (s, 3 H), 6.96-6.99 (d, 2 H), 7.29-7.32 (m, 1 H), 7.37-7.41 (m, 2 H), 7.50-7.57 (m, 4 H) ppm

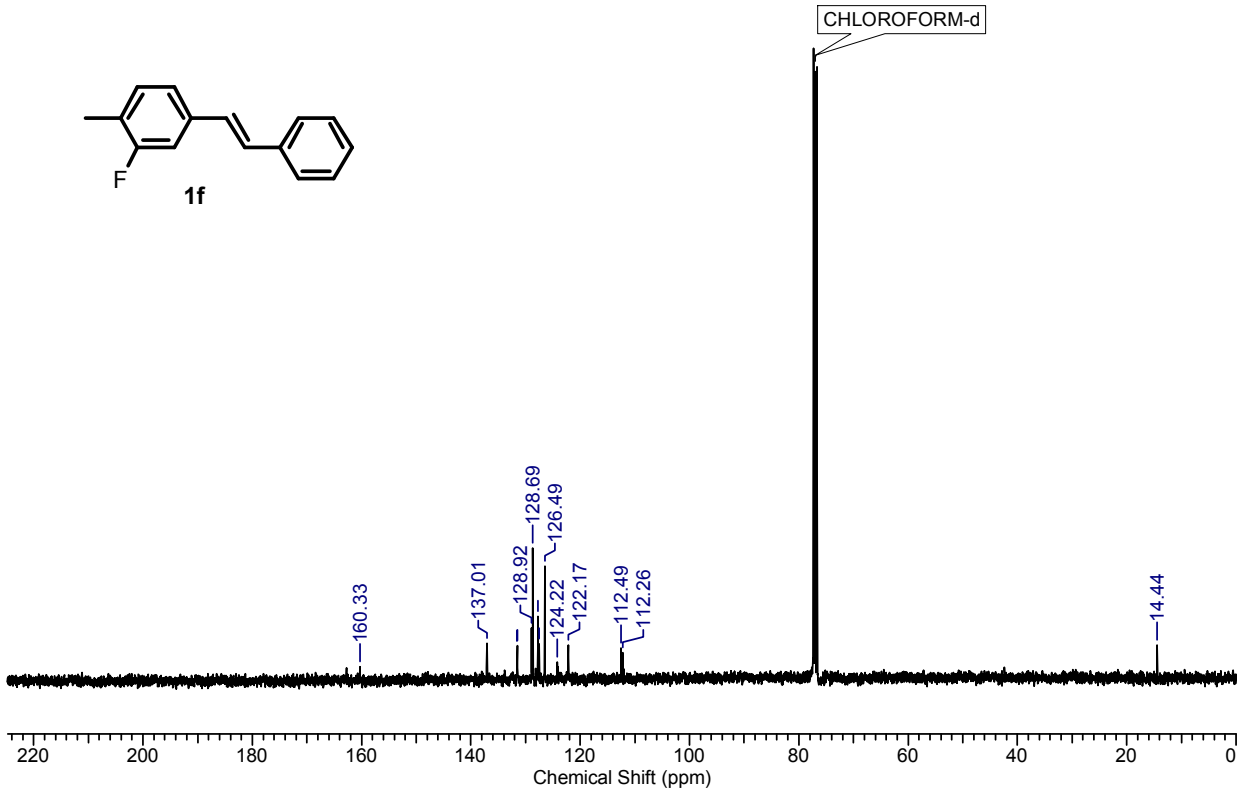
^{13}C NMR ($CDCl_3$, 100MHz): δ = 55.38, 114.26, 126.71, 126.78,128.20, 128.77, 133.83, 140.88, 159.21 ppm

