Asymmetric Synthesis of Pyrazolidines, Pyrrolidines, Indolines and Tetrahydroquinolines *via* Organocatalyzed Sequential Reactions

A THESIS

SUBMITTED TO THE

UNIVERSITY OF PUNE

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

By

B. SENTHIL KUMAR

UNDER THE GUIDANCE OF

Dr. A. Sudalai

Chemical Engineering & Process Development Division,

CSIR-National Chemical Laboratory

Pune - 411008, INDIA

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DEDICATED TO MY BELOVED PARENTS AND DEAR WIFE

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled ***"Asymmetric Synthesis of Pyrazolidines, Pyrrolidines, Indolines and Tetrahydroquinolines via Organocatalyzed Sequential Reactions"*** which is being submitted to the ***University of Pune*** for the award of ***Doctor of Philosophy*** in ***Chemistry*** by ***Mr. B. Senthil Kumar*** was carried out by him under my supervision at the National Chemical Laboratory, Pune. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

March 2014 **Dr. A. Sudalai**
Pune (Research Guide)

NATIONAL CHEMICAL LABORATORY

DECLARATION

I hereby declare that the thesis entitled ***"Asymmetric Synthesis of Pyrazolidines, Pyrrolidines, Indolines and Tetrahydroquinolines via Organocatalyzed Sequential Reactions"*** submitted for the degree of Doctor of Philosophy in Chemistry to the University of Pune, has not been submitted by me to any other university or institution. This work was carried out at the National Chemical Laboratory, Pune, India.

March 2014
Pune

B. Senthil Kumar
CE & PD Division
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CONTENTS

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Above all, I thank God Almighty for His enormous blessings.

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B. Senthil Kumar

ABBREVATIONS

Ac	Acetyl
Ar	Aryl
Bn	Benzyl
Boc	*N-tert*-Butoxycarbonyl
$(Boc)_2O$	Ditert-butyl dicarbonate
n-Bu	*n*-Butyl
n-BuLi	*n*-Butyl Lithium
t-Bu	*tert*-Butyl
Cbz	Benzyloxy carbonyl
CH_2Cl_2	Methylene chloride
$CHCl_3$	Chloroform
CH_3CN	Acetonitrile
$CuSO_4$	Copper(II) sulfate
DBU	1,8-Diazabicyclo[5.4.0]undecene-7
DIBAL-H	Diisobutyl alulinum hydride
DMF	Dimethyl formamide
DMSO	Dimethyl sulphoxide
DMAP	*N,N*-dimethyl-4-aminopyridine
dr	Diastereomeric ratio
ee	Enantiomeric excess
Et	Ethyl
Et_3N	Triethylamine
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethyl alcohol
g	Grams
h	Hours
HCl	Hydrochloric acid
HPLC	High pressure liquid chromatography
H_2SO_4	Sulfuric acid
HNO_3	Nitric acid
IR	Infra red
IBX	2-Iodoxybenzoic acid
K_2CO_3	Potassium carbonate
KOH	Potassium hydroxide
$LiAlH_4$	Lithium aluminum hydride
LiHMDS	Lithium hexamethyldisilazide
M+	Molecular ion
Me	Methyl

MeOH	Methyl alcohol
MOM	Methoxymethyl
min	Minutes
mg	Miligram
mL	Milliliter
mp	Melting point
MS	Mass spectrum
Ms	Mesyl
$NaBH_4$	Sodium borohydride
$NaHCO_3$	Sodium bicarbonate
NaOH	Sodium hydroxide
Na_2SO_4	Sodium sulfate
NH_4Cl	Ammonium chloride
NH_4OH	Ammonium hydroxide
NBS	*N*-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
NMO	*N*-Methyl morpholine *N*-oxide
PCC	Pyridinium chlorochromate
Pd/C	Palladium on activated charcoal
PDC	Pyridinium dichromatel
$Pd(OH)_2$	Palladium hydroxide
Ph	Phenyl
p-TSA	*p*-Toluene sulfonic acid
PhNO	Nitrosobenzene
Py	Pyridine
TBS	*tert*-Butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TBAF	Tetrabutylammonium fluoride
TBDMSCl	*tert*-Butyldimethylsilyl chloride
TBDPSCl	*tert*-Butyldiphenylsilyl chloride
TFA	Trifluoroacetic acid
Ts	Tosyl

GENERAL REMARKS

1. All solvents were distilled and dried before use.

2. Petroleum ether refers to the fraction collected in the boiling range 60-80 °C.

3. Organic layers after every extraction were dried over anhydrous sodium sulfate.

4. Column Chromatography was performed over silica gel (230-400 mesh).

5. TLC analyses were performed over aluminum plates coated with silica gel (5-25 m) containing UV active G-254 additive.

6. IR spectra were recorded on a Perkin-Elmer model 683 B or 1605 FT-IR and absorptions were expressed in cm^{-1}.

7. ^{1}H and ^{13}C NMR spectra were recorded on Brucker FT AC-200 MHz instruments using TMS as an internal standard. The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet, dd = doublet of doublet, dt = doublet of triplet and ddd = doublet of doublet of doublet.

8. Optical rotations were carried out on JASCO-181 digital polarimeter at 25 °C using sodium D light.

9. Enantiomeric excesses were determined on Agilent HPLC instrument equipped with a chiral column.

10. HRMS data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump.

11. All melting points and boiling points are uncorrected and the temperatures are in centigrade scale.

12. Elemental analysis was done on Carlo ERBA EA 110B instrument.

13. The compounds, scheme and reference numbers given in each chapter refers to that particular chapter only.

ABSTRACT

The thesis entitled "**Asymmetric Synthesis of Pyrazolidines, Pyrrolidines, Indolines and Tetrahydroquinolines *via* Organocatalyzed Sequential Reactions**" is divided into four chapters. The title of the thesis clearly reflects the objective, which is to synthesize enantiomerically pure bioactive compounds and to develop useful synthetic methodologies involving organocatalyzed sequential reactions. **Chapter 1** deals with a new protocol involving sequential proline-catalyzed α-amination and Pd-catalyzed reductive cyclization of *o*-nitrohydrocinnamaldehydes that leads to facile synthesis of chiral tetrahydroquinolin-3-amines and its application in the asymmetric synthesis of inotropic agent, 1-[(*S*)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1-(2*H*)-yl]propan-1-one, (*S*-903). **Chapter 2** describes the organocatalyzed sequential α-amination or *syn*-Mannich/Corey-Chaykovsky reaction for the synthesis of substituted 4-hydroxypyrazolidines and 4-hydroxypyrrolidines. **Chapter 3** presents the asymmetric synthesis of substituted indolines and cinnolines *via* Cu-catalyzed intramolecular N-arylation of chiral hydrazine derivatives derived from proline-catalyzed α-amination of *o*-bromohydrocinnamaldehydes. **Chapter 4** presents organocatalyzed asymmetric synthesis of (*R*)-(+)-goniothalamin oxide, a trypanocidal active agent and one-pot tandem azidation, intramolecular [3+2]-cycloaddition of various ethyl acrylates for the regioselective synthesis of substituted 1,2,3- triazoles**.**

CHAPTER 1

A new Organocatalytic Route to Chiral 3-Aminated Tetrahydroquinoline Derivatives and its Application in the Synthesis of 1-[(*S*)-3-(Dimethylamino)-3,4-Dihydro-6,7-Dimethoxyquinolin-1-(2*H*)-yl]propan-1-one, (*S*)-903

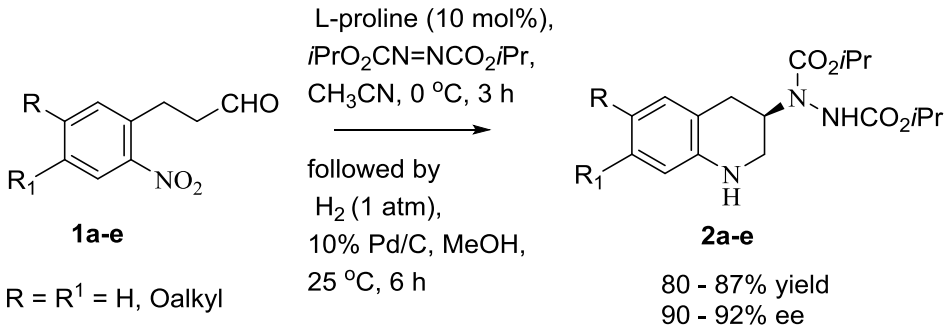
SECTION I: Proline-catalyzed asymmetric organic transformations

The field of asymmetric organocatalysis is rapidly developing and attracts an increasing number of research groups around the world. Proline, an abundant, inexpensive amino acid available in both enantiomeric forms, has emerged as the most practical and versatile organocatalyst.[1] In particular, proline catalyzed α-functionalization and its sequential reactions are arguably one of the most extensively studied and developed asymmetric catalytic reaction.[2] This section briefly describes

the modes of proline catalysis, its mechanism and its application in asymmetric synthesis.

<u>SECTION II</u>: Proline-catalyzed Sequential α -Amination/ Reductive Cyclization of *o*-Nitrohydrocinnamaldehydes: A High Yield Synthesis of Chiral 3-Aminated Tetrahydroquinolines

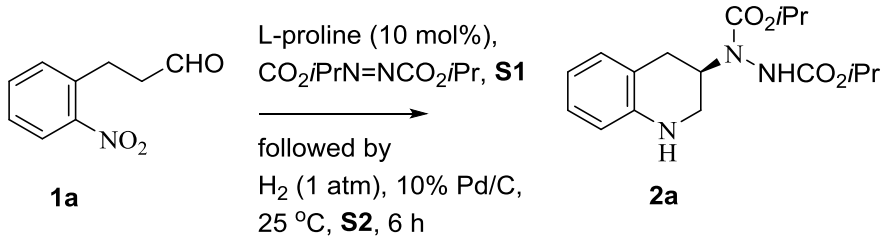
The 1,2,3,4-tetrahydroquinoline (THQ) is a very common structural motif found in numerous biologically active natural products and pharmacologically relevant therapeutic agents.[3] Due to the significance of these scaffolds in drug discovery and medicinal chemistry,[4] the development of new methodologies for the synthesis of 3-substituted THQ derivatives continues to be a very active field of research in recent years. Proline-catalyzed direct α-amination of aldehydes and its sequential reactions have become one of the most extensively studied organocatalytic reactions that provides for the efficient enantioselective synthesis of nitrogen containing structurally diverse molecular architectures.



<u>Scheme 1</u>: Sequential α-amination and reductive cyclization of *o*-nitrohydro cinnamaldehydes

In this section, we wish to disclose, for the first time, a sequential protocol involving α-amination of *o*-nitrohydrocinnamaldehydes and Pd-catalyzed intramolecular reductive cyclization that provides easy access to chiral 3-aminated THQs **2a-e** in high yields (**Scheme 1**). As a model substrate, α-amination of *o*-nitrohydro cinnamaldehyde **1a** with diisopropyl azodicarboxylate (DIAD) as an amine source was carried out in the presence of L-proline (10 mol%) followed by its reductive cyclization using 10% Pd/C as catalyst. The results of such a systematic study to identify the most suitable condition are presented in Table 1.

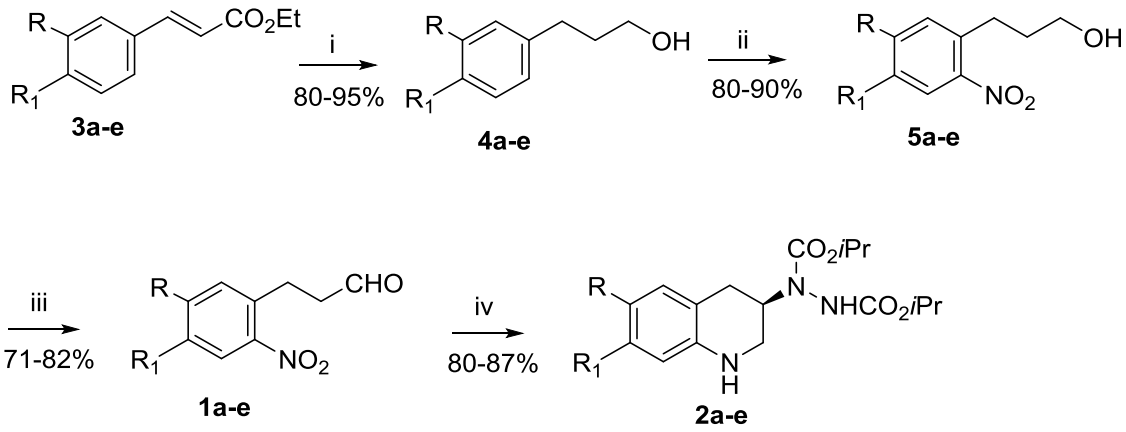
Table 1. Proline-catalyzed sequential α-amination/reductive cyclization of *o*-nitrohydrocinnamaldehyde.[a]



			product **(2a)**	
entry	S1	S2	yield (%)[b]	ee (%)[c]
1	CH_3CN	MeOH	85	60
2[d]	**CH_3CN**	**CH_3CN/MeOH**	**82**	**90**
3[d]	CH_2Cl_2	CH_2Cl_2/MeOH	65	nd
4	CH_2Cl_2	MeOH	70	75
5	THF	MeOH	35	nd
6	$CHCl_3$	MeOH	45	nd

[a]L-proline (10 mol%), *o*-nitrohydrocinnamaldehyde (5.5 mmol), *i*PrCO$_2$N=NCO$_2$*i*Pr (5 mmol), 3 h; [b] isolated yield after column chromatography; [c] ee determined by chiral HPLC analysis; [d] solvent ratio S2 (1:3).

Scheme 2 shows the synthetic sequences for the preparation of chiral 3-aminated THQ's. Several *α, β*-unsaturated esters **3a-e** were prepared and then subjected to $CoCl_2$-mediated reduction in the presence of $NaBH_4$ to give the corresponding saturated alcohols **4a-e** in 80-95% yields. The alcohols **4a-e** were then subjected to nitration with HNO_3 as nitrating agent and CH_2Cl_2 as solvent.



Scheme 2: (i) $NaBH_4$, $CoCl_2{\cdot}6H_2O$, $^iPr_2NH$, EtOH, 60 °C, 24 h; (ii) HNO_3, CH_2Cl_2, 0-25 °C, 1 h; (iii) PCC, dry CH_2Cl_2, 25 °C, 5 h; (iv) (a) DIAD, L-Proline, CH_3CN, 0 °C, 3h; (b) H_2 (1 atm), 10% Pd/C, MeOH, 25 °C, 6 h.

The resulting primary alcohols **5a-e** on PCC oxidation furnished aldehydes **1a-e.** Subsequently, *o*-nitrohydrocinnamaldehydes **1a-e** were subjected to sequential α-amination/reductive cyclization protocol that afforded the corresponding THQs **2a-e** in high yields (80-87%) and enantiomeric excess up to 91% (**Table 2**).

Table 2 : α-Amination-reductive cyclization: Substrate scope

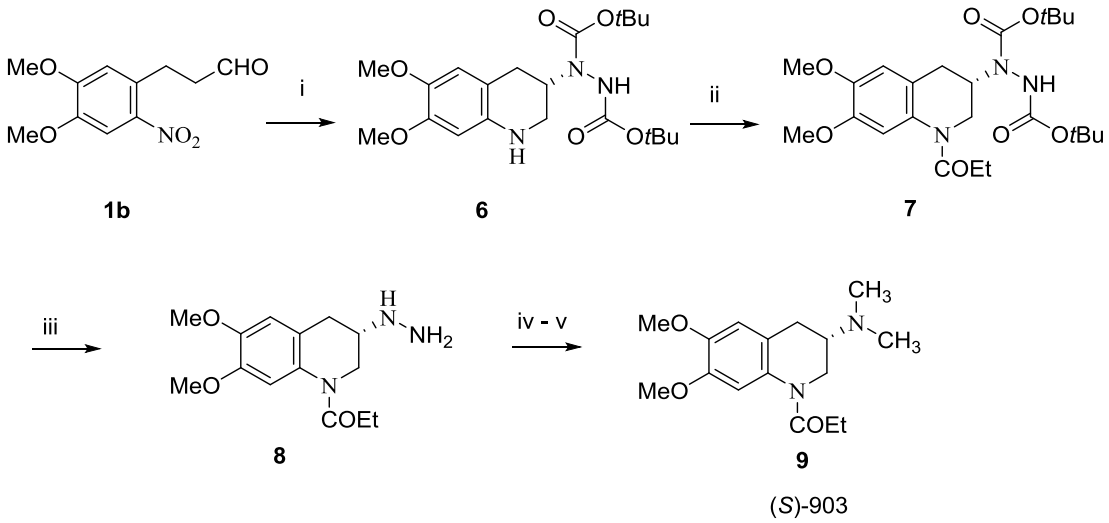
entry	substrates	products **2a-e**	
	1a-e	Yield (%)[a]	ee (%)[b]
a	R = R^1 = H	82	90
b	R = R^1 = OMe	85	90
c	R, R^1 = -O-CH_2-O-	87	91
d	R = O-pentyl ; R^1 = OMe	81	91
e	R = OTBDPS ; R^1 = OMe	80	90

[a] isolated yieds of 3-amino THQ's; [b] ee of THQ-3-amine determined by HPLC analysis.

SECTION III: A Concise Enantioselective Synthesis of 1-[(*S*)-3-(Dimethylamino)-3,4-Dihydro-6,7-Dimethoxyquinolin-1-(2*H*)-yl]propan-1-one, (*S*)-903

Although excellent diuretics and ACE inhibitors are available for the treatment of congestive heart failures, the only current approach that relies on the stimulation of cardiac contractility is the use of cardiac glycosides with a variety of therapeutic limitations. 1-[(*S*)-3-(Dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1(2*H*)-yl] propanone, (*S)*-903 **9** have recently been identified as potentially interesting positive inotropic agents.[5] The synthesis of **9** was started with readily accessible *o*-nitrohydrocinnamaldehyde derivative **1b**. The sequential α-amination of **1b** using D-proline as catalyst and di-*tert*-butyl azodicarboxylate as amine source and reductive cyclization under catalytic hydrogenation condition [H_2 (1 atm),10% Pd/C] gave 3-aminated THQ **6** in 82% yield. Amine functionality in THQ **6** was subsequently acylated [$(EtCO)_2O$, NEt_3, CH_2Cl_2] to give the corresponding amide **7** in 91% yields. The two Boc groups in the hydrazine functionality of **7** were then deprotected using trifluoroacetic acid to give hydrazine **8** in 91% yield. With the free hydrazine **8** in hand, the next step towards its completion was its hydrogenolysis under Raney Ni

reduction condition and subsequent reductive methylation (HCHO, HCO_2H) which afforded **9** in 73% yield and 92% ee (**Scheme 3**).



Scheme 3: (i) D-proline (20 mol%), *t*BuCO$_2$-N=N-CO$_2$*t*Bu, CH_3CN, 0 ^oC, 3 h; followed by H_2 (1 atm), 10% Pd/C MeOH, 6 h, 82%; (ii) $(CH_3CH_2CO)_2O$, Et_3N, CH_2Cl_2, 0 °C, 91%; (iii) TFA, CH_2Cl_2, 0-25 °C, 91%; (iv) H_2 (80 psig), Raney Ni, AcOH (cat.), MeOH, 25 °C, 24 h. (v) HCHO (40 % aq. solution), HCO_2H, 80 °C, 3 h, 73%.

CHAPTER 2

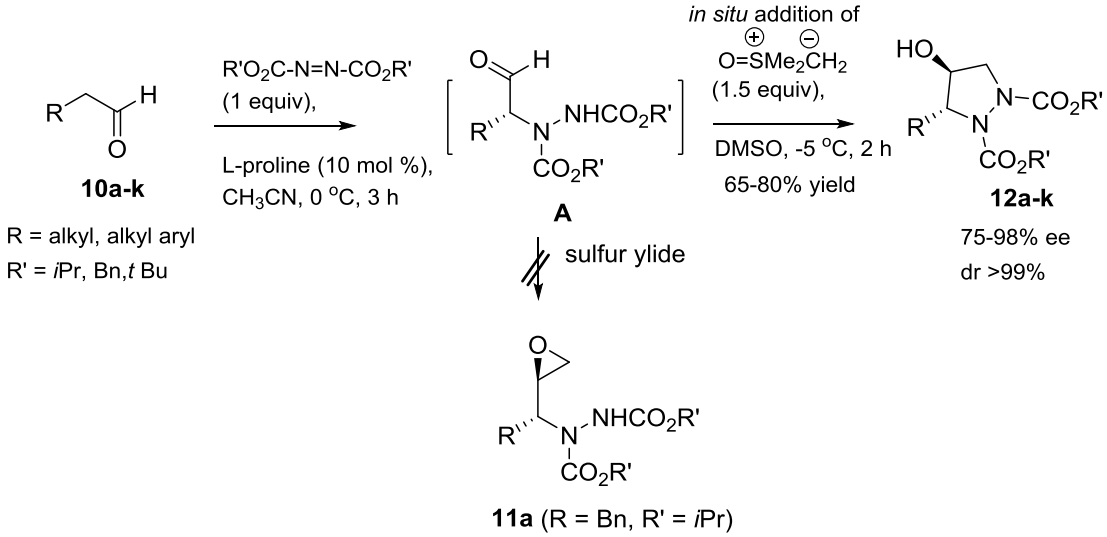
Organocatalyzed Sequential α-Amination or *syn*-Mannich/Corey-Chaykovsky Reaction of Aldehydes for the Asymmetric Synthesis of Substituted 4-Hydroxypyrazolidines and 4-Hydroxypyrrolidines

Five-membered nitrogenous heterocycles, in particular, pyrazolidines and pyrrolidines, are the key structural motifs prevalent in numerous biologically significant molecules and natural alkaloids. In this chapter we have presented the *in situ* trapping of chiral α- and β- amino aldehydes derived from proline-catalyzed α-amination and *syn*-Mannich reaction with Corey's reagent for the enantio- and diastereoselective synthesis of 4-hydroxypyrazolidine **12a-k** and 4-hydroxy pyrrolidine derivatives **17a-k** respectively.

SECTION I: Organocatalytic Sequential α-Amination/Corey-Chaykovsky Reaction of Aldehydes: A High Yield Synthesis of 4-Hydroxypyrazolidine Derivatives

Pyrazolidines**,** pyrazolines and pyrazoles are the interesting class of heterocyclic units found in many complex bioactive natural products.[6] Among them chiral hydroxypyrazolidine derivatives **12a-k** represent not only useful building blocks in the pharmaceutical industry but also powerful intermediates in the preparation of

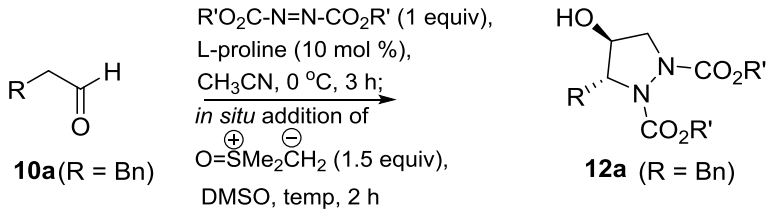
enantiopure 1,3-diamines.[7] In this section, a "one-pot" procedure of tandem α-amination/Corey-Chaykovsky reaction of aldehydes **10a-k** that proceeds to give 4-hydroxypyrazolidine derivatives **12a-k** in high enantio- and diastereoselectivity is described (**Scheme 4**).



Scheme 4: *In situ* trapping of α-amino aldehydes **A** with dimethyloxo sulfonium methylide

As a model substrate, the amination of hydrocinnamaldehyde **10a** was carried out following the List protocol[8] that produced the corresponding α-amino aldehyde **A** *in situ*. As the intermediate **A** is prone to racemization, several experiments were conducted to identify the most effective and suitable reaction condition for Corey-Chaykovsky reaction; the results of which are presented in **Table 3.**

Table 3. Proline-catalyzed α-amination/Corey-Chaykovsky reaction of hydrocinnamaldehyde



no.	amine (R')	temp (°C)	yield of **12a** (%)[b]	ee (%)[c]	de (%)[d]
1	*i*Pr	25	80	5	99
		10	75	75	99
		-5	73 (45)[e]	91 (79)[e]	99
		-20	52	88	99

		-40	48	84	99
2	Bn	-5	71	90	100
3	*t*Bu	-5	60	80	100

[a] aldehyde (5 mmol), amine ($R'O_2C$-N=N-CO_2R') (5 mmol), L-proline (10 mol %), dimethyloxosulfonium methylide (7.5 mmol); [b] isolated yield after column chromatographic purification; [c] determined from chiral HPLC analysis (Chiracel OD-H, Whelk-01columns; n-hexane/2-propanol); [d] Product is obtained as a single diastereomer as determined from ^1H, ^{13}C NMR and HPLC analysis; [e] refers to 2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilanyloxymethyl]pyrro-lidine is used as catalyst.

With the optimized reaction condition in hand, aldehydes bearing various functionalities were subjected to the sequential protocol and the products **12a-k** were indeed obtained in high yields (65-80%), and excellent enantioselectivities (75-98% ee) with dr >99% (**Table 4**).

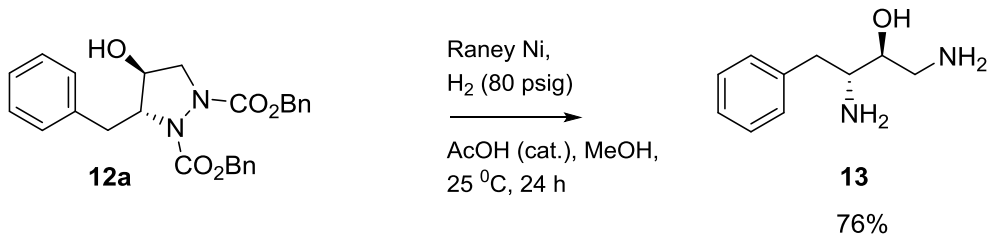
Table 4. Proline-catalyzed asymmetric tandem α-amination/Corey-Chaykovsky reaction [a]

no.	substrates **10a-k** (R)	amine (R')	products[a] **12a-k**	
			yield (%)[b]	ee (%)[c]
1	benzyl (**10a**)	*i*Pr	73	91
2	3,4-dimethylbenzyl (**10b)**	*i*Pr	71	94
3	3,4-methylenedioxybenzyl (**10c**)	Bn	80	90
4	2-Br-4,5-methylenedioxybenzyl (**10d**)	*i*Pr	74	95
5	2-CN-4,5-methylenedioxybenzyl (**10e**)	*i*Pr	75	75
6	naphthalene-1-yl-methyl (**10f**)	*i*Pr	70	90
7	2-NO_2-4,5-dimethoxybenzyl (**10g**)	*i*Pr	68	90
8	n-butyl (**10h**)	Bn	65	92
9	4-azidopropyl (**10i**)	Bn	66	91
10	3-benzyloxymethyl (**10j**)	Bn	70	90
11	3-benzyloxypropyl (**10k**)	*i*Pr	72	98

[a] aldehyde (5 mmol), amine source ($R'O_2C$-N=N-CO_2R') (5 mmol), L-proline (10 mol %), dimethyloxosulfonium methylide (7.5 mmol). [b] isolated yield after column chromatographic purification, [c] determined from chiral HPLC analysis (Chiracel OD-H, Whelk-01column; n-hexane/2-propanol).

A single-step transformation of **12a** under catalytic hydrogenation conditions [Raney Ni, H_2, (80 psig)] gave the corresponding *anti*-1,2-aminoalcohol **13,** which are common structural subunits present in phytospingosines[9a,b] and HIV protease

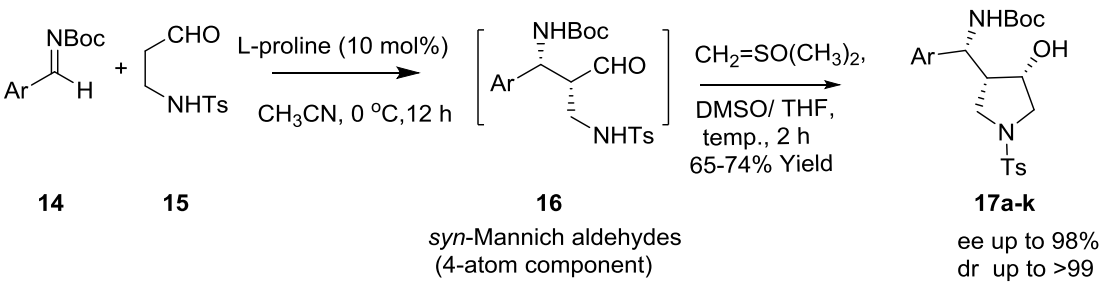
inhibitors,[9c,d] thus constituting an important application of this methodology (**Scheme 5**).



Scheme 5: Synthesis of *anti*-1,2-aminoalcohol

SECTION II: Proline-Catalyzed *syn*-Mannich/Corey-Chaykovsky Reaction Cascade *via* [4+1]-Annulation. A High Yield Synthesis of 4-Hydroxypyrrolidine Derivatives

Five-membered nitrogen-containing heterocycles are structural components of many bioactive compounds, natural products and building blocks in organic and diversity-oriented synthesis.[10] Also, these find wide applications such as chiral auxillaries,[11] chiral ligands,[12] and organocatalysts[13] in asymmetric synthesis. As part of our research program directed toward asymmetric synthesis of bioactive molecules employing proline as organocatalysts, we were interested in investigating the feasibility of a new diastereoselective formal [4+1]-annulation reaction for the asymmetric synthesis of substituted 4-hydroxypyrrolidines **17a-k**, by employing chiral β, β'-diamino aldehydes **16** (generated from proline-catalyzed *syn*-Mannich reaction) as 4-atom component coupled with dimethylsulfoxonium methylide (**Scheme 6**).[14]

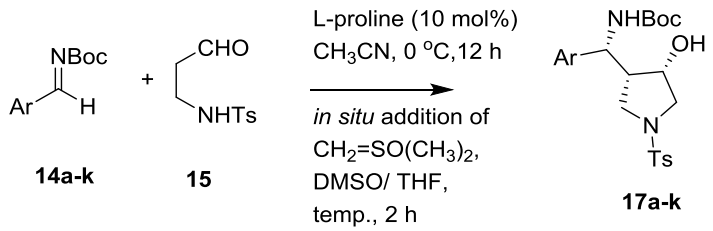


Scheme 6. Proline-catalyzed *syn*-Mannich/Corey-Chaykovsky reaction

In a preliminary study, β-amino aldehyde **15** was treated with N-Boc imine **14a** following the List protocol[15] that produced the corresponding β, β'-diamino aldehyde **16a** (*syn*-Mannich adduct) *in situ*. Several experiments were then conducted to

identify the most effective and suitable condition for this sequential protocol; the results of which are presented in **Table 5**.

Table 5. Synthesis of substituted 4-hydroxypyrrolidine **17a-k**[a]



entry	substrates Ar	temp (°C)	products **(17a-k)** yield (%)[b]	ee (%)[c]	dr (%)[d]
1	phenyl (**17a**)	25	68	92	4:1
	phenyl	0	72	92	9:1
	phenyl	**-10**	**72**	**93**	**>99**
	phenyl	-20	60	92	>99
2	4-OMe-phenyl (**17b**)	-10	74	96	>99
3	4-CF_3-phenyl (**17c**)	-10	70	92	>90
4	4-tolyl (**17d**)	-10	70	94	>99
5	2-naphthyl (**17e**)	-10	63[e]	98	>99
6	4-Br-phenyl (**17f**)	-10	61[e]	98	>99
7	4-F-phenyl (**17g**)	-10	66[e]	96	>99
8	4 –CN-phenyl (**17h**)	-10	71[f]	nd	4:1
9	4-SMe-phenyl (**17i**)	-10	65	93	>99
10	thiophenyl (**17j**)	-10	68[g]	92	>90
11	furfuryl (**17k**)	-10	64[g]	91	>90

[a]imine (5 mmol), aldehyde (5.5 mmol), *L*-proline (10 mol %), dimethyloxosulfonium methylide (7.5 mmol), DMSO/THF (1:1), -10 °C, 2 h; [b]isolated yield after column chromatographic purification; [c] % ee determined from chiral HPLC analysis (Chiracel OD-H, Chiracel AS-H n-hexane/2-propanol); [d]dr determined from ^{1}H NMR analysis; [e] corresponding oxazolidinones were isolated by using 15 mmol of ylide for 12 h at rt; [f]product obtained as inseparable diastereomers; [g] isolated yield of major diastereoisomer separated *via* flash column chromatography; nd = not determined.

Having established the optimal reaction conditions for the [4+1]-annulation, we next examined the scope of the reaction. Substrates having fluoro, bromo, cyano, methoxy, methyl, trifluoromethyl and thiomethyl groups on the aromatic nucleus as well as

heteroaromatic compounds such as thiophenyl and furfuryl were well-tolerated under the reaction conditions. For all the cases studied, the products **17a-k** were indeed obtained in high yields (65-74%) with excellent enantio- and diastereoselectivities (90-98% ee and dr up to >99%) (**Table 5**).

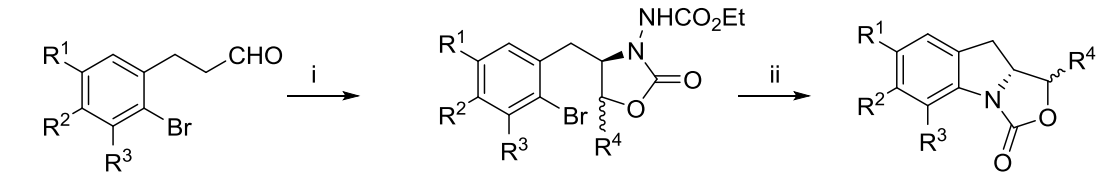
CHAPTER 3

Asymmetric Synthesis of 2-Substituted Indolines and 3-Substituted Cinnolines *via* Cu-Catalyzed Intramolecular N-Arylation of Chiral Hydrazine Derivatives, Derived from Proline-catalyzed α-Amination of *o*-Bromohydrocinnamaldehydes

Substituted cinnoline and indoline derivatives are important skeletons that are found in natural products and pharmaceuticals and thus are potential candidates for biologically important molecules. In this chapter, we have described for the first time, proline-catalyzed amination route for the asymmetric synthesis of substituted indolines and cinnolines involving Cu-catalyzed intramolecular N-arylation.

SECTION I: Asymmetric Synthesis of 2-Substituted Indolines *via* "One-Pot" N-Alkylation/E1cB/Intramolecular N-Arylation of Chiral Hydrazines, Derived from Proline-catalyzed α-Amination of *o*-Bromohydrocinnamaldehyes

Chiral indoline frameworks are found as sub-structure in many naturally occurring alkaloids and biologically active molecules.[16] It exhibit wide spread application not only as chiral auxillary and building blocks in total synthesis of bioactive natural products,[17] but also as a common motif in design of new biologically significant compounds.



18a-g **19a-g** **21a-g**

$R^1 = R^2 = R^3$ = H, OH, OMe, $-OCH_2O-$, NO_2

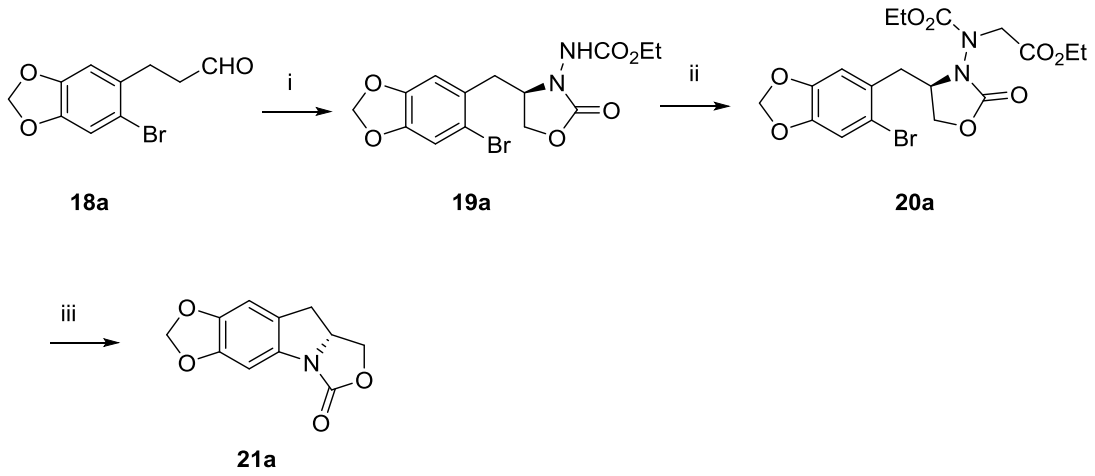
R^4 = H, allyl

80-87% yield
>98% ee

Scheme 7: (i) (a) DEAD, L-Proline, CH_3CN, 0 °C, 3 h then MeOH, $NaBH_4$, 0 °C, 45 min or allyl bromide, Zn, aq. NH_4Cl, 0 °C, 2 h b) K_2CO_3, EtOH, 70 °C, 12 h or NaOH, EtOH: H_2O (4:1), 0-25 °C, 6 h; (ii) $BrCH_2CO_2Et$ (1.2 equiv), Cs_2CO_3 (2.0 equiv), CH_3CN, 50 °C, 5 h; then CuI (10 mol%), DMEDA (10 mol%) Cs_2CO_3 (1.5 equiv), 95 °C, 12 h.

In particular, enantioenriched 2-substituted indolines are considered as privileged structures due to their diverse pharmacological activities[18] as found in many compounds such as benzastatin E, pentopril etc.

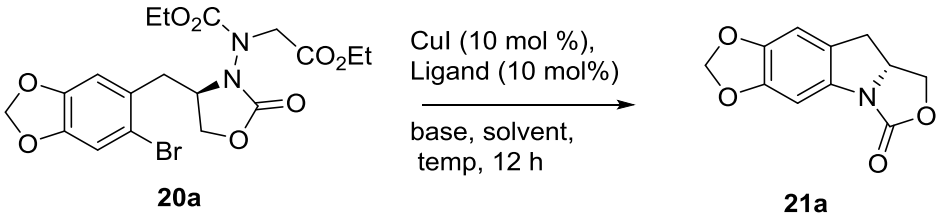
This section discloses an elegant method that provides for the asymmetric synthesis of 2-substituted indolines **21a-g** directly from chiral hydrazine derivatives **19a-g** *via* N-alkylation-E1cB[19]-N-arylation cascade (**Scheme 7**).In a preliminary study, *o*-bromohydro cinnamaldehyde **18a** was subjected to L-proline (10 mol%)-catalyzed asymmetric α-amination, followed by *in situ* reduction of aldehyde with $NaBH_4$ in MeOH to furnish the crude amino alcohol. Conversion of crude amino alcohol to the corresponding oxazolidinone **19a** proceeded smoothly using K_2CO_3 in 85% yield and >99% ee. Further, treatment of **19a** with bromoethyl acetate gave N-alkylated product **20a** in 92% yield (**Scheme 8**).



Scheme 8: (i) (a) L-Proline (10 mol%), DEAD, CH_3CN, 0 ^oC, 3 h then MeOH, $NaBH_4$; after work up K_2CO_3, MeOH, 70 ^0C, 6 h, 85% yield, >99% ee; (ii) $BrCH_2CO_2Et$, Cs_2CO_3, CH_3CN, 50 ^oC, 5 h, 92%; (iii) CuI (10 mol%), DMEDA (10 mol%), Cs_2CO_3 (1.5 equiv), 95 ^oC, 12 h 85%.

N-Alkylated hydrazine derivative **20a** was then subjected to several optimization studies to identify the best condition for E1cB-intramolecular N-arylation cascade to deliver the corresponding chiral indoline **21a**; the results of which are presented in **Table 6**.

Table 6. Optimization studies for E1cB elimination/N-arylation cascade[a]



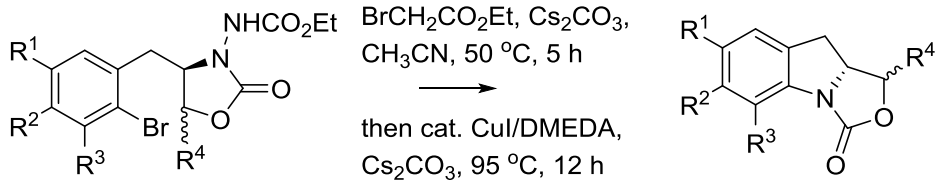
20a **21a**

entry	solvent	ligand	temp (^oC)	base	Yield **67a** (%)[b]
1	DMSO	L-proline	100	K_2CO_3	-
2	DMSO	L-proline	100	Cs_2CO_3	60
3	DMF	L-proline	100	Cs_2CO_3	45
4	CH_3CN	L-proline	100	Cs_2CO_3	56
5	**CH_3CN**	**DMEDA**	**95**	**Cs_2CO_3**	**85**
6	CH_3CN	DMEDA	65	Cs_2CO_3	35

[a] **66a** (1 mmol), CuI (10 mol%), ligand (10 mol%), base (2 equiv), solvent (10 mL), [b]isolated yield after chromatographic purification. DMEDA: N,N'-dimethylethylenediamine.

With this result in hand, we then turned our attention to convert chiral hydrazine **19a** directly to 2-substituted indoline **21a** in a "one-pot" sequential manner without isolating the intermediate **20a** (**Scheme 8**). Accordingly, N-alkyaltion of **19a** was carried out with bromoethyl acetate which gave N-alkylated product **20a**. Further, *in situ* generated **20a** was reacted with CuI/DMEDA catalyst and Cs_2CO_3 at 95 ^oC for 12 h, which gave the corresponding indoline **21a** in excellent yield (83%) (entry 1,**Table 7**). It was found that, this cascade protocol took place smoothly to provide **21a-g** in a "one-pot" reaction which comprises of several sequential reactions taking place in single step. As can be seen, chiral hydrazines bearing electron-releasing groups such as hydroxy, methoxy and methylenedioxy and electron-withdrawing substituent like nitro group on the aromatic nucleus underwent this cascade reaction smoothly to give the corresponding 2-substituted indolines in good yields. Substrates with differently substituted methoxy group which alters the electronic environment of the aromatic ring were also well-tolerated for the cascade reaction (entries 1, 3 and 5 **Table 7**).

Table 7. Asymmetric synthesis of 2-substituted indolines [a]



19a-g **21a-g**

entry	substrates **(19a-g)**				indolines **(21a-g)**
	R^1	R^2	R^3	R^4	Yield (%)[b]
1	-OCH_2O-		H	H	83
2	OMe	OH	H	H	87
3	OMe	H	OMe	H	81
4	OMe	OMe	OMe	H	80
5[c]	H	H	H	H	88
6	OMe	OMe	H	$CH_2CH{=}CH_2$	87
7[c]	H	NO_2	H	H	86

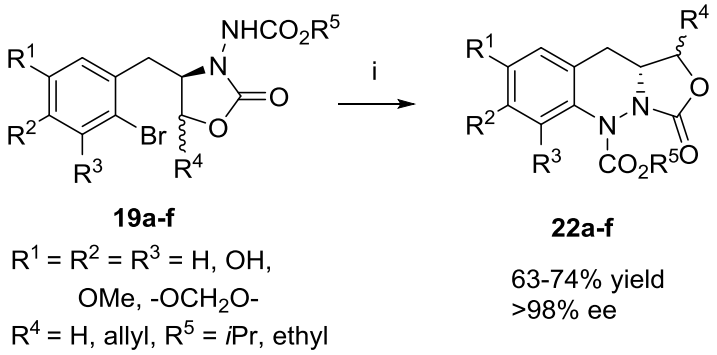
[a] **19a-g** (1 mmol), $BrCH_2CO_2Et$ (1.2 equiv), Cs_2CO_3 (2.0 equiv), CH_3CN (7mL), 50 °C, 4 h; then CuI (10 mol%), DMEDA (10 mol%), Cs_2CO_3 (1.5 equiv), 95 °C, 12 h; [b]isolated yield after chromatographic purification. DMEDA: N,N'-dimethylethylenediamine;[c] chiral hydrazino alcohol was used as indoline precursor.

Additionally, more sterically hindered hydrazines with two chiral centres could also be employed successfully for this reaction (**21g**). For all the cases studied, indoline derivatives **21a-g** was indeed obtained in high yields (80-87%).

<u>SECTION II</u>: Asymmetric Synthesis of 3-Substituted Dihydrocinnoline Derivatives *via* Cu-Catalyzed Intramolecular N-Arylation of Chiral Hydrazines derived from Proline-Catalyzed *α*-Amination of *o*-Bromohydrocinnamaldehyes

The cinnoline scaffold is considered as a previleged structural motif in agriculture, biology, and medicine.[20] For example, cinoxacine is a cinnoline analogue of quinoline antibacterials used for urinary tract infection while ICI-D-7569 is an anxiolytic agent. Significant commercial interest in the development of cinnoline derivatives is evidenced by the large number of patents filed in this area.[21] Chiral 3-substituted cinnolines **22,** which are not only structural analogs of cinnolines but also resemble chiral piperazic acid derivative. Hence, chiral cinnolines can be an attractive target for pharmaceuticals, since piperazic acids are components of several naturally-

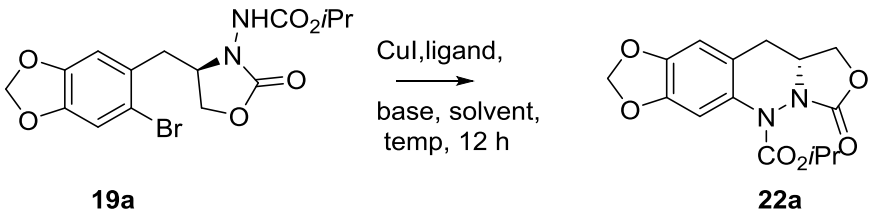
occurring cyclodepsipeptides with remarkable biological activities.[22],This section describes CuI/DMEDA-catalyzed intramolecular N-arylation of chiral hydrazine derivatives **19a-f** that led to the asymmetric synthesis of 3-substituted dihydrocinnolines **22a-f** in high yields (**Scheme 9**).



Scheme 9: CuI (10 mol%), DMEDA (10 mol%), Cs_2CO_3 (2 equiv), 95 ^oC, 12 h.

A systematic study of intramolecular N-arylation of chiral hydrazine **19a** was conducted to identify the optimized condition for the synthesis of cinnoline derivatives (**Table 8**).

Table 8. Optimization studies for cinnoline synthesis[a]



entry	solvent	ligand	temp (^oC)	base	yield (%)[b]
1	DMSO	L-proline	120	K_2CO_3	36
2	DMF	L-proline	120	K_2CO_3	30
3	**CH_3CN**	**DMEDA**	**100**	**Cs_2CO_3**	**72**
4	DMSO	DMEDA	100	Cs_2CO_3	35

[a]**19a** (1 mmol), CuI (10 mol%), ligand (10 mol%), base (1 equiv.), solvent (7mL), [b]isolated yield after chromatographic purification. DMEDA: N,N'-dimethylethylenediamine.