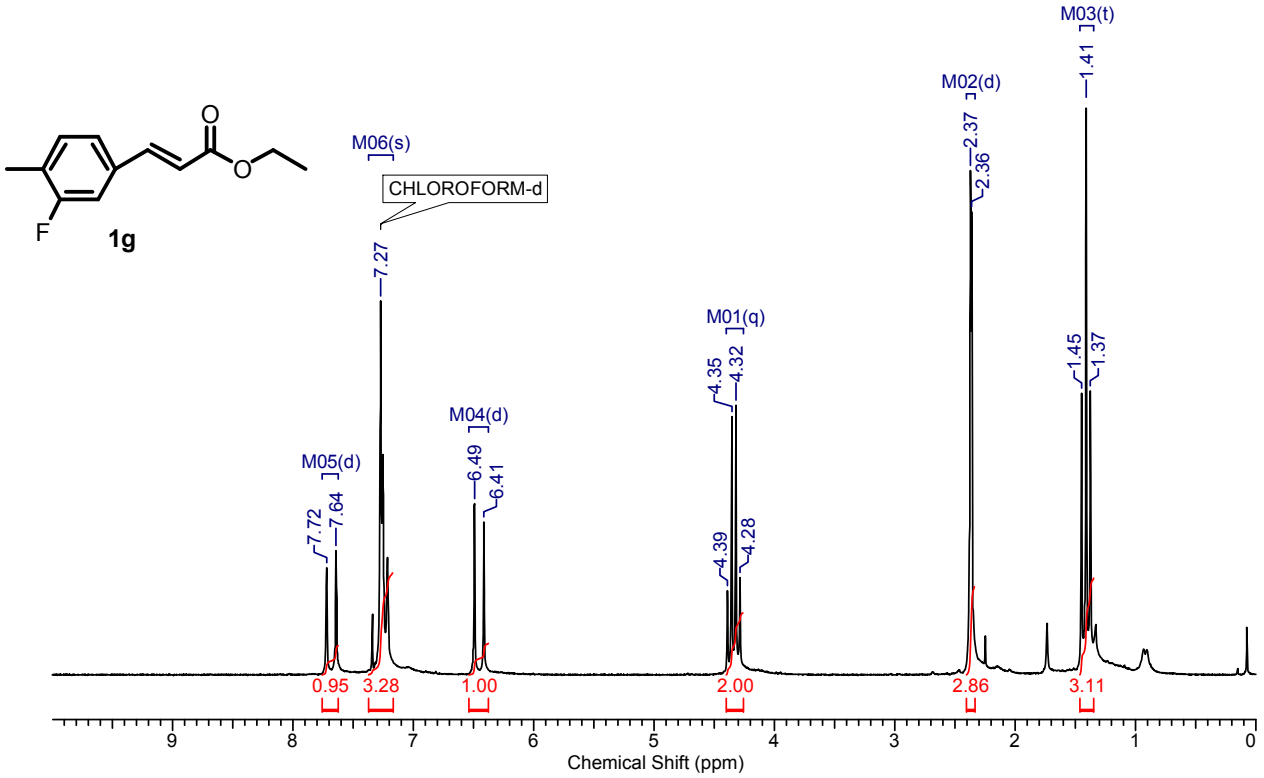
GC-MS (m/z):184 [M]+

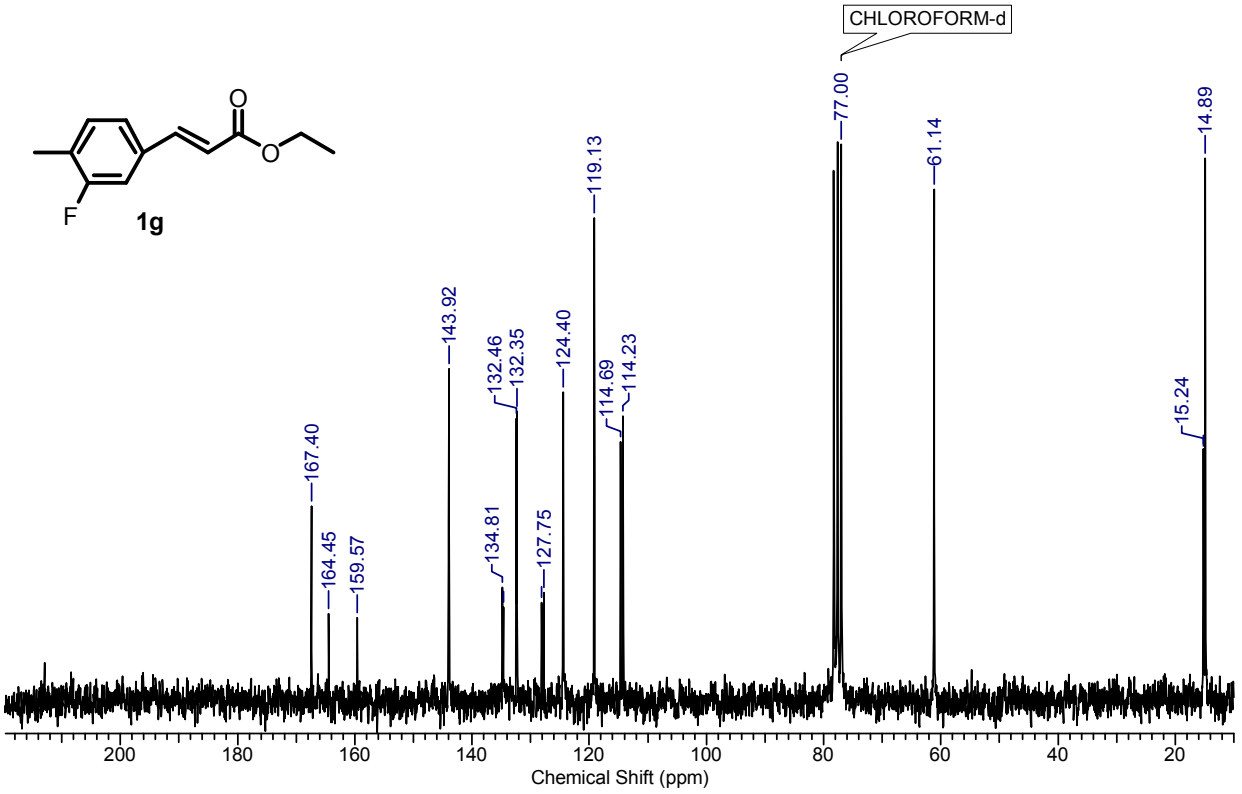
4.6: Selected Spectra

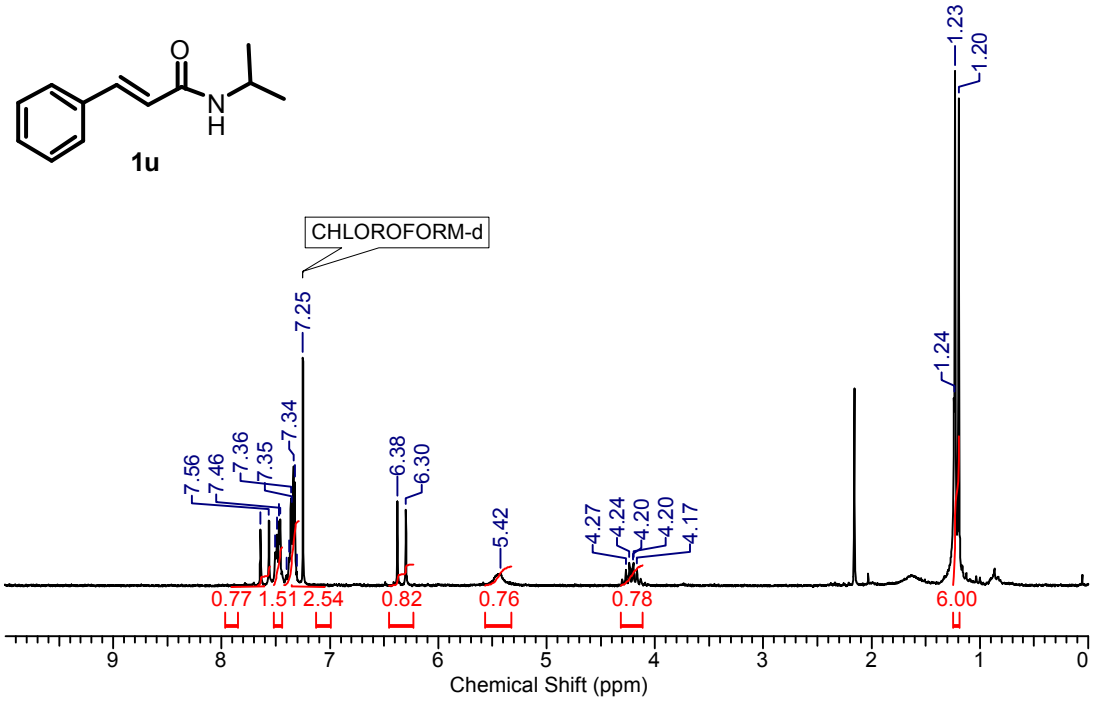
^{1}H and ^{13}C spectra of compound **1f**
^{1}H and ^{13}C spectra of compound **1g**
^{1}H and ^{13}C spectra of compound **1u**
^{1}H and ^{13}C spectra of compound **2c**
^{1}H and ^{13}C spectra of compound **2i**
^{1}H and ^{13}C spectra of compound **3f**
^{1}H and ^{13}C spectra of compound **3g**
^{1}H and ^{13}C spectra of compound **3n**