With the optimized reaction conditions in hand (entry 3, **Table 8**), we then investigated the scope of the reaction by subjecting several chiral hydrazines (**19a-f**) to this intramolecular N-arylation protocol. As can be seen, this N-arylation reaction

took place smoothly with other aromatic substrates having different electronic environments to provide the corresponding chiral cinnolines **22a-f** in good yields (63-72%) (**Table 9**).

Table 9 : Asymmetric synthesis of 3-substituted cinnolines *via* N-arylation of chiral hydrazine derivatives[a]

entry	substrates (**19a-f**)				cinnolines **(22a-f)**
	R^1	R^2	R^3	R^4	Yield (%)[b]
1	$-OCH_2O-$		H	H	72
2[c]	OMe	OH	H	H	70
3	OMe	H	OMe	H	72
4[c]	OMe	OMe	OMe	H	65
5	H	H	H	H	70
6	OMe	OMe	H	$CH_2CH=CH_2$	63

19a-f (1 mmol), CuI (10 mol%), DMEDA (10 mol%), Cs_2CO_3 (1.5 equiv), CH_3CN (8 mL). [b]isolated yield after chromatographic purification.[c] hydrazinoalcohol was used directly as cinnoline precursor with Cs_2CO_3 (2.2 equiv). DMEDA = N,N'-dimethylethylenediamine.

CHAPTER 4

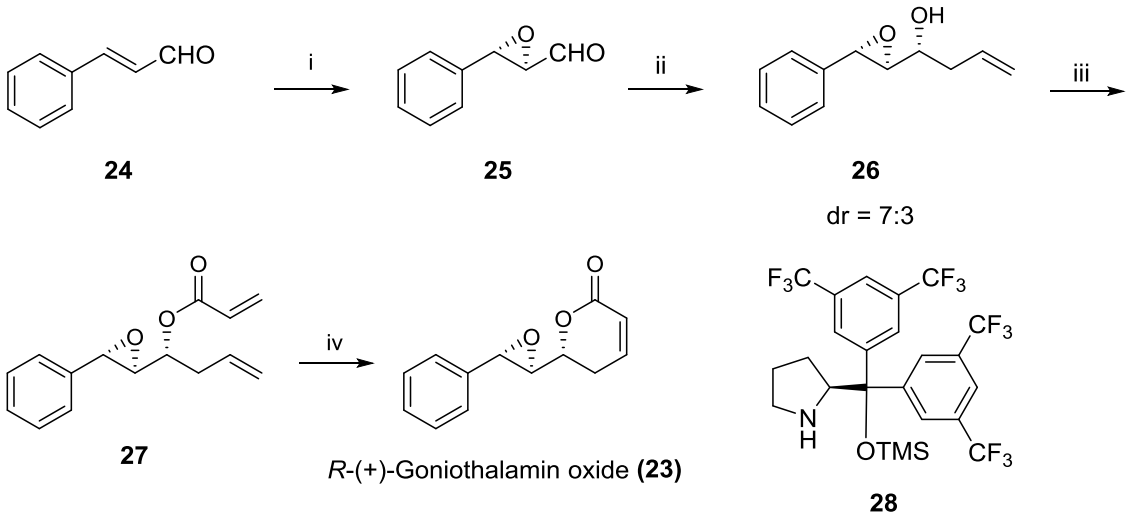
A Concise Enantioselective Synthesis of *R*-(+)- Goniothalamin oxide and Tandem Azidation, Intramolecular [3+2]-Cycloaddition of Acrylates for the Regioselective Synthesis of Triazole Derivatives

In this chapter we have described a short enantioselective synthesis of (*R*)-(+)-goniothalamin oxide using organocatalyzed asymmetric epoxidation of α, β -unsaturated aldehyde followed by diastereoselective allylation strategy and a novel one-pot protocol for the regioselective synthesis of substituted triazoles.

SECTION I: A Concise Enantioselective Synthesis of *R*-(+)-Goniothalamin Oxide, a Trypanocidal Active Agent *via* Organocatalyzed Asymmetric Epoxidation and Diastereoselective Allylation of Aldehydes

Styryl lactones are a group of secondary metabolites commonly isolated from the genus Goniothalamus.These bioactive natural products with relatively small and densely functionalized molecules are found to exhibit cytotoxicity on a variety of cells lines including: MCF-7, T47D, and MDA-MB-231 (breast carcinoma); HeLa (human cervical carcinoma); HL-60 (leukemia carcinoma); Caov-3 (ovarian carcinoma). In particular, R-(+)-goniothalamin oxide (2) shows significant trypanocidal activity

against free trypomastigotes forms of trypanosome cruzi.[23] In continuation of our research work on organocatalyzed reactions as applied in the asymmetric synthesis of bioactive molecules and natural products, we undertook the synthesis of *R*-(+)-goniothalamin oxide (**23**) employing organocatalyzed epoxidation of cinnamaldehyde **24** followed by Lewis acid - mediated diastereoselective allylation of epoxy aldehyde **25** as the key reactions (**Scheme 10**).

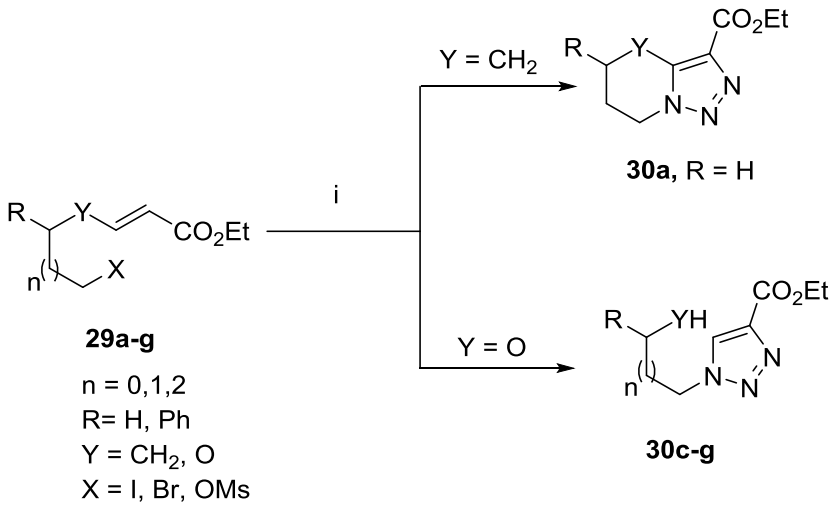


Scheme 10: (i) 35% H_2O_2 (w/w) in water, **28** (10 mol%), CH_2Cl_2, 25 ^oC, 5 h; (ii) tributyl allyl stannane, $LiClO_4$, diethylether, 0-25 ^oC, 7 h, 70% (2 steps), dr = 7:3; (iii) acrylic acid, DMAP, DCC, CH_2Cl_2, 0 ^oC-25 ^oC, 8 h, 91%; (iv) Grubbs' IInd generation catalyst (10 mol %), CH_2Cl_2, 45 ^oC, 8 h, 85%.

The synthesis of *R*-(+)-goniothalamin oxide (**23**) started from commercially available cinnamaldehyde **24**, which on asymmetric epoxidation with Jorgensen protocol[24] using aq. H_2O_2 in the presence of prolinol derivative **28** as the catalyst resulted in the formation of the labile epoxy aldehdye **25**. *In situ* generated chiral epoxy aldehdye **25** was subjected to $LiClO_4$ mediated diastereoselective allylation to furnish the key intermediate homoallylic alcohol **26** in 70% yield with dr = 7:3. However, the Steglich esterification of homoallylic alcohol **26** with acrylic acid, (DCC, DMAP, CH_2Cl_2) gave the acrylate ester **27** as a separable diastereomers which were seperated *via* flash column chromatography. Finally, the ring closing metathesis of acrylate ester **27** with Grubbs' IInd generation catalyst afforded *R*-(+)-goniothalamin oxide (**23**) in 76% yield.

<u>SECTION II:</u> Tandem Azidation, Intramolecular [3+2]-Cycloaddition and Aromatization of Substituted Ethyl Acrylates: A "One-Pot" Sequential Process for the Regioselective Synthesis of Substituted 1,2,3-Triazoles

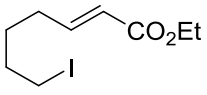
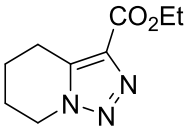
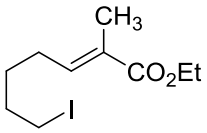
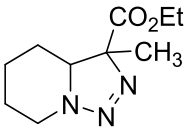
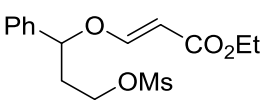
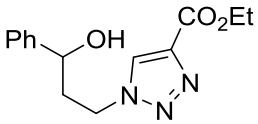
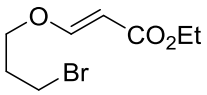
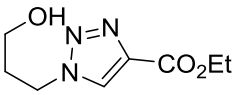
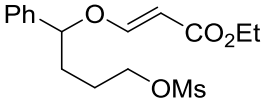
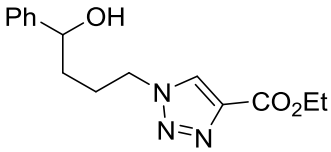
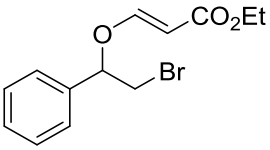
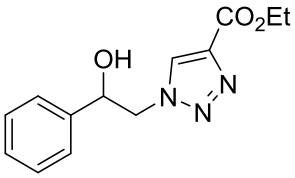
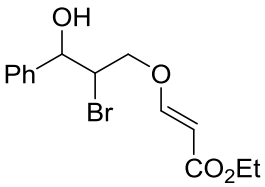
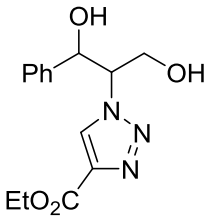
Substituted 1,2,3-triazoles have received considerable interest because of their useful applications in organic synthesis, chemical biology, and materials science.[25] Not present in natural products, however, there are large number of synthetic molecules that contain these substituted 1,2,3-triazole moieties with a wide range of biological activities such as, anti-HIV, anti-allergic, anti-fungal, anti-viral and anti-microbial activities. In this section, a metal-free, "one-pot" method of regioselective synthesis of substituted 1,2,3-triazoles proceeding through tandem azidation, intramolecular [3+2]-cycloaddition and aromatization of substituted acrylates[26] all occurring in that sequence is described (**Scheme 11**).



<u>Scheme 11</u>: (i) NaN_3 (1.5 equiv), DMF, 80 ^oC, 12 h, 15-88%.

Initially, azidation of β-alkyl substituted ethyl acrylate 29a (n = 1, R = H, Y = CH_2, X = I) was carried out with NaN_3 in DMF at 80 ^oC for 12 h, surprisingly it resulted in the formation of substituted 1,2,3-triazole **30a** in 82% yield (**Table 10**). We believed that, the formation of triazole **30a** could be reasoned from sequential reactions involving azidation followed by intramolecular [3+2]-cycloaddition and dehydrogenative aromatization respectively (**Table 10**, entry a). Encouraged by the above results, we explored this reaction by employing various alkoxy ethyl acrylates **29c-h** as substrates, the results of which are summarized in **Table 10**.

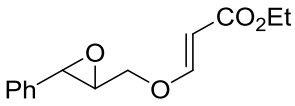
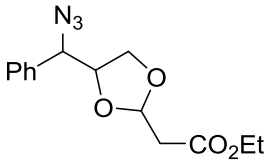
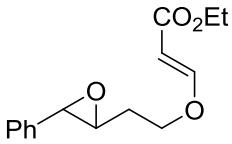
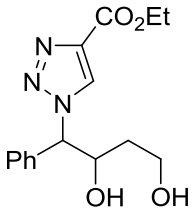
Table 10. Tandem azidation, intramolecular [3+2]-cycloaddition and aromatization[a]

entry	substrates (**29a-g**)	products (**30a-g**)	yields (%)[b]
a			82
b			78
c			84
d			81
e			88
f			85
g			15

[a]**29a-g** (5 mmol), NaN_3 (7.5 mmol), DMF (20 mL), 80 ^oC, 12 h. [b] isolated yield after chromatographic purification.

Substrates with variations in carbon chains similarly underwent this tandem protocol to afford the corresponding 1,2,3-triazole derivatives as a single regioisomer in high yields.With the above obtained results, our next task was to extend the scope of the reaction with epoxide functionality associated with acrylates. Thus, epoxy acrylate **29h** was subjected to triazole formation using NaN_3 (1.5 equiv) in MeOH/H_2O (4:1) at 80 ^oC for 12 h.

Table 11. Tandem epoxide opening, intramolecular [3+2]-cycloaddition and aromatization[a] of epoxy acrylates

entry	substrates (**29h-i)**	products (**30h-i)**	yield (%)[b]
1			90 (dr = 3:2)
2			82

[a]**29h-i** (5 mmol), NaN_3 (7.5 mmol), MeOH/H_2O (16/4 ml), 80 ^oC, 12 h; [b]isolated yield after chromatographic purification

Unexpectedly, oxa-Michael adduct **30h** was obtained in 90% yield with dr = 3:2 (determined from ^1H NMR analysis), probably due to more favourable 5-membered acetal formation over cycloaddition (**Table 11**, entry 1). However, the reaction of one-carbon homologated epoxy acrylate **29i** under the same reaction conditions, gave the desired triazole derivative **30i** in 82% *via* this tandem protocol.

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CHAPTER I

A new Organocatalytic Route to Chiral 3-Aminated Tetrahydroquinoline Derivatives and its Application in the Synthesis of 1-[(*S*)-3-(Dimethylamino)-3,4- Dihydro-6,7-Dimethoxy quinolin-1-(2*H*)-yl]propan-1-one, (*S*)-903

Section I

Proline-catalyzed Asymmetric Organic Transformations: Review

1.1.1 Introduction to asymmetric organocatalysis

The broad utility of synthetic chiral molecules as single-enantiomer pharmaceuticals, in electronic and optical devices, as components in polymers with novel properties, and as probes of biological function, has made asymmetric catalysis a prominent area of investigation. Until a few years ago, it was generally established that transition metal complexes and enzymes were the two main classes of very efficient asymmetric catalysts. Synthetic chemists have hardly used small organic molecules as catalysts throughout the last century, even though some of the very first asymmetric catalysts were purely organic molecules. Simple organic molecules can be highly effective enantioselective catalysts for a variety of important organic transformations.[1] This rediscovery has initiated an explosive growth of research activities in organocatalysis both in industry and in academia. The 1970s brought a milestone in the area of asymmetric organocatalysis, when two industrial groups led by Hajos and Wiechert published the first and highly enantioselective catalytic aldol reactions using simple amino acid proline as the catalyst.

Organocatalysis is the catalysis of chemical transformations using a purely organic molecule, which is composed of mainly carbon, hydrogen, nitrogen, sulfur, and phosphorus, and does not contain any metals. The advantages of organocatalysts include their lack of sensitivity to moisture and oxygen, their ready availability, low cost, and low toxicity, which confers a huge direct benefit in the production of pharmaceutical intermediates when compared with transition metal catalysts. Organic molecules not only have ease of manipulation and a "green" advantage but also can be very efficient catalysts. Asymmetric organocatalysis may begin to catch up with the spectacular advancements of enantioselective transition metal catalysis.

Recently, List[1] introduced a system of classification based on the mechanism of catalysis (**Fig. 1**). The four categories are Lewis base, Lewis acid, Bronsted base and Bronsted acid catalysis. 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* a (partial) deprotonation or protonation, respectively.

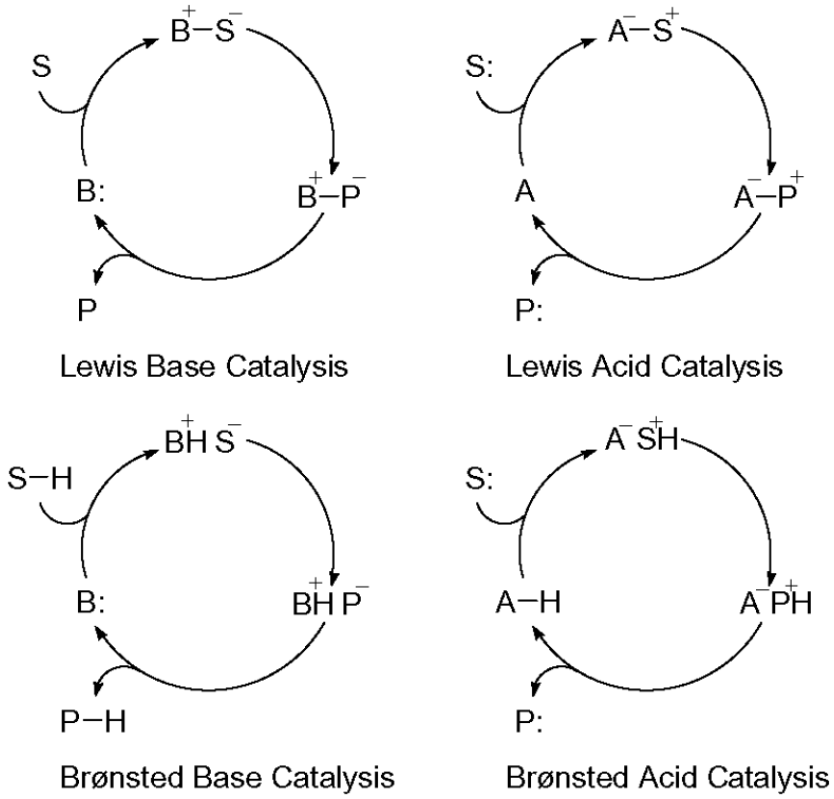


Fig. 1: Organocatalytic cycles

1.1.2 Proline a "Universal catalyst"

Proline (**1**) has been defined as a "universal catalyst" because of its high utility in a variety of asymmetric organic transformations. It 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).

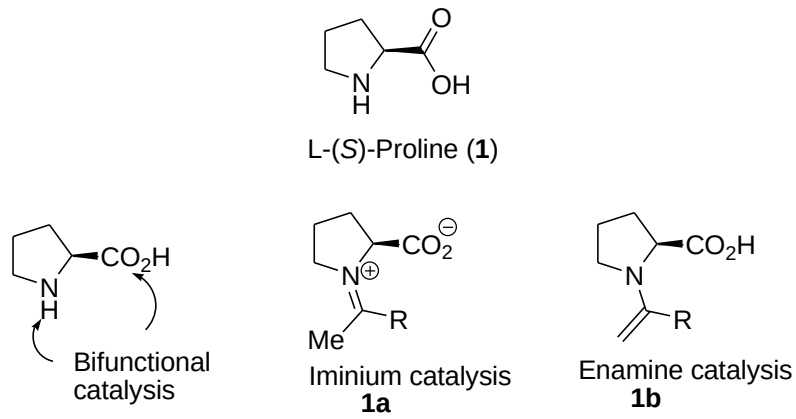


Fig. 2: Modes of proline catalysis

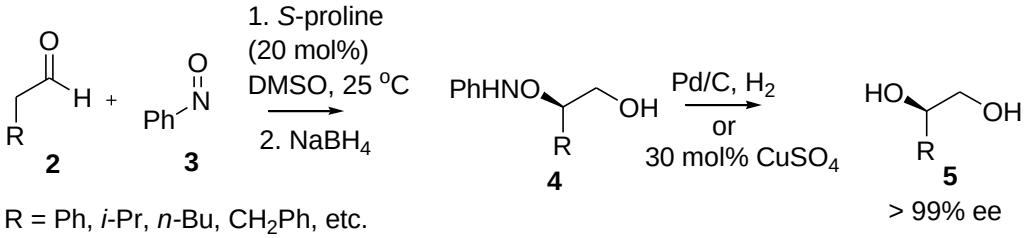
It can be regarded as a bifunctional catalyst as the secondary amine acts as Lewis base and the acid group acts as Bronsted acid (**Fig. 2**). The high stereoselectivity in the proline-catalyzed reactions is possibly due to its formation of organized transition states with many hydrogen bonding frameworks. Proline is not the only molecule to promote catalysis, but it still seems to be one of the best in the diversity of transformations. It is known to catalyze aldol,[2] Diels-Alder,[3] Michael addition[4] and α-functionalization[5] among many other organic transformations.[6] Particularly proline-catalyzed α-aminooxylation[7] and α-amination[8] of carbonyl compounds have emerged as powerful methods because chiral building materials can be synthesized in an effective manner starting from easily available materials.

1.1.3 Proline-catalyzed α-Aminooxylation

Optically active α-hydroxyaldehydes and ketones are important intermediates in organic synthesis as they are direct precursors to 1,2-diols. Because of this utility many methods have been developed for their preparation. The more prominent, well-established methods of enantioselective α-oxygenations include the use of Davis oxaziridine,[9a] Sharpless dihydroxylation of enol ethers,[9b] manganese–salen

epoxidation of enol ethers,[9c] and Shi epoxidation of enol ethers.[9d] It is only rather recently that direct catalytic, asymmetric variants have been reported.[10] Most of these methods, however, require multiple manipulations and there is no direct method, nor catalytic asymmetric method for their synthesis from the corresponding aldehyde.

Recently, proline has been found to be an excellent asymmetric catalyst for α-aminooxylation[7] of carbonyl compounds. When an aldehyde **2** without substitution at α-position was reacted with nitrosobenzene **3** in presence of L-proline in DMSO at ambient temperature, aminooxylation of the aldehyde takes place at the α-position. Aldehyde can be reduced *in situ* with sodium borohydride and the aminooxyl moiety undergoes hydrogenolysis with Pd/C, H_2 or $CuSO_4$ to give the corresponding diols **5** in very high enantioselectivities (**Scheme 1**).



Scheme 1: α-Aminooxylation of aldehydes

The catalytic cycle of the α-aminooxylation reaction is shown in **Fig. 3**. The observed enantioselectivitiy of the catalytic α-aminooxylation of aldehydes can be rationalized by invoking an enamine mechanism operating through a chair transition state where the *Si* face of an *E*-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. Since proline is commercially available in both enantiopure forms, a one-pot sequential catalytic α-aminooxylation of aldehydes followed by *in situ* reduction with $NaBH_4$ affords *R*- or *S*- configured 1,2-diol units (the secondary

alcohol "protected" by an *O*-amino group) with excellent enantioselectivities and in good yields.

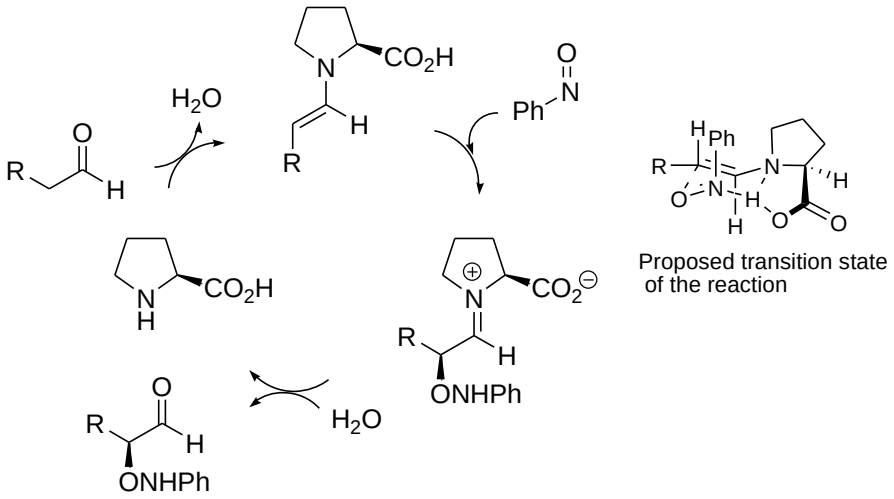


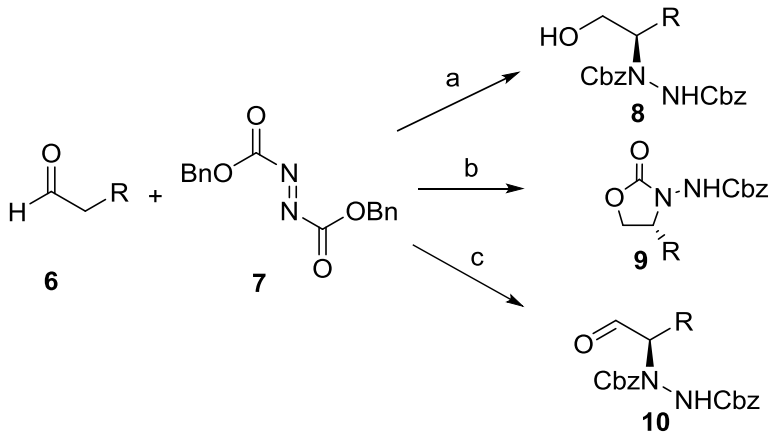
Fig. 3: Proposed mechanism of the α-aminooxylation reaction

1.1.4 Proline-catalyzed α-Amination

The motivation to investigate enantioselective α-amination of carbonyl compounds is provided by valuable synthetic targets such as α-amino acids and α-amino alcohols. The importance of optically active α-amino acids, α-amino aldehydes, and α-amino alcohols, formed by asymmetric catalysis, has stimulated an enormous development in synthetic strategies, and two different catalytic, enantioselective approaches are attractive: the C-C and the C-N bond-forming reactions. The catalytic enantioselective C-C bond-forming reactions include the addition to imines, such as the Strecker and Mannich reactions. The catalytic, enantioselective, direct C-N bond-forming reaction using aldehydes and a nitrogen source, such as azodicarboxylates, would constitute one of the simplest procedures for the construction of a stereogenic carbon center attached to a nitrogen atom.

Asymmetric α-amination[8] of aldehydes using proline-catalyzed reactions represent a burgeoning field of synthetic research as it is a tool for synthesizing chiral building blocks such as α-amino acids, α-amino aldehydes, and α-amino alcohols. The use of

organocatalysis, in particular proline represents a drastic change in approach to asymmetric α-amination. Recently, both List[8a] and Jørgensen[8b] disclosed the asymmetric α-amination of aldehydes (**Scheme 2**) using catalytic quantities of proline. While these approaches parallel each other in many ways, minor variations in reaction conditions result in different products (**8-10**), as well as differences in yields and enantiomeric ratios.



Scheme 2: (a) L-proline (10 mol%), CH_3CN, 0 °C, 3 h; $NaBH_4$, EtOH; (b) L-proline (10 mol%), CH_2Cl_2, 25 °C; $NaBH_4$, MeOH; 0.5 N NaOH; (c) L-proline (10 mol%), CH_2Cl_2, 25 °C; H_2O.

The reaction involves the addition of (*S*)-proline (10 mol%) to a solution of aldehyde **6** and azodicarboxylate ester **7**. List found that optimal enantiomeric enrichment of alcohol product **8** was obtained when the reaction temperature of 0 °C and *in situ* reduction with sodium borohydride was employed. Alternatively, Jørgensen found that aldehydes could be isolated directly, with diminished enantiomeric enrichment as reaction times increased, if the reaction was carried out in methylene chloride at room temperature. This procedure furnishes aldehyde products **10** (path c); these could be converted to the fully protected α-amino acids *via* a multi-step protocol of oxidation, deprotection, protection, and hydrogenolysis. To access *N*-amino oxazolidinones, precursors to α-amino alcohols, Jørgensen's standard proline protocol was used,

followed by addition of sodium borohydride and subsequent treatment with sodium hydroxide to facilitate cyclization to the desired product **9** (path b). These additional steps resulted in significantly diminished yields compared to List's route to α-amino alcohol precursors (path a). Both List and Jørgensen were able to achieve high yields and excellent enatiomeric ratios using sterically hindered substrates. This method is easily performed on gram scale using inexpensive chiral catalyst and can be performed in the absence of solvent.

The key shortcoming of this method is that excess aldehyde **6** is required, a serious disadvantage when using valuable aldehydes. Both List and Jørgensen proposed transition states that rationalize the observed stereochemical outcome. While these transition structures involve the anticipated enamine intermediate, they differ substantially in the prediction of the lowest energy conformation of the transition state. Jørgensen proposed a boatlike transition state **11**, whereas List a chairlike transition state **12**, analogous to that proposed for proline-catalyzed intramolecular aldol reaction.[11] It is worth mentioning that transition structure **12** lacks the hydrogen bond to the proline nitrogen, as Houk and coworkers have recently shown through a series of calculations that the N-H hydrogen bond does not lower the transition state energy in the corresponding aldol reaction[12] (**Fig. 4**).

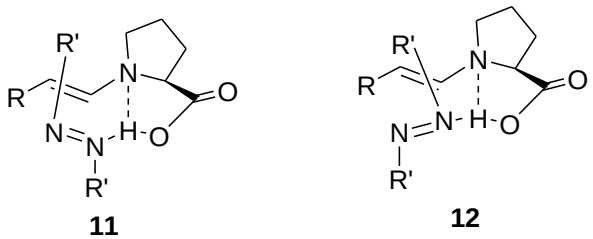


Fig. 4: Transition states for α-amination

While both transition structures lead to identical products directed by the hydrogen bond from the carboxylic acid of proline, they presumably possess unique energies, so

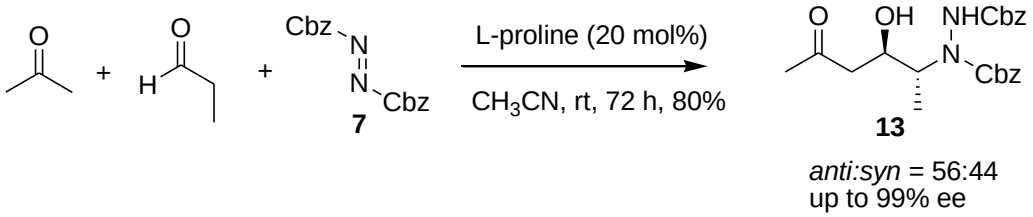
one transition state should be the favored. However, the operative transition state has yet to be established.

1.1.5 Proline-catalyzed sequential transformations in organic synthesis

Proline-catalyzed sequential transformation,[13] is an emerging area of current research in organic synthesis of complex organic molecules can be synthesized in one-pot procedure. Recently a variety of such transformations has been developed by different research groups, some of which are described below.

1.1.5.1 Sequential amination-aldol[13a]

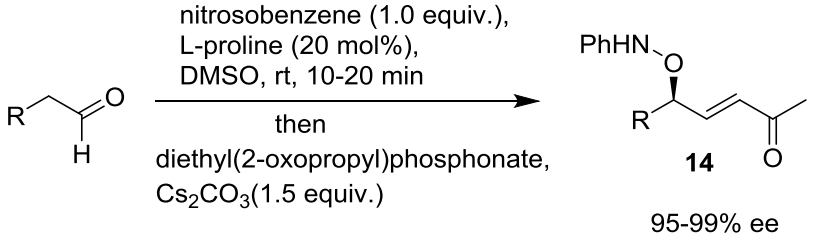
Barbas III *et al*. have developed a one-pot protocol for the synthesis of functionalized β-amino alcohols **13** directly from a mixture containing aldehydes, ketones and azodicarboxylates (**Scheme 3**).



Scheme 3: Sequential amination-aldol reaction

1.1.5.2 Sequential aminooxylation-olefination of aldehydes[13b]

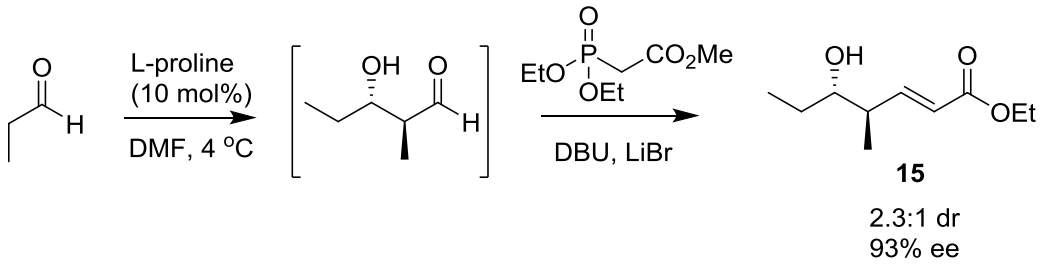
Zhong *et al*. have reported a sequential α-aminoxylation/Wadsworth-Emmons-Horner olefination of aldehydes for the synthesis of optically active *O*-amino-substituted α, β-unsaturated ketones**14** in excellent enantioselectivities using Cs_2CO_3 (**Scheme 4**).



Scheme 4: Sequential aminooxylation-olefination

1.1.5.3 Sequential aldol-olefination of aldehydes[13c]

Cordova *et al*. have reported a one-pot organocatalytic tandem cross-aldol/ Horner-Wittig-Emmons olefination of aldehyde that gave δ-hydroxy α, β-unsaturated ester **15** (**Scheme 5**).

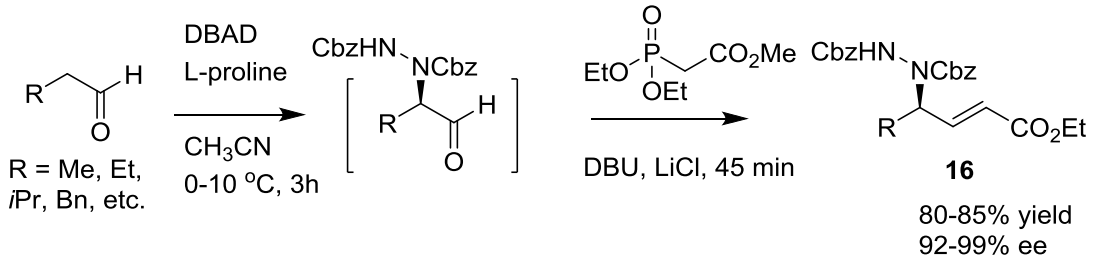


Scheme 5: Sequential aldol-olefination reaction

Apart from this transformation, Cordova *et al*. have also reported tandem Mannich-olefination reaction.[13d]

1.1.5.4 Sequential α-amination-olefination[13e]

Sudalai *et al*. have reported an organocatalytic sequential α-amination-Horner-Wadsworth-Emmons olefination of aldehydes that produces *γ*-amino-α, *β*-unsaturated esters 16 (**Scheme 6**).

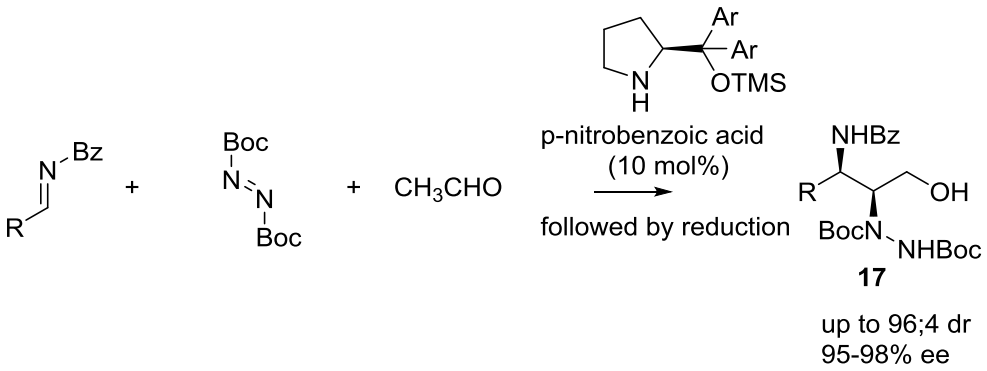


Scheme 6: Sequential α-amination- HWE olefination of aldehydes

1.1.6 Tandem Mannich reaction-electrophilic amination[13f]

Greck *et al*. have disclosed an organocatalytic "one-pot" α, α-bifunctionalization of acetaldehyde by a tandem Mannich reaction/electrophilic amination that leads to the

stereoselective synthesis of *syn*-2,3-diaminoalcohols **17** in high yields and excellent enantioselectivities (**Scheme 7**).



Scheme 7: Tandem Mannich reaction-electrophilic α-amination of aldehdes

Section II

Proline Catalyzed Sequential α -Amination/ Reductive Cyclization of *o*-Nitrohydrocinnamaldehydes: A High Yield Synthesis of Chiral 3-Aminated Tetrahydroquinolines

1.2.1 Introduction

The 1,2,3,4-tetrahydroquinoline (THQ) is a very common structural motiff found in numerous biologically active natural products and pharmacologically relevant therapeutic agents.[14,15] For example, (-)-sumanirole **18** (PNU-95666E) is a selective and high affinity agonist at the dopamine D_2 receptor subtype and has proven as a potential agent for the treatment of Parkinson's disease and restless leg syndrome.[16] Also,1-[(*S*)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1(2*H*)yl] propan-1-one [(*S*)-903] **19** has recently been identified as a potentially interesting positive inotropic agent,[17] while (+)-duocarmycin D_1 **20** has exhibited potent antitumor activity (**Fig. 5**).

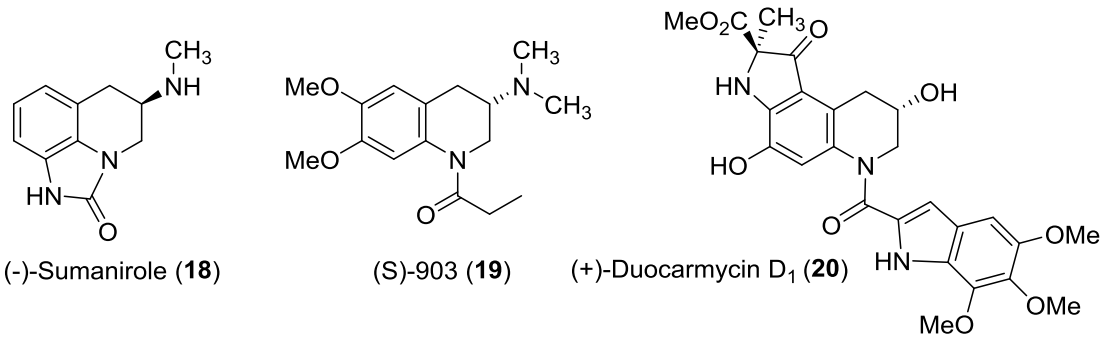


Fig. 5: Structures of some THQ containing bioactive molecules

Moreover, besides pharmaceutical applications, tetrahydroquinoline derivatives are useful as pesticides,[18] antioxidants,[19] and corrosion inhibitors,[20] Also tetrahydroquinolines are widely used as active components of dyes[21] and photosensitizers in photography.[22] Due to the significance of these scaffolds in drug discovery and medicinal chemistry,[23] the development of new methodologies for the

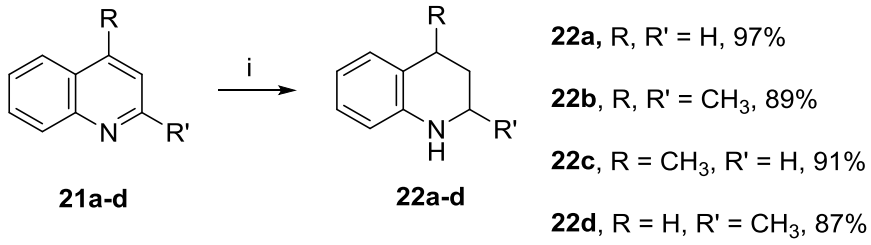
synthesis of 3-substituted THQs derivatives continue to be very active field of research in recent years.[24]

1.2.2 Review of literature

Literature search revealed that there are various reports available for the synthesis of tetrahydroquinoline derivatives; some of which are described below.

Murahashi's approach (1987) [25]

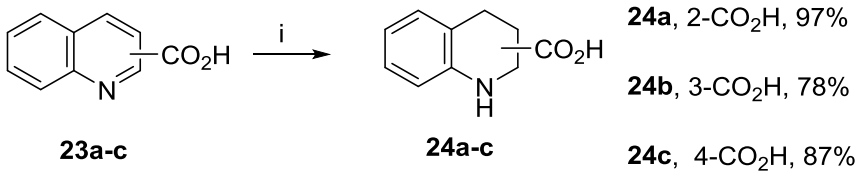
Murahashi *et al*. have used hexarhodiumhexadecacarbonyl complex as catalyst for the synthesis of tetrahydroquinolines **22a-d** from quinolines **21a-d** using carbon monoxide and water as efficient reducing agent (**Scheme 8**).



Scheme 8: (i) Catalytic $Rh_6(CO)_{16}$, CO, H_2O.

Gracheva's approach (1988) [26]

Gracheva *et al.* have reported the use of Ni-Al alloy for the reduction of quinolinecarboxylic acids **23a-c** to obtain tetrahydroquinoline carboxylic acid **24a-c** (**Scheme 9**).

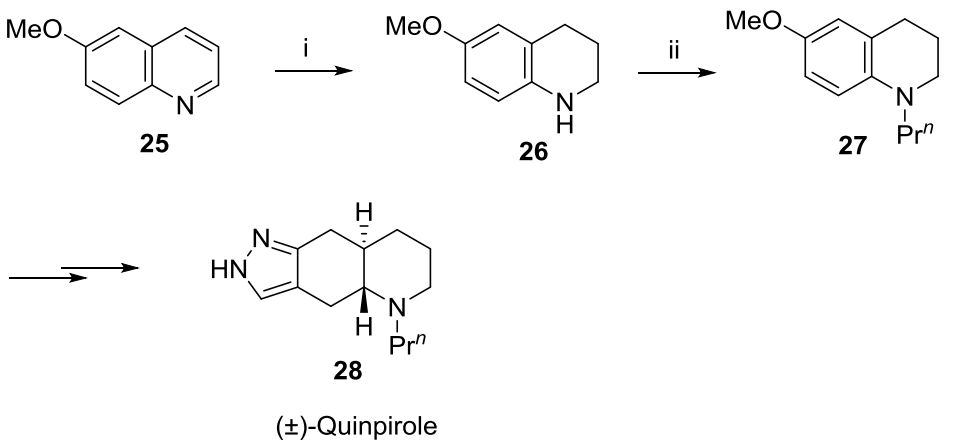


Scheme 9: (i) Ni-Al, aq. NaOH, 50 °C, 12 h.

Schaus's approach (1990) [27]

Schaus *et al.* have reported the synthesis of (±)-quinpirole **28** using hydrogenation [catalytic PtO_2, H_2 (60 psig)] of 6-methoxyquinoline **25** which afforded 6-methoxy-l,2,3,4-tetrahydroquinoline **26**. Reductive alkylation of **26** [propanaldehyde, 10% Pd/C, H_2 (60 psig)] furnished tetrahydroquinoline **27** in 36 % yield over two steps.

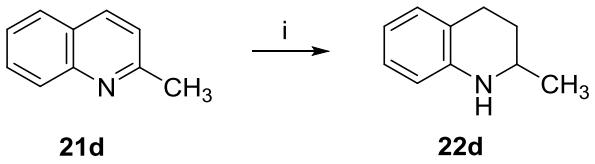
Further, **27** was converted into (±)-quinpirole **28** by employing a sequence of reactions (**Scheme 10**).



Scheme 10: (i) PtO_2 (10 wt%), H_2 (60 psig), 50 °C, 12 h, MeOH, 66%; (ii) 10% Pd/C, H_2 (60 psig), EtCHO, EtOH, 50 °C, 12 h, 54%.

Bouyssou's approach (1992) [28]

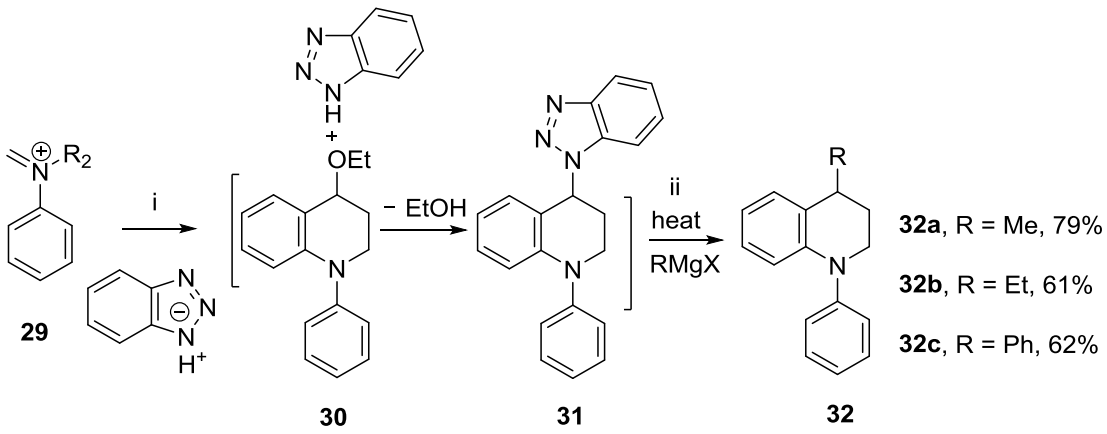
Bouyssou *et al.* have employed transfer hydrogenation (10% Pd/C, HCO_2H/Et_3N) as a method for reducing quinoline **21d** to afford the corresponding tetrahydroquinoline **22d** in 85 % yield (**Scheme 11**).



Scheme 11: (i) 10% Pd/C, HCOOH, Et_3N, 50 °C, 12 h, 85%.

Katritzky's approach (1995) [29]

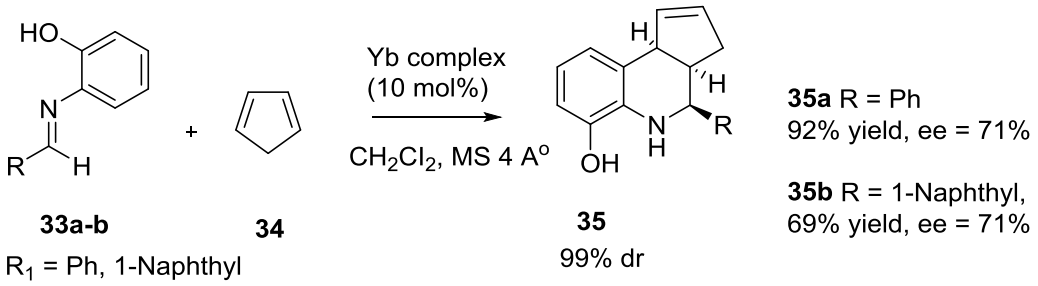
Katritzky *et al.* have reported acid catalyzed Diels-Alder reaction of *N*-methylaniline derivative **29** with ethyl vinyl ether to give reactive intermediate 4-ethoxy-1,2,3,4-tetrahydroquinoline **30** which underwent *in situ* substitution by benzotriazole to provide 4-(benzotriazolyl)-1,2,3,4-tetrahydroquinoline **31** in 48% yield. At elevated temperatures, ionization of **31** gives immonium cation which can be trapped *in situ* by Grignard reagent to provide 4-substituted tetrahydroquinolines **32** in good yields (**Scheme 12**).