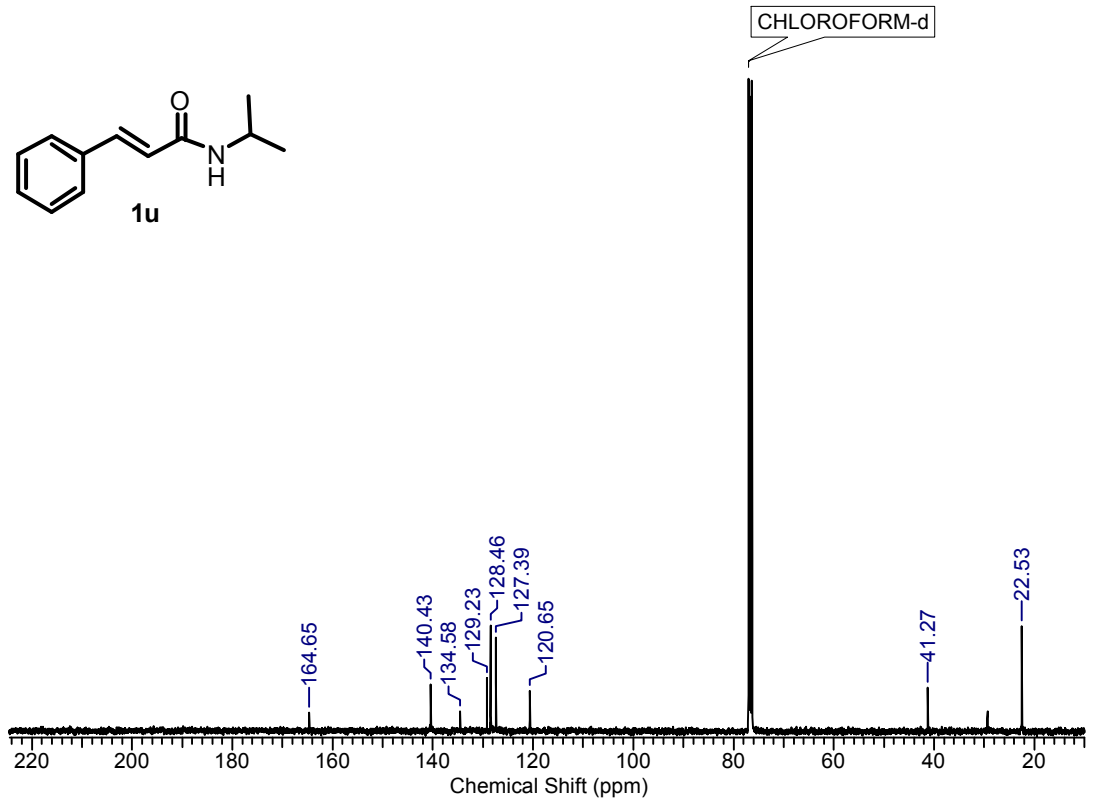

F
1f
CHLOROFORM-d
7.27
7.06
7.18
7.50
7.37
7.53
7.54
7.01
6.98
2.30
2.29
2.34
2.25
1.86
2.61
3.38
2.49
3.00
Chemical Shift (ppm)

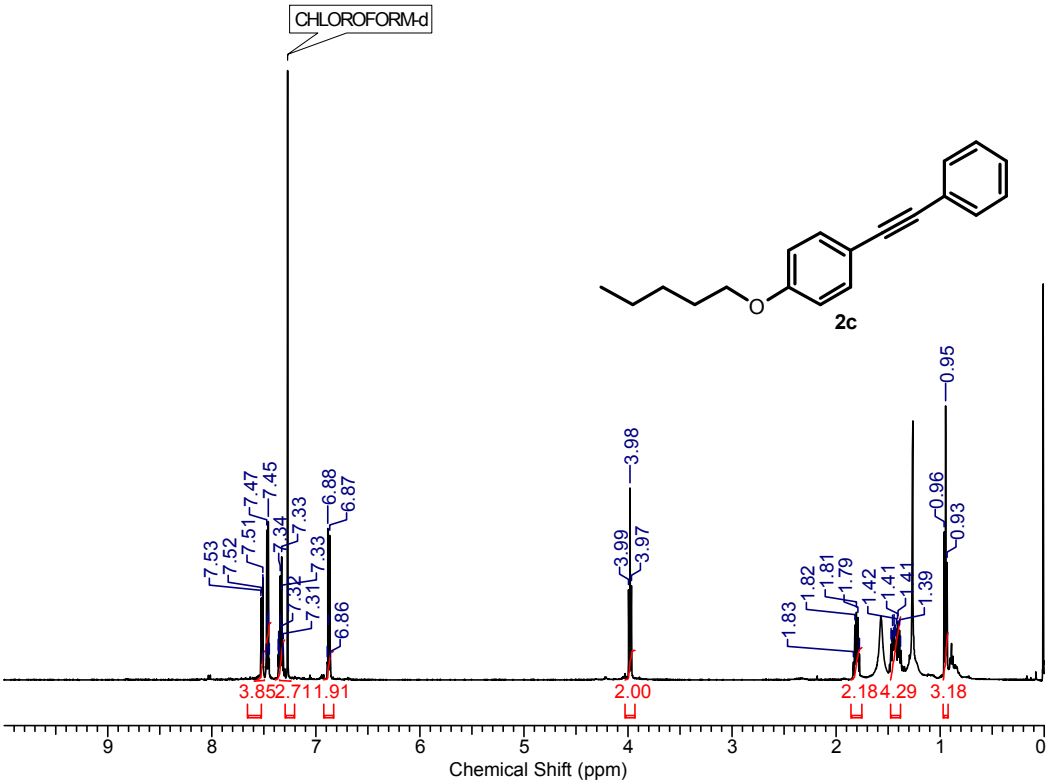

F
1f
CHLOROFORM-d
160.33
137.01
128.92
128.69
126.49
124.22
122.17
112.49
112.26
14.44
Chemical Shift (ppm)