Scheme 12: (i) ethyl vinyl ether, PTSA, 22 ºC, 30 min. then 120 ºC, 10 min; (ii) RMgX, Et_2O, reflux, 1 h.

Kobayashi's approach (1996) [30]

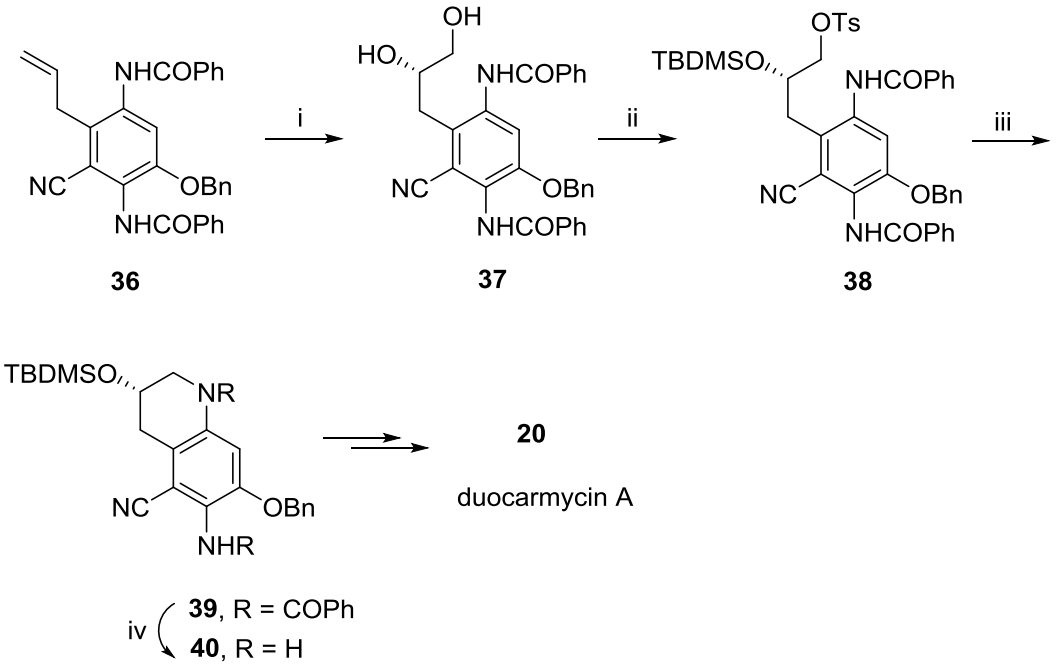
Kobayashi *et al*. have used asymmetric aza Diels-Alder reactions of imine **33a-b** and cyclopentadiene **34** catalysed by a $Yb(OTf)_3$·(*R*)-BINOL catalyst to provide tetrahydroquinoline derivatives **35a-b** in 69-92% yields and 71% ee (**Scheme 13**).



Scheme 13: (i) $Yb(OTf)_3$:(*R*)-BINOL:DBU (20 mol%), 2,6-di-*tert*-butylpyridine, CH_2Cl_2, 4 A^o MS, -15-0 ºC, 20 h.

Boger's approach (1997) [31]

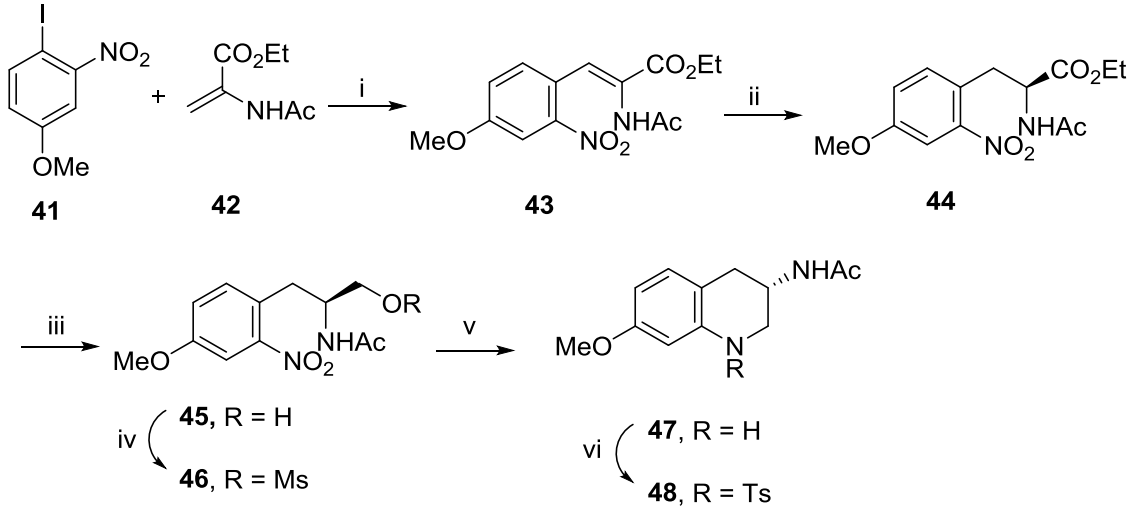
Boger *et al.* have used asymmetric dihydroxylation as a key step for the synthesis of duocarmycin-A **20**. Asymmetric dihydroxylation of olefin **36** gave diol **37** in 95 % yield. Tosylation of primary alcohol and protection of secondary alcohol as silyl ether in **37** gave **38**. Intramolecular nucleophilic displacement of tosylate **38** with amide anion provided key intermediate **39**, which on hydrolysis (N_2H_4, sealed tube, 140 ºC) gave diamine **40**. By sequential transformations, **40** was further converted to duocarmycin A **20** (**Scheme 14**).



Scheme 14: (i) OsO_4, $(DHQD)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, THF:H_2O (4:1), 0-25 °C, 24 h, 92%; (ii) (a) Bu_2SnO, toluene-THF (10:1), reflux, 6 h; (b) TsCl, Et_3N, CH_2Cl_2, 25 °C, 12 h, 89%; (c) TBDMS-OTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 3 h, 67%; (iii) NaH, THF, 0 °C, 2 h, 92%; (iv) NH_2NH_2, EtOH, 140 ºC, 12 h, sealed tube, 85%.

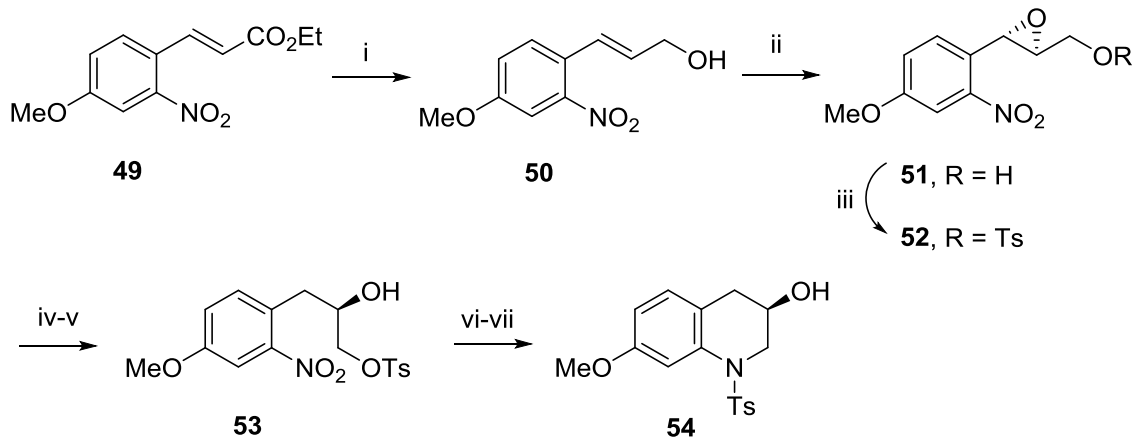
Rajan Babu's approach (2001)[32]

Rajan Babu *et al.* have used Rh-catalyzed asymmetric hydrogenation as a key reaction for the synthesis of aminotetrahydroquinoline **48**. Rh-catalyzed asymmetric hydrogenation of α-acetamido-2-nitrocinnamate ester **43** gave α-acetamido ester **44** in 96% yield and 98% ee. Further reduction of ester functionality with super hydride afforded the corresponding alcohol **45** which was subsequently transformed into its mesylate **46**. Reduction (H_2, 10% Pd/C) of nitro in **46** to amine followed by cyclization provided 3-aminotetrahydroquinoline **47** which was transformed (TsCl/ Et_3N) as its tosylamide **48** (**Scheme 15**).



Scheme 15: (i) $Pd(OAc)_2$, Bu_4NCl, $NaHCO_3$, sealed tube, 80 ºC, 24 h, 80%; (ii) Rh catalyst, H_2 (40 psig.), THF, 96%, 98% ee; (iii) super hydride, 0 ºC; (iv) MsCl, Et_3N, CH_2Cl_2, 0 ºC, 30 min; (v) H_2, Pd/C, 1 h, 25 ºC; (vi) TsCl, Et_3N, CH_2Cl_2, 0 ºC.

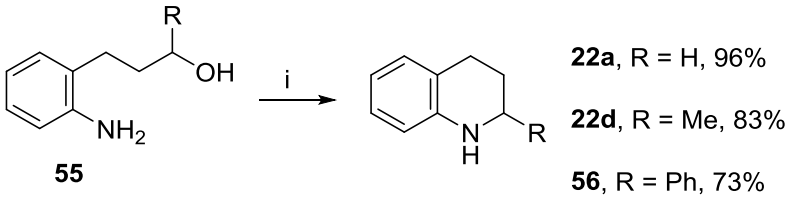
In another approach, 2-nitrocinnamate **49** was reduced to the corresponding allyl alcohol **50** using DIBAL-H. Sharplesss asymmetric epoxidation of allyl alcohol **50** gave the chiral epoxy alcohol **51,** which was transformed into its tosylate **52** (TsCl, Et_3N)**.** Reductive ring opening of epoxide **52** over PtO_2 furnished alcohol **53** in 70 % yield. Finally reduction (Fe/HCl, H_2O and DMF) of nitro functionality to amine gave 3-hydroxy tetrahydoquinoline, which on tosylation gave tosylamide **54** in 66% yield (**Scheme 16**).



Scheme 16: (a) DIBAL-H, toluene, 0 ºC, 75%; (b) $Ti(O^iPr)_4$, (+)-diethyl tartrate, ^tBuOOH, CH_2Cl_2, -30 ºC, 6 days, 60%, >90% ee; (c) TsCl, Et_3N, CH_2Cl_2, DMAP, 0 ºC, 80%; (d) MgI_2, toluene, -55 ºC; (e) PtO_2, H_2 (40 psig), Et_3N, THF, 70% over two steps; (f) Fe, HCl, H_2O, DMF, 70 ºC; (g) TsCl, Et_3N, CH_2Cl_2, 66% (over two steps).

Fujita's approach (2002)[33]

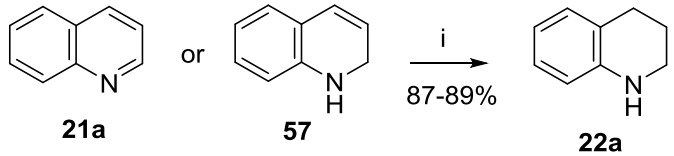
Fujita *et al.* have employed $[CpIrCl_2]_2/K_2CO_3$ catalyzed cyclization of 3-(2-aminophenyl)propanol (**55**) to give tetrahydroquinoline (**22a, 22d** and **56**) in high yields (**Scheme 17**).



Scheme 17: (i) $[CpIrCl_2]_2$ (5 mol % Ir), K_2CO_3 (10 mol%), toluene, 111 °C, 20 h.

Fujita's approach (2004) [34]

Fujita *et al.* have used Ir-catalyzed transfer hydrogenation of quinoline **21a** and dihydroquinoline **57** to provide tetrahydroquinoline **22a** in high yields. Addition of acid (CF_3CO_2H or $HClO_4$) considerably accelerates the rate of the reaction whereas addition of water minimizes the formation of byproducts (**Scheme 18**).

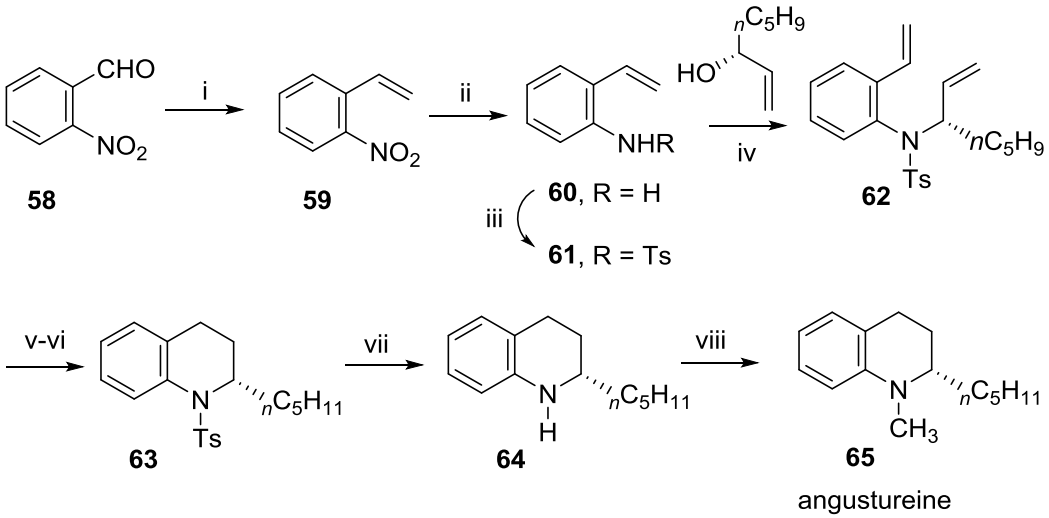


Scheme 18: (i) $[CpIrCl_2]_2$ (1mol %), aq. $HClO_4$, 2-propanol, H_2O, reflux, 17 h.

Nishida's approach (2005)[35]

This approach utilized Ru-catalyzed ring closing metathesis (RCM) to construct dihydroquinoline core. Wittig olefination of *o*-nitrobenzaldehyde **58** gave nitrostyrene **59**, which was subjected to reduction of nitro group (Zn/AcOH) to give the corresponding *o*-aminostyrene **60**. Protection of amine in **60** as tosymide **61** (TsCl, Py, CH_2Cl_2), followed by Mitsunobu reaction with (*R*)-oct-1-en-3-ol (99% ee) [DEAD and PPh_3] provided the desired diene **62** in 78% yield. The diene **62** was subjected to ring closing metathesis (RCM) with Grubbs' II catalyst to give the

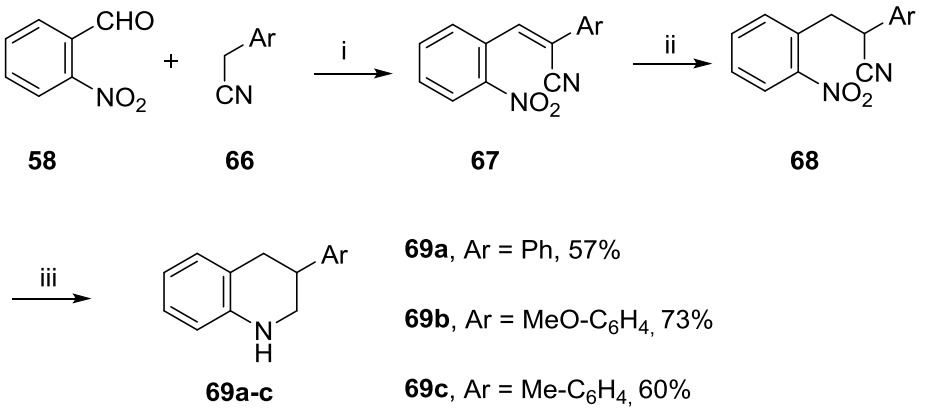
corresponding 1,2-dihydroquinoline in 92% yield which was subsequently hydrogenated over Adam's catalyst in MeOH to provide tetrahydroquinoline **63** in 94% yield and 99.7% ee. Finally detosylation of **63** to free amine **64** and subsequent methylation of the free nitrogen gave (+)-(*S*)-angustureine **65** in 80% yield (**Scheme 19**).



Scheme 19: (i) Ph_3PMeBr, $KN(TMS)_2$, THF, 25 ºC, 1 h, 90%; (ii) Zn powder, AcOH, 25 ºC, overnight, 72%; (iii) TsCl, pyridine, CH_2Cl_2, 25 ºC, 1 h, 86%; (iv) DEAD, PPh_3, THF, 25 ºC, 2 h, 78%; (v) Grubbs II, CH_2Cl_2 (0.01 M), 50 ºC, 1 h, 92%; (vi) PtO_2, H_2, MeOH, 25 ºC, 12 h, 94%; (vii) anthracene sodium, DME, -65 ºC, 10 min, 99%; (viii) MeI, K_2CO_3, THF, reflux, 10 h, 80%.

Yang's approach (2006) [36]

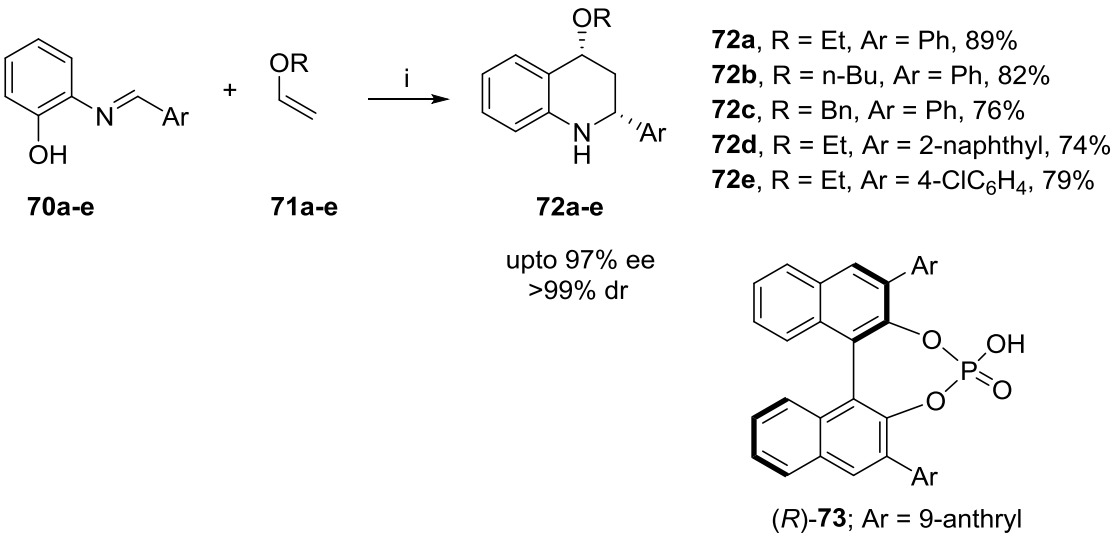
Yang *et al*. have reported reductive cyclization of **68** using H_2 over Pd/C to give 3-aryl tetrahydroquinoline **69a-c**. Condensation of 2-nitrobenzaldehyde **58** with aryl propionitrile **66** and subsequent reduction of double bond with $NaBH_4$ provided **67,** which was subjected to reduction with H_2 over 30% Pd/C followed by reductive cyclization with cyano group afforded 3-aryltetrahydroquinoline **69a-c** in 57-73% yields (**Scheme 20**).



Scheme 20: (i) Na, C_2H_5OH, 5 h; (ii) $NaBH_4$, THF, CH_3OH; (iii) H_2, 30% Pd/C, THF, CH_3OH.

Akiyama's approach (2006) [37]

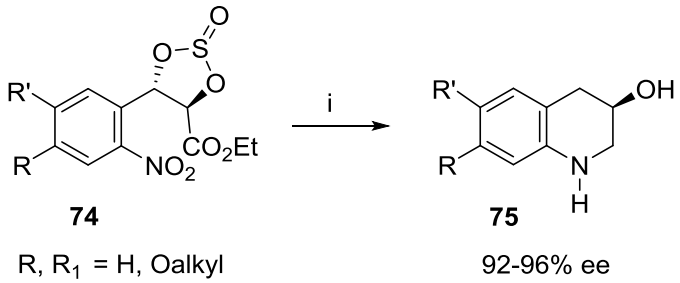
Akiyama's *et al.* have described inverse electron-demand aza Diels-Alder reaction of aldimines **70a-e** with electron-rich alkene enol ethers **71a-e** catalyzed by a chiral Brønsted acid **73** to provide tetrahydroquinoline derivatives **72a-e** in 74-89% yields and upto 97% ee (**Scheme 21**).



Scheme 21: (i) catalyst (R)-**73** (10 mol%), toluene, 10 - 55 h, 25 ºC

Sudalai's approach (2009)[38]

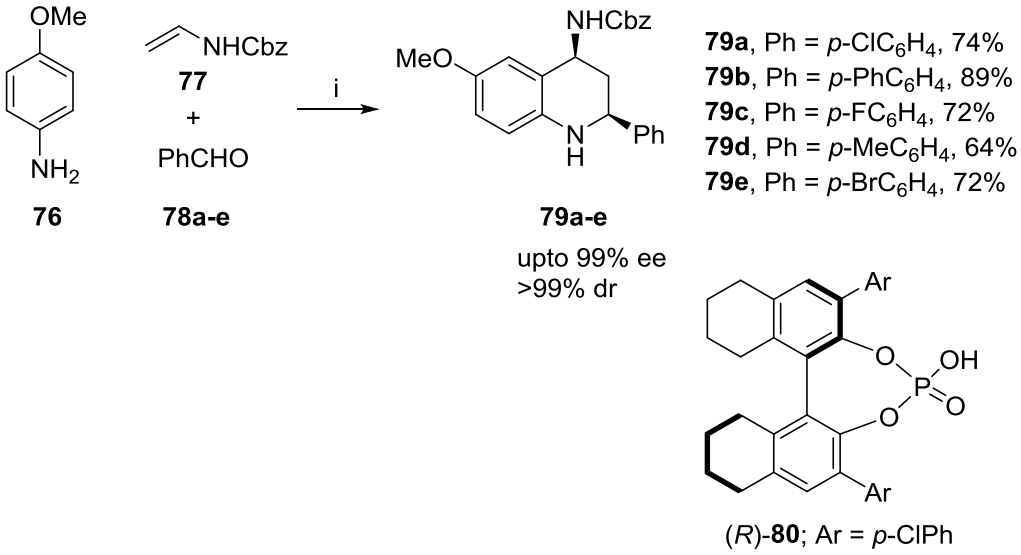
Sudalai's approach describes a new method for the construction of chiral 3-substituted tetrahydroquinoline derivatives **75** based on asymmetric dihydroxylation and $CoCl_2$-catalyzed reductive cyclization of nitro cyclic sulfites **74** with $NaBH_4$ (**Scheme 22**).



Scheme 22: (a) 1 mol% $CoCl_2$, $6H_2O$, $NaBH_4$, EtOH, 0-25 °C, 12 h.

Zhu's approach (2009) [39]

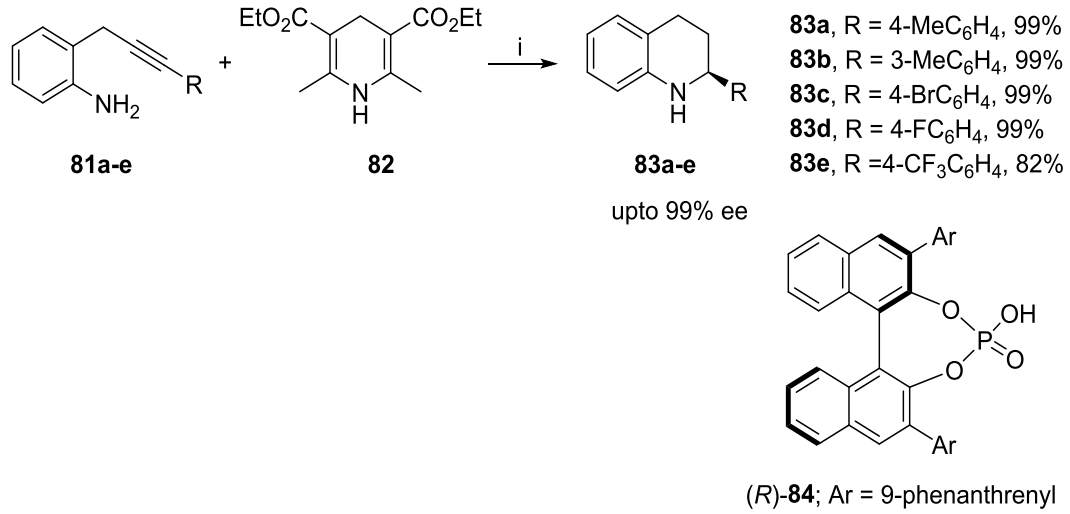
This approach utilized the first catalytic three-component Povarov reaction of aldehydes **78a-e**, aniline **76** and benzyl N-vinylcarbamate **77** in the presence of 0.1 equiv of chiral phosphoric acid **80** that afforded *cis*-2,4-disubstituted tetrahydroquinolines **79a-e** in good yields and enantiomeric excesses (upto 99% ee) (**Scheme 23)**.



Scheme 23: (i) catalyst (*R*)-**69** (0.1 equiv.), CH_2Cl_2, 1 h, 0 ºC.

Gong's approach (2009) [40]

Gong *et al.* have developed a new protocol which directly transformed 2-(2-propynyl) aniline **81a-e** derivatives into tetrahydroquinolines **83a-e** in one operation with excellent enantioselectivity under the relay catalysis of an achiral Au complex and a chiral phosphoric acid **84** (**Scheme 24**).

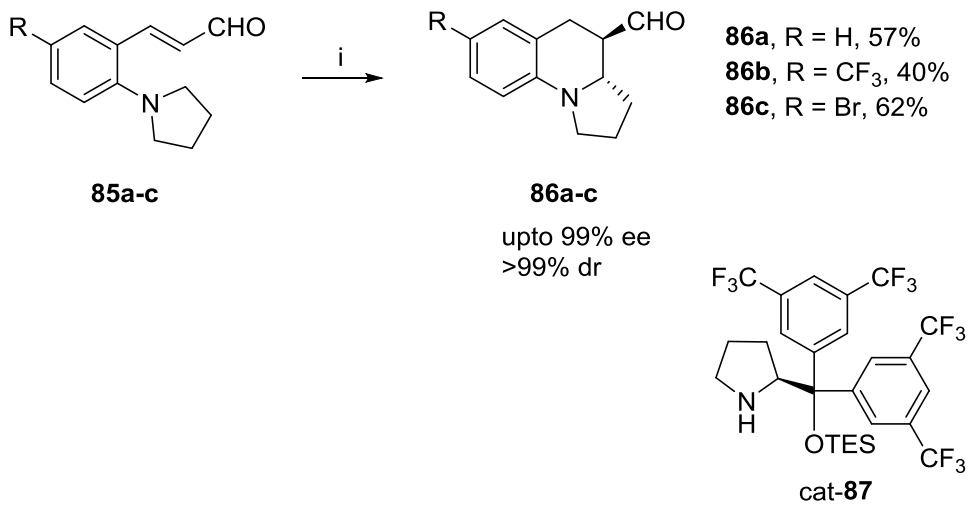


Scheme 24: (i) catalyst (*R*)-**84** (15 mol%.), Ph_3PAuCH_3 (5 mol%), toluene, 25 ^oC 16 h.

This reaction was considered a consecutive catalytic process consisting of Au-catalyzed intramolecular hydroamination of a C-C triple bond and a Brønsted acid catalyzed enantioselective transfer hydrogenation to provide tetrahydroquinolines **83a-d** in 99% yield with 99% ee.

Kim's approach (2010)[41]

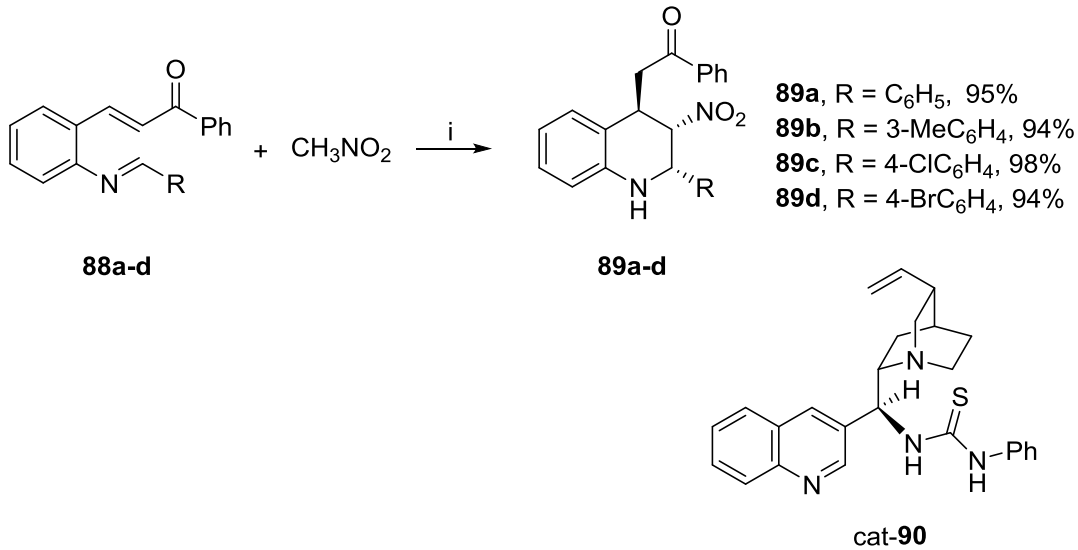
Kim et al. have reported the first enantioselective intramolecular 1,5-hydride transfer/ring closure reaction cascade. In this organocatalytic redox neutral reaction, *o*-dialkylaminosubstituted cinnamaldehydes **85a-c** were reacted in the presence of prolinol derivative **87** (30 mol%) as an organocatalyst and (-)-CSA (30 mol%) as an additive in TCE provided tetrahydroquinolines **86a-c** in high enantioselectivities with moderate yield (**Scheme 25**).



Scheme 25: (i) cat-**87** (30 mol%), (-)-CSA (30 mol%), TCE, 5 - 9 d, 25 ºC.

Xu's approach (2011)[42]

Xu *et al.* have described a novel synthetic method for polysubstituted tetrahydroquinoline derivatives **89a-d** *via* organocatalytic asymmetric tandem Michael addition and the aza-Henry reaction, in which chalcone **88a-d** and nitromethane were employed as the starting materials. The reaction yields were high (94%-98%), and highly diastereo- and enantioenriched tetrahydroquinoline derivatives **89a-d** with a substantial substitution diversity were smoothly delivered (up to >99% ee, dr up to 20:1) (**Scheme 26**).

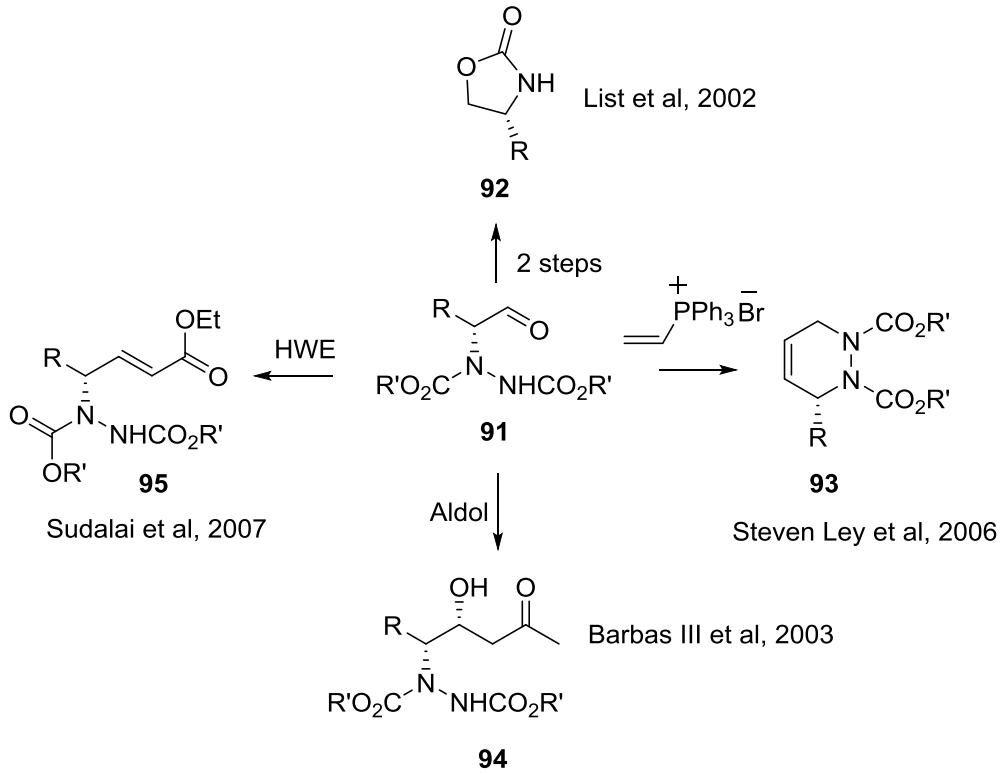


Scheme 26: (i) cat-**90** (20 mol%), Ph_3PAuCH_3 (5 mol%), toluene, 25 ºC, 4 h.

1.2.3 Present Work

1.2.3.1 Objective

As can be seen from the above discussion, only a few methods exist in the literature for the asymmetric synthesis of 3-substituted tetrahydroquinolines, most of which are based on chiral pool resources. The use of expensive chiral reagents, lengthy reaction sequence, use of protection and deprotection of various functional groups along with low overall yield are some of the drawbacks of the existing routes. In this regard, an organocatalytic protocol that provides for the efficient synthesis of chiral 3-substituted THQs is highly desirable. Proline catalyzed α-functionalization and its sequential reactions are arguably one of the most extensively studied and developed asymmetric catalytic reaction.[13,43,44] Yet the full synthetic potential of the use α-functionalized aldehydes that are readily available by this route in excellent enantioselectivity, remains to be further exploited.

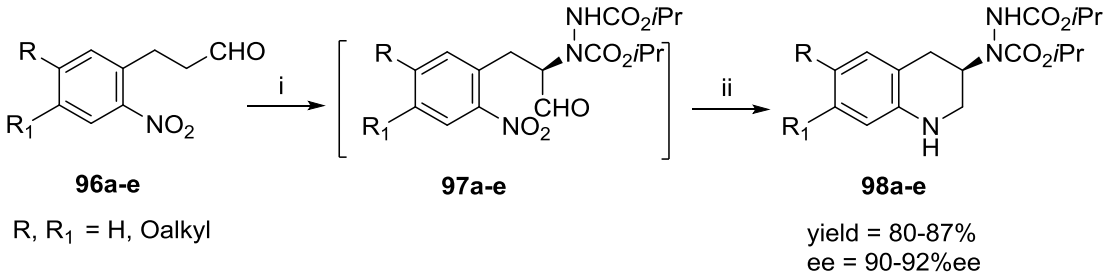


Scheme 27: *In situ* trapping of α-amino aldehydes

In proline-catalyzed direct α-amination of aldehydes, the reactive intermediate **91**, generated *in situ* was transformed into several functionalized organic derivatives: for instance, it was reduced and cyclized to oxazolidinone **92**,[8a] cyclized by intramolecular Wittig olefination to 3, 6-dihydropyridazines **93**,[44b] condensed under aldol conditions to form functionalized β-amino alcohols **94**,[13a] or trapped with Horner-Wadsworth-Emmons olefination conditions to produce γ-amino-α, β-unsaturated esters[13d] **95** (**Scheme 27**). In this connection it is of interest to design experiments in trapping intermediate **91** *via* intramolecular reductive cyclization. In this section, we wish to disclose, for the first time, a sequential protocol involving α-amination of *o*-nitrohydrocinnamaldehydes and Pd-catalyzed intramolecular reductive cyclization that provides easy access to chiral 3-aminated THQs **98a-e** in high yields.

1.2.3.2 Results and Discussion

In continuation of our work on the utilization and application of enantiomerically-enriched α-functionalized aldehydes, [13d, 45] we envisaged that sequential trapping of α-aminated *o*-nitrohydrocinnamaldehydes **97a-e** with Pd-catalyzed reductive cyclization should provide enantiomerically pure 3-aminated THQs **98a-e** (**Scheme 28**).

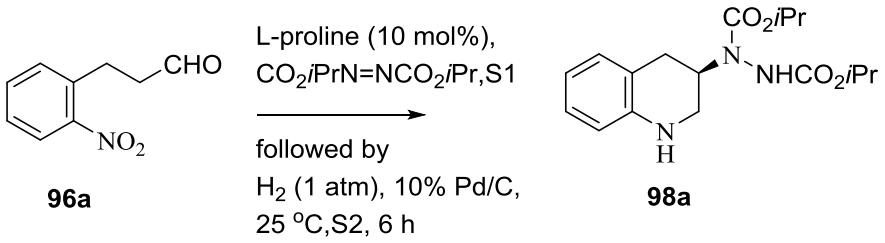


Scheme 28: (i) L-proline (10 mol%), *i*PrO$_2$CN=NCO$_2$*i*Pr, CH$_3$CN, 0 ^{o}C, 3 h; (ii) 10 % Pd/C, H$_2$ (1 atm), 25 ^{o}C, 6 h.

In a preliminary study, α-amination of o-nitrohydrocinnamaldehyde **96a** with diisopropyl azodicarboxylate (DIAD) as amine source in the presence of L-proline (10 mol%) as a catalyst in CH$_3$CN was carried out using List's protocol[8] that indeed

gave the corresponding chiral α-aminated aldehyde **97a** *in situ*. Then, CH_3CN was distilled off under reduced pressure and subsequently the reductive cyclization [10% Pd/C, H_2 (1 atm), MeOH] was carried out to afford the desired 3-amino THQ **98a** in high yields (85%) with low ee (60%). Several other solvents were also screened simultaneously in order to improve the yield and ee of the amination process, but with little success (yield 35–70%). After several experimentations, when α-amination was carried out in CH_3CN and reductive cyclization in a solvent mixture of CH_3CN–MeOH (1 : 3), The best yield (82%) and enantioselectivity (90%) of **98a** could be realized (**Table 1**).

Table 1. L-Proline-catalyzed sequential α-amination/reductive cyclization of *o*-nitrohydrocinnamaldehyde[a]



			product **(98a)**	
entry	S1	S2	yield (%)[b]	ee (%)[c]
1	CH_3CN	MeOH	85	60
2[d]	**CH_3CN**	**CH_3CN/MeOH**	**82**	**90**
3[d]	CH_2Cl_2	CH_2Cl_2/MeOH	65	nd
4	CH_2Cl_2	MeOH	70	75
5	THF	MeOH	35	nd
6	$CHCl_3$	MeOH	45	nd

[a]L-proline (10 mol%), *o*-nitrohydrocinnamaldehyde (5.5 mmol), *i*PrCO_2N=NCO_2*i*Pr (5 mmol), 3 h; [b] isolated yield after column chromatography; [c] ee determined by chiral HPLC analysis; [d] solvent ratio S2 CH_3CN:MeOH (1:3).

Other amine sources like di-*tert*-butyl and diethyl azodicarboxylate could be conveniently employed under the reaction conditions[46a] giving the desired 3-aminated

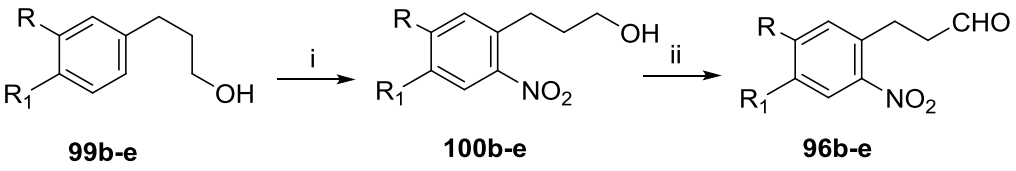
THQs in high yields and enantioselectivity; however, the reactions were not efficient in the case of other commercially available L-proline-based catalysts.[46b](**Table 1)**. With the optimized conditions in hand, we then turned our attention to briefly investigate the scope of the reaction by subjecting several o-nitrohydrocinnamaldehydes **96a–e** to a sequential α-amination/reductive cyclization protocol. When subjected to L-proline catalyzed α-amination with 1 equiv of DIAD followed by catalytic [H_2 (1 atm), Pd/C] intramolecular reductive cyclization, several o-nitrohydrocinnamaldehydes [46c] **96a**–e gave the corresponding (*R*)-3-aminated tetrahydroquinoline derivatives **98a–e** in 80–87% yields with excellent enantioselectivities. Results of such studies are presented in Table 2. For substrates with easily removable groups like TBDPS, the corresponding 3-aminated THQs were obtained in excellent enantioselectivities (entry e, **Table 2**).

Table 2 : α-Amination-reductive cyclization: Substrate scope

Entry	Substrates **96a-e**	Products **98a-e**	
		Yield (%)[a]	ee (%)[b]
a	R = R^1 = H	82	90
b	R = R^1 = OMe	85	90
c	R, R^1 = -O-CH_2-O-	87	91
d	R = O-pentyl ; R^1 = OMe	81	91
e	R = OTBDPS ; R^1 = OMe	80	90

[a] isolated yieds of THQ-3-amines; [b] ee of 3-aminated THQ's determined by HPLC.

o-Nitrohydrocinnamaldehydes **96b-e**, the starting materials, were efficiently prepared from the corresponding hydrocinnamyl alcohols **99b-e** in two steps. Thus, regiospecific aromatic nitration of **99b-e** with conc. HNO_3 gave the corresponding nitro compounds **100b-e** in 80-95% yields (**Scheme 29**).



Scheme 29: (i) conc.HNO_3, CH_2Cl_2, 0 ^oC, 80-95%; (ii) PCC, CH_2Cl_2, 25 ^oC, 80-85%.

For example, the formation of *o*-nitrohydrocinnamyl alcohol **100c** was confirmed from its ^1H NMR spectrum, which showed a triplet at δ 3.70 (J = 6.2 Hz, 2H) corresponding to methylene (-**CH_2**-OH) protons. Two singlets at δ 6.8 (1H) and 7.5 (1H) indicated the presence of aromatic protons.

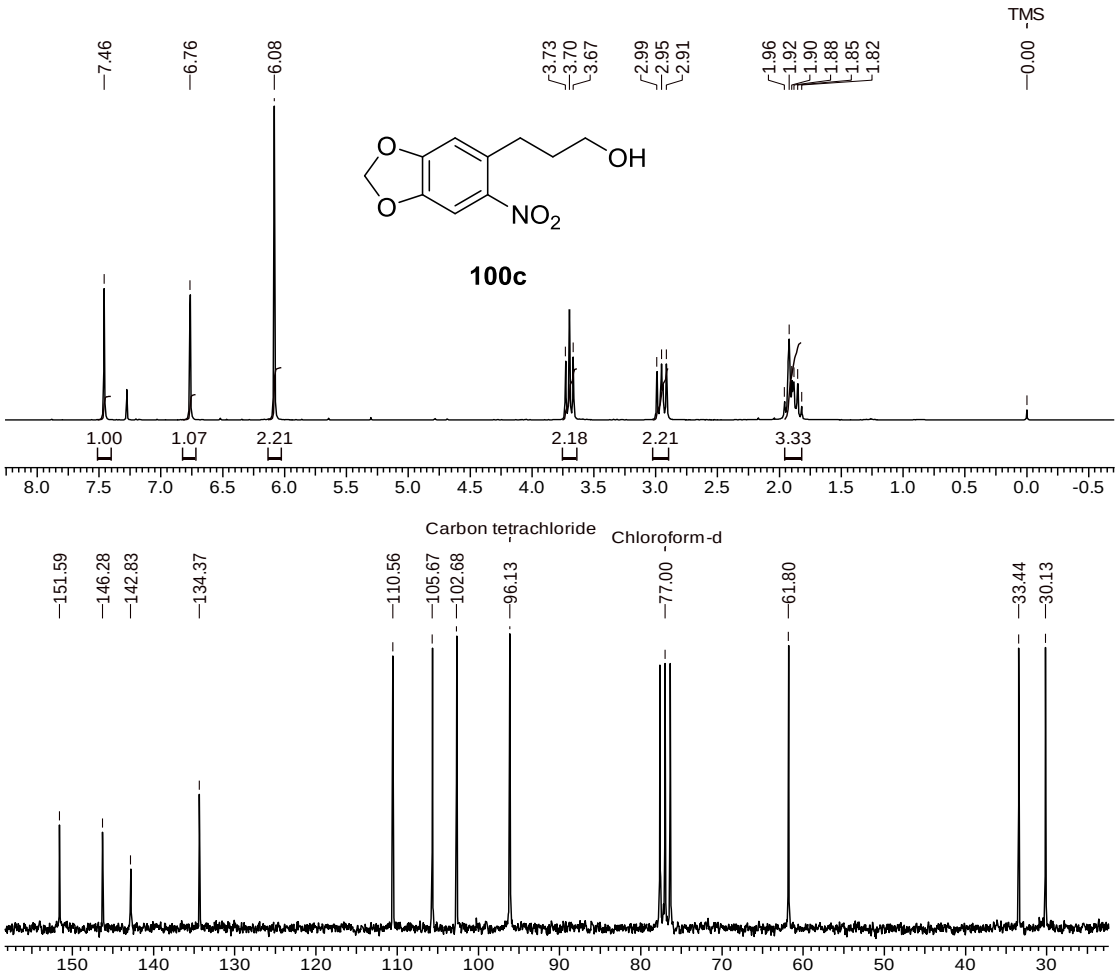


Fig. 6: ^1H and ^{13}C NMR spectra of *o*-nitrohydrocinnamyl alcohol **100c**

Its ^{13}C NMR spectrum showed a typical carbon signal at δ 102.7 indicative of the methylene carbon having dioxo linkage (-O-**CH_2**-O) (**Fig. 6**). Subsequent oxidation of

nitro alcohols **100b-e** with PCC gave nitroaldehydes **96b-e** in 80-85% yield. The ^{1}H NMR spectrum of *o*-nitrohydrocinnamaldehyde **96c** showed a characteristic proton signal at δ 9.82 for aldehydic proton. This was further evidenced by its ^{13}C NMR spectrum, which showed a typical carbon signal at δ 200.1 corresponding to aldehydic carbon (**Fig. 7**). The formation of all intermediates along with the final products (THQs **98a-e**) was established unambiguously from their corresponding ^{1}H & ^{13}C NMR, IR and HRMS spectral data. Their optical purity was determined from their chiral HPLC analyses.