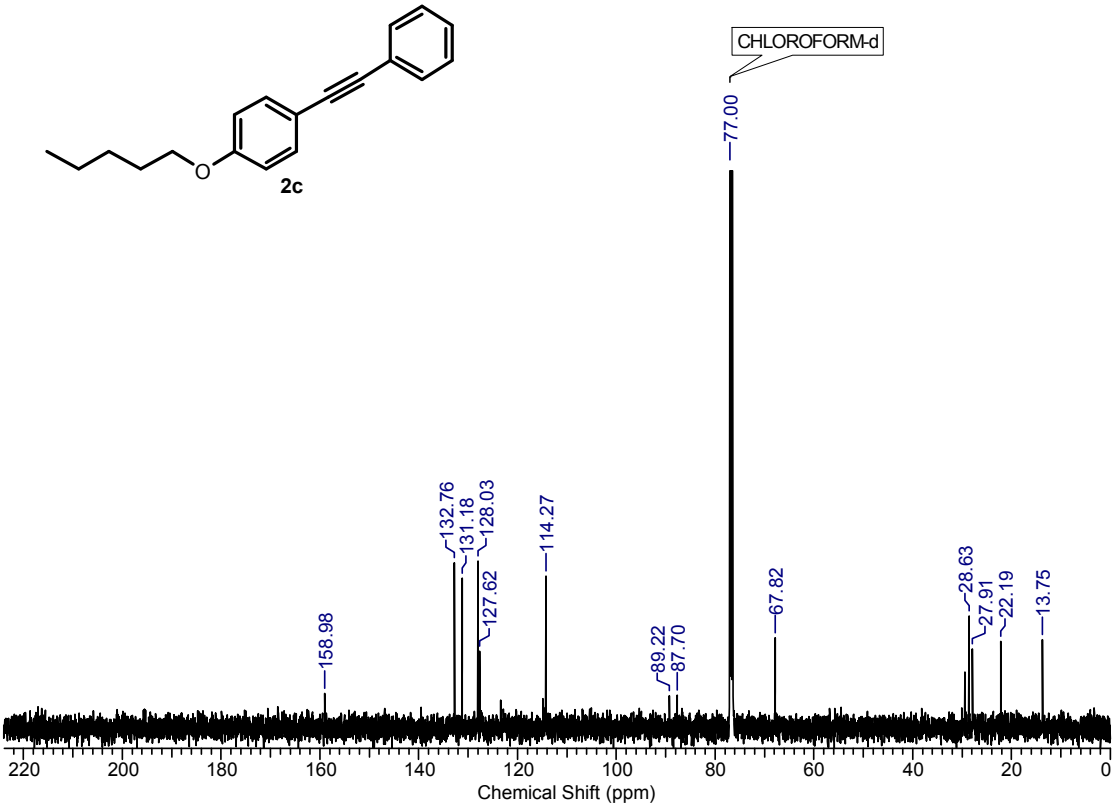

1g
M06(s)
CHLOROFORM-d
M05(d)
M04(d)
M01(q)
M02(d)
M03(t)
7.72
7.64
7.27
6.49
6.41
4.39
4.35
4.32
4.28
2.37
2.36
1.45
1.41
1.37
0.95
3.28
1.00
2.00
2.86
3.11
Chemical Shift (ppm)

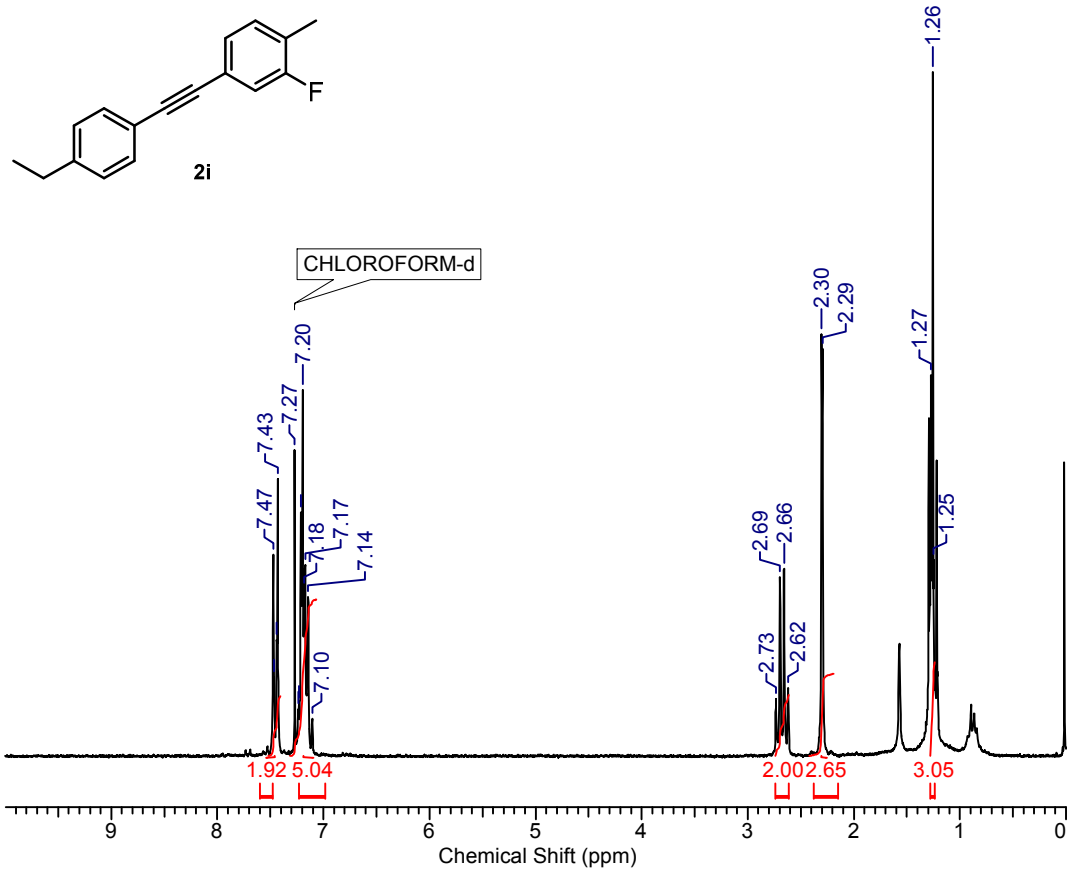

1g
CHLOROFORM-d
167.40
164.45
159.57
143.92
134.81
132.46
132.35
127.75
124.40
119.13
114.69
114.23
77.00
61.14
15.24
Chemical Shift (ppm)

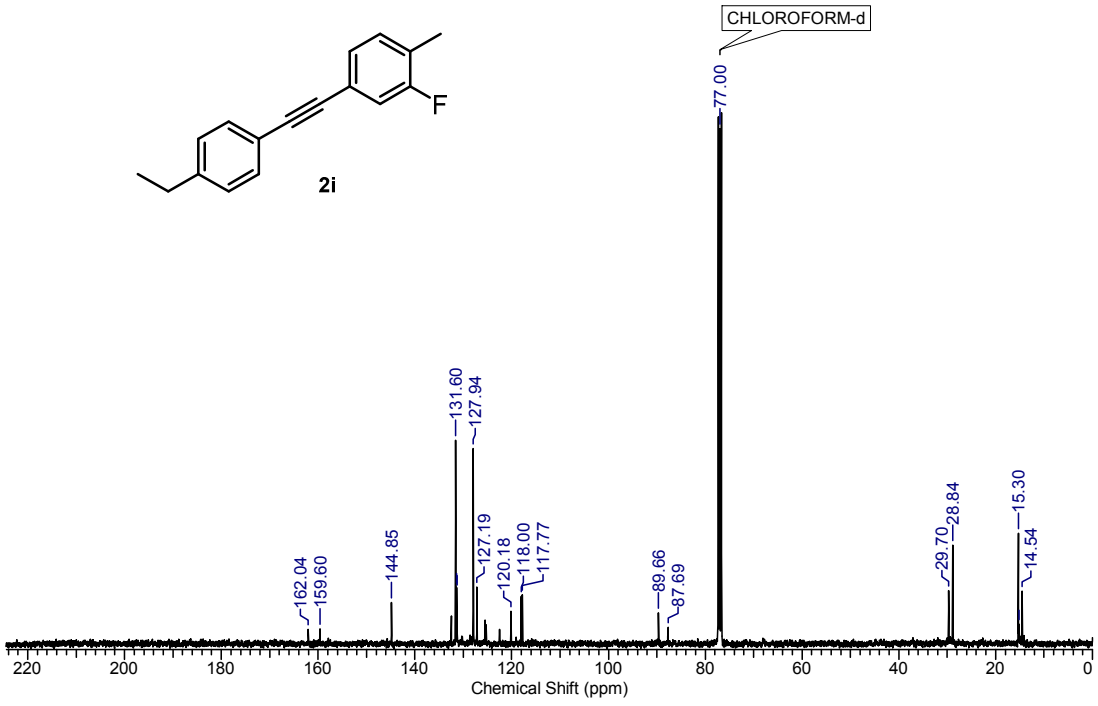

1u
CHLOROFORM-d
7.25
7.56
7.46
7.36
7.35
7.34
6.38
6.30
5.42
4.27
4.24
4.20
4.20
4.17
1.24
1.23
1.20
0.77
1.51
2.54
0.82
0.76
0.78
6.00
Chemical Shift (ppm)

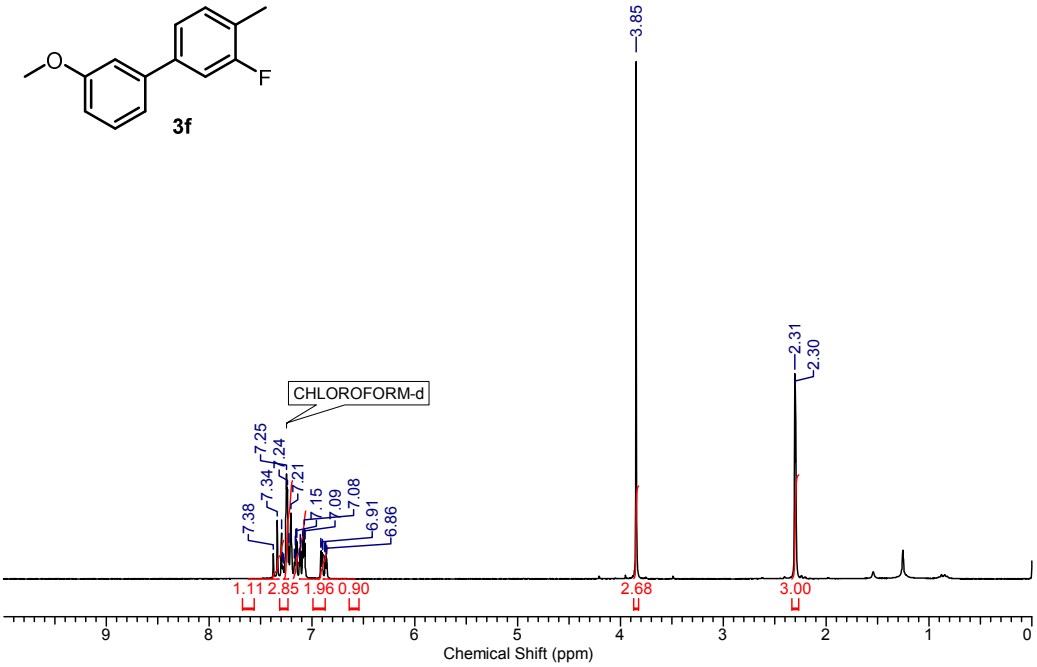

1u
CHLOROFORM-d
164.65
140.43
134.58
129.23
128.46
127.39
120.65
41.27
22.53
Chemical Shift (ppm)