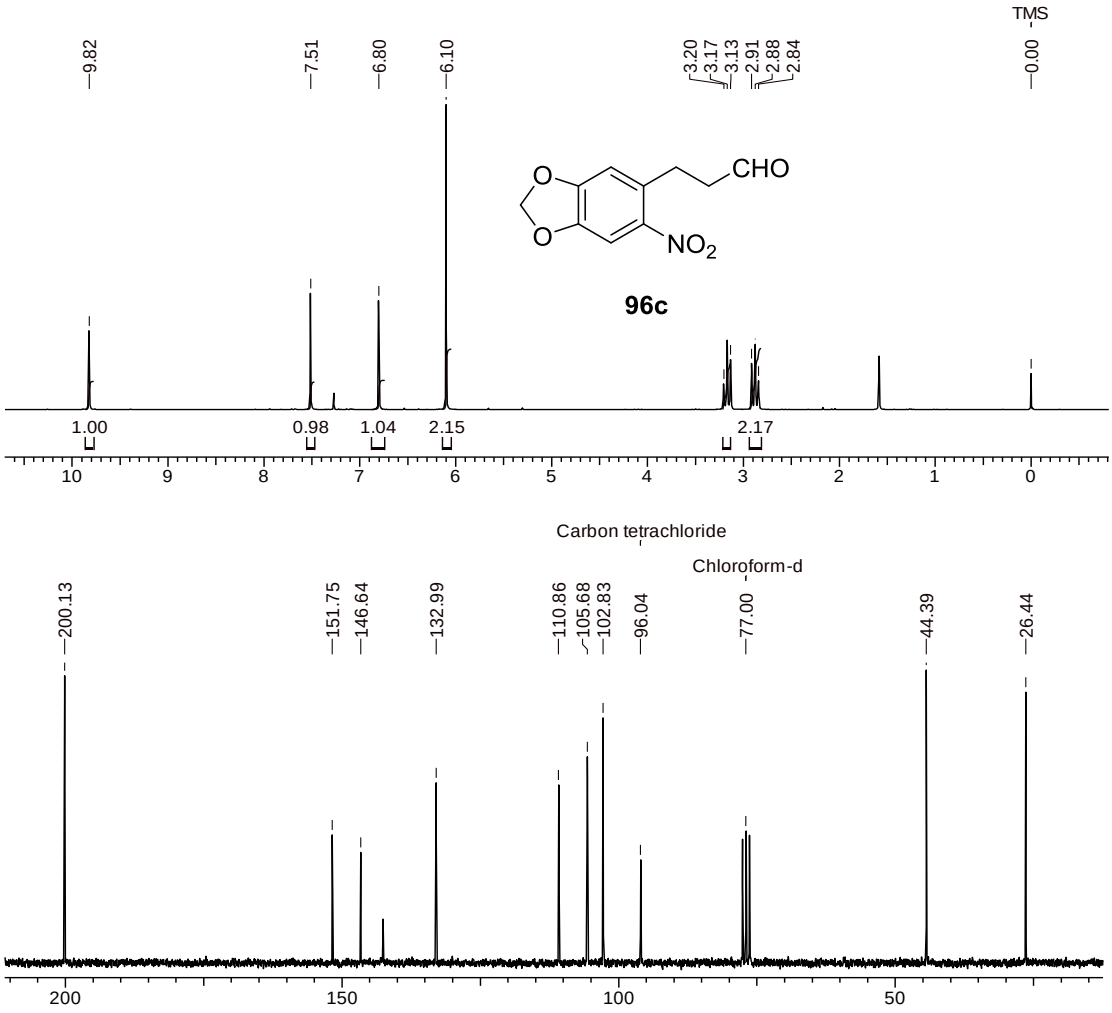


Fig. 7: ^{1}H and ^{13}C NMR spectra of *o*-nitrohydrocinnamaldehyde **96c**

For example, the formation of THQ **98b** was confirmed from its ^{1}H NMR spectrum, which showed a broad multiplet at δ 4.54-4.58 corresponding to methine (-**CH**-NR_2)

proton, while a multiplet at δ 3.21-3.43 indicated the presence of methylene (-**CH_2**-NH-) protons. The multiplets at δ 4.94-4.97 were due to methine (-O-CHR_2) protons of the carbamate. The ^{13}C NMR spectrum of THQ **98b** showed characteristic carbon signals at δ 99.7, 111.0, 113.4, 137.1, 141.8 and 148.2 corresponding to aromatic carbons, while the other carbon signals at δ 69.4 and 69.9 were indicative of methyoxy carbons (-O**C**H_3) respectively (**Fig. 8**).

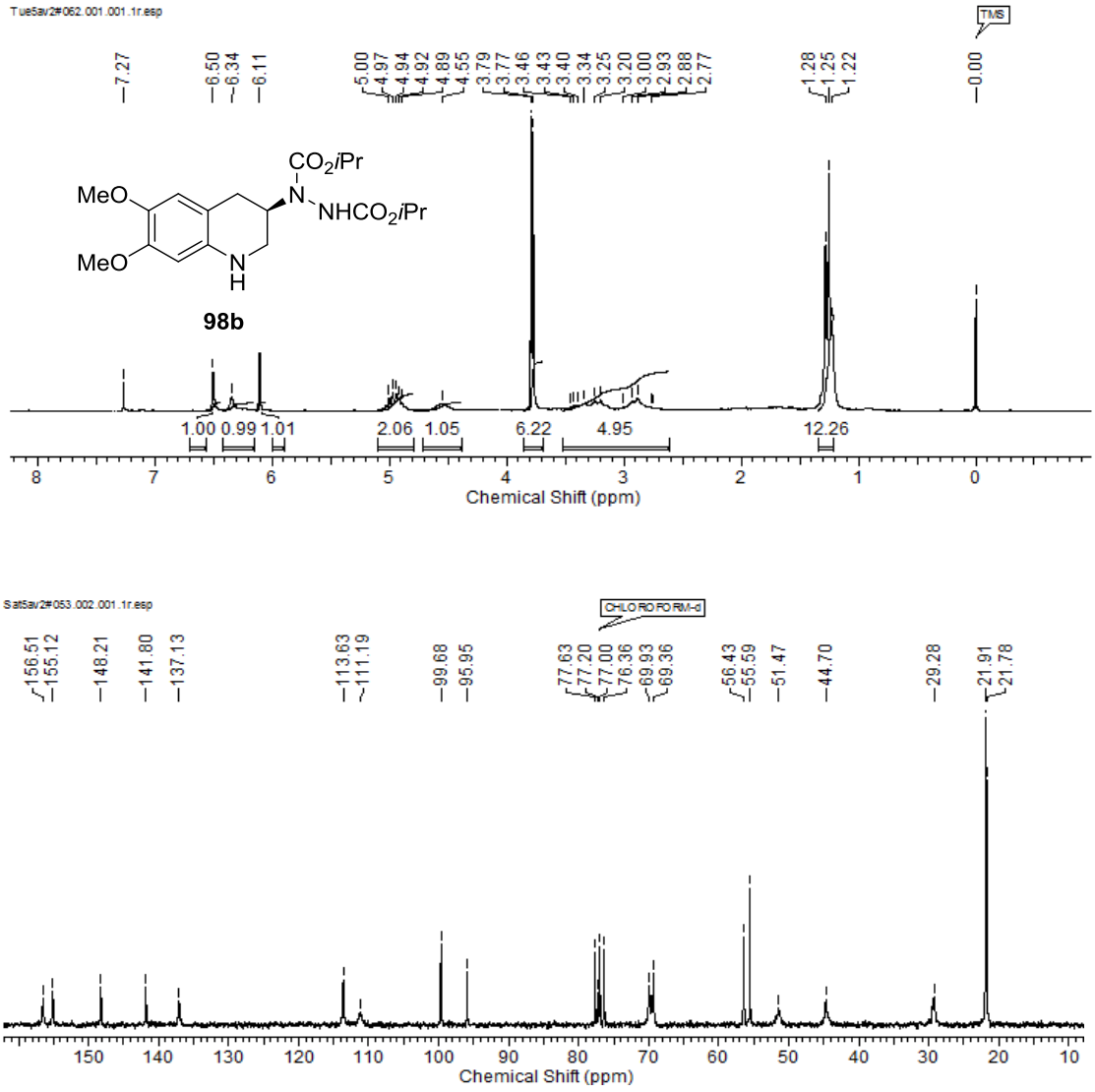
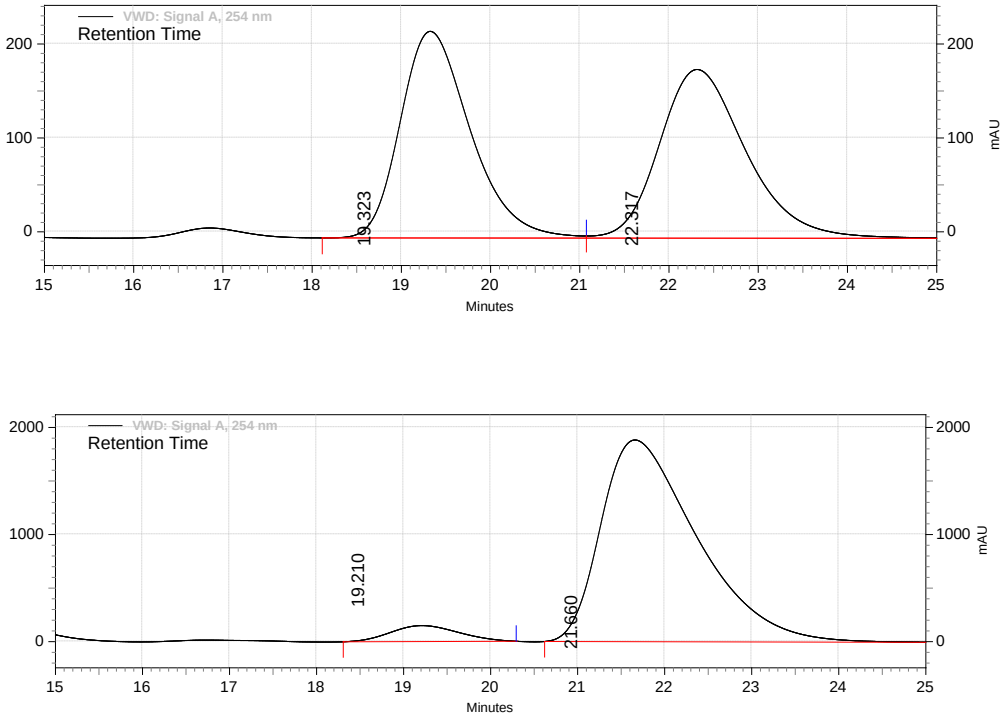


Fig. 8: ^{1}H & ^{13}C NMR spectra of THQ **98b**

The optical purity of THQ **98b** was determined from chiral HPLC analysis, Chiracel OD-H column **(Fig. 9).**



Retention Time	Area	Area %	Height	Height %
19.210	135951973	5.31	2499796	7.33
21.660	2422085955	94.69	31593077	92.67
	2558037928	100.00	34092873	100.00

Fig. 9: HPLC chromatogram of THQ **98b**

Similarly, the ^{1}H NMR spectrum of THQ **98c** showed a broad multiplet at δ 4.44-4.54 corresponding to methine (-**CH**-NR_2) proton, while a multiplet at δ 3.07-3.42 confirmed the presence of methylene (-**CH_2**-NH-) protons. Its ^{13}C NMR spectrum of showed typical carbon signals at δ 100.1, 108.9, 111.6, 137.9, 139.8 and 146.3 corresponding to aromatic carbons, while the other carbon signals at δ 44.7 and 51.3 were indicative of methylene (-**C**H_2-NHAr) and methine (-**CH**-NR_2) carbons respectively (**Fig. 10**).

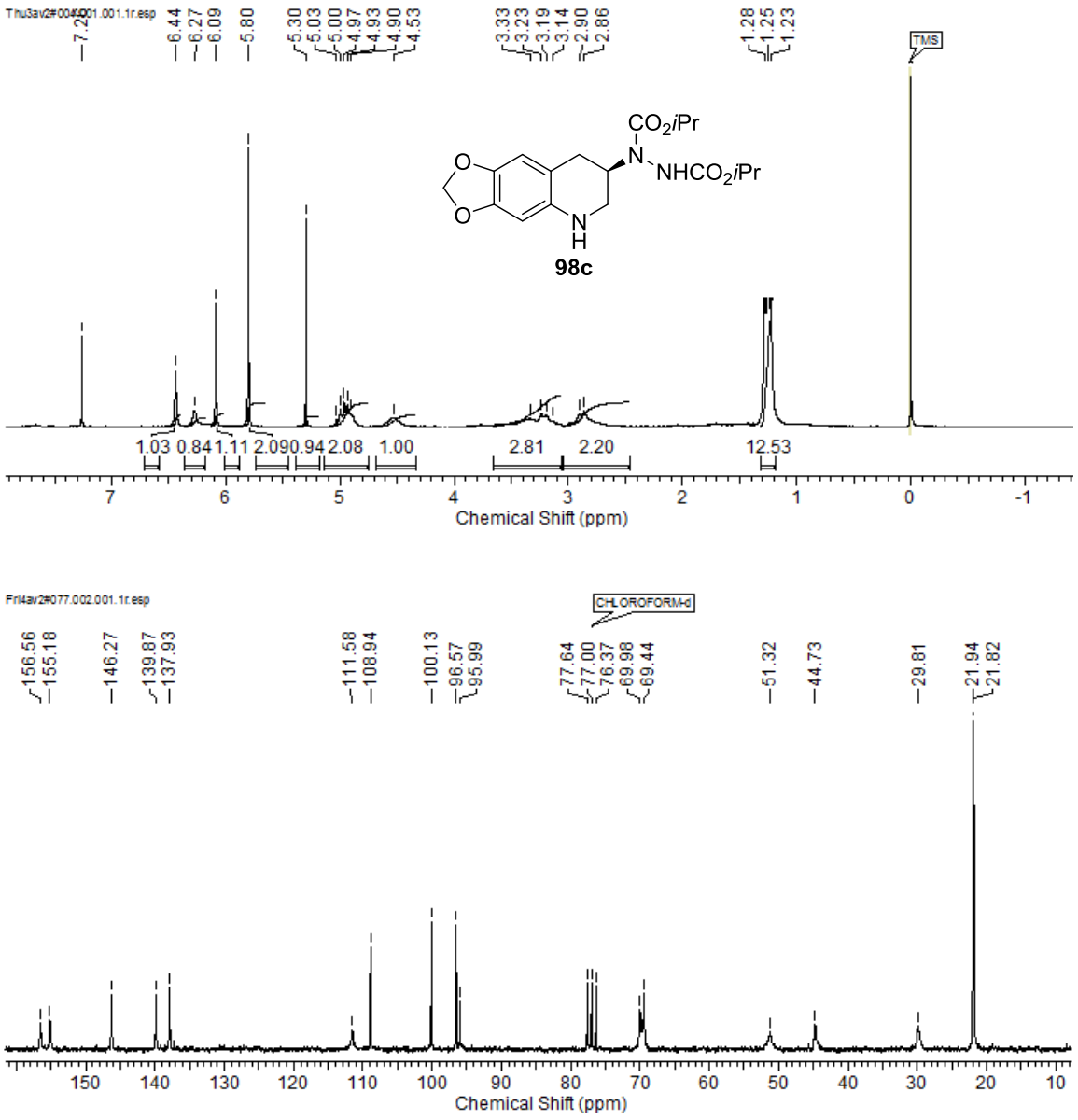


Fig. 10: ^{1}H & ^{13}C NMR spectra of THQ **98c**

1.2.4 Conclusion

In conclusion, we have developed a new sequential strategy for the construction of chiral 3-substituted THQs in high yields. The reaction is convenient to carry out under milder conditions with a sequential operation and the enantioselectivity is excellent. We believe that this strategy will find applications in the synthesis of optically pure 3-aminated terahydroquinoline owing to the flexible nature of synthesis of substituted *o*-nitrohydrocinnamaldehydes and the ready availability of both enantiomers of proline.

1.2.5 Experimental Section:

A general experimental procedure for the preparation of *o*-nitrohydrocinnamyl alcohol (100b-e)

To a stirred solution of alcohol **99b-e** (10 mmol) in CH_2Cl_2 (40 mL), conc. HNO_3 (2 mL, *d* =1.4) was added dropwise at 0 °C. Reaction mixture was stirred for 30 min and the progress of reaction was monitored by TLC. After completion of reaction, 50 mL of water was added. Organic layer was separated and aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). Combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and then passed through a thick pad of silica gel (230-400 mesh) with CH_2Cl_2 as eluent. The organic layer was concentrated under reduced pressure to give **100b-e** in pure form.

3-(4,5-Dimethoxy-2-nitrophenyl)propan-1-ol (100b)

Yield: 95% (2.3 g); gum, **IR** ($CHCl_3$, cm^{-1}): υ_{max} 745, 945, 1120, 1378, 3412; **^{1}H NMR** (200 MHz, $CDCl_3$): 1.87-1.95 (m, 2H), 2.97-3.05 (m, 2H), 3.71 (t, *J* = 6.2 Hz, 2H), 3.92 (s, 3H), 3.94 (s, 3H), 6.74 (s, 1H), 7.57 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 30.1, 33.5, 56.2, 61.9, 108.2, 113.4, 132.4, 141.2, 147.2, 153.0; **Anal.** Calcd for $C_{11}H_{15}NO_5$ requires C, 54.77; H, 6.27; N, 5.81; found C, 54.86; H, 6.33; N, 5.97%.

3-(6-Nitrobenzo[1,3]dioxol-5-yl)propan-1-ol (100c)

Yield: 93% (2.1 g); gum, **IR** ($CHCl_3$, cm^{-1}): υ_{max} 857, 968, 1060, 1460, 3498; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.82-1.96 (m, 3H), 2.91-2.99 (m, 2H), 3.73 (t, *J* = 6.2 Hz, 2H), 6.08 (s, 2H), 6.76 (s, 1H), 7.46 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 30.1, 33.4, 61.8, 102.7, 105.7, 110.6, 134.4, 142.8, 146.3, 151.6; **Anal.** Calcd for $C_{10}H_{11}NO_5$ requires C, 53.33; H, 4.92; N, 6.22; found C, 53.43; H, 4.98; N, 6.27%.

3-(4-(Cyclopentyloxy)-5-methoxy-2-nitrophenyl)propan-1-ol (100d)

Yield: 87% (2.6 g); gum, **IR** ($CHCl_3$, cm^{-1}): υ_{max} 754, 1129, 1324, 1460, 3467; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.58 (br s, 1H), 1.82-2.03 (m, 10H), 3.01 (t, *J* = 7.5 Hz, 2H), 3.72 (t, *J* = 6.0 Hz, 2H), 3.92 (s, 3H), 4.78-4.82 (m, 1H), 6.71 (s, 1H), 7.56 (s, 1H); **^{13}C NMR** (50 MHz $CDCl_3$): 23.9, 30.0, 32.5, 33.3, 56.0, 61.7, 80.6, 110.7, 113.5, 131.9, 140.8, 145.6, 153.8; **Anal.** Calcd for $C_{15}H_{21}NO_5$ requires C, 61.00; H, 7.17; N, 4.74; found C, 61.08; H, 7.23; N, 4.89%.

3-(4-(*tert*-Butyldiphenylsilyloxy) - 5 -methoxy-2-nitrophenyl) propan-1-ol (100e)

Yield: 80% (3.7g); gum, **IR** ($CHCl_3$, cm^{-1}): υ_{max} 907, 1172, 1068, 1531, 3367; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.13 (s, 9H), 1.31(br s, 1H), 1.61-1.71 (m, 2H), 2.93 (t, *J* = 7.4 Hz, 2H), 3.54 (s, 3H), 3.65 (t, *J* = 6.1 Hz, 2H), 6.55 (s, 1H), 7.34-7.44 (m, 8H), 7.64-7.69 (m, 4H); **^{13}C NMR** (50 MHz $CDCl_3$): δ 19.9, 26.7, 30.1, 33.5, 55.3, 62.0, 113.7, 117.2, 127.7, 130.0, 132.5, 132.8, 135.3, 141.1, 143.2, 154.6 ; **Anal.** Calcd for $C_{26}H_{31}NO_5Si$ requires C, 67.07; H, 6.71; N, 3.01; found C, 67.12; H, 6.79; N, 3.09%.

A general experimental procedure for the oxidation of alcohols to aldehydes (96b-e)

To a stirred solution of alcohol **100a-e** (5 mmol) in dry CH_2Cl_2 (10 mL), PCC (10 mmol) was added slowly at 25 °C. It was then stirred for further 6 h. After completion of the reaction (monitored by TLC), it was passed through a short pad of silica gel (230-400 mesh) using CH_2Cl_2 as eluent. The combined organic layers were concentrated under reduced pressure to give the aldehyde **96a-e** which was pure enough to be used in the next step.

3-(2-Nitrophenyl)propanal (96a)

Yield: 85% (761 mg); gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 765, 1166, 1225, 1235, 1454, 1712, 2989, 3123; **NMR** (200 MHz, $CDCl_3$): δ 2.89 (t, *J* = 7.3 Hz, 2H), 3.20 (t, *J* = 7.3 Hz, 2H), 7.28-7.59 (m, 3H), 7.92 (d, *J* = 7.9, 1H), 9.82 (s, 1H); **^{13}C NMR** (50

MHz, $CDCl_3$): 25.6, 44.4, 124.9, 127.5, 132.3, 133.1, 135.7, 199.9; **Anal.** Calcd for $C_9H_9NO_3$ requires: C, 60.33; H, 5.06; N, 7.82; found: C, 60.45; H, 5.13; N, 7.91%.

3-(4,5-Dimethoxy-2-nitrophenyl)propanal (96b)

Yield: 85% (1.07 g); gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1155, 1215, 1278, 1371, 1720, 2935, 2983; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.91 (t, *J* = 7.1 Hz, 2H), 3.23 (t, *J* = 7.3 Hz, 2H), 3.94 (s, 3H), 3.97 (s, 3H), 6.82 (s, 2H), 7.61 (s, 1H), 9.83 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 26.4, 44.4, 56.2, 108.1, 113.8, 131.0, 140.8, 147.4, 153.1, 200.4; **Anal.** Calcd for $C_{11}H_{13}NO_5$ requires: C, 55.23; H, 5.48; N, 5.86; found: C, 55.29; H, 5.57; N, 5.90%.

3-(6-Nitrobenzo[d][1,3]dioxol-5-yl)propanal (96c)

Yield: 85% (948 mg); gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1253, 1348, 1496, 1608, 1718, 2987; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.84 (t, *J* = 7.2 Hz, 1H), 3.17 (t, *J* = 7.0 Hz, 1H), 6.10 (s, 2H), 6.80 (s, 1H), 7.51 (s, 1H), 9.82 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 26.4, 44.4, 102.8, 105.7, 110.7, 133.0, 146.6, 151.7, 200.1; **Anal.** Calcd for $C_{10}H_9NO_5$ requires: C, 53.82; H, 4.06; N, 6.28; found: C, 53.72; H, 3.93; N, 6.21%.

3-(4-(Cyclopentyloxy)-5-methoxy-2-nitrophenyl)propanal (96d)

Yield: 82% (1.20 g); gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1233, 1312, 1608, 1718, 2913, 3018; **^{1}H NMR** (200 MHz, CDCl3): 1.64-2.02 (m, 8H), 2.90 (t, *J* = 6.9 Hz, 2H), 3.21 (t, *J* = 7.2 Hz, 2H), 3.92 (s, 3H), 4.76-4.84 (m, 1H), 6.78 (s, 1H), 7.59 (s, 1H), 9.83 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 23.9, 26.3, 32.5, 44.4, 56.0, 80.6, 110.6, 113.9, 127.2, 130.0, 130.4, 137.2, 140.6, 145.9, 153.9, 200.2; **Anal.** Calcd for $C_{15}H_{19}NO_5$ requires: C, 61.42; H, 6.53; N, 4.78; found: C, 61.46; H, 6.48; N, 4.87%.

3-(4-(*tert*-Butyl diphenyl silyloxy)-5-methoxy- 2 - nitrophenyl) propanal (96e)

Yield: 80% (1.85 g); gum; **IR** ($CHCl_3$): **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1155, 1215, 1357, 1718, 2984; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.12 (s, 9H), 2.82 (t, *J* = 7.1 Hz, 2H),

3.13 (t, *J* = 7.2 Hz, 2H), 3.56 (s, 3H), 6.61 (s, 1H), 7.34-7.39 (m, 8H), 7.64-7.68 (m, 4H), 9.78 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 19.8, 26.5, 26.7, 44.6, 55.4, 114.2, 117.2, 127.7, 130.0, 131.4, 132.6, 135.3, 143.5, 154.8, 200.6; **Anal.** Calcd for $C_{26}H_{29}NO_5Si$ requires: C, 67.36; H, 6.31; N, 3.02; found: C, 67.43; H, 6.41; N, 3.09%.

A general experimental procedure for the preparation of (*R*)-1,2,3,4-tetrahydro-6,7-dialkyloxyquinolin-3-amine (98a-e)

To a stirred solution of nitro hydrocinnamaldehyde **96a-e** (5.5 mmol) and DIAD (5 mmol) in CH_3CN (10 mL), L-proline (20 mol %) was added at 0 ºC and allowed to stir for 3 h. After completion of reaction, as indicated by the disappearance of yellow color, was added MeOH (30 mL) and 10% Pd/C (5 wt%). The reaction mixture was then stirred at 25 ^{o}C for additional 12 h under H_2 atmosphere (1 atm.). After the completion of reaction (monitored by TLC), it was filtered through celite and the solvent evaporated under reduced pressure. Chromatographic purification of the crude product over flash silica gel (230-400 mesh) and pet. ether:EtOAc gave the pure (*R*)-tetrahydroquinolin-3-amines **98a-e**.

(*R*)-Diisopropyl-1-(1,2,3,4-tetrahydroquinolin-3-yl)hydrazine-1,2-dicarboxylate (98a)

Yield: 82% (1.37 g); gum, $[\alpha]^{D}_{25}$ -720 (*c* 0.8, $CHCl_3$); 90% ee from **HPLC analysis**; Column: Chiracel OD-H (250 x 4.6 mm), mobile phase: isopropyl alcohol/n-hexane (5/95), wavelength: 254 nm, flow rate: 0.5 mL/ min, conc.: 1.5 mg/mL, injection vol.: 10µL, retention time: 31.73 min (-)-isomer, 34.6 min (+)-isomer; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1107, 1180, 1230, 1246, 1306, 1375, 1408, 1511, 1711, 1721, 2932, 2981, 3298; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.23-1.28 (m, 12H), 2.97-3.47 (m, 4H), 4.62(brs, 1H), 4.94-5.00 (m, 2H), 6.37(brs, 1H), 6.48 (d, *J* = 7.4 Hz, 1H), 6.61 (t, *J* = 7.2 Hz, 1H), 6.96 (m, 2H) **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.8, 21.9, 30.0, 44.5, 51.0, 69.7,

70.1, 96.0, 113.9, 117.4, 119.5, 126.8, 129.5, 143.5, 155.2, 156.6; **HRMS (ESI, m/z):** Calculated for $C_{17}H_{25}N_3O_4$ (M+H)+ 336.1923, found: 336.1923; **Analysis**: $C_{17}H_{25}N_3O_4$ requires: C, 60.88; H, 7.51; N, 12.53; found: C, 60.88; H, 7.51; N, 12.53%.

(*R*) - Diisopropyl 1 - (6,7-dimethoxy-1,2,3,4-tetrahydroquinolin-3-yl) hydrazine - 1,2 - dicarboxylate (98b)

Yield: 85% (1.68 g); gum, $[\alpha]^{D}_{25}$ -1379.0 (*c* 1.2, $CHCl_3$); 90% ee from **HPLC analysis**; Column: Chiracel OD-H (250 x 4.6 mm), mobile phase: isopropyl alcohol/n-hexane (5/95), wavelength: 254 nm, flow rate: 0.5 mL/ min, conc.: 1.5 mg/mL, injection vol.: 10µL, retention time: 19.3 min (-)-isomer, 22.3 min (+)-isomer; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1036, 1108, 1133, 1179, 1385, 1398, 1519, 1707, 2999, 3313, 3378; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.22-128 (m, 12H), 2.81-2.93 (m, 2H), 3.20-3.41 (m, 2H), 3.77 (s, 3H), 3.79 (s, 3H), 4.54-4.58 (m, 1H), 4.94-4.97 (m, 2H), 6.11 (s, 1H), 6.32 (br. s, 1H), 6.50 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.0, 29.6, 44.9, 51.6, 56.5, 69.2, 70.0, 96.1, 99.6, 111.2, 113.7, 137.5, 141.7, 148.3, 155.3, 156.7; **HRMS (ESI, m/z):** Calculated for $C_{19}H_{29}N_3O_6$ (M+H)+ 396.2135, found: 396.2131; **Analysis**: $C_{19}H_{29}N_3O_6$ requires: C, 57.71; H, 7.39; N, 10.63; found: C, 57.72; H, 7.33; N, 10.67%.

(*R*)-Diisopropyl 1-(5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]quinolin-7-yl)hydrazine-1,2-dicarboxylate (98c)

Yield: 87% (1.65 g); gum, $[\alpha]^{D}_{25}$ -1694.1(*c* 0.7, $CHCl_3$); 91% ee from **HPLC analysis**; Column: Chiracel OD-H (250 x 4.6 mm), mobile phase: isopropyl alcohol/n-hexane (5/95), wavelength: 254 nm, flow rate: 0.5 mL/ min, conc.: 1.5mg/mL, injection vol.: 10µL, retention time: 20.3 min (-)-isomer, 27.9 min (+)-isomer; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1038, 1106, 1161, 1182, 1216, 1235, 1299, 1374, 1386, 1468, 1503, 1707, 2916, 2980, 3304; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.23-1.28

(m, 12H), 2.82-2.98 (m, 2H), 3.13-3.42 (m, 2H), 4.51 (m, 1H), 4.94-4.97 (m, 2H), 5.30 (s, 1H), 5.80 (s, 2H), 6.09 (s, 1H), 6.28 (br. s, 1H), 6.44 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.9, 29.8, 44.7, 51.3, 69.4, 70.0, 96.6, 108.9, 111.6, 137.5, 139.9, 146.3, 155.0, 156.6; **Analysis**: $C_{18}H_{25}N_3O_6$ requires: C, 56.98; H, 6.64; N, 11.08; found: C, 56.52; H, 6.51; N, 11.18%.

(*R*)-Diisopropyl-1-(7-(cyclopentyloxy)-6-methoxy-1,2,3,4-tetrahydroquinolin-3-yl)hydrazine-1,2-dicarboxylate (98d)

Yield: 81% (1.82 g); gum, $[\alpha]^{D}_{25}$ -327.6 (*c* 3.4, $CHCl_3$); 91% ee from **HPLC analysis**; Column: Chiracel OD-H (250 x 4.6 mm), mobile phase: isopropyl alcohol/n-hexane (5/95), wavelength: 254 nm, flow rate: 0.5 mL/ min, conc.: 1.5 mg/mL, injection vol.: 10µL, retention time: 29.9 min (-)-isomer, 37.6 min (+)-isomer; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1035, 1108, 1135, 1198, 1227, 1253, 1299, 1340, 1374, 1385, 1397, 1515, 1712, 2978, 3296; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.23-128 (m, 12H), 1.56-1.82 (m, 8H), 2.75-3.37 (m, 4H), 3.75 (s, 3H), 4.59 (m, 2H), 4.94-5.00 (m, 2H), 6.01 (s, 1H), 6.28 (br. s, 1H), 6.51 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.8, 22.0, 24.9, 29.6, 44.8, 51.2, 56.8, 69.4, 69.8, 80.1, 103.1, 111.1, 114.9, 137.4, 142.8, 146.8, 155.0, 156.5; **Analysis**: $C_{23}H_{35}N_3O_6$ requires: C, 61.45; H, 7.85; N, 9.35; found: C, 61.38; H, 7.84; N, 9.15%.

(*R*)- Diisopropyl 1-(7-(*tert*-butyldiphenylsilyloxy)-6-methoxy-1,2,3,4-tetrahydro-quinolin-3-yl)hydrazine-1,2-dicarboxylate (98e)

Yield: 80% (2.46 g); gum, $[\alpha]^{D}_{25}$ -434.5 (*c* 3.2, $CHCl_3$); 90% ee from **HPLC analysis**; Column: Chiracel OD-H (250 x 4.6 mm), mobile phase: isopropyl alcohol/n-hexane (5/95), wavelength: 254 nm, flow rate: 0.5 mL/ min, conc.: 1.5mg/mL, injection vol.: 10µL, retention time: 35.5 min (-)-isomer, 41.99 min (+)-isomer; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 702, 1109, 1143, 1228, 1255, 1298, 1385, 1518, 1710, 2856, 2931, 2979, 3283; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.9 (s, 9H), 1.08-1.30 (m,

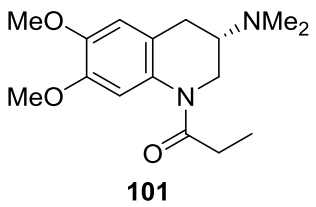
12H), 2.83-3.18 (m, 4H), 3.49 (s, 3H), 4.51 (m, 1H), 4.87-5.0 (m, 2H), 5.93 (s, 1H), 6.13 (brs, 1H), 6.26 (br s, 1H), 6.42 (brs, 1H), 7.33-7.67 (m, 5H), 7.68-7.73 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 19.7, 21.9, 26.6, 29.5, 51.2, 56.5, 69.4, 69.7, 107.1, 115.1, 127.4, 129.4, 133.6, 135.2, 137.2, 143.2, 144.3; **Analysis**: $C_{34}H_{45}N_3O_6Si$ requires: C, 65.88; H, 7.32; N, 6.78; found: C, 65.80; H, 7.02; N, 6.56 %.

Section III

A Concise Enantioselective Synthesis of 1-[(*S*)-3-(Dimethylamino)-3, 4-Dihydro-6,7-Dimethoxyquinolin-1(2*H*)-yl] Propan-1-one, [(*S*)-903]

1.3.1 Introduction

Although excellent diuretics and ACE inhibitors are available for the treatment of congestive heart failures, the only current approach that relies on the stimulation of cardiac contractility is the use of cardiac glycosides with a variety of therapeutic limitations. 1-[(*S*)-3-(Dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1(2*H*)-yl] propanone **101** have recently been identified as potentially interesting positive inotropic agents (**Fig. 11**). [47]



101

Fig. 11: *S*-903, a positive inotropic agent

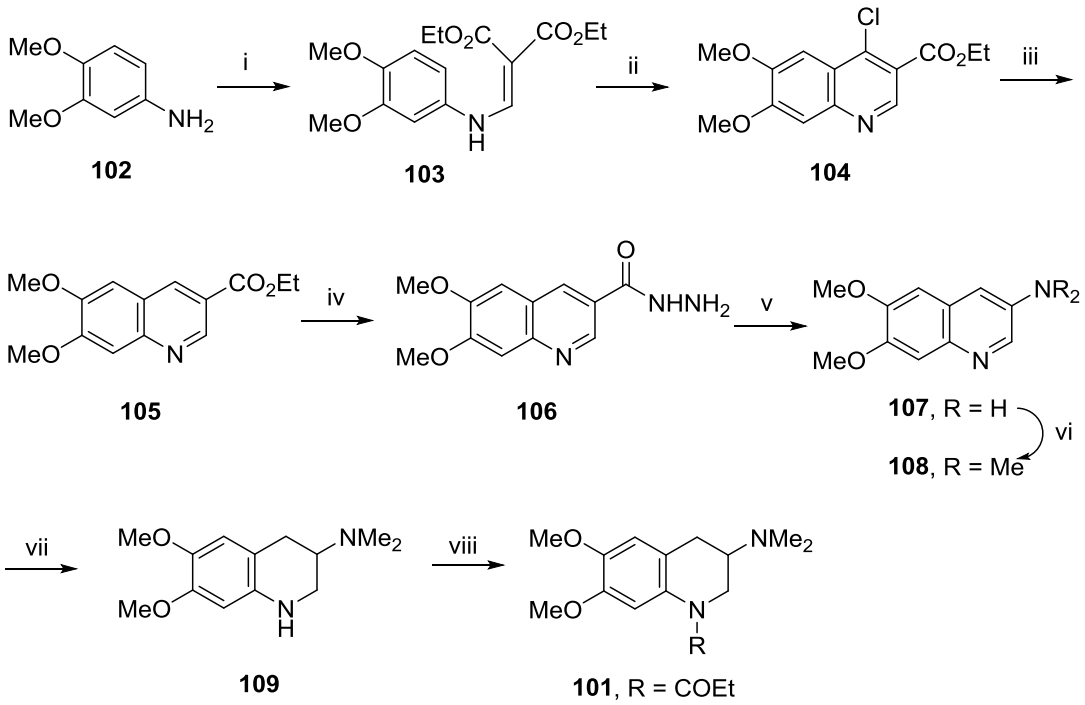
1.3.2 Review of literature

Literature search revealed that there are only few reports available for the synthesis of 1-[(*S*)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1(2*H*)-yl] propanone which is described below.

Vecchietti's Approach (1994)[47]

Vecchietti *et al.* have reported racemic synthesis of 1-[(*S*)-3-(Dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1(2*H*)-yl] propanone. Diethyl 2-[(3,4-dimethoxyphenylamino)methylene]malonate **103,** obtained by the condensation of ethoxymethylene malonate with 3,4-dimethoxyaniline (**102**), was cyclized ($POCl_3$ and DMF) to give chloro tetrahydroquinoline derivative **104**. Subsequent dechlorination (10% Pd/C, H_2 and AcOH) was achieved to give quinoline derivative **105.** This was

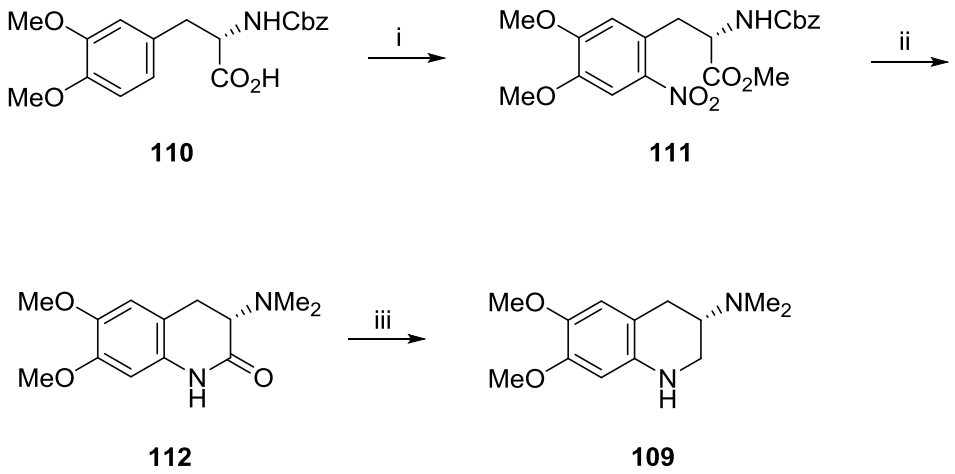
subjected to Curtius rearrangement *via* hydrazine amide **106** to provide 3-aminoquionoline **107** in good yields. Subsequently, its reductive amination (HCHO and HCO_2H) gave **108,** which was subjected to ionic hydrogenation under high pressure (10%Pd/C, H_2 and AcOH) to give *N*,*N*-dimethyl amino tetrahydroquinoline **109.** Finally, acylation of amine **109** (acid chloride and CH_2Cl_2) furnished amide **101** in good yields (**Scheme 30**).



Scheme 30: (i) $C_2H_5OCH{=}C(COOC_2H_5)_2$, heat; (ii) $POCl_3/PCl_5$; (iii) H_2, 10% Pd/C, acetic acid; (iv) $NH,NH_2{\cdot}H_2O$; (v) $NaNO_2$; (vi) HCHO/HCOOH; (vii) H_2, 10% Pd/C, acetic acid, 80%; (viii) acyl chloride, CH_2Cl_2.

In another approach, the same authors have described the asymmetric synthesis of diamine intermediate **109** starting from chiral starting material. *N*-Cbz protected L–DOPA derivative **110** was esterified to give methyl ester**,** which was regioselectively nitrated (conc. HNO_3 and AcOH) to give nitro derivative **111**. Nitro ester **111** was reduced (10% Pd/C, H_2 (4 atm) and AcOH) to give (*S*)-3-amino-3,4-dihydro-6,7-dimethoxyquinolin-2(1*H*)-one**,** which on reductive amination (10% Pd/C, HCHO and

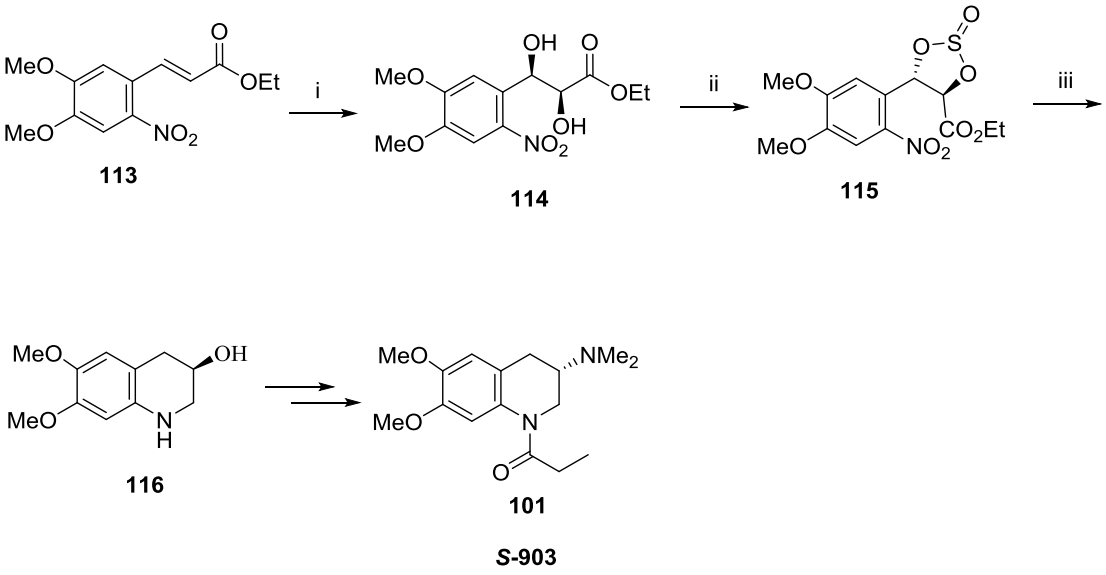
MeOH) gave *N, N*-dimethylaminoquinolin-2-one **112**. Finally, $LiAlH_4$ reduction of **112** gave very low yield (28%) of 3-**(***N, N*-dimethylamino)quinoline **109** (**Scheme 31**).



Scheme 31: (i) (a) CH_3I, K_2,CO_3, acetone, 60 °C, 6 h, 73%; (b) HNO_3, CH_3CO_2H, 15 °C, 3 h 76%; (ii) (a) 10% Pd/C, H_2 (4 atm), CH_3CO_2H, 91%; (b) 10% Pd/C, HCHO, 2N HCl, Et_2O, 40-50 °C, 90%; (iii) $LiAlH_4$, DME, reflux, 24 h, 28%.

Sudalai's approach (2009)[48]

Sudalai *et al.* have used a novel $CoCl_2$-catalyzed reductive cyclization of nitro cyclic sulfites with $NaBH_4$ for the formal synthesis of S-903. Unsaturated nitroesters **113** prepared from Wittig-Horner olefination of the corresponding nitrobenzaldehyde was converted to the corresponding diol **114** in 82% yield *via* Os-catalyzed asymmetric dihydroxylation using $(DHQD)_2$-PHAL as chiral ligand. The diol **114** was readily converted into the corresponding nitro cyclic sulphite **115** ($SOCl_2$ and Et_3N in CH_2Cl_2) in 95% yield. Catalytic one-pot reduction of cyclic sulphite **115** using $CoCl_2$ (1 mol%) and $NaBH_4$ gave the 3-hydroxy tetrahydroquinoline **116** in 81% yield. **116** was then converted into the title compound **101** in five additional steps (**Scheme 32**).



Scheme 32: (i) K_2OsO_4 (0.2 mol%), $(DHQD)_2$-PHAL (1 mol%), $K_3Fe(CN)_6$ (3 equiv), K_2CO_3 (3 equiv.), $MeSO_2NH_2$ (1 equiv), *tert*-BuOH:H_2O (1:1), 25 °C, 24 h, 82%; (ii) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 1 h, 95%; (iii) $CoCl_2 \cdot 6H_2O$ (1 mol%), $NaBH_4$, EtOH, 0-25 °C, 6 h, 81%.