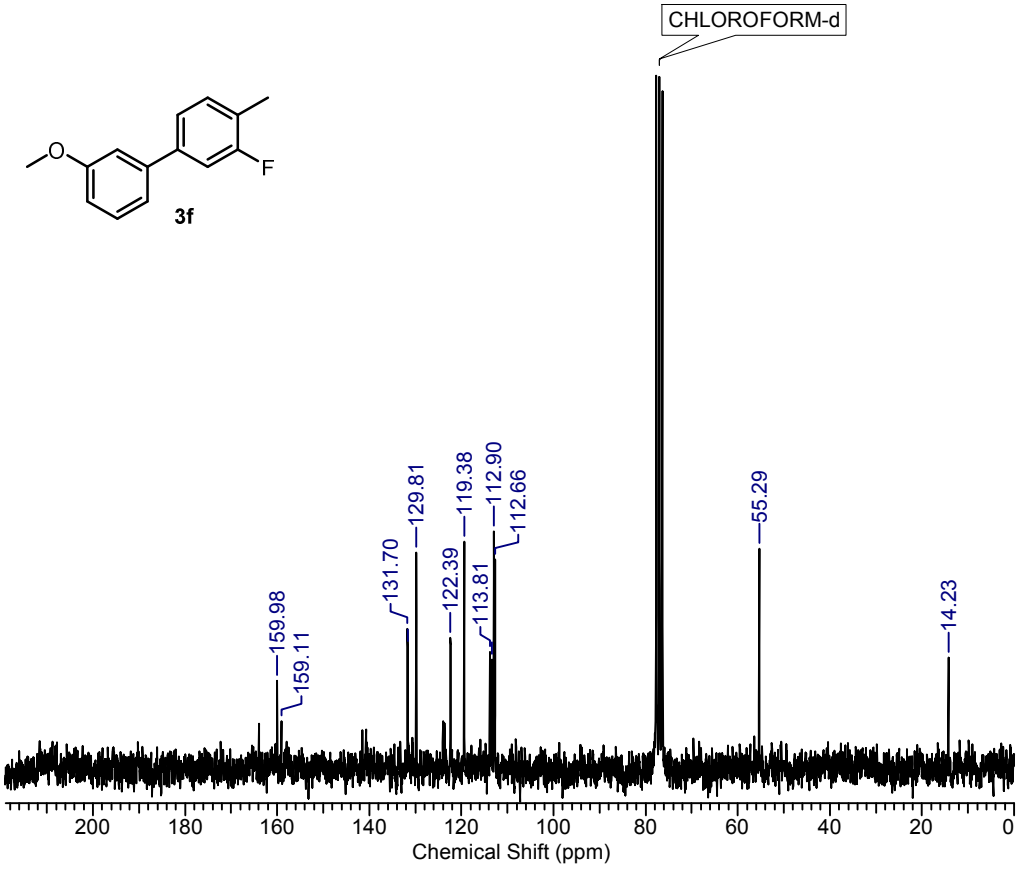

CHLOROFORM-d
2c
7.53
7.52
7.51
7.47
7.45
7.34
7.33
7.33
7.32
7.31
6.88
6.87
6.86
3.98
3.99
3.97
1.83
1.82
1.81
1.79
1.42
1.41
1.41
1.39
0.96
0.95
0.93
3.85
2.71
1.91
2.00
2.18
4.29
3.18
Chemical Shift (ppm)

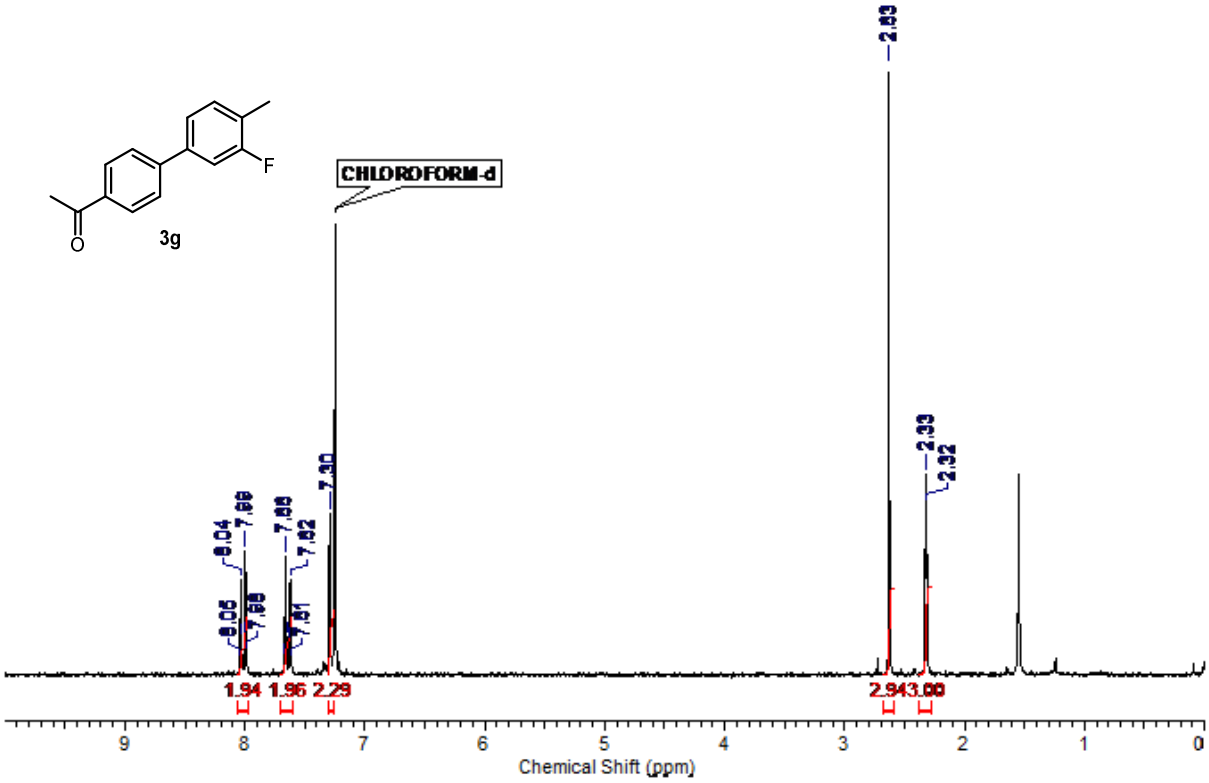

2c
CHLOROFORM-d
77.00
158.98
132.76
131.18
128.03
127.62
114.27
89.22
87.70
67.82
28.63
27.91
22.19
13.75
Chemical Shift (ppm)

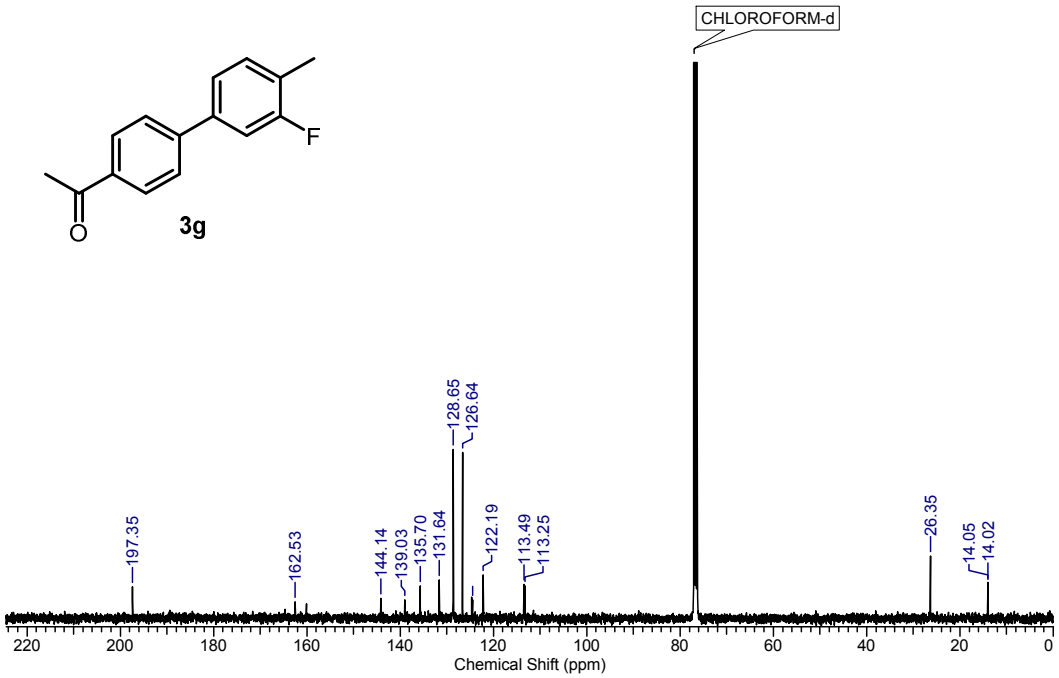

F
2i
CHLOROFORM-d
7.43
7.27
7.20
7.47
7.18
7.17
7.14
7.10
2.69
2.66
2.73
2.62
2.30
2.29
1.27
1.26
1.25
1.92
5.04
2.00
2.65
3.05
Chemical Shift (ppm)

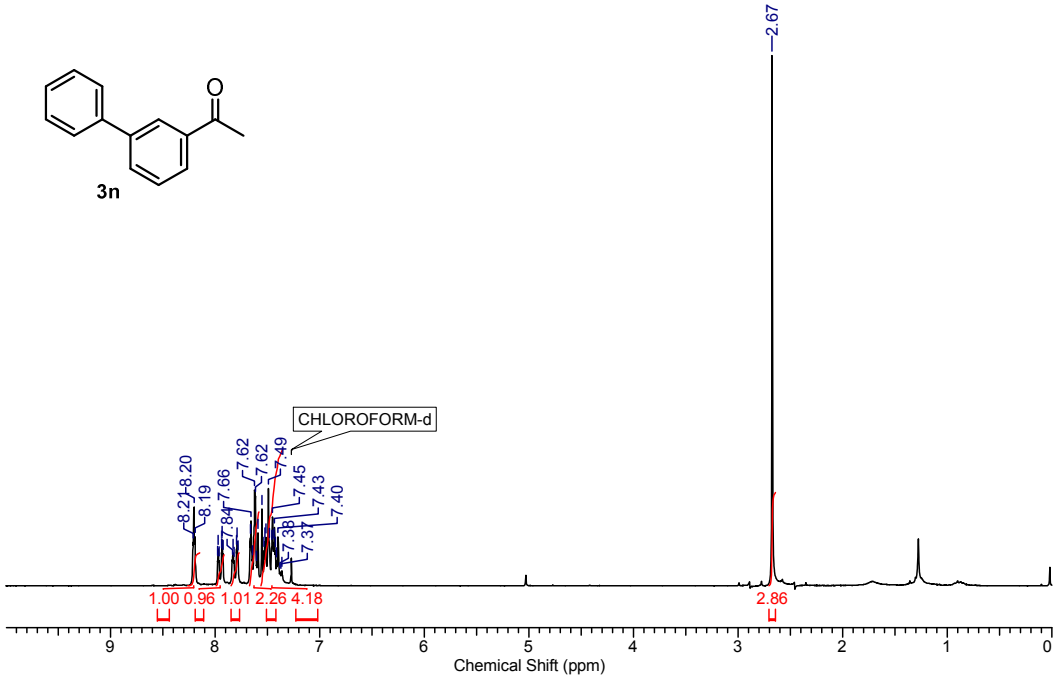

F
2i
CHLOROFORM-d
77.00
131.60
127.94
127.19
120.18
118.00
117.77
162.04
159.60
144.85
89.66
87.69
29.70
28.84
15.30
14.54
Chemical Shift (ppm)