1.3.3 Present work

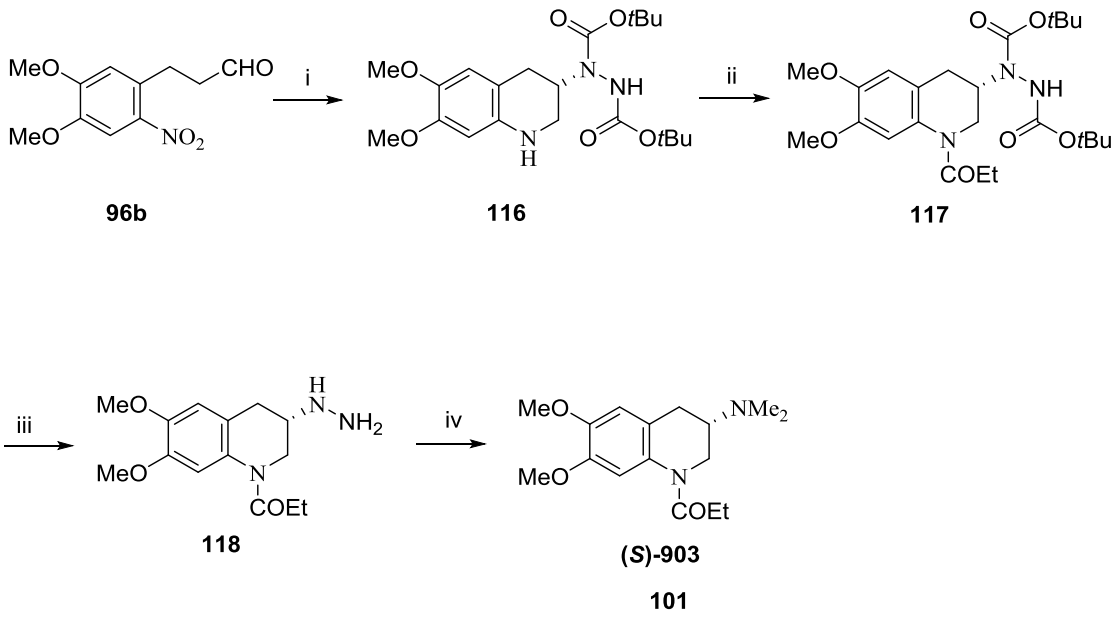
1.3.3.1 Objective

Review of literature reveals that there are only limited reports available for the synthesis of *S*-903. Additionally, use of chiral starting material as well as the need for several protecting groups in the synthesis, make the existing method uneconomical. In section II of this Chapter, we have described a proline-catalyzed α-amination-reductive cyclization method for the synthesis of 3-aminated tetrahydroquinoline derivatives **98a-e**. To demonstrate the direct application of the methodology, a concise enantioselective synthesis of (*S*)-903 **101** is described in this section (**Scheme 33**)

1.3.3.2 Results and Discussion

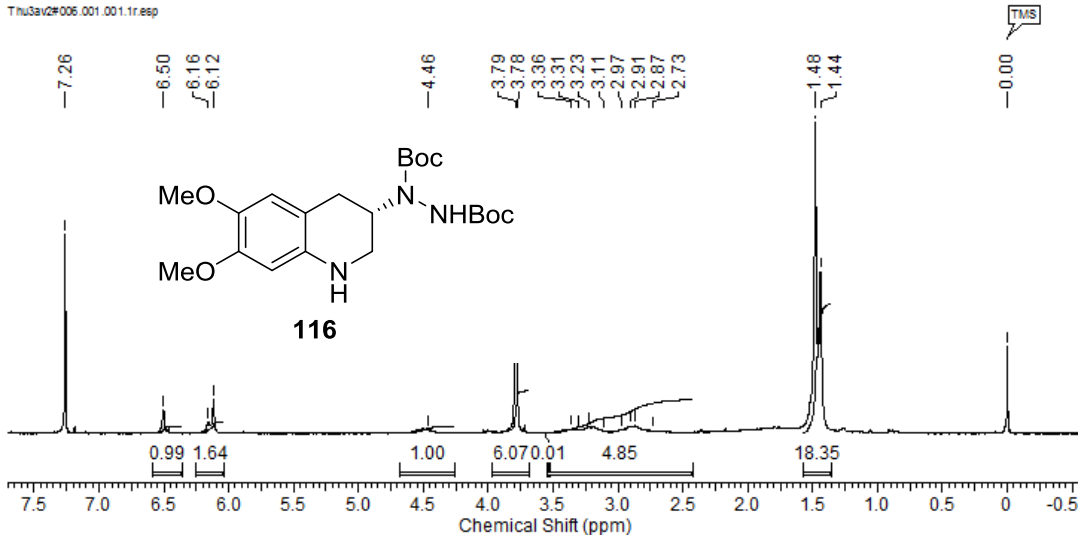
The synthesis of S-903 **101** was started with readily accessible *o*-nitrohydrocinnamaldehyde derivative **96b**. The sequential α-amination of **96b** using D-proline as catalyst and di-*tert*-butyl azodicarboxylate as amine source followed by

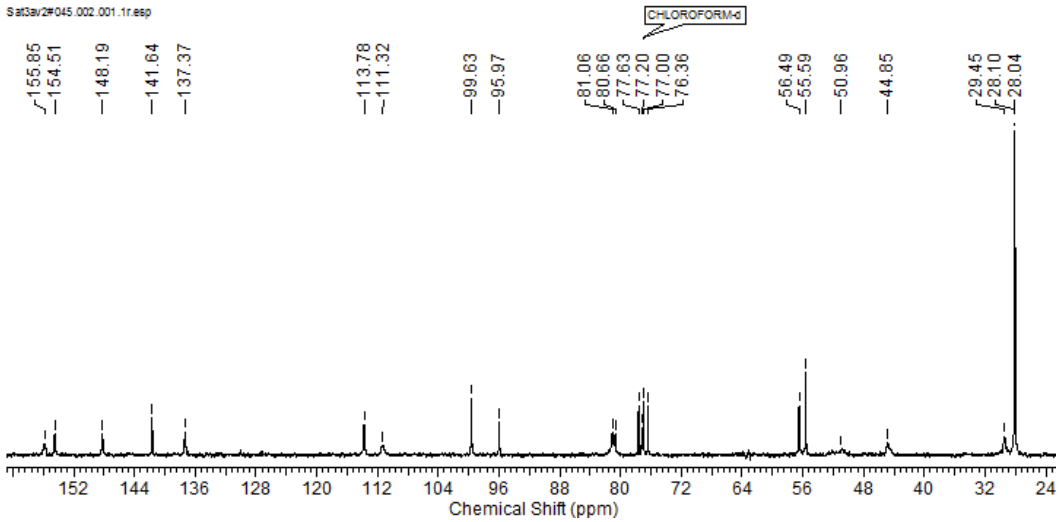
in situ reductive cyclization under catalytic hydrogenation condition [H_2 (1 atm),10% Pd/C] gave 3-aminated THQ **116** in 82% yield; $[\alpha]^{D}_{25}$ -409.6 (*c* 2.0, $CHCl_3$).

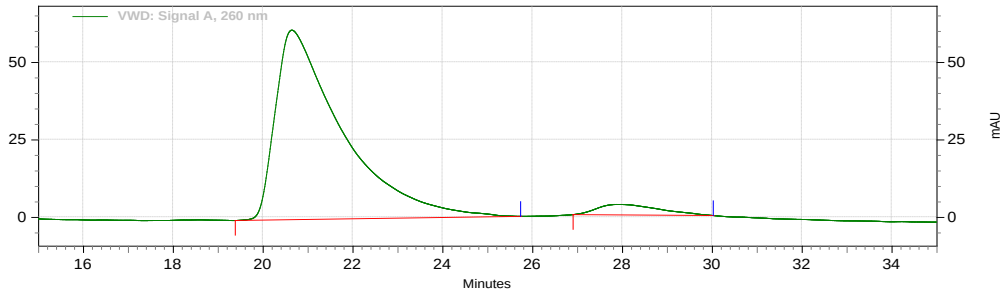


Scheme 33: (i) D-proline (20 mol%), *t*BuO_2C-N=N-CO_2*t*Bu, CH_3CN, 0 °C, 3 h followed by H_2 (1 atm), 10% Pd/C, MeOH, 6 h, 83%; (ii) $(EtCO)_2O$, Et_3N, CH_2Cl_2, 0 °C, 91%; (iii) TFA, CH_2Cl_2, 0-25 °C, 12 h, 91%; (iv) (a) H_2 (80 psig), Raney Ni, AcOH (cat.), MeOH, 25 °C, 24 h;(b) HCHO, HCO_2H, 80 °C, 3 h, 73% (over two steps).

The formation of THQ **116** was confirmed by its ^{1}H NMR spectrum which showed a typical multiplet at δ 3.16-3.47 (m) and a broad singlet at 4.52 (brs) corresponding to methylene (N-C**H**$_2$) and methine (-C**H**-NR_2) protons respectively, while singlets at δ 3.78 and 3.79 were due to methoxy protons. Its ^{13}C NMR spectrum displayed two methylene and one methine (-**CH**-OH) carbons appearing typically at δ 29.4, 44.8 and 50.9 respectively, while the other signals at δ 55.6 and 56.5 were due to methyl carbons attached to oxygen atom (**Fig. 12**). The optical purity of THQ **116** was analyzed from chiral HPLC analysis; Chiracel OD-H column (**Fig. 12**).







Ret. Time	Area	Area %	Height	Height %
20.640	105537842	96.05	1025503	94.78
27.930	5494182	3.95	56517	5.22
	111032024	100.00	1082020	100.00

Fig. 12: ^{1}H & ^{13}C NMR spectra and HPLC chromatogram of THQ **116**

Amine functionality in THQ **116** was subsequently acylated [$(EtCO)_2O$, NEt_3, CH_2Cl_2] to give the corresponding amide **117** in 91% yields; $[\alpha]^{D}_{25}$ -382.6 (*c* 2.0, $CHCl_3$)**.** Its ^{1}H NMR spectrum showed typical proton signals at δ 1.12-1.21 (m, 3H) and 1.48-1.68 (m, 2H) corresponding to the methyl (-$COCH_2$**CH_3**) and methylene (-CO**CH_2**CH_3) protons respectively. A broad singlet at δ 4.58 (brs, 1H) was due to methine (-C**H**-NR_2) proton. Its ^{13}C NMR spectrum showed a typical carbonyl signal at δ 173.3; thus confirming the formation of amide carbonyl group (**Fig 13**).

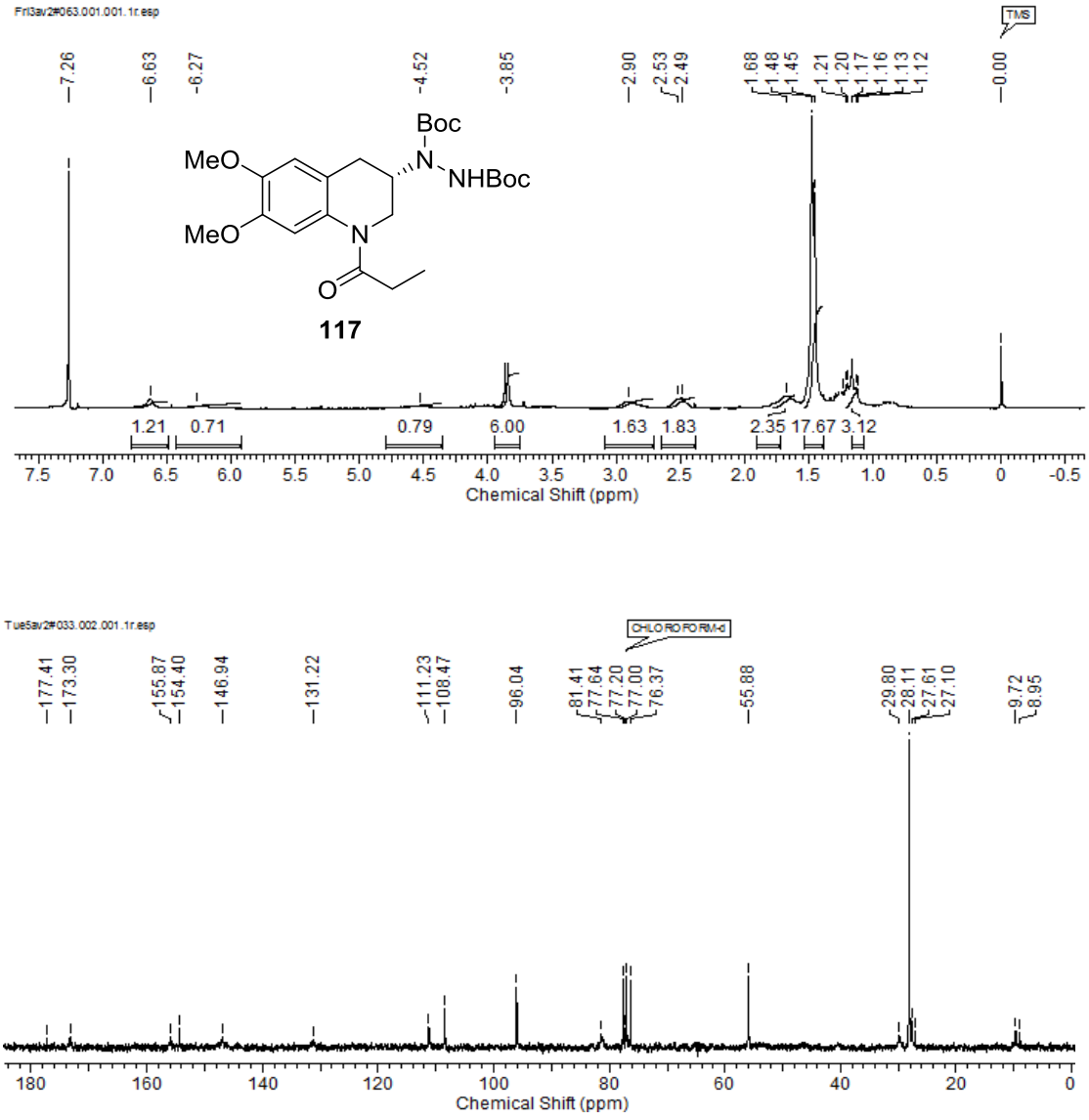


Fig. 13: ^{1}H and ^{13}C NMR spectra of amide **117**

The two Boc groups in the hydrazine functionality of **117** were then deprotected using trifluoroacetic acid to give hydrazine **118** {$[\alpha]^{D}_{25}$ +18.3 (*c* 1.1, MeOH)} in 91% yield. The disappearance of peaks at δ 1.45-1.48 for 18 protons in its ^{1}H NMR spectrum confirmed the complete deprotection of both the Boc groups. Also, the absence of carbon signals at δ 154.4 and 155.8 corresponding to carbamate carbonyls in its ^{13}C NMR spectrum confirmed the formation of compound **118**. Its HRMS (ESI, m/z) showed typical mass peak at 280.1664 calculated for $C_{14}H_{21}N_3O_3$ $(M+H)^+$ 280.1661 (**Fig. 14**).

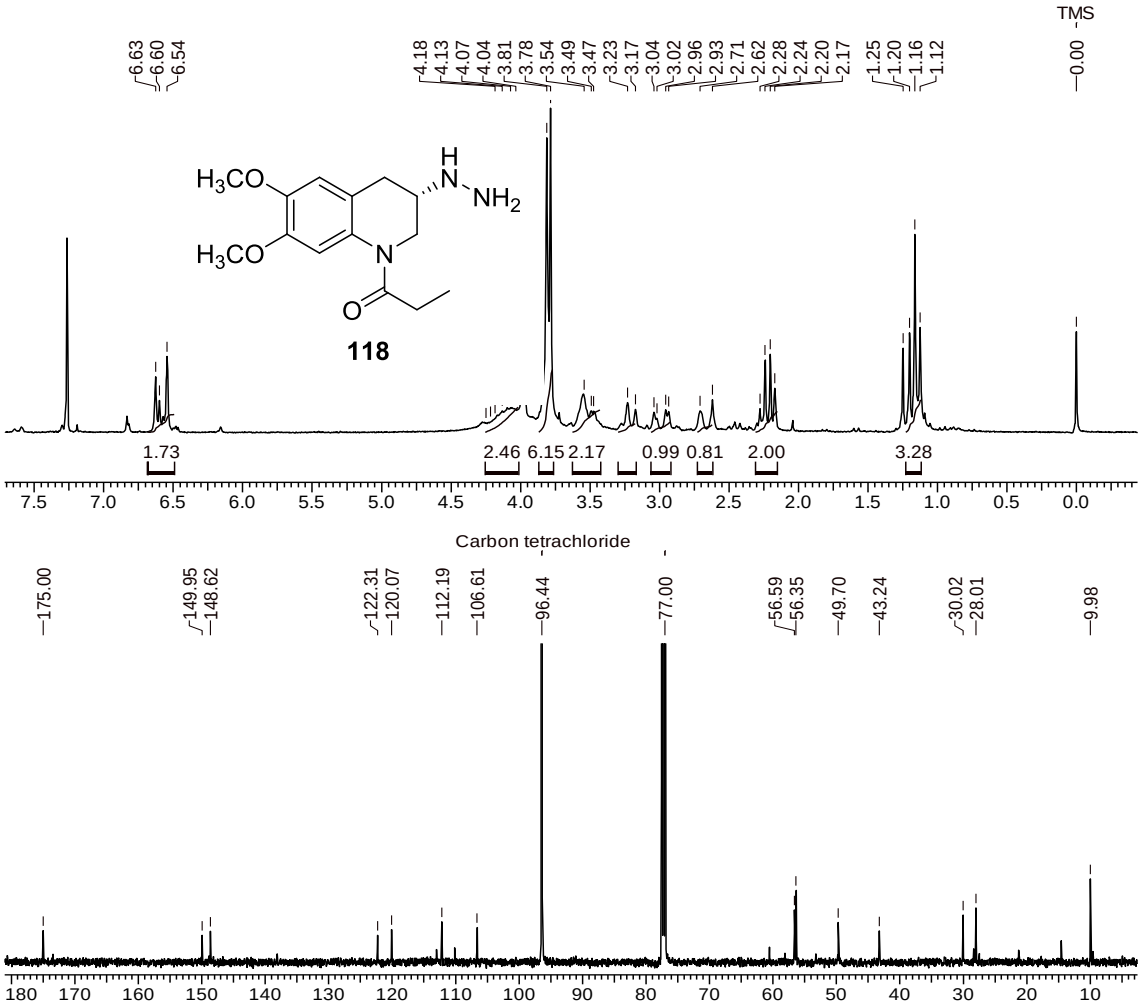


Fig. 14: ^{1}H and ^{13}C NMR spectra of hydrazine **118**

With the free hydrazine **118** in hand, the next step towards its completion was its hydrogenolysis under Raney Ni reduction condition followed by reductive methylation (HCHO, HCO_2H), which afforded the target molecule **101** in 73% yield and 92% ee (**Scheme 33**). The ^{1}H NMR spectrum of **101** showed a typical singlet at δ 2.35 due to methyl amine protons [-N($\mathbf{CH_3}$)$_2$]. The other signals at δ 41.33 and 41.46 in its ^{13}C NMR spectrum were due to methyl amine carbons (**Fig. 15**).

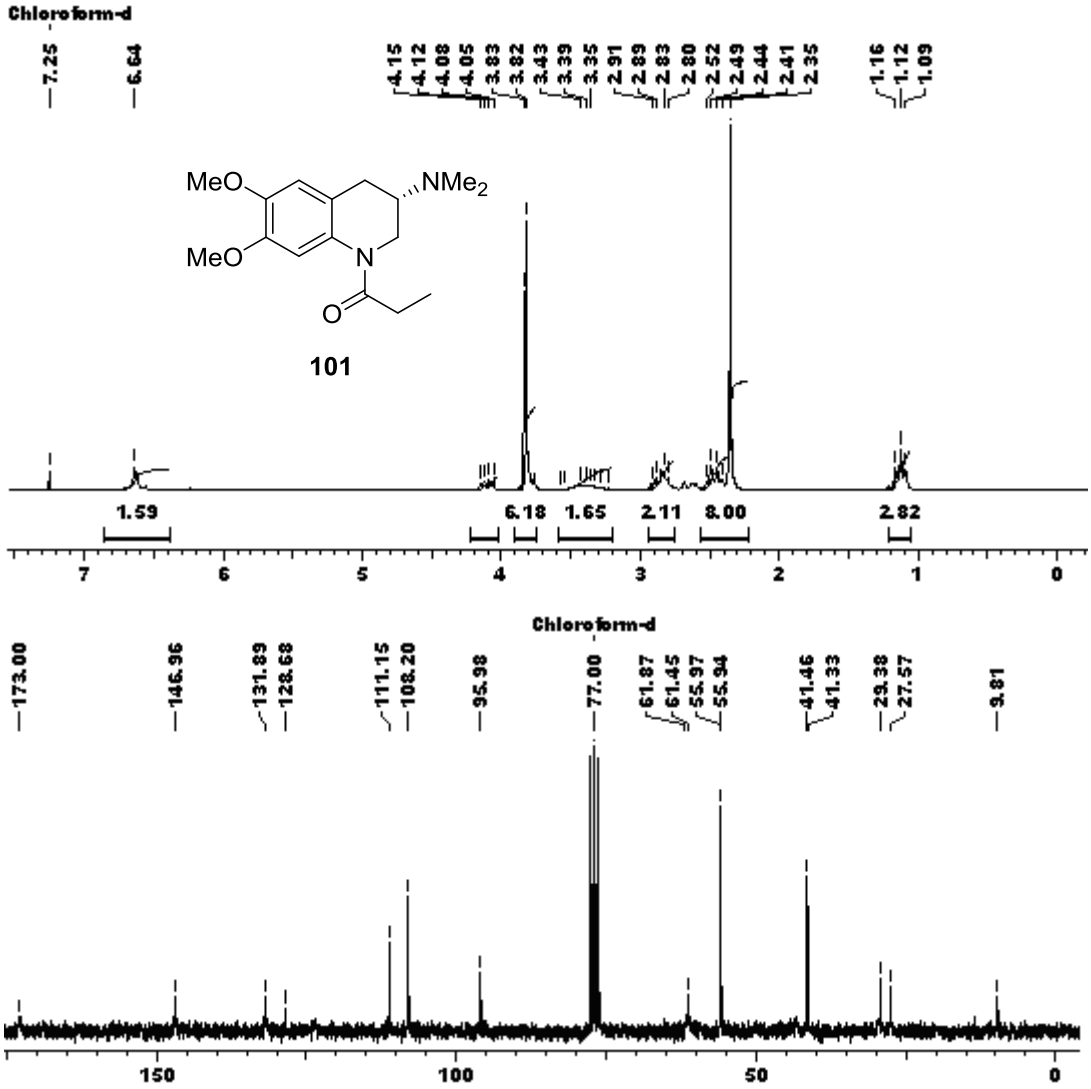


Fig. 15: ^{1}H and ^{13}C NMR spectra of **101** (*S*)-903

1.3.4 Conclusion

In conclusion, we have achieved a concise enantioselective synthesis of 1-[(*S*)-3-(dimethylamino)-6,7-dimethoxytetrahydroquinoline propanone (**101)** (50.1% overall

yield from **96b** with 92% ee). We have successfully utilized a novel sequential protocol based on α-amination followed by reductive cyclization of *o*-nitrohydrocinnamaldehydes as key steps for the synthesis of (*S*)-903**.**

1.3.5 Experimental section

(*S*)-Di-*tert*-butyl-1-(6,7-dimethoxy-1,2,3,4-tetrahydroquinolin-3-yl)hydrazine-1,2-dicarboxylate (116)

To a stirred solution of nitrohydrocinnamaldehyde **96b** (1.31 g, 5.5 mmol) and di-*tert*-butyl azodicarboxylate (1.15 g, 5.0 mmol) in CH_3CN (10 mL), was added D-proline (20 mol %) at 0 ºC and allowed to stir for 3 h. After the completion of reaction as indicated by the disappearance of yellow color, was added MeOH (30 mL) and 10% Pd/C (5 wt%). The reaction mixture was then stirred at 25 ^oC for additional 6 h under H_2 atmosphere (1atm, balloon pressure). After the completion of reaction (monitored by TLC), it was filtered through a pad of celite and the solvent evaporated under reduced pressure. Chromatographic purification of the crude product [flash silica gel (230-400 mesh) and pet. ether:EtOAc (70:30)] gave the pure **116**.

Yield: 83% (1.76 g); gum, $[\alpha]^D_{25}$ +409.1 (*c* 1.5, $CHCl_3$); 92% ee from **HPLC analysis**; Column: Chiracel OD-H (250 x 4.6 mm), mobile phase: isopropyl alcohol/n-hexane (5/95), wavelength: 254 nm, flow rate: 0.5 mL/ min, conc.: 1.5 mg/mL, injection vol.: 10µL, retention time: 20.6 min (-)-isomer, 27.9 min (+)-isomer; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1158, 1207, 1252, 1366, 1391, 1518, 1704, 2929, 2977, 3323; ^1H **NMR** (200 MHz, $CDCl_3$): 1.44-1.48 (m, 18H), 1.80 (brs, 1H), 2.85-3.01 (m, 2H), 3.09-3.46 (m, 2H), 3.78 (s, 3H), 3.7 (s, 3H), 4.44-4.54 (m, 1H), 6.1 (s, 1H), 6.16 (brs, 1H), 6.50 (s, 1H); ^{13}**C NMR** (50 MHz, $CDCl_3$): δ 28.0, 29.4, 44.8, 50.7, 55.5, 56.4, 77.0, 80.6, 81.0, 95.9, 99.6, 111.3, 113.7, 137.3, 141.6, 148.0, 154.5, 155.8; **Analysis** for $C_{21}H_{33}N_3O_6$ requires C, 59.56; H, 7.85; N, 9.92; found: C, 59.52; H, 7.81; N, 9.88%.

Synthesis of (*S*)-Di-*tert*-butyl-1-(6,7-dimethoxy-1-propionyl-1,2,3,4-tetrahydroquinolin-3-yl)hydrazine-1,2-dicarboxylate (117)

To the stirred solution of tetrahydroquinolin-3-hydrazine *tert*-butyl ester **116** (1.5 g, 3.6 mmol) and Et_3N (0.722 g, 7.2 mmol) in 25 mL of CH_2Cl_2, was added propionic anhydride (0.930 g, 7.2 mmol) at 25 ^oC. Reaction mixture was then stirred for 3 h and after completion of reaction (monitored by TLC), it was washed sequentially with saturated aq. $NaHCO_3$ and brine, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude product. Chromatographic purification of crude product [silica gel (230-400 mesh) and pet. ether:EtOAc (60:40)] gave amide **117** in pure form.

Yield 91% (1.56 g); gum, $[\alpha]^D_{25}$ -382.6 (*c* 2.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 758, 1044, 1172, 1275, 1367, 1393, 1643, 1706, 1737, 2934, 2977, 3328: **^{1}H NMR** (200 MHz, $CDCl_3$): 1.12-1.23 (m, 3H), 1.45-1.48 (m, 18H), 1.65-1.71 (m, 2H), 2.43-2.58 (m, 2H), 2.84-3.00 (m, 2H), 3.85 (s, 6H), 4.43-4.59 (m, 1H), 6.22 (s, 1H), 6.63 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 8.9, 9.7, 27.0, 27.6, 28.1, 29.8, 55.8, 81.4, 108.4, 111.2, 154.4; **Analysis** for $C_{24}H_{37}N_3O_7$ requires C, 60.11; H, 7.78; N, 8.76; found C, 60.08; H, 7.74; N, 8.72%.

(*S*)-1-(3-Hydrazinyl-6,7-dimethoxy-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (118)

To an ice-cooled solution of **117** (1.40 g, 2.9 mmol) in dry CH_2Cl_2 (15 mL) was added trifluoro acetic acid (2.0 g, 17.5 mmol). The reaction mixture was stirred at room temperature for 12 h. After the completion of the reaction (monitored by TLC), it was then quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were washed with brine and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product. Chromatographic

purification [silica gel (230-400 mesh) of the crude product using MeOH:EtOAc (5:95)] gave pure hydrazine **118** as colorless solid.

Yield 90% (0.736 g): solid, **mp** 104-108 °C; $[\alpha]^{D}_{25}$ +18.3 (*c* 1.1, MeOH); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 749, 838, 1144, 1207, 1229, 1254, 1523, 1643, 2931, 2990, 3184, 3283; **^{1}H NMR** (200 MHz,$CDCl_3$): 1.17 (t, *J* = 7.6 Hz, 3H), 2.17 (dd, *J* = 7.4, 15.0 Hz, 2H), 2.57 (dd, *J* = 4.3, 15.5 Hz, 2H), 2.89 (dd, *J* = 4.3, 16.3 Hz, 1H), 3.23-3.40 (m, 5H), 3.78 (s, 6H), 6.20 (s, 1H), 6.50 (s, 1H), 7.54 (brs, 1H**); ^{13}C NMR** (50 MHz, $CDCl_3$): δ 9.6, 14.2, 27.7, 29.7, 42.9, 49.4, 56.3, 106.3, 111.8, 119.7, 122.0, 148.3, 149.6, 174.7; **HRMS (ESI, m/z):** Calculated for $C_{14}H_{21}N_3O_3$ (M+H)+ 280.1661, found: 280.1664; **Analysis** for $C_{14}H_{21}N_3O_3$ requires C, 60.20; H, 7.58; N, 15.04; found: C, 60.15; H, 7.52; N, 15%.

1-[(*S*)-3-(Dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1(2*H*)-yl]-propan-1-one (101)

A solution of hydrazine **118** (560 mg, 2 mmol) in MeOH (10 mL), and AcOH (10 drops) was treated with Raney nickel (2 g, excess) under H_2 (80 psig) atmosphere for 24 h. After the completion of reaction (monitored by TLC), it was passed through a column packed with celite and concentrated under reduced pressure to afford the crude amine. To the crude amine, 40% aq. solution of HCHO (1 mL) and HCO_2H (2 mL) were added and the resulting mixture was refluxed for 3 h. After completion of the reaction, a saturated aq. $NaHCO_3$ solution (10 mL) was added and the mixture extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine (2 x 20 mL), dried over anhyd. Na_2SO_4, concentrated under reduced pressure. Chromatographic purification of the crude product [silica gel (230-400 mesh) and pet. ether: ethyl acetate: Et_3N (60:38:2) as eluent] gave pure **(*S*)-903** (**101**).

Yield: 73% (0.425 mg); **mp** 136 °C [lit.[18] 135-137 °C]; $[\alpha]^{D}_{25}$ –3.2 (*c* 1, EtOH) {lit.[18] $[\alpha]^{D}_{25}$ –3.3 (*c* 1, EtOH)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 760, 1049, 1211, 1511, 1647, 1743,

3018, 3450; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.12 (t, *J* = 7.3 Hz, 3H), 2.35 (s, 6H), 2.46 (q, *J* = 7.3 Hz, 2H), 2.80-2.91 (m, 2H), 3.23-3.54 (m, 2H), 3.82 (s, 3H), 3.83 (s, 3H), 6.64 (bs, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 9.8, 27.5, 29.5, 41.3, 41.4, 55.9, 55.9, 61.4, 61.8, 108.2, 111.1, 128.6, 131.8, 146.9, 173.0; **Analysis** for $C_{15}H_{21}N_2O_3$ requires C, 64.96; H, 7.63; N, 10.10; found: C, 64.82; H, 7.60; N, 10.27%.

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46 (a) A complex mixture was observed when dibenzyl azodicarboxylate was used for this sequential protocol; (b) Use of (S)-α,α-diarylprolinol silyl ether as a modified proline catalyst was found to be less effective for the reaction; (c) ArX (X = Cl, Br, I) were found to undergo dehalogenation under the present protocol of reductive cyclization. Further, attempts to prepare substrates with other electronwithdrawing groups (F, –CN, $–CO_2Et$) on the aryl ring were unsuccessful due to lengthy sequence of reactions involving formation of undesired regioisomers.

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CHAPTER II

Organocatalyzed Sequential α-Amination or *syn*-Mannich/Corey-Chaykovsky Reaction of Aldehydes for the Asymmetric Synthesis of Substituted 4-Hydroxypyrazolidines and 4-Hydroxypyrrolidines

Section I

Organocatalytic Sequential α-Amination/Corey-Chaykovsky Reaction of Aldehydes: A High Yield Synthesis of 4-Hydroxy pyrazolidine Derivatives

2.1.1 Introduction

Pyrazolidines (**1**)**,** pyrazolines (**2**) and pyrazoles are an interesting class of heterocyclic units found in many complex bioactive natural products.[1] Among them chiral hydroxypyrazolidine derivatives represent not only useful building blocks in pharmaceutical industry[2] but also powerful intermediates in the preparation of enantiopure 1,3-diamines (**3**) (**Fig. 1**).[3] More importantly, the derivatives of densely functionalized pyrazolidines exhibit a wide variety of biological acitivities including anticonvulsant,[4] antidepressant[5] and antitumour[6] properties along with other minor uses (**e.g**. as brightening agent).[7]

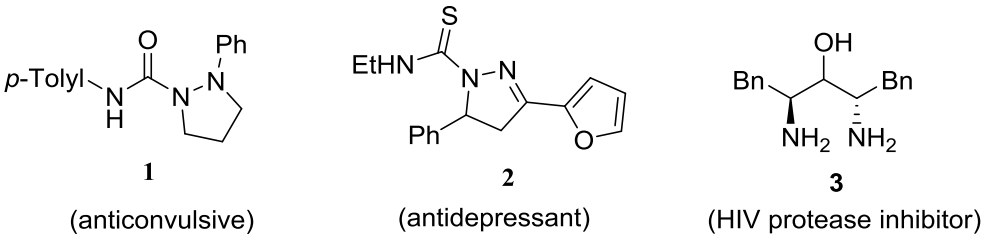


Fig. 1: Some of bioactive molecules

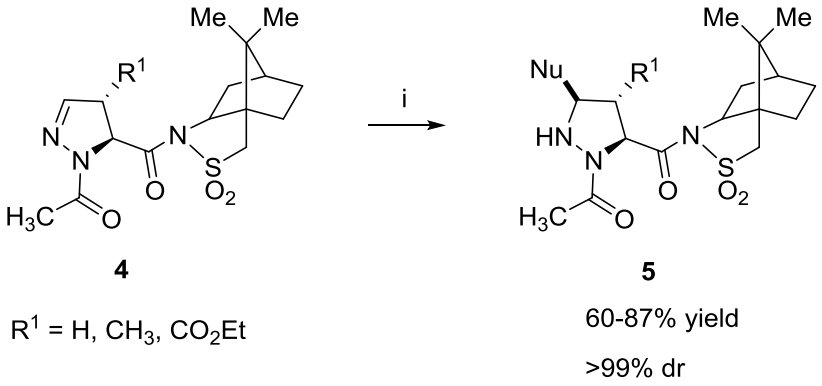
Due to the significance of these chiral pyrazolidines in drug discovery and medicinal chemistry, the development of new methodologies for their synthesis is highly desirable.

2.1.2 Review of literature

Literature search revealed that there are various reports available for the asymmetric synthesis of substituted pyrazolidine derivatives; some of which are described below.

Carreira's approach (2000)[8]

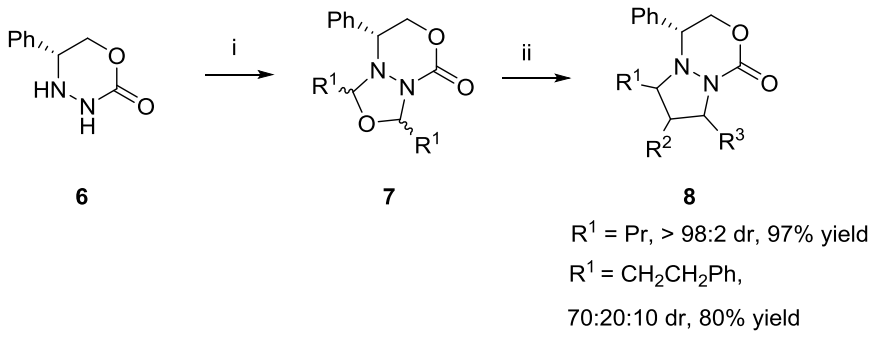
Carreira *et al.* have employed the Lewis acid promoted nucleophilic additions of allyl tributylstannane, the methyl acetate derived silyl ketene acetal, and trimethylsilyl cyanide to a number of chiral *N*-acyl pyrazolines **4** to provide highly functionalized pyrazolidines **5** in a highly diastereoselective fashion (**Scheme 1**).



Scheme 1: $TiCl_4$ (1.2 equiv), **Nu**$^-$ (allyl tributylstannane, methyl acetate derived silyl ketene acetal, and trimethylsilyl cyanide) CH_2Cl_2, –78° C to 23 °C.

Chauveau's approach (2002)[9]

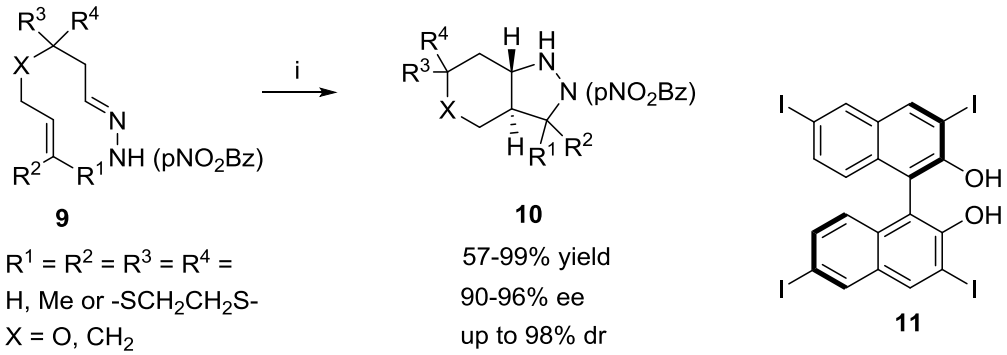
Chauveau *et al.* have described an asymmetric three-component reaction involving a diastereoselective 1,3-dipolar cycloaddition of a chiral non-racemic azomethine imine ylide **7** with dipolarophile for the synthesis of densely functionalized bicyclic hydrazines **8** (**Scheme 2**).



Scheme 2: (i) R^1CHO, $CHCl_3$, 65 °C (ii) dipolarophile, toluene, 80–100 °C, 3 d.

Kobayashi's approach (2002)[10]

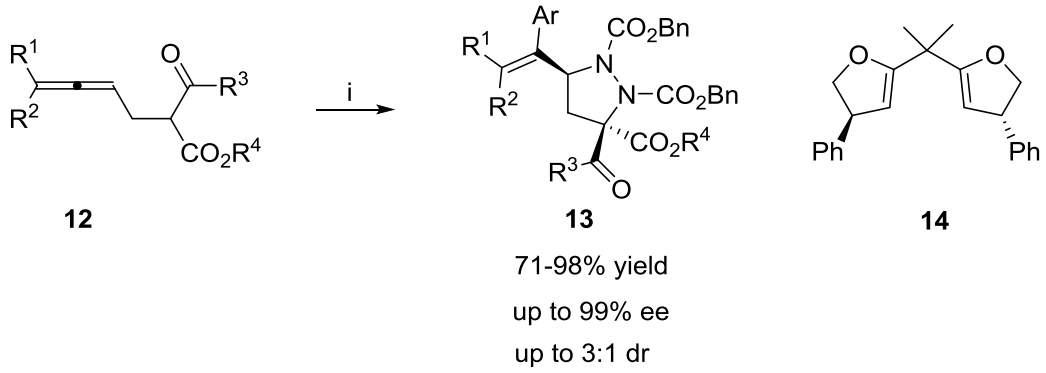
Kobayashi *et al*. have reported the asymmetric intramolecular [3 + 2] cycloaddition reactions of acylhydrazones/olefins **9** employing a chiral zirconium catalyst for the synthesis of pyrazolidine derivatives **10** in high yields with excellent enantio- and diastereoselectivity **(Scheme 3)**.



Scheme 3: $Zr(OPr)_4$ (10 mol %), **11** (12 mol%), PrOH (50 mol %), CH_2Cl_2, 25 °C.

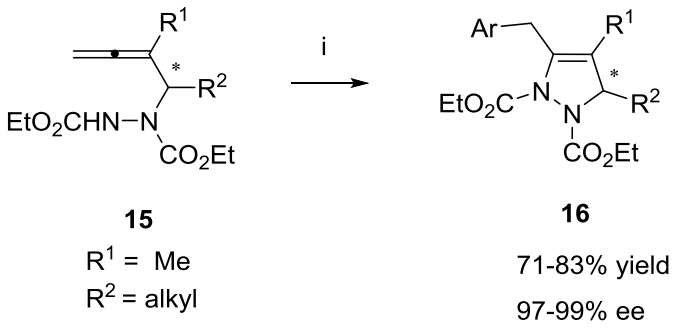
Shengming Ma's approach (2004)[11]

Shengming Ma *et al.* have reported the synthesis of optically active pyrazolidine derivatives **13** in high yields with ees by the Cu- and Pd-catalyzed asymmetric one-pot tandem addition-cyclization reaction of 2-(2',3'-dienyl)-*β*-ketoesters **12**, aryl halides, and dibenzyl azodicarboxylate (**Scheme 4**).



Scheme 4: (i) (a) **14** (10 mol%), $Cu(OTf)_2$, ArI, dibenzylazodicarboxylate, CH_2Cl_2, 0 °C; (b) K_2CO_3 (2 equiv), $Pd(PPh)_3$ (5 mol%), 1,4-dioxane, 100 °C, 4 h.

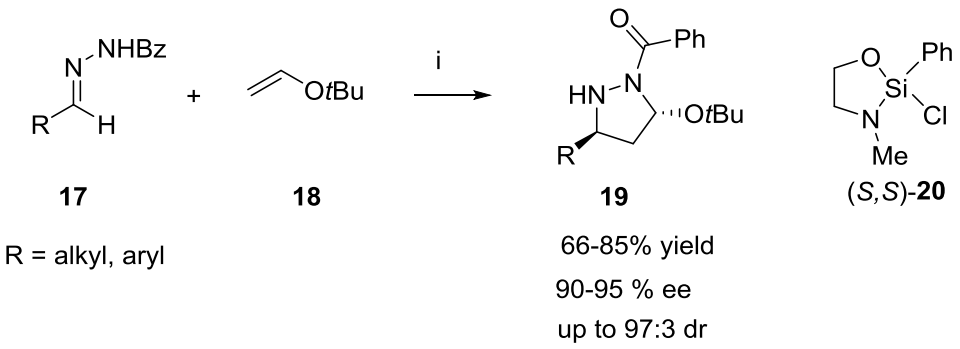
In a similar approach[11b] Shengming Ma *et al.* have developed a method for the regioselective synthesis of 2,3-dihydro-1H-pyrazoles **16** *via* the Pd(0)-catalyzed coupling-cyclization reaction of readily available enantiomerically enriched 2,3-allenyl hydrazines **15** with aryl iodides in moderate to good yields (**Scheme 5**).



Scheme 5: (i) ArI, $Pd(PPh_3)_4$ (5 mol%), Cs_2CO_3 (1.2 equiv), CH_3CN, 80 ^oC, 3 h.

Leighton's approach (2005)[12]

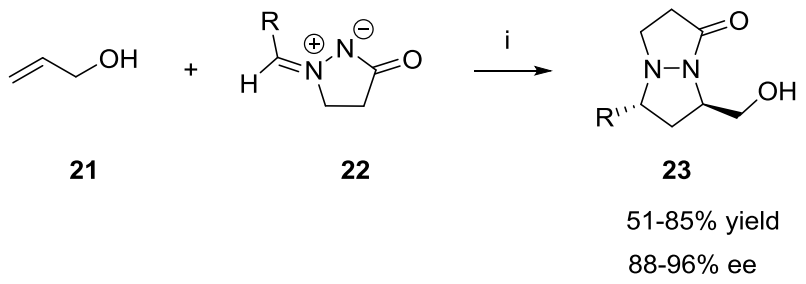
Leighton *et al.* have reported the use of chiral silane Lewis acid **20** for the highly diastereo- and enantioselective synthesis of pyrazolidines **19** *via* [3 + 2] cycloaddition of benzoylhydrazone **17** with enol ether **18** (**Scheme 6**).



Scheme 6: (i) (*S*,*S*)-**20** (1.5 equiv), toluene, 23 ^oC, 24 h.

Inomata's approach (2008)[13]

In this approach Inomata *et al.* have applied the asymmetric 1,3-dipolar cycloaddition of azomethine imines **22** with allyl alcohol **21** by utilizing diisopropyl(*R*,*R*)-tartrate as a chiral auxiliary to afford the corresponding optically active *trans*-pyrazolidines **23** with excellent regio-, diastereo-, and enantioselectivities (**Scheme 7**).



21 **22** **23**

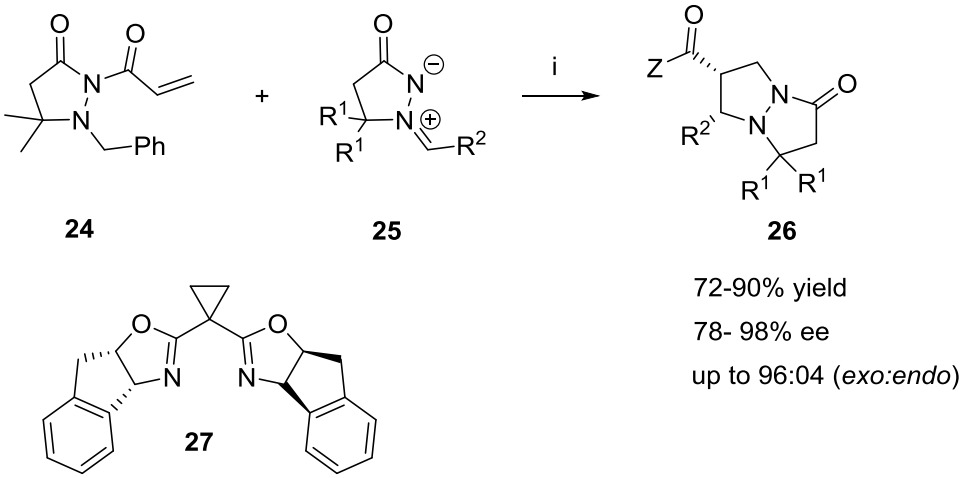
51-85% yield

88-96% ee

Scheme 7: (i) *n*-Bu_2Mg (1 equiv), (*R*,*R*)-DIPT (1 equiv), *n*-BuMgBr, **22** (1 equiv), CH_3CN, 80 ^oC, 2 d.

Mukund's approach (2008)[14]

Mukund *et al*. have illustrated an efficient method for exo and enantioselective cycloaddition of azomethine imines **25** with pyrazolidinone acrylates **24** to give 2-acryloyl-3-pyrazolidinone **26**. The cycloadducts are isolated with high diastereoselectivities (up to >96:4 *exo/endo*) and enantioselectivities (up to 98% ee) (**Scheme 8**).



24 **25** **26**

27

72-90% yield

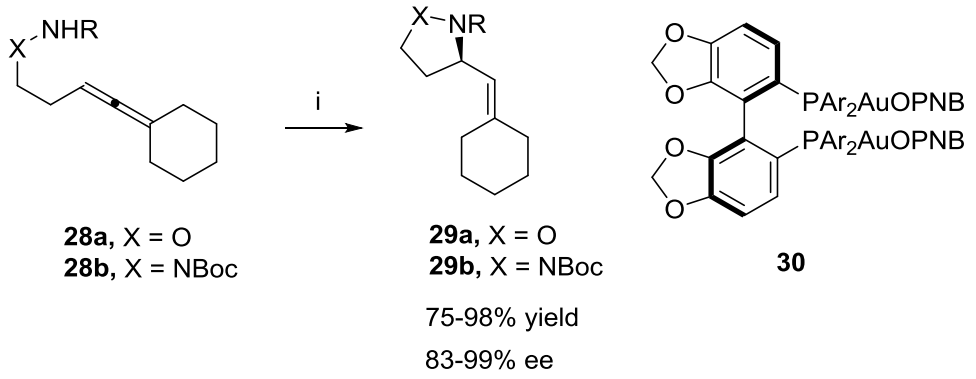
78- 98% ee

up to 96:04 (*exo:endo*)

Scheme 8: (i) **27** (10 mol%), $Cu(OTf)_2$, 4 A° MS, CH_2Cl_2, 0 ^oC, 6 h.

Toste's approach (2010)[15]

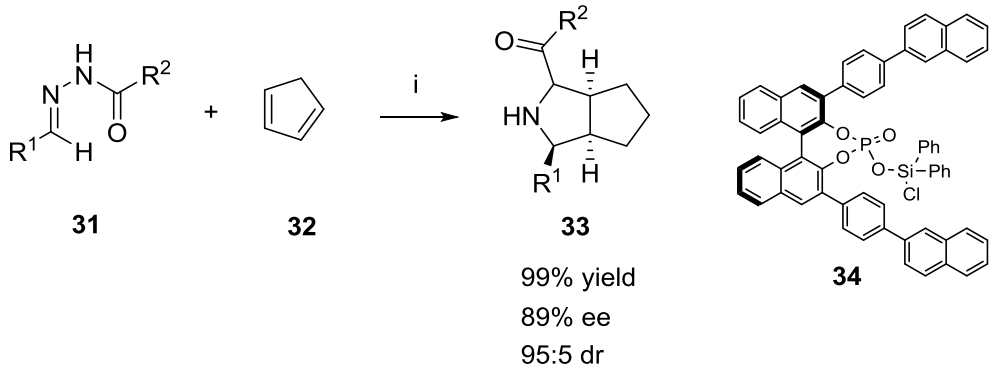
Toste *et al*. have developed an enantioselective gold (I)-catalyzed hydroaminations and hydroalkoxylations of allenes **28** with hydroxylamines and hydrazines using chiral biarylphosphinegold(I) complexes **30** as catalyst. This method allows rapid access to chiral oxazines **29a**, and differentially protected pyrazolidines **29b** in good yields and enantioselectivity (**Scheme 9**).



Scheme 9: (i) **30** (5 mol%), $MeNO_2$, 50 °C, 15 h.

Tsogoeva's approach (2011)[16]

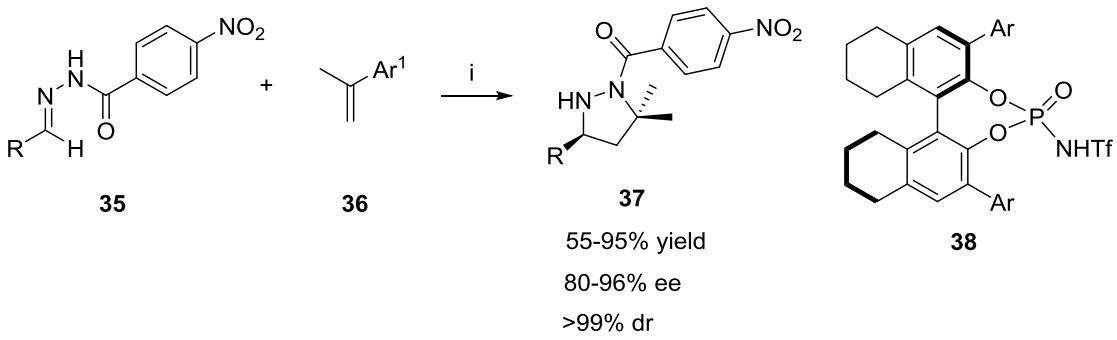
Tsogoeva *et al.* have used BINOL-phosphate-derived silicon Lewis acid **34**, for the [3+2] cycloaddition of *N*-benzoylhydrazone **31** with cyclopentadiene **32** to afford cycloadduct **33** in high enantiomeric excess (89%) and diastereomeric ratio (*syn*/*anti* = 95:5) (**Scheme 10**).



Scheme 10: (i) TMSOTf (10 mol%), CH_2Cl_2, -10 °C, 24 h.

Rueping's approach (2012)[17]

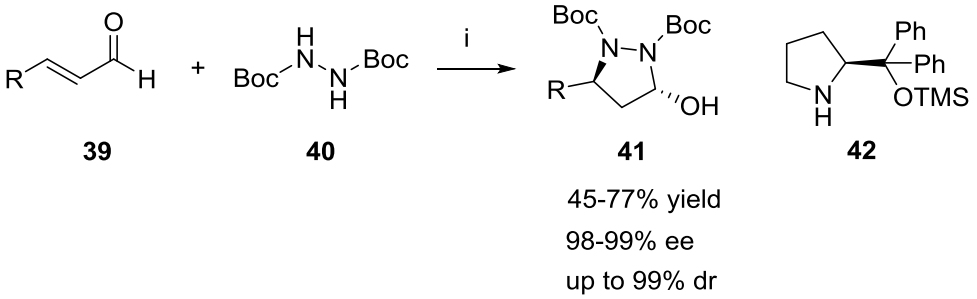
Rueping *et al.* have developed a general metal-free highly enantioselective cycloaddition between hydrazones **35** and alkenes **36** that affords pyrazolidine derivatives **37** in high yields and excellent diastereo- and enantioselectivities. The acidic N-triflylphosphoramide Brønsted acid **38** proved to be very effective catalysts and promoted the highly enantioselective cycloaddition reaction (**Scheme 11**).



Scheme 11: (i) **38** (5 mol%), $CHCl_3$, 0-25 °C, 18 h.

Cordova's approach (2012)[18]

Cordova *et al*. have developed a highly chemo- and enantioselective 1,3-diamination of α, β unsaturated aldehydes **39** with diprotected hydrazine derivatives **40** as the dinitrogen source. The transformation was catalyzed by readily available chiral amine **42** and proceeds *via* a direct catalytic metal-free aza-Michael/hemiaminal cascade sequence and delivers functional 3-hydroxypyrazolidine derivatives **41** with 98–99% ee in one step (**Scheme 12**).

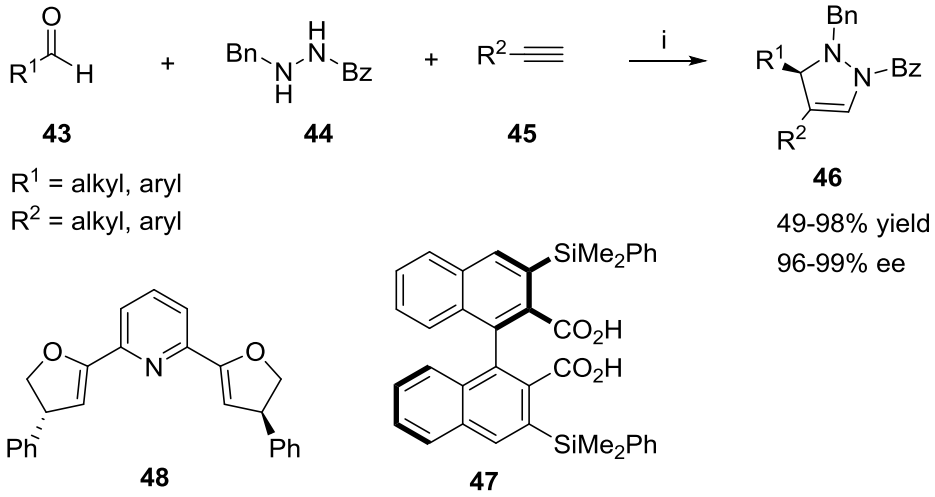


Scheme 12: 39 (1 equiv), **40** (0.8 equiv), **42** (20 mol%), toluene, 4-8 °C, 144 h.

Maruoka's approach (2013)[19]

Maruoka *et al.* have reported the synthesis of substituted pyrazolidines **46** using catalytic asymmetric three-component 1,3-dipolar cycloaddition of aldehydes **43,** hydrazides **44**, and alkynes **45**. The corresponding products were obtained in good yields with high enantioselectivities (**Scheme 13**). The use of CuOAc/Ph-pybox **48**

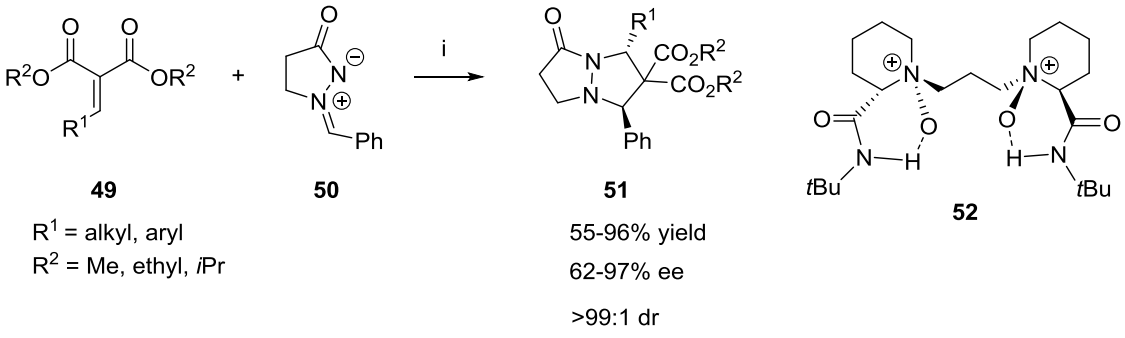
and axially chiral dicarboxylic acid cocatalysts, **47** for the synthesis of variety of 3,4-disubstiuted pyrazolines in high enantioselectivities is demonstrated.



Scheme 13: (i) CuI (10 mol%), **47** (5 mol%), **48** (6 mol%), 4 A° MS, CH_2Cl_2, 40 °C, 3 d.

Feng's approach (2013)[20]

Feng *et al.* have demonstrated an asymmetric 1,3-dipolar cycloaddition of azomethine betaines **50** with alkylidene malonates **49** by using a chiral N,N'-dioxide– Ni(II) complex **52** as a catalyst. A range of *trans*-pyrazolone derivatives **51** was exclusively obtained with excellent yields (up to 99% yield) and good enantioselectivities (up to 97% ee) under the reaction conditions (**Scheme 14**).



Scheme 14: (i) **52**–$Ni(ClO_4)_2$ (1:1, 10 mol%), **49** (1 equiv), **50** (1 equiv), CH_2Cl_2, 30 °C.

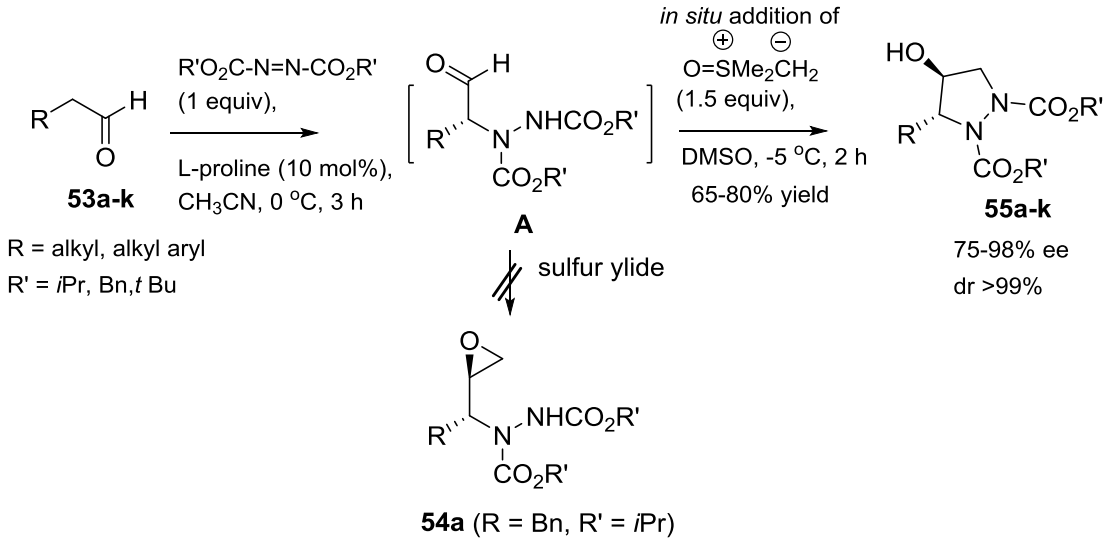
2.1.3 Present Work

2.1.3.1 Objective

The literature survey reveals that there are many methods available for the synthesis of substituted pyrazolidines; most of the strategies involve construction by [3+2]-cycloadditions under strongly acidic as well as thermal conditions. Its asymmetric versions have been reported employing chiral Lewis acid derivatives, and transition metal (Pd, Ni, Au)-catalyzed intramolecular annulations. However, these methods are reasonably limited because of harsh reaction conditions, complex chiral pool resources, expensive chiral ligands and metal catalysts often involving multi-step reaction sequences. Hence, an operationally simple and efficient method, which overcomes the above limitations, is of continuing interest to chemists.

2.1.3.2 Results and Discussion

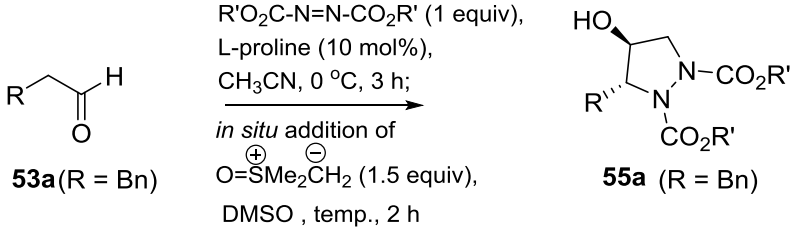
In recent years, proline-catalyzed direct α-amination of aldehydes has emerged as a reliable method for the enantioselective synthesis of α-amino acid derivatives.[21] In this regard, the *in situ* generated amino aldehyde **A**, was readily transformed into several functionalized organic derivatives: e.g. 1,2-aminoalcohols,[21a] 3,6-dihydropyridazines,[22a] functionalized β-aminoalcohols[22b] and γ-amino-α, β-unsaturated esters.[22c] As part of our program directed toward asymmetric synthesis of bioactive molecules employing organocatalysts,[22c,23] we envisaged that *in situ* trapping of amino aldehyde **A** with Corey's sulfur ylide (dimethyloxosulfonium methylide)[24,27a] under basic conditions should provide the corresponding highly functionalized terminal amino epoxides **54a**. Surprisingly, the reaction took a different course to furnish the corresponding 4- hydroxypyrazolidine derivatives **55a-k** in high yields with excellent ees (**Scheme 15**).



Scheme 15: *In situ* trapping of α-amino aldehydes **A** with dimethyloxosulfonium methylide

As a model substrate, the amination of hydrocinnamaldehyde **53a** was carried out following the List protocol[21a] that produced the corresponding α-amino aldehyde **A** *in situ*. As the intermediate **A** is prone to racemization[25] under basic conditions, several experiments were conducted to identify the most effective and suitable condition for Corey-Chaykovsky reaction; the results of which are presented in Table 1. Firstly, a solution of dimethyloxosulfonium methylide in DMSO [sulfur ylide (1.5 equiv), prepared *in situ* from $O=SMe_3I$/NaH in DMSO][26a] was added to intermediate **A** at 25 °C, which gave **55a** as a single diastereomer in 80% yield with 5% ee; low % ee may be due to racemization (entry 1). A dramatic improvement in enantioselectivity (75% ee) was however realized by performing the reaction at 10 °C for 2 h. Finally, the best results could be obtained when the addition of ylide was conducted at -5 °C (91% ee with 73% yield). However, further lowering of temperature to either -20 or -40 °C had deleterious effect both in yield and enantioselectivity. Also (*S*)-α,α-diarylprolinol silyl ether as a modified proline catalyst was found to be less effective for the reaction (**Table 1**, foot-note e).

Table 1. Proline-catalyzed α-amination/Corey-Chaykovsky reaction of hydrocinnamaldehyde[a]



no	amine (R')	temp. (°C)	yield of **55a** (%)[b]	ee (%)[c]	de (%)[d]
1	*i*Pr	25	80	5	99
		10	75	75	99
		-5	73 (45)[e]	91 (79)[e]	99
		-20	52	88	99
		-40	48	84	99
2	Bn	-5	71	90	100
3	*t*Bu	-5	60	80	100

[a] aldehyde (5 mmol), amine (R'O_2C-N=N-CO_2R') (5 mmol); L-proline (10 mol%); dimethyloxosulfonium methylide (7.5 mmol); [b] isolated yield after column chromatographic purification; [c] determined from chiral HPLC analysis (Chiracel OD-H, Whelk-01columns; n-hexane/2-propanol); [d] Product is obtained as a single diastereomer as determined from ^{1}H,^{13}C NMR and HPLC analysis; [e] refers to 2-[bis(3,5 bistrifluoromethylphenyl) trimethyl-silanyloxymethyl] pyrrolidine is used as catalyst.

We then turned our attention to briefly investigate the scope of amine sources; the results of which indicated that diisopropyl- and dibenzylazadicarbxylates were found to be better candidates (entries 2 & 3). Use of other solvents such as THF and CH_2Cl_2 for the tandem protocol resulted in a sluggish reaction with poor yields (~30%). With the optimized reaction conditions in hand,[26b] we next examined the scope of the reaction. Aldehydes bearing bromo, cyano, nitro, methoxy and methylene dioxy groups on the aromatic nucleus and azide and benzyl ether substitutions in aliphatic

compounds were well-tolerated under the reaction conditions. For all the cases studied, the products **55a-k** were indeed obtained in high yields (65-80%), and excellent enantioselectivities (75-98% ee) with dr >99% (**Table 2**).

Table 2. Proline-catalyzed asymmetric tandem α-amination/Corey-Chaykovsky reaction [a]

no	substrates **53a-k** (R)	amine (R')	products[a] **55a-k**	
			yield (%)[b]	ee (%)[c]
1	benzyl (**53a**)	*i*Pr	73	91
2	3,4-dimethylbenzyl (**53b)**	*i*Pr	71	94
3	3,4-methylenedioxybenzyl (**53c**)	Bn	80	90
4	2-Br-4,5-methylenedioxybenzyl(**53d**)	*i*Pr	74	95
5	2-CN-4,5-methylene-dioxybenzyl (**53e**)	*i*Pr	75	75
6	naphthalene-1-yl-methyl (**53f**)	*i*Pr	70	90
7	2-NO_2-4,5-dimethoxybenzyl (**53g**)	*i*Pr	68	90
8	*n*-butyl (**53h**)	Bn	65	92
9	4-azidopropyl (**53i**)	Bn	66	91
10	3-benzyloxymethyl (**53j**)	Bn	70	90
11	3-benzyloxypropyl (**53k**)	*i*Pr	72	98

[a] aldehyde (5 mmol), amine source (R'O_2C-N=N-CO_2R') (5 mmol), L-proline (10 mol%), dimethyloxosulfonium methylide (7.5 mmol); [b] isolated yield after column chromatographic purification;[c] determined from chiral HPLC analysis (Chiracel OD-H, Whelk-01column; n-hexane/2-propanol).

The formation of 4-hydroxypyrazolidines (**55a-k**) was established unambiguously from the corresponding ^{1}H & ^{13}C NMR, IR and HRMS spectral data. Their optical purity was established from their chiral HPLC analyses. For example, the formation of 4-hydroxypyrazolidine **55a** was confirmed from its ^{1}H NMR spectrum, which

showed a doublet at δ 3.36 (d, *J* = 11.9 Hz, 1H) and a doublet of doublet at δ 3.94-4.02 (dd, *J* = 5.4, 11.9 Hz, 1H) corresponding to the methylene (-**CH$_2$**-NR$_2$) protons. A multiplet at δ 4.33-4.40 (2H) indicated the presence of methine protons (-C**H**-OH and -C**H**-NR$_2$). Its ^{13}C NMR spectrum displayed two carbon signals at δ 53.9 and 68.8 due to the methylene (-**CH$_2$**-NR$_2$) and methine (-**C**H-NR$_2$) carbons respectively. Also, a characteristic signal at δ 74.2 is due to the methine carbon (-**C**H-OH) attached to the hydroxyl group which proves the formation of cyclized product **55a** (**Fig. 2**).

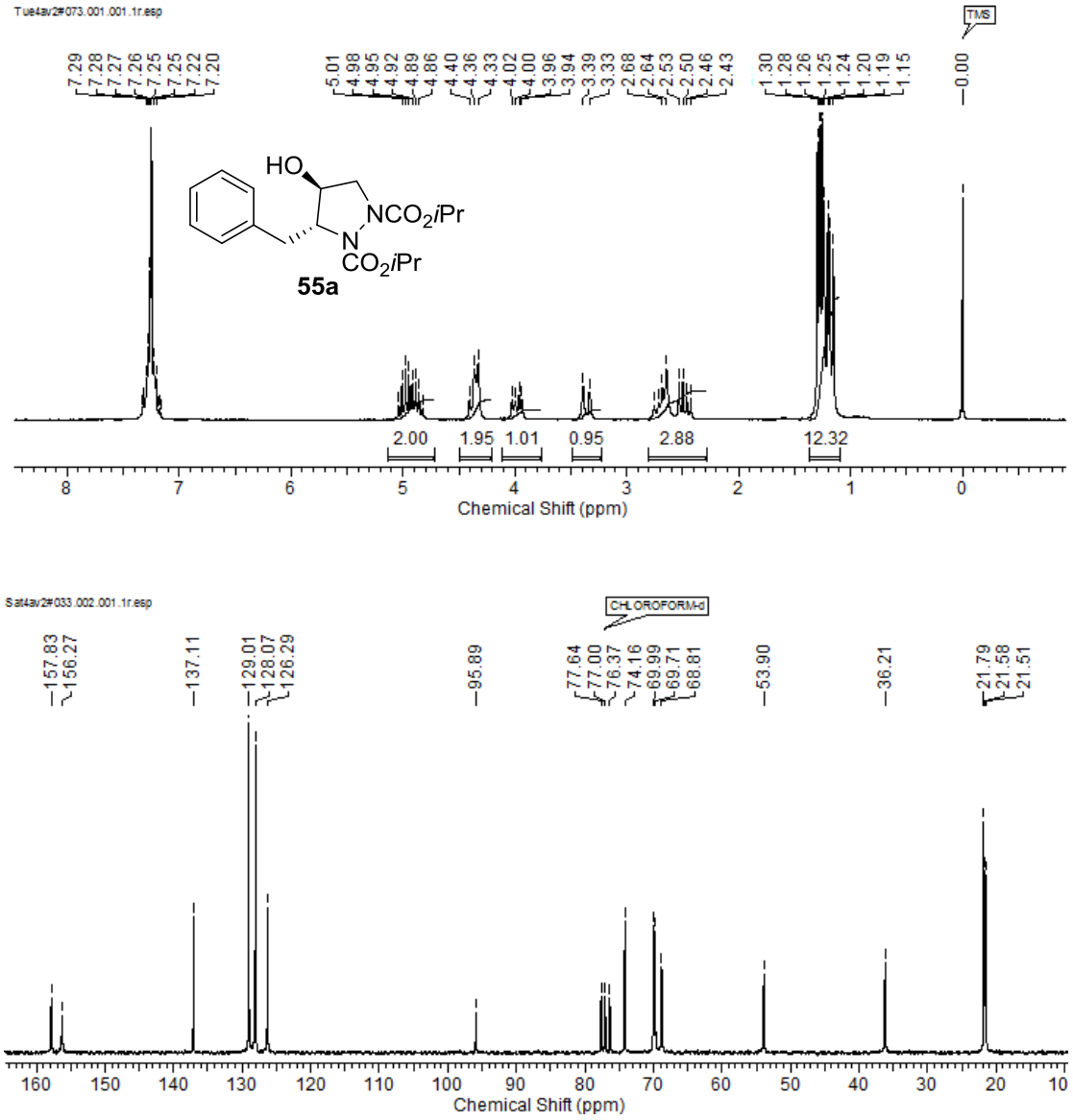


Fig. 2: ^{1}H and ^{13}C NMR spectra of 4-hydroxypyrazolidine derivative **55a**

Similarly, the ^{1}H NMR spectrum of 4-hydroxypyrazolidine **55i** showed a doublet at δ 3.36 (d, *J* = 12.1, 1H) and a doublet of doublet at δ 3.95-4.01 (dd, *J* = 5.4, 12.0 Hz, 1H) corresponding to methylene -**CH_2**-NR_2 protons, while another doublet of doublet

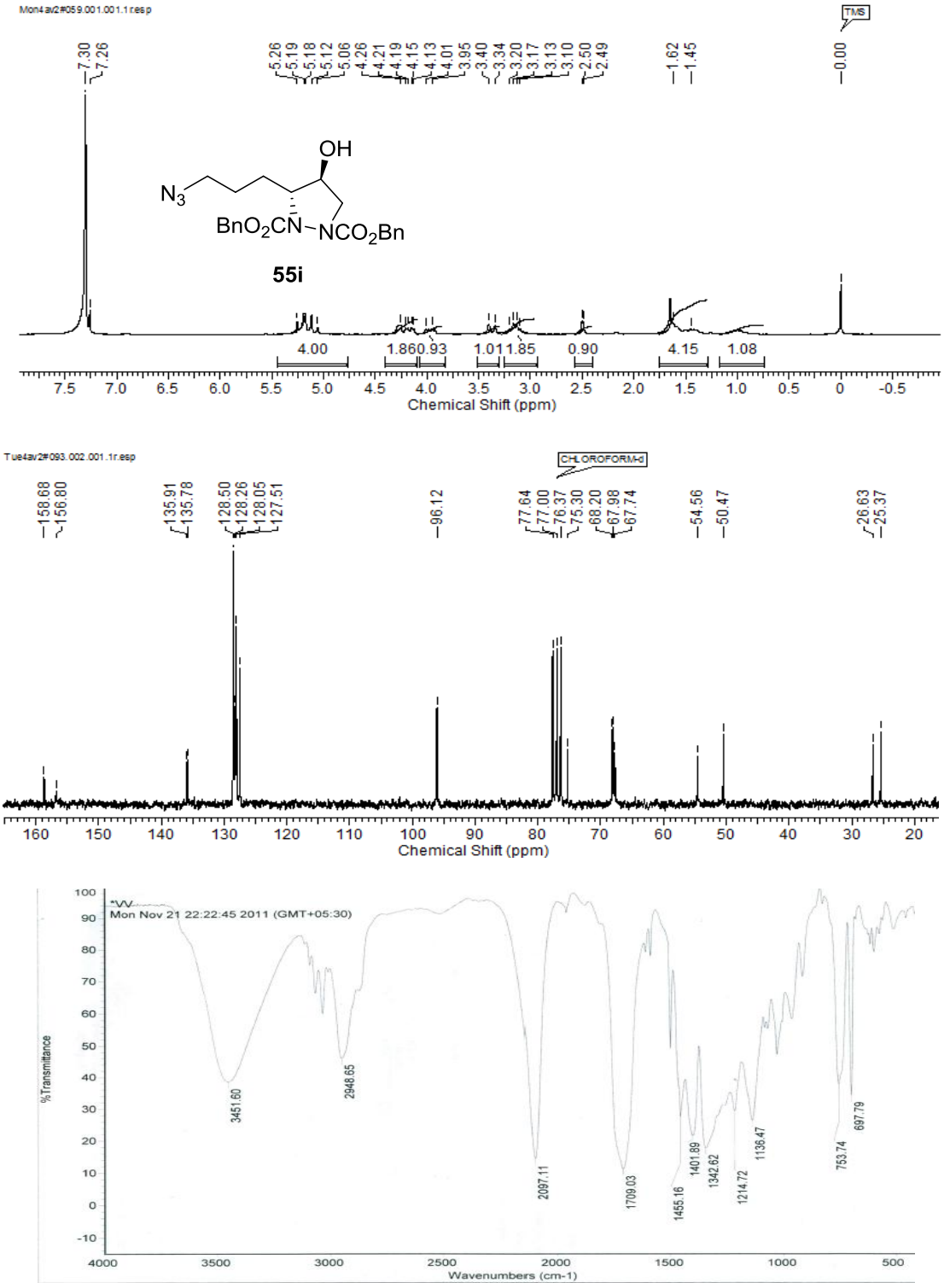
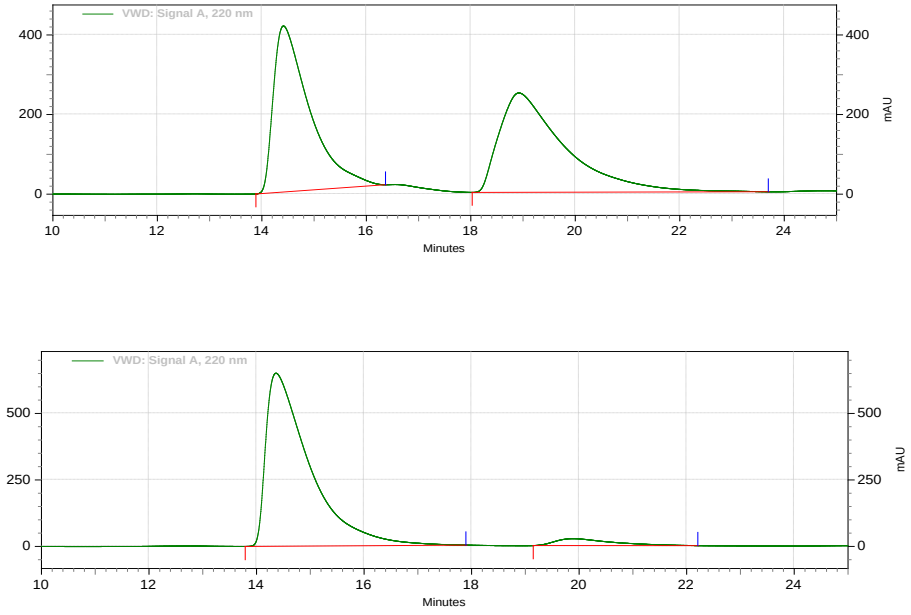


Fig. 3: ^{1}H and ^{13}C NMR and IR spectra of 4-hydroxypyrazolidine **55i**

at δ 4.13-4.21 (dd, *J* = 4.05, 11.37 Hz, 1H) and a typical multiplet at δ 4.26- 4.28 (m, 1H) correspond to the methine (-**CH**-NR_2-) and (-C**H**-OH) protons respectively. Its ^{13}C NMR spectrum displayed a typical carbon signal at δ 54.56 corresponding to methylene carbon **C**H_2-NR_2, while the other carbon signals at δ 68.2 and 75.3 were indicative of two methine (-**C**H-NR_2 and -**C**H-OH) carbons respectively. The other carbon resonance signals at δ 67.7 and 67.9 are due to benzyloxy (Ph-**C**H_2-OR) carbons (**Fig. 3**). Further, the formation of **55i** was substantiated by strong IR absorption bands at 2097 and 3451 cm^{-1} due to the azide and secondary hydroxyl groups respectively (**Fig. 3**). The enantiomeric excess of 4-hydroxypyrazolidine **55i** was determined from chiral HPLC analysis; Whelk-01 column (**Fig. 4**).



Ret. time	Area	Area %	Height	Height %
14.363	618479535	95.55	10915444	96.16
19.887	28817027	4.45	435555	3.84
	647296562	100.00	11350999	100.00

Fig. 4: HPLC chromatogram of 4-hydroxypyrazolidine derivative **55i**

The absolute configuration of the newly generated amine center was assigned on the basis of the previously established configuration of α-amino aldehydes.[12a] The *anti*-stereochemistry in pyrazolidines **55a-k** is, however, proven unambiguously from COSY and NOESY NMR studies,[27] X-ray crystallographic analysis (**Fig. 5**) and also in conformity with Felkin-Ahn model. [28]

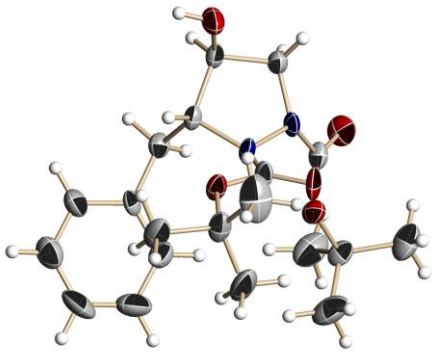
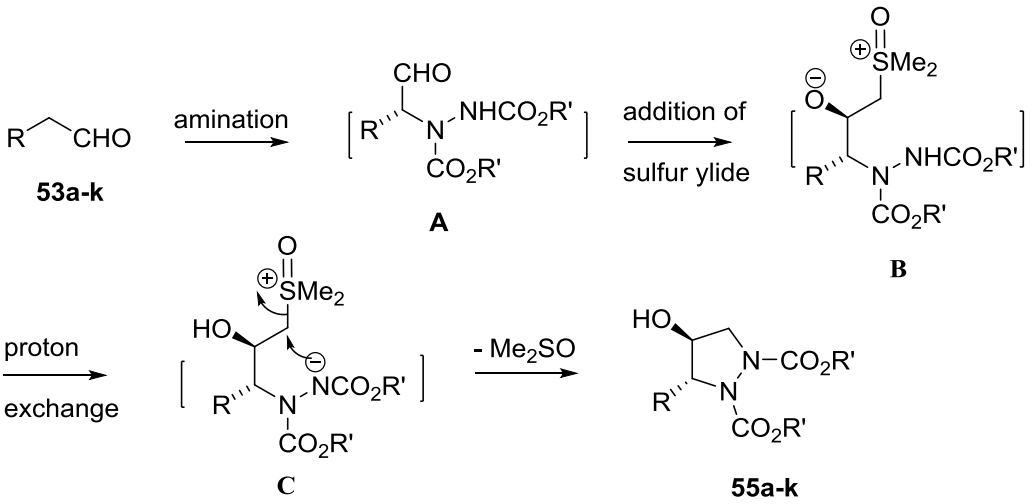


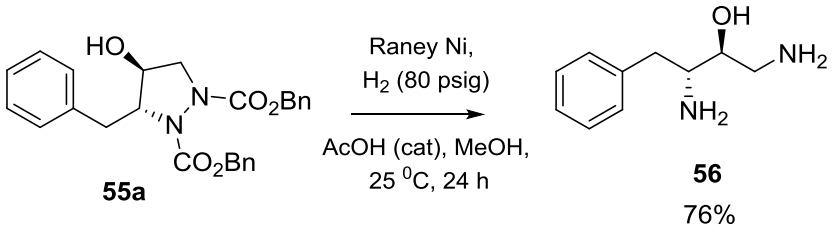
Fig. 5: ORTEP diagram of hydroxypyrazolidine **55a** (R'= *t*Bu)

A probable mechanistic pathway is shown in **Scheme 16**. This pathway is supported by the following experimental facts: (a) no aminoepoxide **54a** was detected (GC & ^{1}H NMR) even at -40 °C when the reaction was monitored every 10 min; (b) alternatively, **54a** was prepared separately in two steps from aldehyde **A** *via* Wittig reaction ($Ph_3P^+MeI^-$, $KOBu^t$, THF, 0-25 °C, 90%) followed by epoxidation (MCPBA, CH_2Cl_2, 25 °C, 92%) and found to be quite stable under the reaction conditions. This leads us to believe that addition of sulfur ylide onto aldehyde **A** generates the intermediate **B**. This in turn is followed by a facile proton exchange[29] from carbamate nitrogen to basic oxide ion to give the stable species C, which then subsequently undergoes intramolecular cyclization with the removal of DMSO to afford the products **55a-k**.



Scheme 16: Probable mechanistic pathway

A single step transformation of **55a** under catalytic hydrogenation conditions [Raney Ni, H_2, (80 psig)] gave the corresponding *anti*-1,2-aminoalcohol **56**, which are common structural subunits present in phytospingosines[30a,b] and HIV protease inhibitors;[30c,d] thus constituting an important application of this methodology (**Scheme 17**).



Scheme 17: Synthesis of *anti*-1,2-aminoalcohol (**56**)

2.1.4 Conclusion

In conclusion, we have described, for the first time, a novel one pot procedure of sequential amination-Corey-Chaykovsky reaction of aldehydes that leads to synthesis of 4-hydroxypyrazolidine derivatives **55a-k** with good yields and excellent enantio-

and diastereoselectivities. The salient features of the methodology are: (1) metal-free synthesis (2) milder reaction conditions (3) functional group tolerance (4) high yields with excellent enantio- and diastereoselectivity.

2.1.5 Experimental Section:

General Experimental Procedure:

(a) **Preparation of sulfur ylide**: 0.18 g (7.5 mmol) of NaH (previously washed with petroleum ether to remove oil) was taken in an oven-dried three-necked flask, followed by the addition of dry DMSO (10 mL) through a septum to it and the the whole slurry was stirred at 25 °C under N_2 atmosphere. Then trimethyloxosulfonium iodide (1.67g, 7.5 mmol) was added to the slurry over a period of 5 min *via* a solid addition funnel until it becomes a homogenous solution.

(b) **Sequential α-amination-Corey Chaykovsky reaction of aldehydes**: To a cooled solution of azadicarboxylate (5.0 mmol) and L-proline (10 mol%) in dry CH_3CN (20 ml) at 0 ^oC was added α-unsubstituted aldehyde (**53a-k**, 5 mmol) and the mixture was stirred for 3 h at 0 ^oC. This was followed by the addition of a solution of dimethyloxosulfonium methylide in DMSO at -5 °C and allowed to stir for 2h at the same temperature. The progress of the reaction was monitored by TLC. It was then quenched by the addition of aq. NH_4Cl solution. The mixture was concentrated in vacuum to remove acetonitrile and concentrate extracted with diethylether (3 x 40 ml). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4, and concentrated under reduced pressure to give the crude products, which were then purified by flash column chromatography (100-200 mesh) using petroleum ether and ethyl acetate as eluents to afford the pure products **55a-k**.

(3*R*, 4*S*)-Diisopropyl-3-benzyl-4-hydroxypyrazolidine-1,2-dicarboxylate (R' = *i*Pr) (55a)

Yield: 73%; colorless liquid; 91% ee from **HPLC analysis**; Column: Chiracel OD-H, (2-propanol:*n*-hexane = 5:95, flow rate 0.5 mL/min, λ = 220 nm). Retention time (min): 22.05 (minor) and 26.25 (major), $[\alpha]^{D}_{25}$ +22.78 (*c* 0.8, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 422, 546, 599, 623, 666, 700, 750, 834, 920, 1000, 1043, 1496, 1585, 1604, 1716, 2936, 2981, 3063, 3087, 3446; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.15-1.30 (m, 12H,), 2.43-2.76 (m, 3H), 3.36 (d, *J* = 11.9 Hz, 1H), 3.94 -4.02 (dd, *J* = 5.43, 11.9 Hz, 1H), 4.33-4.40 (m, 2H), 4.79-5.07(m, 2H), 7.17-7.32 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.5, 21.6, 21.8, 36.2, 53.9, 68.8, 69.7, 69.9, 74.2, 126.3, 128.1, 129.0, 137.1, 156.3, 157.8; ESI-MS: *m*/*z* 373.3294 $[M+Na]^+$ **Analysis**: $C_{18}H_{26}N_2O_5$ requires: C, 61.70; H, 7.48; N, 7.99%; found: C, 61.73; H, 7.44; N, 7.95%.

(When R' = Bn) (3*R*, 4*S*)-Dibenzyl 3-benzyl-4-hydroxypyrazolidine-1,2 -dicarboxylate (55a)

Yield: 71%; colorless liquid; 90% ee from **HPLC analysis**; Column: Whelk -01 (2-propanol:*n*-hexane = 20:80, flow rate 0.5 mL/min, λ = 260 nm). Retention time (min): 12.77 (major) and 16.71 (major),; $[\alpha]^{D}_{25}$ +13.66 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 697, 750, 971, 1027, 1077, 1139, 1215, 1343, 1402, 1454, 1497, 1604, 1716, 2955, 3030, 3064, 3450; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.37-2.72 (m, 3H), 3.41 (d, *J* = 11.7 Hz, 1H), 3.95-4.06 (m, 1H), 4.32-4.45 (m, 2H), 5.11-5.24 (m, 4H), 7.10-7.29 (m, 15H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.1, 54.2, 67.8, 69.2, 74.1, 76.4, 126.4, 127.1, 127.7, 127.8, 127.9, 128.2, 128.3, 129.0, 135.7, 136.8, 156.5, 158.3; **Analysis**: $C_{26}H_{26}N_2O_5$ requires: C, 69.94; H, 5.87; N, 6.27%; found: C, 69.91; H, 5.85; N, 6.24%.

(When R'= *t*Bu) (3*R*, 4*S*)-Di-*tert*-butyl 3-benzyl-4-hydroxypyrazolidine-1,2-dicarboxylate (55a)

Yield: 68%; colorless solid; **mp**: 126-128 °C; 80% ee from **HPLC analysis**; Column: Chiracel OD-H (2-propanol:*n*-nexane = 5:95, flow rate 0.5 mL/min, λ = 220 nm). Retention time (min): 14.09 (minor) and 16.47 (major), $[\alpha]^{D}_{25}$ +24.48.28 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 699, 755, 853, 998, 1033, 1076, 1091, 1142, 1255, 1367, 1455, 1477, 1496, 1697, 2931, 2977, 3444; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.39 (s, 9H), 1.49 (s, 9H), 2.08 (dd, *J* = 2.1, 3.1 Hz, 1H,), 2.46-2.75 (m, 2H), 3.30-3.37 (dd, *J*=1.6, 12.0 Hz, 1H,), 3.95-4.04 (dd, *J* = 5.6, 12.1 Hz, 1H,), 4.26-4.34 (m, 2H), 7.26 (brs, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.0, 28.2, 36.6, 53.9, 68.8, 74.6, 80.9, 81.2, 126.4, 128.2, 129.3, 137.5, 155.8, 156.9; **HRMS (ESI, m/z):** Calculated for $C_{20}H_{30}N_2O_5Na$ $(M+Na)^+$ 401.2052, found 401.2060. **Analysis**: $C_{20}H_{30}N_2O_5$ requires: C, 63.47; H, 7.99; N, 7.40% found: C, 63.50; H, 7.93; N, 7.44%.

(3*R*, 4*S*)-Diisopropyl-3-(3,4-dimethylbenzyl)-4-hydroxypyrazolidine-1,2-dicarboxylate (55b)

Yield: 71%; gum; 94% ee from **HPLC analysis**; Column: Chiracel OD-H (2-propanol:*n*-hexane = 10:90, flow rate 0.5 mL/min, λ = 220 nm). Retention time (min): 8.95 (minor) and 9.95 (major), $[\alpha]^{D}_{25}$ +7.12 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 663,771, 926, 1101, 1211, 1315, 1380, 1697, 2345, 2397, 2973, 3012, 3679; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.19-1.30 (m, 12H), 2.09 (brs, 1H), 2.23 (s, 6H), 2.28-2.40 (dd, *J* = 8.3, *J* =13.9 Hz, 1H), 2.68-2.79 (dd, *J* = 7.1, 13.7 Hz, 1H), 3.33 (d, *J* = 12.13 Hz, 1H), 3.96-4.04 (dd, 1H, *J* = 5.30, *J* = 11.9 Hz), 4.30-4.37 (m, 2H), 4.86-5.04 (m, 2H), 6.93-7.05 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 19.1, 19.5, 21.6, 21.7, 21.9, 35.9, 53.9, 68.9, 69.6, 69.9, 74.1, 126.4, 129.4, 130.3, 134.3, 134.5, 136.1, 156.3, 157.9; **HRMS (ESI, m/z):** Calculated for $C_{20}H_{30}N_2O_5Na$ $(M+Na)^+$ 401.2052, found 401.2060. **Analysis**: $C_{20}H_{30}N_2O_5$ requires: C, 63.47; H, 7.99; N, 7.40% found: C, 63.45; H, 7.95; N, 7.45%.

(3*R*, 4*S*)-Dibenzyl-3-((benzo[d][1,3]dioxol-5-yl)methyl)-4-hydroxypyrazolidine-1,2-dicarboxylate (55c)

Yield: 78%; gum; 90% ee from **HPLC analysis**; Column: Whelk - 01 (2-propanol:*n*-hexane = 20:80, flow rate 0.5 mL/min, λ = 260 nm). Retention time (min): 20.64 (major) and 31.49 (minor),; $[\alpha]^{D}_{25}$ +10.17 (*c* 1.1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 757, 1041, 1216, 1248, 1343, 1444, 1491, 1709, 2929, 3021, 3444; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.33-2.60 (m, 3H), 3.40 (d, *J* = 12 Hz, 1H), 3.93-4.02 (dd, *J* =5.1, 11.8 Hz, 1H), 4.32-4.39 (m, 2H), 5.12-5.24 (m, 4H), 5.88 (s, 2H), 6.53-6.67 (m, 3H), 7.18-7.34 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 35.9, 54.3, 67.9, 69.4, 74.3, 100.8, 108.2, 109.5, 122.2, 127.3, 127.9, 128.1, 128.4, 128.5, 130.5, 135.8, 146.3, 147.6, 156.6, 158.4; **Analysis**: $C_{27}H_{26}N_2O_7$ requires: C, 66.11; H, 5.34; N, 5.71%; found: C, 66.15; H, 5.30; N, 5.74%.

(3*R*, 4*S*)-Diisopropyl-3-((5-bromobenzo[d][1,3]dioxol-6-yl)methyl)-4-hydroxypyrazolidine-1,2-dicarboxylate (55d)

Yield: 74%; gum; 95% ee from HPLC analysis; Column: Chiracel OD-H (2-propanol:*n*-hexane = 10:90, flow rate 0.5 mL/min, λ = 254 nm). Retention time (min): 19.69 (minor) and 22.06 (major), $[\alpha]^{D}_{25}$ +33.19(*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 757, 1039, 1106, 1233, 1317, 1384, 1480, 1704, 2984, 3447; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.16-1.30 (m, 12H), 2.46-2.52 (m, 1H), 2.74 -2.79 (dd, *J* = 9.2, 13.5 Hz, 1H), 2.76-2.79 (dd, *J* = 6.1, 14.3 Hz, 1H), 2.95 (brs, 1H), 3.39 (d, *J* = 11.60 Hz, 1H), 4.01-4.05 (dd, *J* = 5.18, 11.59 Hz, 1H), 4.37-4.43 (m, 2H), 4.84-4.90 (m, 1H), 4.96-5.02 (m, 1H), 5.95(s, 1H), 6.85 (s, 1H), 6.98 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.9, 22.1, 36.2, 54.3, 67.9, 70.1, 70.2, 74.6, 101.6, 111.3, 112.5, 114.7, 129.6, 147.3, 156.3, 157.8; **HRMS (ESI, m/z):** Calculated for $C_{19}H_{25}BrN_2O_7Na$ $(M+Na)^+$ 495.0743, found 495.0740. **Analysis**: $C_{19}H_{25}BrN_2O_7$ requires: C, 48.21; H, 5.32; N, 5.92%; found: C, 48.24; H, 5.28; N, 5.88%.