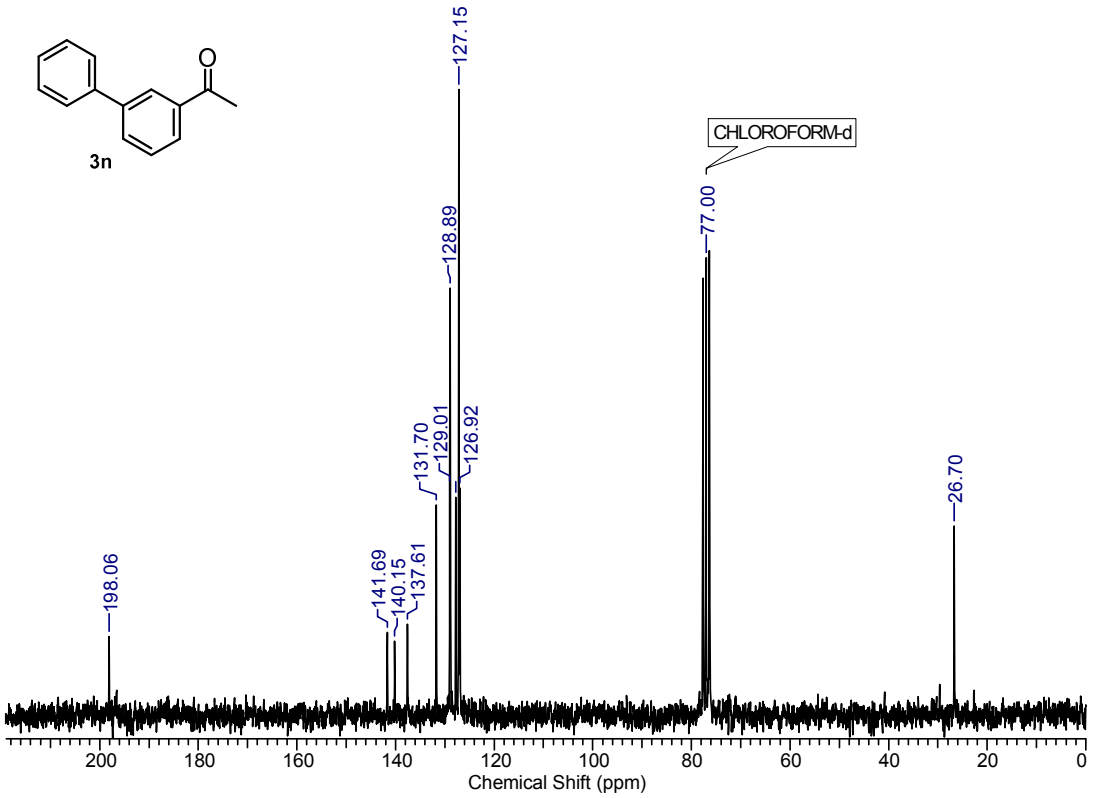

O
F
3f
3.85
2.31
2.30
CHLOROFORM-d
7.25
7.24
7.34
7.21
7.15
7.09
7.08
7.38
6.91
6.86
1.11 2.85 1.96 0.90
2.68
3.00
9 8 7 6 5 4 3 2 1 0
Chemical Shift (ppm)


O
F
3f
CHLOROFORM-d
159.98
159.11
131.70
129.81
122.39
119.38
113.81
112.90
112.66
55.29
14.23
200 180 160 140 120 100 80 60 40 20 0
Chemical Shift (ppm)


3g
CHLOROFORM-d
2.69
2.33
2.32
8.04
7.99
8.05
7.98
7.99
7.82
7.81
7.80
1.94 1.96 2.29
2.94 3.00
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


3g
CHLOROFORM-d
197.35
162.53
144.14
139.03
135.70
131.64
128.65
126.64
122.19
113.49
113.25
26.35
14.05
14.02
220
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


3n
2.67
CHLOROFORM-d
8.21
8.20
8.19
7.84
7.66
7.62
7.62
7.49
7.45
7.43
7.40
7.38
7.31
1.00 0.96 1.01 2.26 4.18
2.86
Chemical Shift (ppm)


3n
127.15
CHLOROFORM-d
128.89
77.00
131.70
129.01
126.92
26.70
198.06
141.69
140.15
137.61
Chemical Shift (ppm)

5.7. References

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Curriculum Vitae

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2009- present	Ph.D. Organic Chemistry, National Chemical Laboratory, Pune, India.
2008	M. Sc. Chemistry, Savitribai Phule Pune University, India .
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Fellowships

2009-2011	Junior Research Fellowship awarded by Council of Scientific and Industrial Research (CSIR), India (www.csir.res.in).
2011-2014	Senior Research Fellowship awarded by Council of Scientific and Industrial Research (CSIR), India.

Examination Qualified

2008	Qualified *National Eligibility Test* (NET) conducted by **Council of Scientific and Industrial Research (CSIR),**

Publications

Carbon-carbon bond forming reactions: Application of covalently anchored 2,4,6-triallyloxy-1,3,5-triazine (TAT) Pd(II) complex over modified surface of SBA-15 to Heck, Suzuki, Sonogashira and Hiyama cross coupling reactions Chandani Singh, Kiran Jawade, Priti Sharma, Anand P. Singh, Pradeep Kumar, *Cat. Comm*, **2015**, *69*,11.

Research experience

Ph.D. thesis	"Synthesis of Naturally Occurring Polyhydroxylated δ-lactones, aryne mediated synthesis of Phenyl indolines and Pd-SBA-TAT catalyzed C-C Cross Coupling Reactions"
Supervisor	Dr. Pradeep Kumar (CSIR-National Chemical Laboratory)

Conference & Presentations

2014 Poster presentation at **"10th Junior National Organic Symposium Trust (JNOST)"** conference IIT-Madras, Madras, India.

2015 Poster presentation at **"Humboldt Academy Pune Chapter"** Bogmallo, Goa, India.

Technical Skills

1 Excellent experience in conducting reactions under inert conditions.

2 Purification, and characterization of various organic and organometallic compounds in milligram and multigram scale.

3 Experience in handling HPLC, IR, GC.

Skilled in the interpretation of spectroscopic data (NMR, IR, MS, LCMS, TOF Mass, HRMS, IR, UV-VIS, GC, HPLC) towards the characterization of unknown compounds