(3*R*, 4*S*)-Diiisopropyl-3-((5-cyanobenzo[d][1,3]dioxol-6-yl)methyl)-4-hydroxypyrazolidine-1,2-dicarboxylate (55e)

Yield: 75%; gum; 75% ee from **HPLC analysis**; Chiracel OD-H column (2-propanol:*n*-hexane = 10:90, flow rate 0.5 mL/min, λ = 254 nm). Retention time (min): 33.52 (minor) and 37.22 (major), $[\alpha]^{D}_{25}$ +42.19 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): υ_{max} 546, 666, 754, 870, 930, 1035, 1385, 1618, 1715, 2222, 2983, 3440; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.13-1.31 (m, 12H), 2.42-2.54 (dd, *J* = 10.5, 14.3 Hz, 1H), 2.92-3.01 (dd, *J* = 4.3, 14.3 Hz, 1H), 3.17 (bs, 1H), 3.36-3.43 (dd, *J* = 1.8, 12.0 Hz, 1H), 4.00-4.09 (dd, *J* = 5.7, 12.0 Hz, 1H), 4.33-4.44 (m, 2H), 4.83-5.04 (m, 2H), 6.05 (s, 2H), 6.98 (s, 1H), 7.03 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.7, 21.8, 22.0, 22.1, 34.6, 54.9, 68.6, 70.1, 70.3, 75.0, 102.2, 104.3, 110.9, 111.3, 118.1, 138.1, 146.6, 151.6, 155.9, 157.6; **Analysis**: $C_{20}H_{25}N_3O_7$ requires: C, 57.27; H, 6.01; N, 10.02; found: C, 57.20; H, 6.08; N, 10.09 %.

(3*R*, 4*S*)-Diisopropyl-4-hydroxy-3-((naphthalen-2-yl)methyl)pyrazolidine-1,2-dicarboxylate (55f)

Yield: 70%; gum; 90% ee from HPLC analysis; Chiracel OD-H column (2-propanol:*n*-hexane = 6:94, flow rate 0.5 mL/min, λ = 254 nm). Retention time (min): 14.39 (minor) and 16.49 (major), $[\alpha]^{D}_{25}$ +17.29 (*c* 1.2, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): υ_{max} 757, 1039, 11067, 1233, 1317, 1384, 1480, 1704, 2984, 3447; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.16-1.32 (m, 12H), 2.76-2.88 (dd, *J* = 9.3, 13.9 Hz, 1H), 3.30-3.44 (m, 2H), 4.12-4.20 (m,1H), 4.37 (brs, 1H), 4.48-4.55 (t, *J* = 7.20 Hz, 1H), 4.86-5.04 (m, 2H), 7.26-7.60 (m, 5H), 7.73-7.88 (m, 2H), 8.12 (d, *J* = 7.8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.7, 21.9, 34.4, 54.1, 67.8, 70.0, 74.6, 123.5, 125.3, 125.6, 126.2, 127.5, 128.8, 131.9, 133.1, 133.8, 156.6, 157.4; **HRMS (ESI, m/z):** Calculated for $C_{22}H_{28}N_2O_5Na$ $(M+Na)^+$ 423.1896, found 423.1893. **Analysis**: $C_{22}H_{28}N_2O_5$ requires: C, 65.98; H, 7.05; N, 7.00% found: C, 65.95; H, 7.01; N, 7.05%.

(3*R*, 4*S*)-Diisopropyl-3-(4,5-dimethoxy-2-nitrobenzyl)-4-hydroxypyrazolidine-1,2-dicarboxylate (55g)

Yield: 68%; liquid; 90% ee from **HPLC analysis**; Chiracel OD-H column (2-propanol:*n*-hexane = 10:90, flow rate 0.5 mL/min, λ = 260 nm). Retention time (min): 29.78 (minor) and 33.81 (major), $[\alpha]^{D}_{25}$ -6.64 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 666, 756, 797, 870, 939, 1004, 1519, 1581, 1616, 1731, 2852, 2983, 3443; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.04-1.30 (m, 12H), 2.33-2.61 (m, 2H), 3.32-3.47 (m, 2H), 3.94-4.10 (m, 7H), 4.43-4.49 (m, 2H), 4.81-5.04 (m, 2H), 7.08 (s, 1H), 7.62 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.8, 21.8, 22.1, 22.2, 34.2, 54.5, 56.2, 56.8, 68.5, 69.9, 70.2, 76.1, 107.9, 115.3, 128.3, 140.9, 140.7, 153.2, 156.0, 157.3; **HRMS (ESI, m/z):** Calculated for $C_{20}H_{29}N_3O_9Na$ $(M+Na)^+$ 478.1801, found 478.1804. **Analysis**: $C_{20}H_{29}N_3O_9$ requires: C, 52.74; H, 6.42; N, 9.23%; found: C, 52.70; H, 6.37; N, 9.25 %.

(3*R*, 4*S*)-Dibenzyl-3-butyl-4-hydroxypyrazolidine-1,2-dicarboxylate (55h)

Yield: 76%; gum; 92% ee from HPLC analysis; Whelk -01 column (2-propanol:*n*-hexane = 20:80, flow rate 0.5 mL/min, λ = 220 nm). Retention time (min): 10.07 (major) and 14.01 (minor), $[\alpha]^{D}_{25}$ = -1.42 (*c* 0.8, $CHCl_3$, cm^{-1}); **IR** ($CHCl_3$): υ_{max} 756, 1216, 1701, 3021, 3454; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.81 (t, *J* = 7.1 Hz, 3H), 1.02-1.43 (m, 6H), 2.39 (brs, 1H), 3.36(d, *J* = 12.1 Hz, 1H), 3.91- 4.00 (dd, *J* = 5.4, 12.0 Hz, 1H), 4.13-4.20 (dd, *J* = 4.5, 10.4 Hz, 1H), 4.27 (d, *J* = 5.05 Hz, 1H), 5.07-5.29 (m, 4H), 7.29 (brs, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.9, 22.2, 28.1, 29.4, 54.6, 67.8, 68.0, 68.4, 75.2, 127.4, 127.8, 128.0, 128.1, 128.4, 134.0, 156.9, 158.9; **Analysis**: $C_{23}H_{28}N_2O_5$ requires: C, 66.97; H, 6.84; N, 6.79%; found: C, 66.90; H, 6.89; N, 6.85%.

(3*R*, 4*S*)- Dibenzyl-3-(3-azidopropyl)-4-hydroxypyrazolidine-1,2-dicarboxylate (55i)

Yield: 66%; gum; 91% ee from HPLC analysis; Whelk - 01 column (2-propanol:*n*-hexane = 20:80, flow rate 0.5 mL/min, λ = 220 nm). Retention time (min): 14.41 (major) and 18.92 (minor), $[\alpha]^{D}_{25}$ +4.79(*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 679, 753, 1136, 1214, 1342, 1401, 1455, 1709, 2097, 2984, 3451; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.88-1.09 (m, 1H), 1.39-1.62 (m, 3H), 2.50 (d, *J* = 2.5 Hz, 1H), 3.07-3.23 (m, 2H), 3.36 (d, *J* = 12.1, 1H), 3.95-4.01 (dd, *J* = 5.4, 12.0 Hz, 1H), 4.13-4.21 (dd, *J* = 4.05, 11.4 Hz, 1H), 4.27 (brs, 1H), 5.06-5.26 (m, 4H), 7.30 (s, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 25.4, 25.6, 50.5, 54. 6, 67.6, 68.0, 68.2, 75.3, 127.5, 128.1, 128.3, 128.5, 135.8, 135.9, 156.8, 158.7; **HRMS (ESI, m/z):** Calculated for $C_{22}H_{25}N_5O_5Na$ $(M+Na)^+$ 462.1753, found 462.1751. **Analysis**: $C_{22}H_{25}N_5O_5$ requires: C, 60.13; H, 5.73; N, 15.94%; found: C, 60.21; H, 5.65; N, 15.84%.

(3*R*, 4*S*)-Dibenzyl-3-((benzyloxy)methyl)-4-hydroxypyrazolidine-1,2-dicarboxylate (55j)

Yield: (70%); gummy liquid; 90% ee from **HPLC analysis**; Whelk-01 column (2-propanol:*n*-hexane = 20:80, flow rate 0.5 mL/min, λ = 254 nm). Retention time (min): 17.45 (major) and 19.64 (minor), $[\alpha]^{25}_{D}$: - 10.453 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 697, 753, 1027, 1141, 1216, 1338, 1402, 1455, 1715, 2953, 3032, 3066, 3446; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.43 (d, *J* = 21.2 Hz, 1H), 3.26-3.41 (m, 2H), 3.55-3.62 (dd, *J* = 4.0, 9.9 Hz, 1H,), 4.08-4.16 (dd, *J* = 6.32, 11.1 Hz, 1H), 4.28-4.41 (m, 3H), 4.52 (brs, 1H), 4.96-5.24 (m ,4H), 7.17-7.27 (m, 15H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 55.5, 67.0, 67.7, 68.07, 69.6, 73.4, 73.6, 127.5, 127.7, 128.0, 128.4, 135.9, 136.0, 137.5, 156.8, 157.8; **Analysis:** $C_{27}H_{28}N_2O_6$ requires C, 68.05; H, 5.92; N, 5.88%; found C, 68.15; H, 5.99; N, 5.98%.

(3*R*, 4*S*)-Diisopropyl-3-(3-(benzyloxy)propyl)-4-hydroxypyrazolidine-1,2-dicarboxylate (55k)

Yield: 72%; gum; 98% ee from **HPLC analysis**; Chiracel OD-H column (2-propanol:*n*-hexane = 5:95, flow rate 0.5 mL/min, λ = 254 nm). Retention time (min): 9.75 (minor) and 11.36 (major), $[\alpha]^{25}_{D}$: +1.33 (*c* 0.9, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 666, 699, 760, 919, 1027, 1105, 1147, 1180, 1219, 1321, 1381, 1690, 2394, 2863, 2936, 2980, 3019, 3434; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.19-1.30 (m, 12H), 1.50-1.83 (m, 4H), 2.55 (brs, 1H), 3.28 (d, *J* = 12.5 Hz, 1H), 3.41-3.60 (m, 2H), 3.91-4.00 (dd, *J* = 5.7, 12.0 Hz, 1H), 4.08-4.16 (dd, *J* = 4.9, 10.7 Hz, 1H), 4.23 (brs, 1H), 4.47 (s, 2H), 4.90-4.98 (m, 2H), 7.23-7.37 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 21.9, 22.0, 26.2, 26.7, 54.2, 67.6, 69.4, 69.6, 70.1, 72.9, 75.3, 127.5, 127.6, 128.3, 138.3, 156.7, 158.3; **HRMS (ESI, m/z)**: Calculated for $C_{21}H_{32}N_2O_6Na$ $(M+Na)^+$ 431.2158, found 431.2160**. Analysis:** $C_{21}H_{32}N_2O_6$ requires C, 61.75; H, 7.90; N, 6.86%; found C, 61.75; H, 7.90; N, 6.86%.

Synthesis of *anti*-1, 2-aminoalcohol (**56**)

A solution of hydroxypyrazolidine (R' = Bn) **55a** (0.805 mg, 1.8 mmol) in MeOH (20 ml) and acetic acid (10 drops) was treated with Raney Ni (~ 30 mol%, 20 mg) under H_2 (80 psig) atmosphere for 24 h. After the reaction was complete, it was filtered over Celite and concentrated to give *anti*-1,2-aminoalcohol **56.**

Yield: 76%, gum; $[\alpha]^{25}_{D}$: + 3.9 (*c* 1.2, MeOH). **^{1}H NMR** (500 MHz, MeOH-d_4) δ 2.16 (brs, 5H), 2.78-3.04 (m, 4H), 3.44 (br s, 1H), 3.93 (brs, 1H), 7.26-7.37 (m, 5H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 37.0, 42.7, 57.3, 69.7, 128.3, 130.2, 130.5, 138.1; **Analysis:** $C_{10}H_{16}N_2O$ requires C, 66.63; H, 8.95; N, 15.54; found C, 66.59; H, 8.93; N, 15.52%.

Synthesis of amino epoxide (**54a**)

Step 1. Preparation of amino aldehyde (A)

To a cooled solution of diisopropylazadicarboxylate (1.1 g, 5.0 mmol) and L-proline (57.5 mg, 10 mol %) in dry CH_3CN (20 ml) at 0 ^oC was added hydrocinnamaldehyde 53a (670 mg, 5 mmol) and the mixture was stirred for 3 h at 0 ^oC. The progress of the reaction was monitored by TLC. Then the mixture was concentrated in vacuum at room temperature to remove acetonitrile to give the crude product which was then purified by column chromatography with pet-ether/ ethylacetate (80:20) as eluents to afford the amino aldehyde intermediate **A** (1.52 g, 90% yield) **.**

Yield: 90%, viscous liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 698, 1107, 1180, 1235, 1300, 1385, 1455, 1467, 1496, 1719, 2981, 3286; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.11-1.27 (m, 12H), 2.90-3.11 (m, 1H), 3.21-3.31 (dd, *J* = 5.6, 14.7 Hz, 1H), 4.50-4.77 (m, 1H), 4.84-5.00 (m, 2H), 6.17 (d, *J* = 21.0 Hz, 1H), 7.20- 7.34 (m, 5H), 9.82 (d, *J* = 10.3 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 21.7, 32.3, 70.6, 126.7, 128.5, 128.8, 137.1, 155.2, 198.9; **Analysis:** $C_{17}H_{24}N_2O_5$ requires C, 60.70; H, 7.19; N, 8.33; found C, 60.72; H, 7.17; N, 8.29%.

Step 2. Preparation of amino olefin (epoxide precursor)

To a stirred solution of $Ph_3P^+CH_3I^-$ (3.6 g, 9 mmol) in THF (25 m) was added $KOBu^t$ (1.0 g, 9 mmol) at 0 °C. After 15 min. of stirring, amino aldehyde **A** (1.5 g, 4.5 mmol) in THF (10 ml) was added dropwise over a period of 10 min. The reaction mixture was then stirred for 1 h at 25 °C. After the completion of the reaction, as monitored by TLC, was quenched at 0 °C with aq. NH_4Cl, extracted with diethylether (3X40 ml) and dried over anhyd. Na_2SO_4. The combined organic layer was concentrated under reduced pressure to get the crude product which was then purified by column

chromatography with pet-ether/ ethyl acetate (90:10) as eluents to afford the amino olefin (1.35 g, 90% yield).

Yield: 90%, viscous liquid; $[\alpha]^{25}_{D}$: + 4.67 (*c* 1.2, $CHCl_3$). **IR** ($CHCl_3$, cm^{-1}): υ_{max} 756, 1037, 1107, 1180, 1216, 1296, 1385, 1706, 2983, 3385; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.15-1.27 (m, 12H), 2.83-3.02 (m, 2H), 4.76-5.02 (m, 3H), 5.13 (d, *J* = 10.4 Hz, 2H), 5.83-6.04 (m, 2H), 7.14-7.31 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 21.9, 22.0, 37.9, 69.7, 69.9, 116.9, 126.4, 128.4, 129.1, 135.8, 138.0, 155.0, 156.4; **Analysis:** $C_{18}H_{26}N_2O_4$ requires C, 64.65; H, 7.84; N, 8.38; found C, 64.67; H, 7.85; N, 8.35%.

Step 3. Preparation of amino epoxide (54a)

To a stirred solution of amino olefin (200 mg, 0.59 mmol) in CH_2Cl_2 (5 ml) was added mCPBA (154 mg, 0.9 mmol) at 0 °C. The reaction mixture was then stirred for 12 h at 25 °C. After the completion of the reaction, as monitored by TLC, was washed with aq. $NaHCO_3$ and extracted with CH_2Cl_2 (3x5 ml) and dried over anhyd. Na_2SO_4. The combined organic layer was concentrated under reduced pressure to get the crude product which was then purified by column chromatography with pet-ether/ ethylacetate (90:10) as eluents to afford the amino epoxide **54a** (0.189 g, 92%).

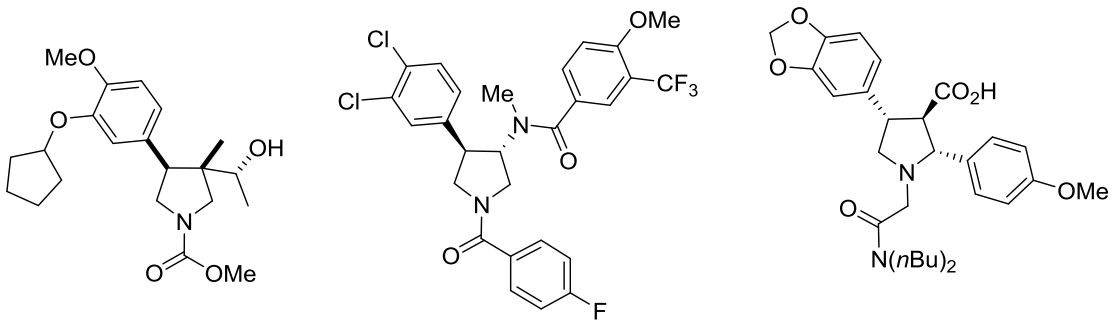
Yield: 92%, viscous liquid; $[\alpha]^{D}_{25}$: + 2.51 (*c* 1.2, $CHCl_3$). **IR** ($CHCl_3$, cm^{-1}): υ_{max} 756, 1037, 1107, 1180, 1216, 1296, 1385, 1706, 2983, 3385; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.20-1.30 (m, 12H), 2.34-2.39 (m, 1H), 2.64-2.94 (m, 2H), 3.01-3.16 (m, 2H), 4.20-4.30 (m, 1H), 4.81-5.04 (m, 2H), 6.27 (brs, 1H), 7.17-7.32 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 21.7, 22.0, 35.7, 46.3, 52.7, 60.5, 69.7, 70.1, 126.6, 128.6, 128.7, 129.1, 137.6, 155.2, 156.2; **Analysis:** $C_{18}H_{26}N_2O_5$ requires C, 61.70; H, 7.48; N, 7.99; found C, 61.72; H, 7.58; N, 7.95%.

Section II

Proline-catalyzed *syn*-Mannich/Corey-Chaykovsky Reaction Cascade *via* [4+1] Annulation. A High Yield Synthesis of 4-Hydroxy pyrrolidine Derivatives

2.2.1 Introduction

Five-membered nitrogen-containing heterocycles are structural components of many bioactive compounds (**Fig. 7**), natural products and building blocks in organic and diversity-oriented synthesis.[31] Also, these find wide applications such as chiral auxillaries,[32] chiral ligands,[33] and organocatalysts[34] in asymmetric synthesis. More importantly, the derivatives of densely functionalized pyrrolidines such as **57**-**59** exhibit a wide variety of pharmaceutical activities such as antitumor, antidepressant, antihypertensive, antiarthritic, antibacterial, antithrombotic, analgesic agents, etc (**Fig. 7**).[35] Consequently, much efforts have been devoted to the development of efficient routes to the asymmetric synthesis of substituted pyrrolidines.



57 (PDE4 inhibitor) **58** (peptide deformylase inhibitor) **59** (anticancer)

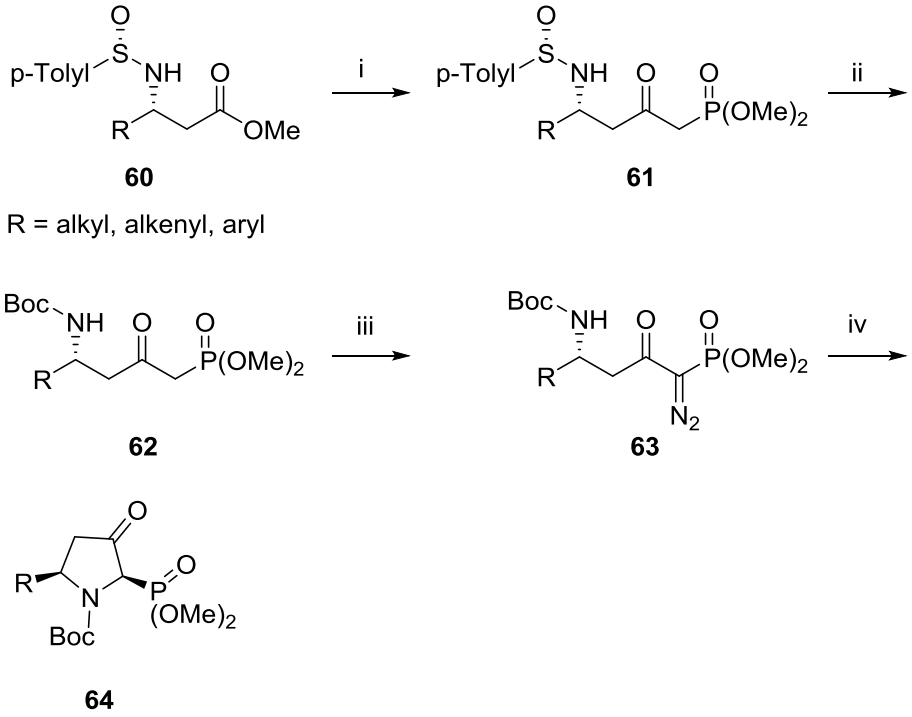
Fig. 7: Some bioactive compounds containing substituted pyrrolidine motif

2.2.2 Review of literature

Literature search revealed that several reports are available for the asymmetric synthesis of substituted pyrrolidines. Some of the recent literature reports are described briefly below.

Davis's approach (2004)[36]

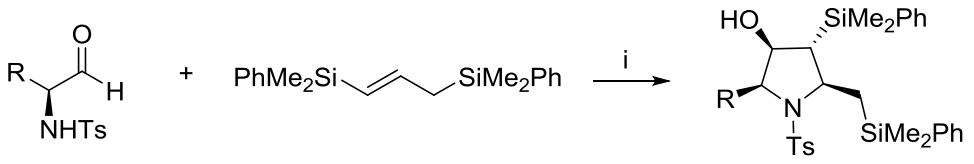
Davis *et al.* have demonstrated the asymmetric synthesis of *cis*-5-substituted pyrrolidine 2-phosphonates **64**, through intramolecular metal carbenoid NH insertion reaction from α-diazophosphonate **63**. These α-diazophosphonates **63** are prepared from *N*-sulfinyl *δ*-amino *α*-keto-β-phosphonates **61**, a new sulfinimine-derived chiral building block (**Scheme 18**)



Scheme 18: (i) $CH_3P(O)(OMe)_2$, *n*-BuLi, -78 ^oC (80-93%); (ii) (a) TFA/MeOH (b) $(Boc)_2O$, NEt_3, DMAP (80-90%); (iii) NaH, 4-acetamidobenzenesulfonyl azide; (iV) $Rh_2(OAc)_4$, CH_2Cl_2, 35 ^oC (65-88%).

Somfai's approach (2006)[37]

Somfai *et al*. have illustrated a highly stereoselective [3 + 2]-annulation approach to hydroxypyrrolidine derivatives **67**, containing four contiguous stereocenters using *N*-Ts-α-amino aldehydes **65** and 1,3-bis(silyl)propene **66**, which functions as 1, 2-dipole equivalent (**Scheme 19**).



65 **66** **67**

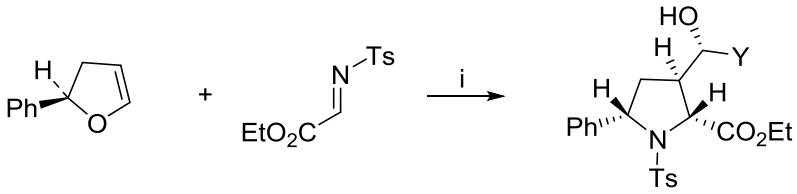
33-69% yield

98:2 dr

Scheme 19: (i) $MeAlCl_2$, CH_2Cl_2, -78 ^oC, 5 h.

Ghosh's approach (2006)[38]

Ghosh *et al*. have developed a $TiCl_4$-catalyzed asymmetric multicomponent coupling reactions of optically active phenyl dihydrofuran **68**, N-tosyl imino ester **69**, and silane reagents in a one-pot operation that afforded highly substituted pyrrolidine derivatives **70** diastereoselectively. The reaction is quite efficient and constructed up to three stereogenic centers in a single operation (**Scheme 20**).



68 **69** **70**

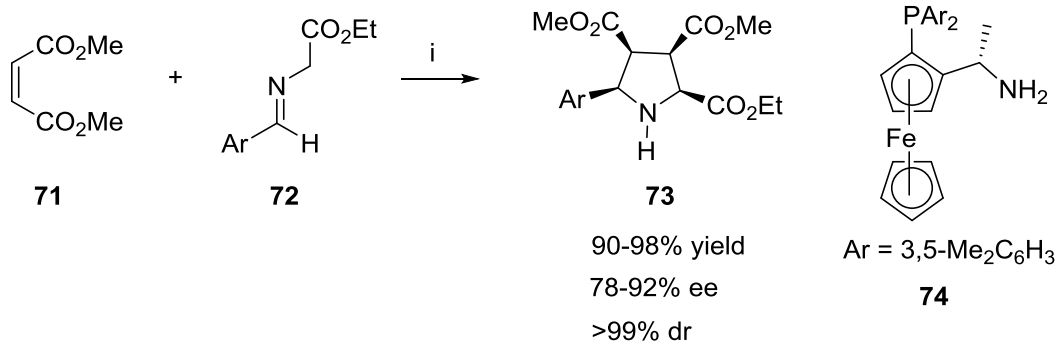
63-83% yield

up to 99:1 dr

Scheme 20: $TiCl_4$, TMS-Y, -78 to 23 ^oC, 2 h.

Li's approach (2007)[39]

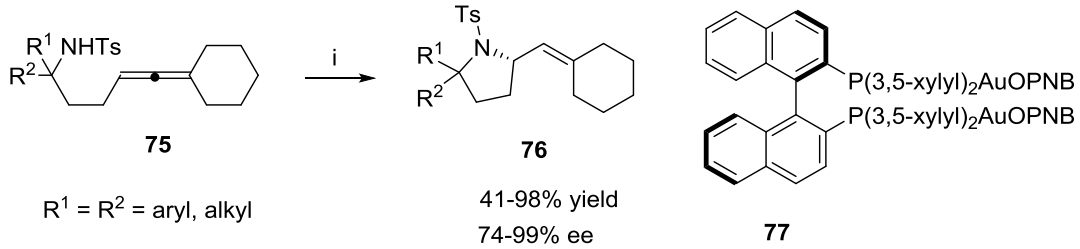
Li *et al.* have employed AgOAc-catalyzed [3+2]-cycloaddition between azomethine ylide of **72** and dimethylmaleate **71** for the asymmetric synthesis of densely substituted pyrrolidine carboxylate **73**. The enantio- and diastereoselectivity was achieved *via* hydrogen bonding between chiral ligand **74** and reactants (**Scheme 21**).



Scheme 21: iminoester **72** (1.0 equiv), dimethyl maleate **71** (1.5 equiv), AgOAc (3 mol %), **74** (3.3 mol %), Et_2O, 8-24 h.

Toste's approach (2007)[40]

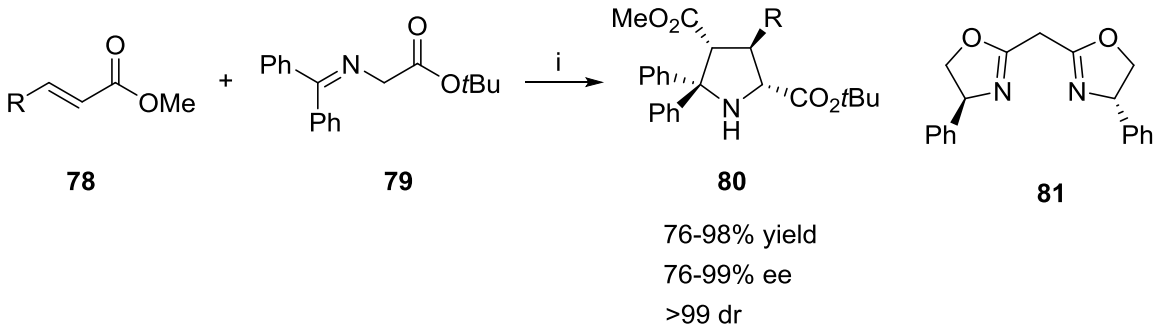
Toste *et al.* have described an enantioselective Au-catalyzed intramolecular hydroamination of allenes **75** for the formation of vinyl-substituted pyrrolidines **76** using of phosphine Au(I)-*bis*-*p*-nitrobenzoate complex **77** as catalysts (**Scheme 22**).



Scheme 22: (i) 3 mol % of **77**, $ClCH_2CH_2Cl$, 23 °C, 15-24 h

Kobayashi's approach (2007)[41]

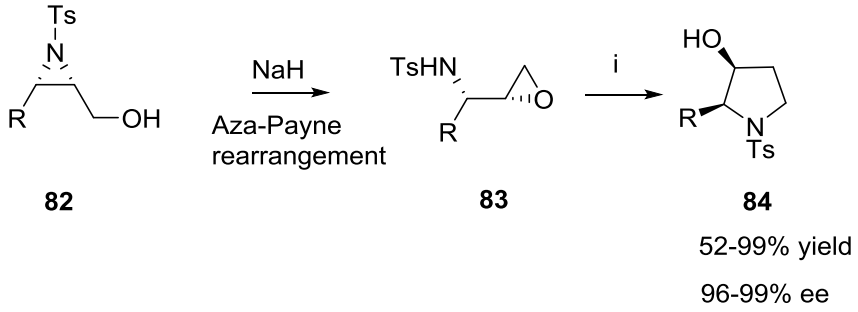
Kobayashi *et al*. have developed novel Ca-Box catalysts, prepared from calcium alkoxides and methylene bridged Box ligand **81**, for the asymmetric synthesis of substituted pyrrolidines **80**. The catalyst promoted two types of catalytic asymmetric additions of α-amino acid derivatives **79** with α, *β*- unsaturated carbonyl compounds **78**; (a) 1,4-addition reactions and (b) [3+2]-cycloaddition recations **(Scheme 23)**.



Scheme 23: Ca(*i*OPr)$_4$ (10 mol %), Ligand **81** (10 mol%), THF, 4A° MS, -30 to 10 °C, 3 h.

Borhan's approach (2007)[42]

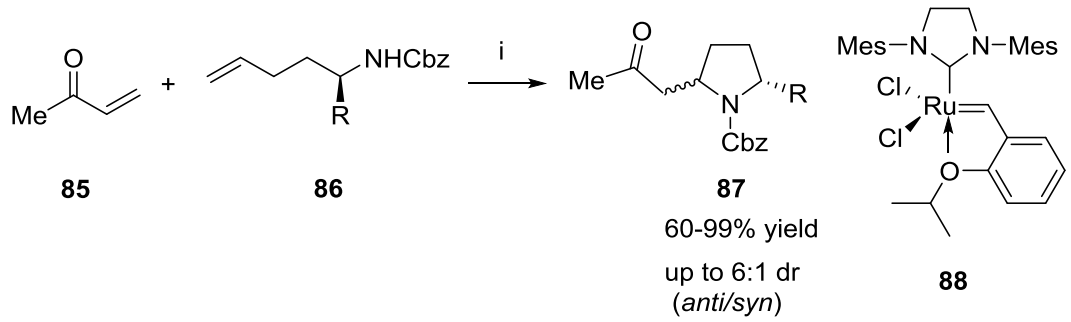
Borhan *et al.* have reported a dimethylsulfoxonium ylide-based aza-Payne rearrangement of optically pure 2, 3-aziridin-1-ols **82** that led to an efficient process for the preparation of substituted hydroxypyrrolidines **84** (**Scheme 24**).



Scheme 24: (i) dimethylsulfoxonium methylide (8 equiv), DMSO, 80-85 °C, 24 h.

Fustero's approach (2007)[43]

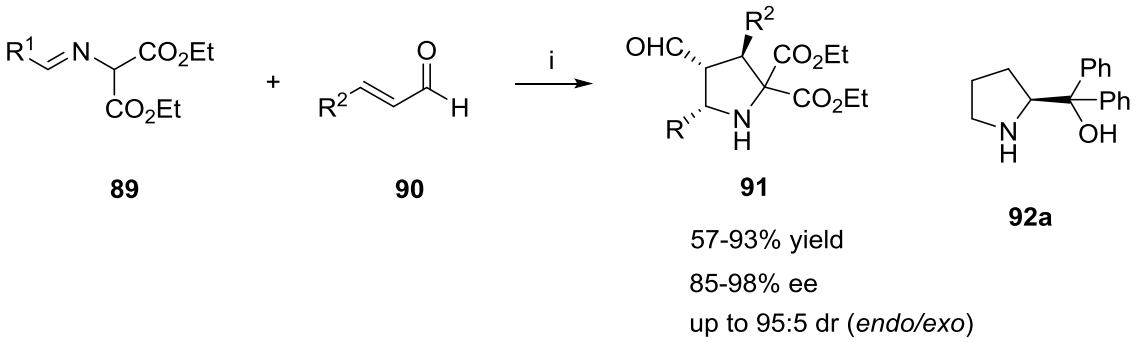
Fustero *et al.* have developed a tandem cross-metathesis intramolecular aza-Michael tandem reaction between α-branched Cbz-protected amines **86** and methyl vinyl ketone **85**, catalyzed by a Hoveyda- Grubbs second generation catalyst **88**/BF_3.OEt_2 system, that allowed rapid access to protected 2,5-substituted pyrrolidines **87** with excellent overall yields (**Scheme 25**).



Scheme 25: (i) **88** (2.5 mol%), $BF_3.OEt_2$, CH_2Cl_2, 45 ^oC, 4 d.

Vicario's approach (2007)[44]

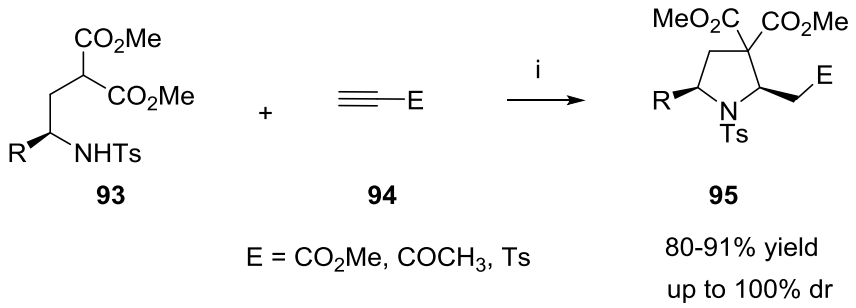
Vicario *et al.* have demonstrated an organocatalytic enantioselective [3+2]-cycloaddition reaction between α,β-unsaturated aldehydes **90** and azomethine ylide of **89**. The reaction proceeded with complete regioselectivity and with very high diastereo- and enantioselectivity to furnish almost stereoisomerically pure highly functionalized polysubstituted pyrrolidines **91** in excellent yields (**Scheme 26**).



Scheme 26: (i) **89** (0.75 mmol), **90** α,β-unsaturated aldehyde (0.70 mmol), H_2O (50 mL), **92a** (0.14 mmol), THF (6 mL), 48 °C, 72 h.

Kwon's approach (2007)[45]

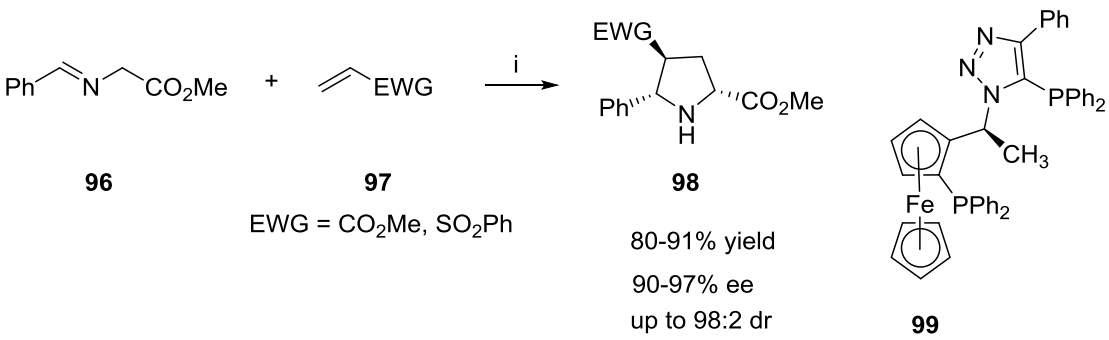
Kwon *et al.* have reported the mixed double-Michael addition of amino acid-derived γ-amino malonate **93** with methyl propiolate or acetylacetylene **94** for the synthesis of substituted pyrrolidines **95**, which were obtained in excellent yields with high diastereoselectivities (**Scheme 27**).



Scheme 27: (i) Diphenylphosphinopropane (10 mol%), 80 °C, 9 h.

Oki's approach (2008)[46]

Oki *et al.* have demonstrated a copper(I)/ClickFerrophos complex **99**-catalyzed asymmetric 1,3-dipolar cycloaddition reaction of methyl *N*-benzylideneglycinate **96** (the source of azomethine ylide) with vinyl sulfone **97** to give the *exo*-2,4,5-trisubstituted pyrrolidine **98** in good yields with high enantioselectivity (99% ee). The complex also effectively catalyzed the reactions of other dipolarophiles such as acrylates, maleates, and maleimides to give *exo*-2,4,5-, and 2,3,4,5-substituted pyrrolidine derivatives with high diastereo- and enantioselectivities (**Scheme 28**).

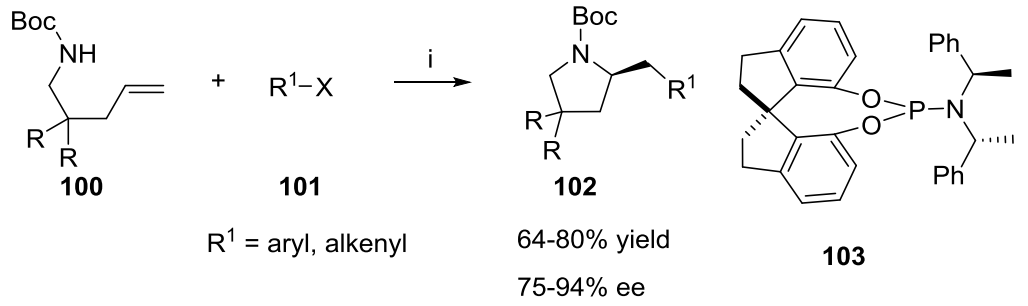


Scheme 28: (i) **96** (0.2 mmol), **97** dipolarophile (0.2 mmol), CuOAc (0.01 mmol), **99** (0.011 mmol), diethyl ether (2 mL), 24 h.

Wolfe's approach (2010)[47]

Wolfe *et al.* have developed an enantioselective Pd-catalyzed alkene carboamination reactions between readily available alkenyl or aryl bromides **101** and *N*-boc-pent-4-

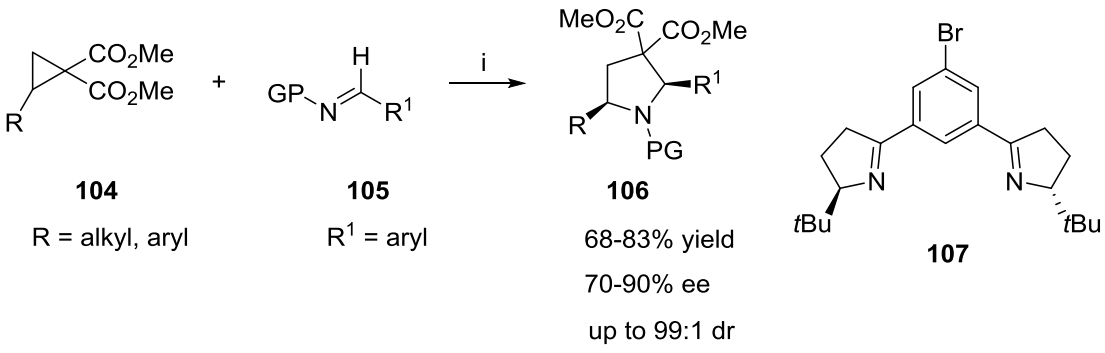
enylamines **100** that afforded 2-(arylmethyl)- or 2-(alkenylmethyl)pyrrolidines **102** in good yields and enantioselectivities (**Scheme 29**).



Scheme 29: (i) **100** (1.0 equiv), ArBr or alkenylBr (2.0 equiv), NaO*t*Bu (1.0-2.0 equiv), $Pd_2(dba)_3$ (2.5 mol %), **103** (7.5 mol %), toluene (0.2 M), 90 °C, 12-15 h.

Johnson's approach (2010)[48]

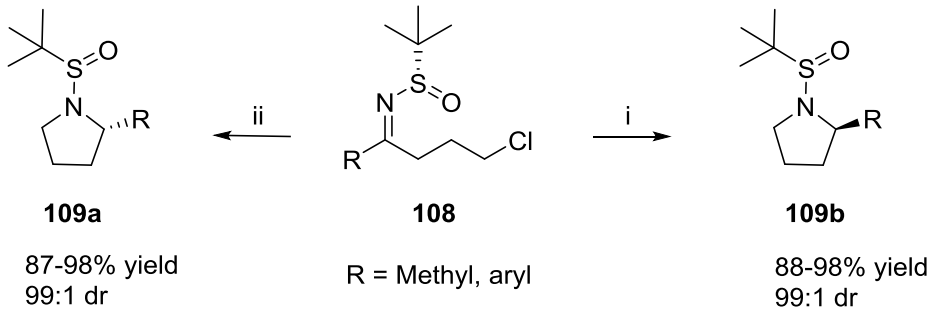
Johnson *et al.* have reported an enantioselective synthesis of 2,5-*cis*-disubstituted pyrrolidines **106** through a dynamic kinetic asymmetric [3 + 2]-annulation of racemic cyclopropanes **104** and (*E*)-aldimines **105**. Substituted *N*-benzyl protecting group of the aldimine **105** and chiral ligand **107** allowed for an increase in enantioselectivity (**Scheme 30**).



Scheme 30: (i) MgI_2 (10 mol%), **107** (10 mol%), CCl_4, 25 °C, 24 h.

Rajender Reddy's approach (2010)[49]

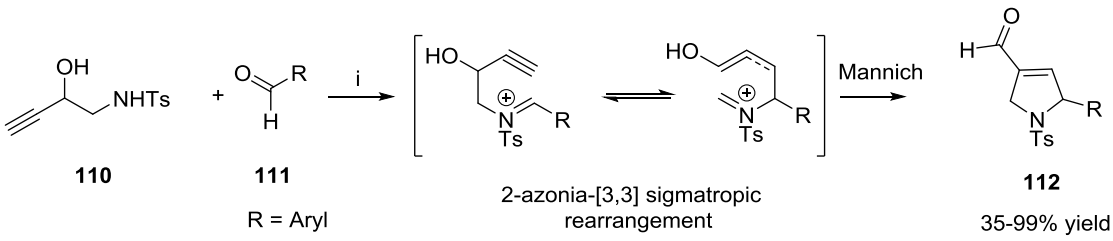
Rajender Reddy *et al.* have described a one-step process for asymmetric synthesis of either stereoisomers of 2-substituted pyrrolidines **109** from (*S,S*)-γ-chloro-N-*tert*-butanesulfinyl ketimines **108** *via* diastereoselective reductive cyclization with excellent yields and high diastereoselectivity (**Scheme 31**). The diastereoselectivity is controlled effectively by the choice of reducing agent.



Scheme 31: (i) $LiBHEt_3$, -78 °C, 3 h, 25 °C, THF, 1 h; (ii) DIBAL-H, -78 °C, 3 h, LiHMDS, 25 °C, toluene, 2 h.

Padrón's approach (2010)[50]

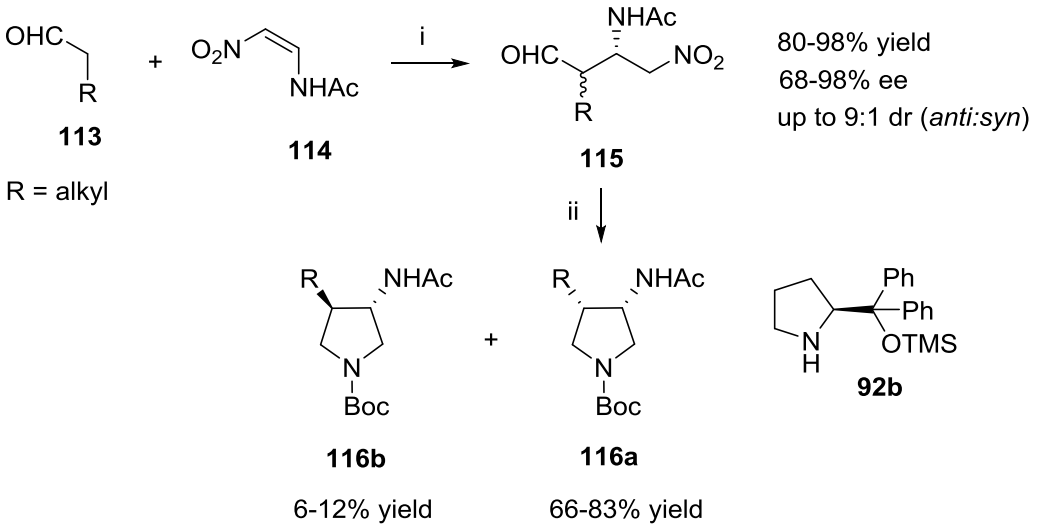
Padrón *et al.* have reported an alkene aza-Cope-Mannich cyclization between 2-hydroxy homoallyl tosylamine **110** and aldehydes **111** in the presence of iron (III) salts to obtain 3-alkyl-1-tosyl pyrrolidines **112** in good yields. The process is based on the consecutive generation of a γ-unsaturated iminium ion, 2-azonia-[3,3]-sigmatropic rearrangement, followed by intramolecular Mannich reaction (**Scheme 32**).



Scheme 32: (i) $FeCl_3$ (10-20 mol%), TMSCl, CH_2Cl_2, 25 °C, 2-24 h.

Dawei Ma's approach (2010)[51]

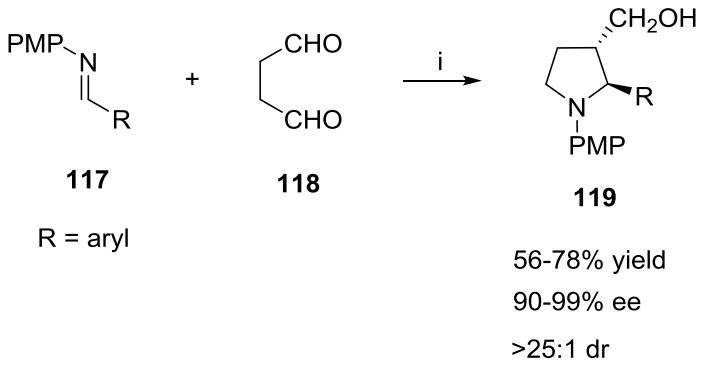
Ma *et al.* have demonstrated that protected 2-nitroethenamine **114** could undergo organocatalytic Michael additions to aldehydes **113** to provide 1,2-diamine precursors **115**. The diamine precursors **115** were then subjected to Pd/C (5 wt%)-catalyzed reductive cyclization leading to the synthesis of substituted 3-aminopyrrolidines **116** in good yields (**Scheme 33**).



Scheme 33: (i) **113** (1.5 equiv), **114** (1 equiv), AcOH (25 mol%), prolinol derivative **92b** (5 mol%), CH_3CN, 0 °C, 2-25 h; (ii) Pd/C H_2 MeOH then $(Boc)_2O$.

Indresh Kumar's approach (2012)[52]

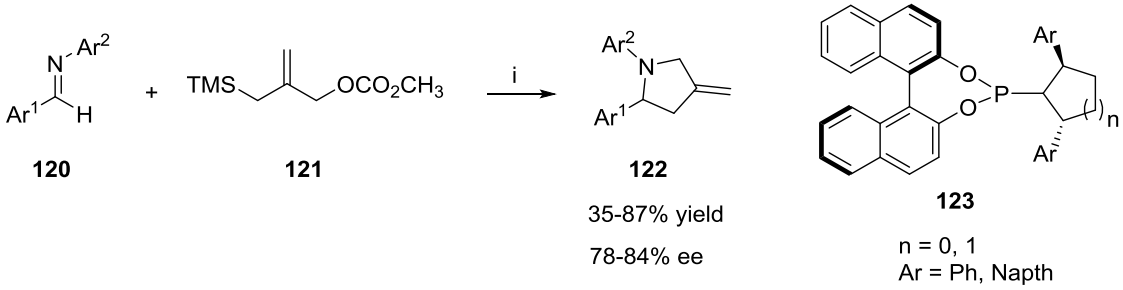
Indresh Kumar *et al.* have developed a stereoselective method for the synthesis of substituted pyrrolidines **119** from readily available precursors like N-PMP aldimines **117** and succinaldehyde **118** as new 1,3-carbon dipoles. This one-pot protocol involves the L-proline-catalyzed direct Mannich reaction and reductive cyclization sequence as a formal [3+2]-cycloaddition strategy, affording a wide access to *trans*-2,3- substituted pyrrolidines (**Scheme 34**).



Scheme 34: (i) (a) L-proline (20 mol%), DMSO, 5 °C, 8-24 h; (b) AcOH (50 mol%), $NaBH_4$, MeOH, 0 °C-25 °C, 3 h.

Trost's approach (2012)[53]

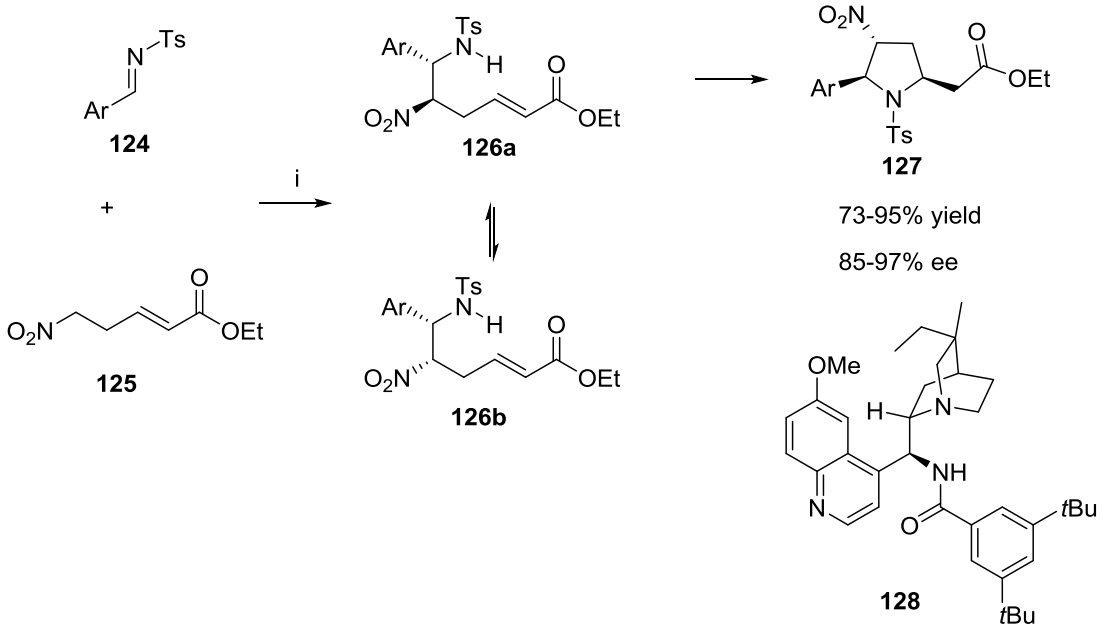
In this approach, Trost *et al.* have developed a chiral Pd-complex **123** that catalyzed asymmetric [3 + 2]-cycloaddition reaction of trimethylenemethane **121** with imine acceptors **120.** This afforded products **122** with high levels of chemo-, diastereo- and enantioselectivity (**Scheme 35**).



Scheme 35: $Pd(dba)_2$ (5 mol%), **123 (**10 mol%) , **120** (1.6 equiv) , **121** (1.0 equiv) , toluene, 45 °C, 4 h.

Huang's approach (2013)[55]

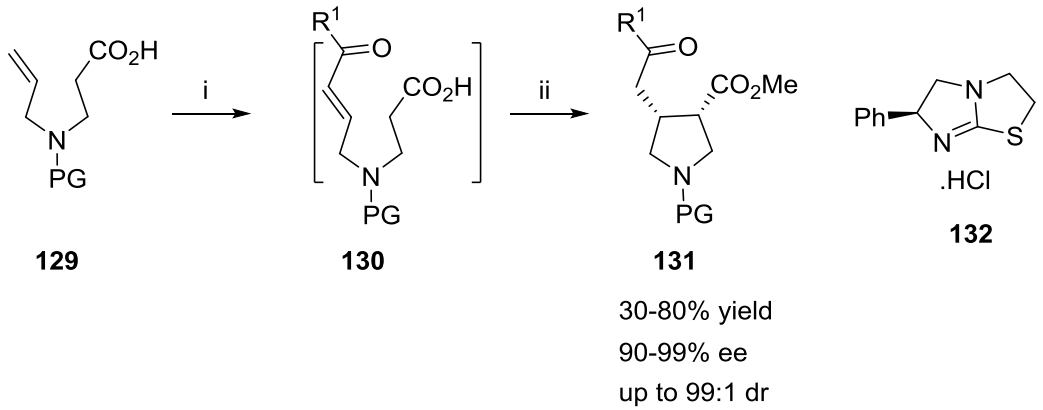
Huang *et al.* have described a highly diastereo- and enantioselective organocatalytic cascade strategy that provided for the synthesis of heavily substituted pyrrolidines **127** with up to three stereogenic centers. This domino reaction relies on a reversible aza-Henry reaction of nitroalkane **125** with tosyl imines **124** and a subsequent DKR aza-Michael cyclization, both catalyzed by a Cinchona alkaloid derivative containing amine/amide **128**, to ensure overall stereoselectivity (**Scheme 36**).



Scheme 36: (i) **128** (10 mol %), **124**/**125**=1:1.5, toluene, 25 °C, 24 h.

Smith's approach (2013)[54]

Smith *et al.* have developed a telescoped and one-pot olefination/asymmetric functionalization approach to 2,3- or 3,4-*syn*-disubstituted pyrrolidines **131** from readily available N-allyl-β-amino acid derivatives **129**. This method provides the corresponding pyrrolidine derivatives with high diastereo-and enantiocontrol (dr up to 99:1, up to 99% ee) using tetramisole chiral reagent **132** (**Scheme 37**).



Scheme 37: (i) O_3, Ph_3P=CHCOR[1]; (ii) (a) Me_3COCl (1.5 equiv), *i*Pr_2NEt (1.5 equiv), CH_2Cl_2, 25 °C; then **132** (5 mol%), *i*Pr_2NEt (2.5 equiv), 25 °C, 1 h; (b) MeOH, DMAP, 25 °C.

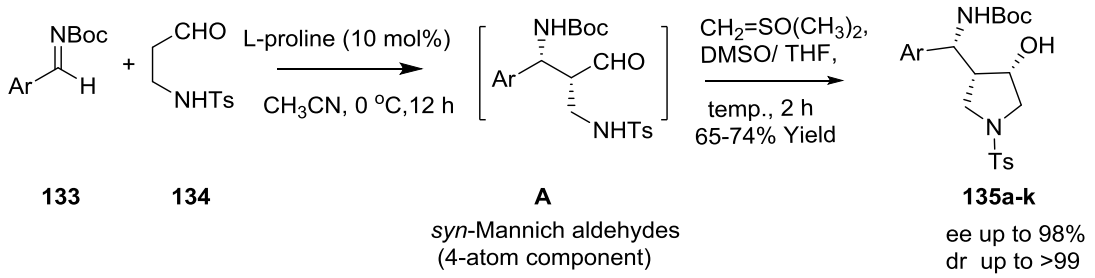
2.2.3 Present Work

2.2.3.1 Objective

The literature survey reveals that several methods are available for the asymmetric synthesis of substituted pyrrolidines. Majority of the routes involve [3+2]-cycloadditions of azomethine ylides with alkenes[46] or cyclopropanes,[48] Pd-catalyzed carboamination reactions,[47] acid-catalyzed cyclization of vinylsilanes,[37] intramolecular carbolithiation of homoallylic amines,[56] Brønsted acid-catalyzed intramolecular hydroamination of alkenylamines,[57] manipulations of sugars from the chiral pool,[58] various other metal-catalyzed cyclizations.[59] However, these methods have limitations such as dependence on complex chiral pool resources, expensive chiral ligands and metal catalysts, often involving multi-step reaction sequences. Hence, an operationally simple method with cheap starting materials and catalysts without compromising the yield and stereoselectivity of product is highly desirable.

2.2.3.2 Results and Discussion

Proline-catalyzed asymmetric reactions have emerged as a reliable method for the construction of structurally diverse molecular architectures.[60] As part of our research program directed toward asymmetric synthesis of bioactive molecules employing proline as organocatalysts,[23] we were interested in investigating the feasibility of a new diastereoselective formal [4+1] annulation reaction for the asymmetric synthesis of substituted 4-hydroxypyrrolidines **135a-k**, by employing chiral β, β'-diamino aldehydes **A** (generated from proline-catalyzed *syn*-Mannich reaction)[61] as 4-atom component coupled with dimethylsulfoxonium methylide as one-carbon source (**Scheme 38**).[24]

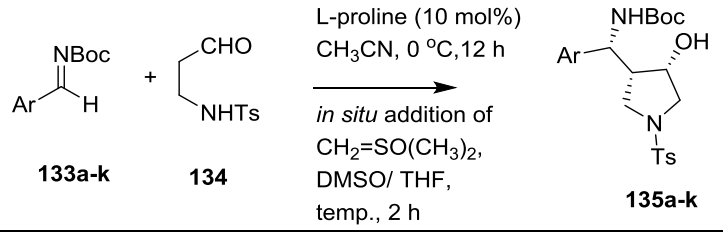


Scheme 38: Proline-catalyzed *syn*-Mannich/Corey-Chaykovsky reaction

Dimethylsulfoxonium methylide, a one-carbon source (1,1'-dipole-type reagent)[62] has been extensively used as a methylene transfer reagent in organic synthesis.[63] Despite the multiple advances, the research for unprecedented reactions involving sulfur ylide continues, with the goal of increasing the diversity of possible substrates and architectural complexity of products in a step-economical fashion. In this section, a one-pot formal [4+1] annulation of *in situ* generated β, β'-diamino aldehydes **A**[61,64] with sulfur ylide to give 4-hydroxypyrrolidine derivatives **135a-k** in a highly enantio- and diastereoselective manner is described (**Scheme 38**).

In a preliminary study, β-amino aldehyde **134** was treated with N-Boc imine **133a** following the List protocol[61] that produced the corresponding β, β'-diamino aldehyde **A**, a *syn*-Mannich adduct *in situ*. A solution of dimethylsulfoxonium methylide in DMSO/THF [sulfur ylide (1.5 equiv), prepared *in situ* from $O=SMe_3I$/NaH in DMSO/THF] was added to the precursor **A,** which gave the desired hydroxypyrrolidine derivative **135a** (**Table 3**).[65] Several experiments were conducted to identify the best condition for the formal [4+1]-annulation protocol; the results of such studies are presented in Table 3. Firstly, when sulfur ylide i.e. $CH_2=SOMe_2$ was reacted with *in situ* generated *syn*-Mannich aldehyde **A** at 25 °C pyrrolidine **135a** was produced in 68% yield with 92% ee and moderate dr (4:1) (entry 1).

Table 3. Synthesis of substituted 4-hydroxypyrrolidine **135a-k**[a]



133a-k **134** **135a-k**

entry	Ar	temp (°C)	products **(135a-k)**		
			yield (%)[b]	ee (%)[c]	dr (%)[d]
1	phenyl (**133a**)	25	68	92	4:1
	phenyl	0	72	92	9:1
	phenyl	**-10**	**72**	**93**	**>99**
	phenyl	-20	60	92	>99
2	4-OMe-phenyl (**133b**)	-10	74	96	>99
3	4-CF_3-phenyl (**133c**)	-10	70	92	>90
4	4-tolyl (**133d**)	-10	70	94	>99
5	2-naphthyl (**133e**)	-10	63[e]	98	>99
6	4-Br-phenyl (**133f**)	-10	61[e]	98	>99
7	4-F-phenyl (**133g**)	-10	66[e]	96	>99
8	4 –CN-phenyl (**133h**)	-10	71[f]	nd	4:1
9	4-SMe-phenyl (**133i**)	-10	65	93	>99
10	thiophenyl (**133j**)	-10	68[g]	92	>90
11	furfuryl (**133k**)	-10	64[g]	91	>90

[a]imine (5 mmol), aldehyde (5.5 mmol), *L*-proline (10 mol %), dimethyloxosulfonium methylide (7.5 mmol), DMSO/THF (1:1), -10 °C, 2 h; [b]isolated yield after column chromatographic purification; [c] % ee determined from chiral HPLC analysis (Chiracel OD-H, Chiracel AS-H n-hexane/2-propanol); [d]dr determined from ^{1}H NMR analysis; [e] corresponding oxazolidinones were isolated by using 15 mmol of ylide for 12 h at 25 °C; [f]product obtained as inseparable diastereomers; [g] isolated yield of major diastereoisomer separated *via* flash column chromatography; nd = not determined.

An improvement in diastereoselectivity (9:1) was realized by performing the reaction at 0 °C for 2 h. Finally, the best results could be obtained when the addition of sulfur ylide was conducted at -10 °C (93% ee, >99 dr with 72% yield). However, further lowering of the temperature for the annulations protocol had a deleterious effect on the yield. Use of other solvents such as THF, $CHCl_3$ and DMF were found to be less effective for the tandem protocol.

Having established the optimal reaction conditions for the [4+1] annulation, we next examined the scope of the reaction. Substrates having fluoro, bromo, cyano, methoxy, methyl, trifluoromethyl and thiomethyl groups on the aromatic nucleus as well as heteroaromatic compounds such as thiophenyl and furfuryl were well-tolerated under the reaction conditions. For all the cases studied, the products **135a-k** were indeed obtained in high yields (65-74%) with excellent enantio- and diastereoselectivities (90-98% ee and dr up to >99%) (**Table 3**). Structures of 4-hydroxypyrrolidine derivatives **135a-k** were established unambiguously from their corresponding ^{1}H & ^{13}C NMR, IR and HRMS spectral data. The optical purity of these pyrrolidine derivatives was determined from chiral HPLC analysis.

Example 1: The formation of 4-hydroxypyrrolidine **135a** was confirmed from its ^{1}H NMR spectrum, which showed two doublets at δ 3.45 (d, J = 11.5 Hz, 1H) and δ 3.58 (d, J = 12.3 Hz, 1H) corresponding to the diastereotopic methylene C**H**$_2$-NR_2 protons (i.e. methylene group transferred from dimethylsulfoxonium methylide) of the pyrrolidine ring. Also, a doublet of doublet at δ 4.51-4.56 (dd, J = 8.1, 10.8 Hz, 1H) indicated the presence of methine C**H**-OH proton of the cyclic moiety. Its ^{13}C NMR spectrum showed two typical signals at δ 52.2 and 53.2 indicative of the methylene (-**CH**$_2$-NR_2) carbons of the pyrrolidine ring. The other resonance signals at δ 55.6 and

69.9 are due to the benzylic (Ph**C**H-NHR) and methine (**C**H-OH) carbons respectively (**Fig. 8**).

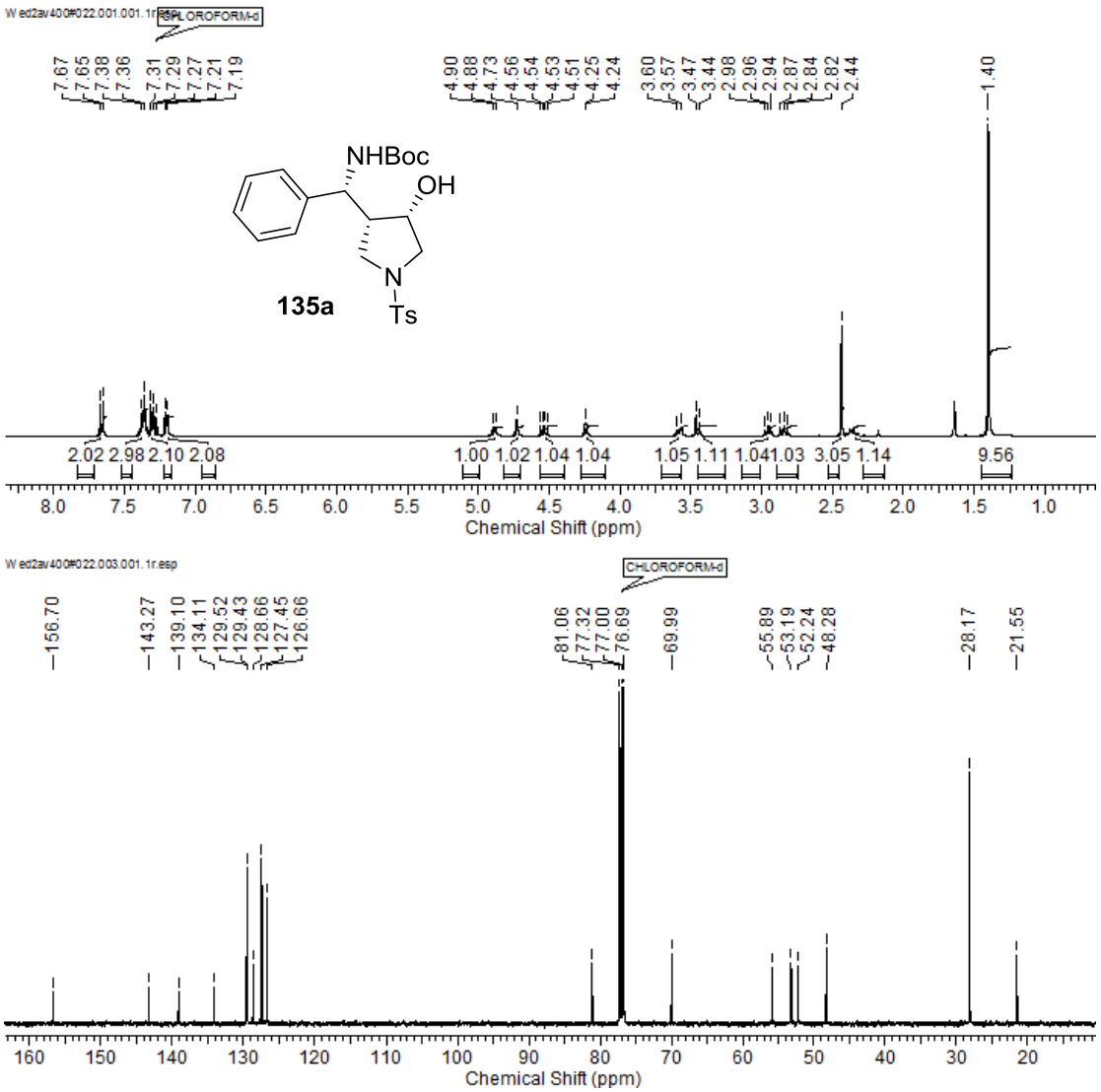


Fig. 8: ^{1}H and ^{13}C NMR spectra of 4-hydroxypyrrolidine derivative **135a**

Example 2: The ^{1}H NMR spectrum of 4-hydroxypyrrolidine derivative **135c** showed a doublet at δ 3.44 (d, *J* = 11.4 Hz, 1H) and a doublet of doublet at δ 3.56-3.58 (dd, *J* = 3.7, 12.9 Hz, 1H) corresponding to methylene (-**CH$_2$**-NR$_2$) protons (i.e. methylene group transferred from dimethylsulfoxonium methylide) of the 5-membered nitrogen heterocycle, while a doublet of doublet at δ 4.60-4.70 (dd, *J* = 8.5, 10.3 Hz, 1H), and

a broad signal at δ 4.23 (br s, 1H) indicated the presence of methine (-C**H**-OH and -**CH**-NR_2) protons of **135c**.

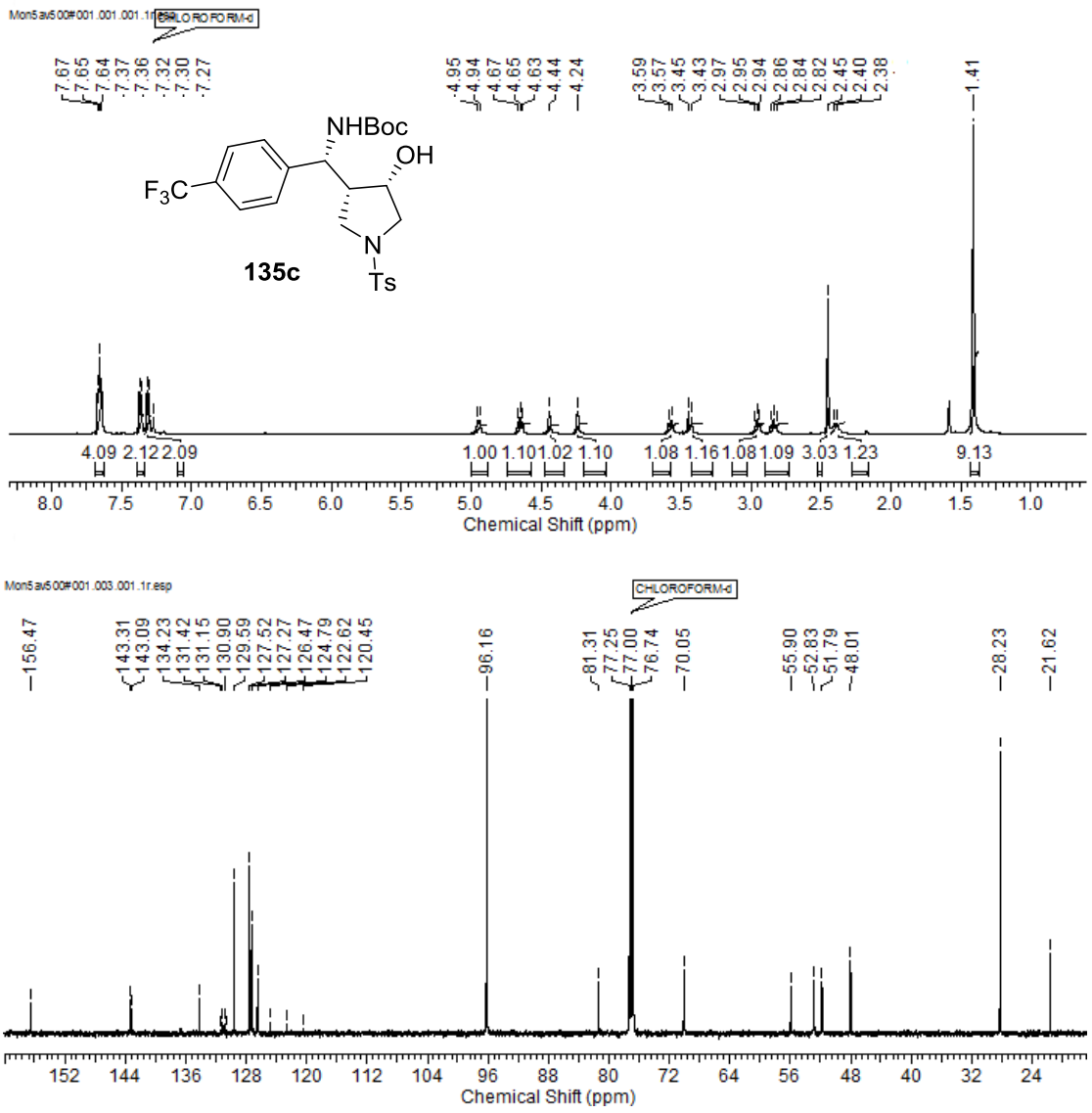
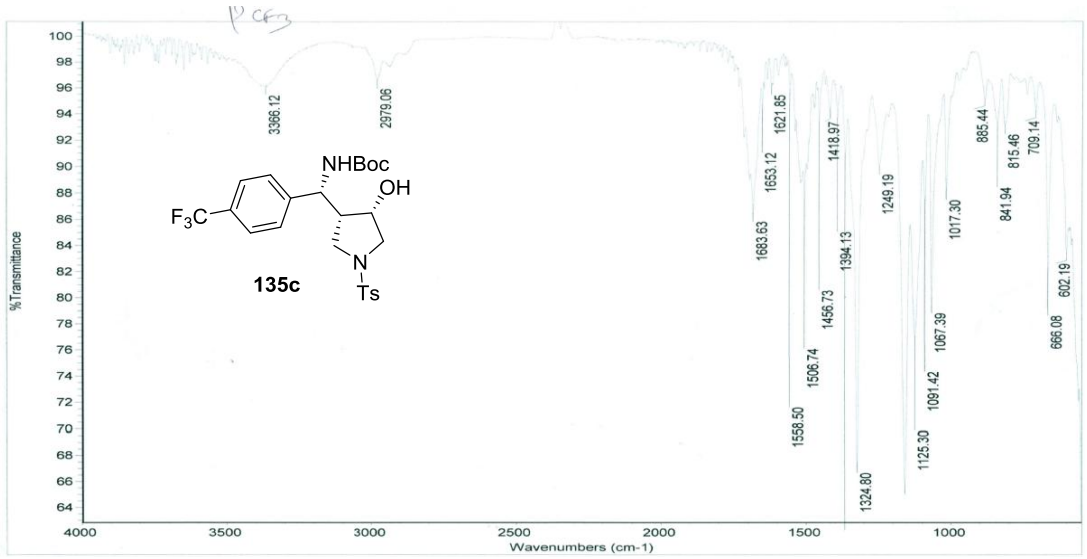
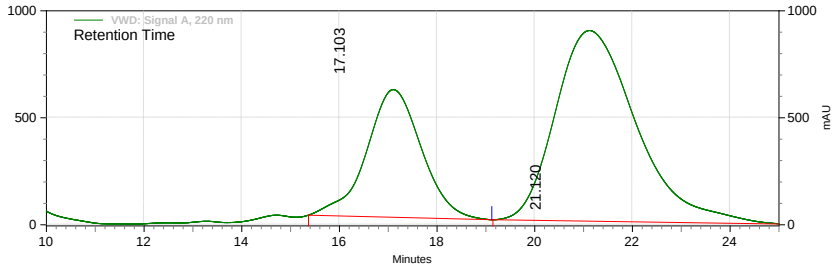


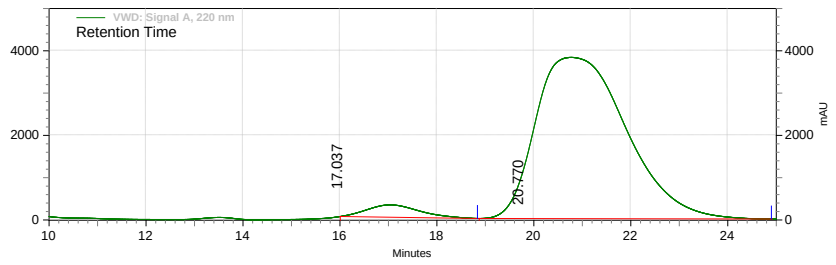
Fig. 9: ^{1}H and ^{13}C NMR spectra of 4-hydroxypyrrolidine derivative **135c**

Its ^{13}C NMR spectrum displayed typical carbon signals at δ 51.2 and 52.8 corresponding to methylene carbon (**C**H_2-NR_2) of the pyrrolidine moiety, while the other carbon signals at δ 55.9 and 70.0 were indicative of two methine (-**C**H-NR_2 and -**C**H-OH) carbons respectively, confirming the formation of **135c**. In addition, a carbon signal at δ 81.3 is due to the tertiary (Me_3-**C**-OR) carbon of the Boc group

(**Fig. 9**). Further, the formation of **135c** was clearly demonstrated by a strong IR absorption band at 3366 cm^{-1} due to the secondary hydroxyl (CH**OH)** group. Also, a strong absorption band at 1683 cm^{-1} indicated the presence of C=O stretching of carbamate functionality (**Fig.10).**







Ret. Time	Area	Area %	Height	Height %
17.037	368551768	4.25	4895632	7.11
20.770	8300669567	95.75	63957823	92.89

Fig. 10: IR Spectrum & HPLC Chromatogram of 4-hydroxypyrrolidine **135c**

The optical purity of **135c** was determined from chiral HPLC analysis; Chiracel-AS-H column (**Fig. 10**).

Example 3: The formation of oxazolidinone ring in **135g** was determined from its ^{1}H NMR spectrum, which indicated the disappearance of a proton signal at δ 1.40 for 9 protons of the *t*Bu group. Also, appearance of an upfield shift in the carbon signal of the carbamate carbonyl group (δ 151.8 from ~156) in its ^{13}C NMR spectrum confirmed the formation of 6-membered oxazolidinone moiety in **135g**. Additionally, a characteristic carbon signal at δ 162.5 (d, J = 249 Hz) indicated the presence of quaternary aromatic carbon attached to fluorine atom (**Fig. 11**).

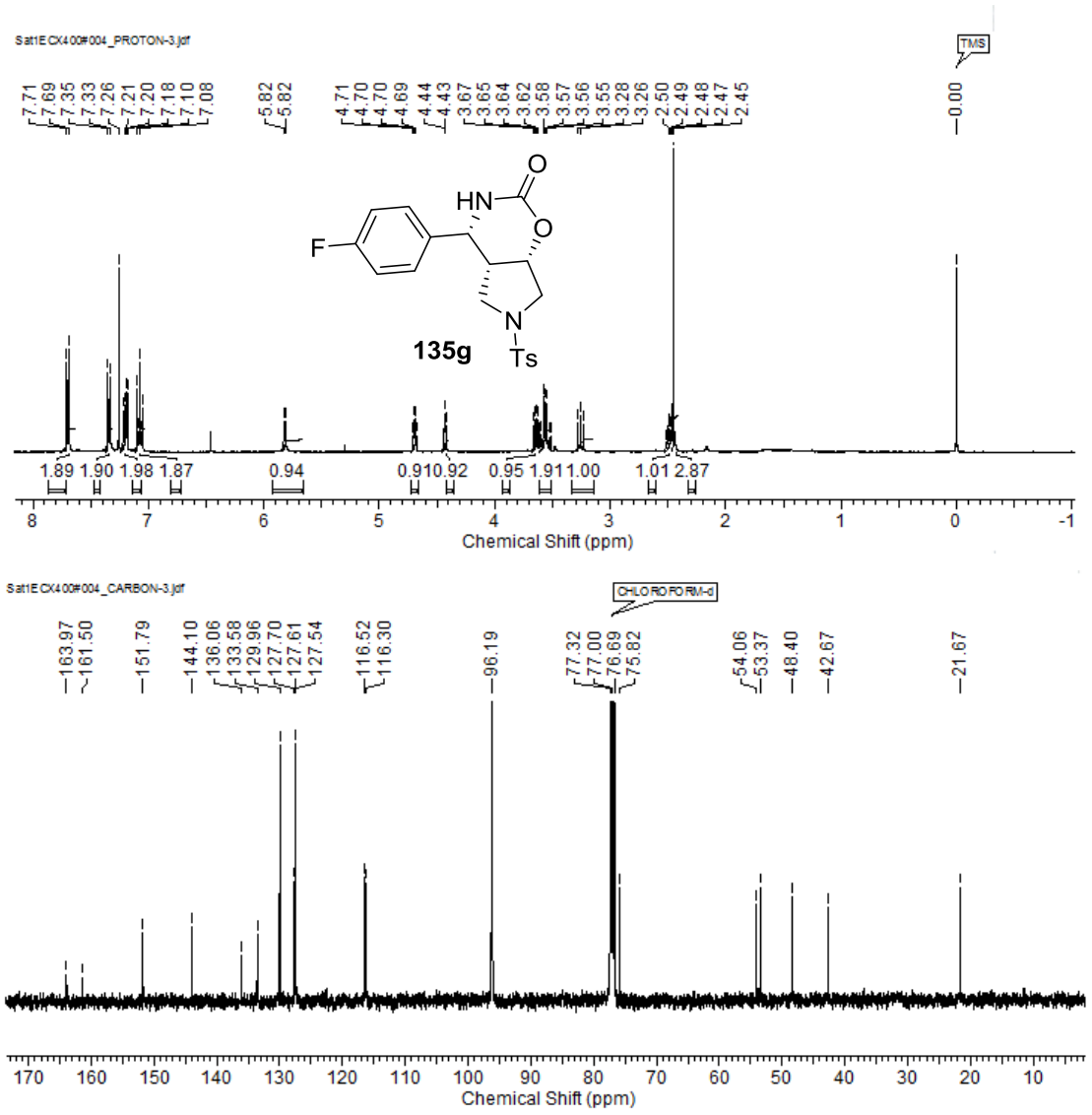


Fig. 11: ^{1}H and ^{13}C NMR spectra of oxazolidinone**135g**

The absolute configuration of the newly generated *syn*-Mannich adduct was assigned on the basis of the previously established configuration of amino aldehydes.[61] The relative stereochemistry of hydroxyl group of the pyrrolidine derivatives **135a-k** is proven unambiguously from X-ray crystallographic analysis of (**Fig 12**).

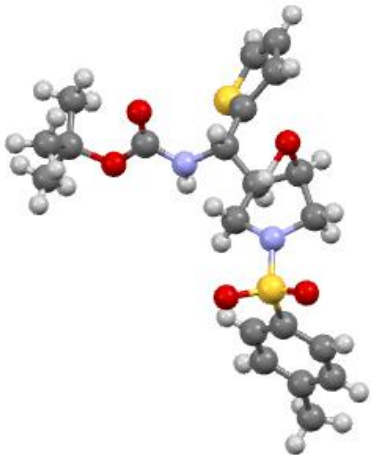
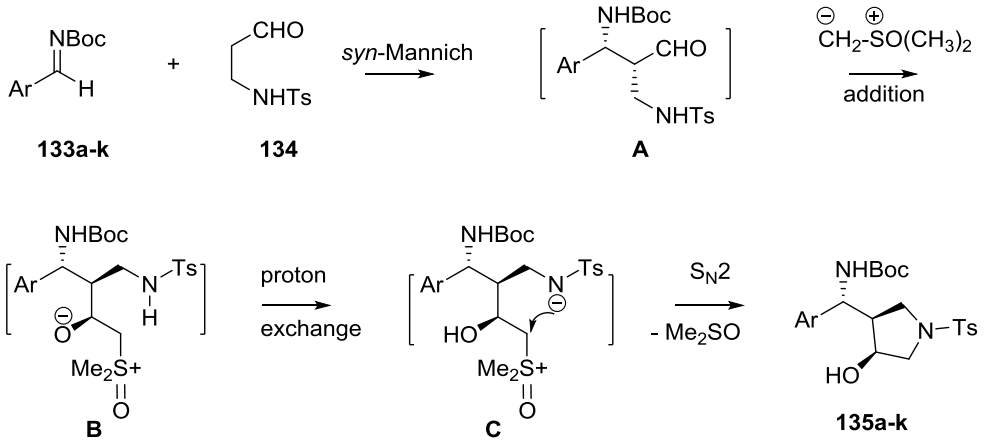


Fig. 12: ORTEP diagram of hydroxypyrrolidine **135j**

Based on our earlier experimental observations (Section I of this Chapter) and literature support,[63] we proposed a probable mechanistic pathway as shown in **Scheme 39**.



Scheme 39: Probable mechanistic pathway

Firstly, addition of sulfur ylide onto the *in situ* formed β, β'-diamino aldehydes **A**, a 4-atom component, generates the alkoxide intermediate **B**. This in turn is followed by a facile intramolecular proton exchange[65] from the more acidic Ts-NH to basic alkoxide ion to give a labile species **C**, which then subsequently undergoes intramolecular S_N2 displacement with the removal of DMSO to afford the pyrrolidine derivatives **135a-k**.

2.2.4 Conclusion

In summary, we have described, for the first time, a novel [4+1] annulation procedure involving *syn*-Mannich/Corey-Chaykovsky reaction that leads to the synthesis of substituted pyrrolidine derivatives **135a-k** with good yields and excellent enantio- and diastereoselectivities. The salient features of the methodology are as follows: (1) metal-free synthesis; (2) ready-availability of the substrates; (3) milder reaction conditions; (3) operationally simple; (4) functional group tolerance, and (5) high yields with excellent enantio- and diastereoselectivity.

2.2.5 Experimental Section:

General Experimental Procedure:

(a) **Preparation of sulfur ylide**: 0.18 g (7.5 mmol) of NaH (previously washed with petroleum ether to remove oil) was taken in an oven-dried three-necked flask, followed by the addition of dry DMSO (10 mL) through a septum to it and the the whole slurry was stirred at 25 °C under N_2 atmosphere. Then, trimethyloxosulfonium iodide (1.67 g, 7.5 mmol) was added to the slurry over a period of 5 min *via* a solid addition funnel until it becomes a homogenous solution.

(b) **Sequential *syn*-Mannich/Corey-Chaykovsky Reaction**: To a cooled solution of N-Boc imines (**133a-k**, 5.0 mmol) and L-proline (10 mol%) in dry CH_3CN (20 mL) at 0 °C was added β-amino aldehyde **134** (5.5 mmol), and the mixture was stirred for 12

h at 0 °C. This was followed by the addition of a solution of dimethyloxosulfonium methylide in DMSO at -10 °C and allowed to stir for 2 h at the same temperature. The progress of the reaction can be monitored by TLC. It was then quenched by the addition of an aq. NH_4Cl solution. The mixture was concentrated in vacuum to remove acetonitrile and the residue extracted with EtOAc (30-40 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4, and concentrated under reduced pressure to give the crude products, which were then purified by flash column chromatography (230-400 mesh) using petroleum ether and ethyl acetate as eluents to afford the pure products **135a-k.**

***tert*-Butyl ((*R*)-((*3R, 4S*)-4-hydroxy-1-tosylpyrrolidin-3yl) (phenyl) methyl) carbamate (135a)**

Yield: 72%; colorless solid; **mp** 197-200 ^oC; $[\alpha]^D_{25}$ +10.4 (*c* 0.2, $CHCl_3$); 93% ee from **HPLC analysis**; Column: Chiracel OD-H (250 x 4.6 mm), mobile phase: isopropyl alcohol/n-hexane (10/90), wavelength: 254 nm, flow rate: 0.5 mL/ min, conc.: 1.5 mg/mL, injection vol.: 10 µL, retention time: 30.13 min (-)-isomer, 33.59 min (+)-isomer; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 763, 1014, 1296, 1418, 1575, 1652, 1669, 1720, 2917, 3366; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.40 (s, 9H), 2.32-2.40 (m, 1H), 2.44 (s, 3H), 2.84 (t, *J* = 11.5 Hz, 1H), 2.96 (t, *J* = 8.8 Hz, 1H), 3.45 (d, *J* = 11.5 Hz, 1H), 3.58 (d, *J* = 11.5, 1H), 4.21-4.27 (m, 1H), 4.51-4.56 (dd, *J* = 8.1, 10.8 Hz, 1H), 4.73 (br s, 1H), 4.89 (d, *J* = 7.8 Hz, 1H), 7.20 (d, *J* = 7.3 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.35-7.40 (m, 3H), 7.66 (d, *J* = 8.1 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.5, 28.2, 48.3, 52.2, 53.2, 55.9, 69.9, 81.1, 126. 7, 127.4, 128.7, 129.4, 129.5, 134.1, 139.1, 143.3, 156.7; **HRMS** (ESI) calcd for $C_{23}H_{30}N_2O_5S$ $[M+H]^+$ 447.1954; found: 447.1951.

***tert*-Butyl((*R*)-((*3R, 4S*)-4-hydroxy-1-tosylpyrrolidin-3-yl)(4methoxyphenyl) methyl) carbamate (135b)**

Yield: 74%; colorless solid; **mp** 199-202 ^{o}C; $[\alpha]^{D}_{25}$ +33.4 (*c* 0.3, $CHCl_3$); 96% ee from **HPLC analysis**; Column: Chiracel OD-H (250 x 4.6 mm), mobile phase: isopropyl alcohol/n-hexane (10/90), wavelength: 254 nm, flow rate: 0.5 mL/ min, conc.: 1.5 mg/mL, injection vol.: 10µL, retention time: 32.07 min (-)-isomer, 35.89 min (+)-isomer; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 887, 1094, 1341, 1369, 1469, 1510, 1561, 1656, 1679, 2974, 3365; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.41 (s, 9H), 2.29-2.40 (m, 1H), 2.45 (s, 3H), 2.74-2.85 (dd, *J* = 9.2, 11.62 Hz, 1H), 2.93-3.01 (dd, *J* = 7.8, 9.22 Hz, 1H), 3.44 (d, *J* = 11.5 Hz, 1H), 3.59 (dd, *J* = 3. 7, 12.9, 1H), 3.83 (s, 3H), 4.18-4.25 (m, 1H), 4.44-4.53 (dd, *J* = 7.8, 10.7 Hz, 1H), 4.73-4.78 (m, 2H), 6.88 (d, *J* = 8.7 Hz, 1H), 7.13 (d, *J* = 8.7 Hz, 2H), 7.13 (d, *J* = 8.7 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.66 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.6, 28.3, 48.3, 52.4, 52.5, 55.3, 55.9, 70.0, 81.0, 114.8, 127.5, 127.9, 129.5, 131.3, 134.4, 143.1, 156.6, 159.7; Analysis: $C_{21}H_{28}N_2O_5S_2$ requires C, 55.73; H, 6.24; N, 17.68; S, 14.17; found C, 55.90; H, 6.47; N, 17.48; S, 14.27%.

***tert*-Butyl ((*R*)-((*3R, 4S*)-4-hydroxy-1-tosylpyrrolidin-3-yl)(4-(trifluoromethyl) phenyl)methyl)carbamate (135c)**

Yield: 70%; colorless solid; **mp** 202-204 ^{o}C; $[\alpha]^{D}_{25}$ +27.3 (*c* 0.3, $CHCl_3$); 92% ee from **HPLC analysis**; Column: Chiracel AS-H (250 x 4.6 mm), mobile phase: isopropyl alcohol/n-hexane (20/80), wavelength: 220 nm, flow rate: 0.5 mL/ min, conc.: 1.5 mg/mL, injection vol.: 10µL, retention time: 17.03 min (-)-isomer, 20.77 min (+)-isomer; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1249, 1418, 1506, 1621, 1653, 1683, 2979, 3366; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.41 (s, 9H), 2.19-2.40 (m, 1H), 2.45 (s, 3H), 2.76-3.00 (m, 2H), 3.44 (d, *J* = 11.4 Hz, 1H), 3.58 (dd, *J* = 3. 7, 12.9, 1H), 4.20-4.28 (br s, 1H), 4.45 (br s, 1H), 4.60-4.70 (dd, *J* = 8.5, 10.4 Hz, 1H), 4.93 (d, *J* = 8.1 Hz,

1H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.7 Hz, 2H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.66 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 21.6, 28.2, 48.0, 51.8, 55.9, 70.1, 81.3, 123.6 (q, *J* = 272.8 Hz) 126.5, 127.3, 127.5, 129.6, 130.1 (q, *J* = 32.4), 134.2, 143.1, 143.3, 156.5; **HRMS** (ESI) calcd for $C_{24}H_{29}F_3N_2O_5S$ $[M+Na]^+$ 537.1647; found:537.1643.

***tert*-Butyl ((*R*)-((*3R, 4S*)-4-hydroxy-1-tosylpyrrolidin-3-yl)(p-tolyl)methyl) carbamate (135d)**

Yield: 70%; colorless solid; **mp** 187-190 ^oC $[\alpha]^D_{25}$ +25.1 (*c* 0.2, $CHCl_3$); 94% ee from **HPLC analysis**; Column: Chiracel OD-H (250 x 4.6 mm), mobile phase: isopropyl alcohol/n-hexane (10/90), wavelength: 254 nm, flow rate: 0.5 mL/ min, conc.: 1.5 mg/mL, injection vol.: 10µL, retention time: 28.07 min (-)-isomer, 31.89 min (+)-isomer; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 884, 1091, 1248, 1339, 1366, 1472, 1507, 1558, 1653, 1683, 2977, 3366; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.40 (s, 9H), 2.31-2.34 (m, 1H), 2.36 (s, 3H), 2.44 (s, 3H), 2.80-2.85 (dd, *J* = 9. 8, 11.5 Hz, 1H), 2.94-2.98 (dd, *J* = 7.6, 9.3 Hz, 1H), 3.45 (d, *J* = 11.5 Hz, 1H), 3.58 (dd, *J* = 3. 7, 12.9, 1H), 4.22-4.28 (m, 1H), 4.47-4.52 (dd, *J* = 8.1, 11.0 Hz, 1H), 4.75 (br s, 1H), 4.84 (d, *J* = 7.8 Hz, 1H), 7.09 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.66 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.1, 21.6, 28.2, 48.3, 52.3, 52.9, 55.9, 69.9, 80.9, 126.6, 127.4, 129.5, 130.0, 134.1, 136.1, 138.5, 143.3, 156.7; Analysis: $C_{24}H_{32}N_2O_5S$ requires C, 62.59; H, 7.00; N, 6.08; S, 6.96; found C, 62.40; H, 7.10; N, 6.28; S, 6.80 %. **HRMS** (ESI) calcd for $C_{24}H_{32}N_2O_5S$ $[M+Na]^+$ 461.1120; found:461.1116.

(*4R, 4aR, 7aS*)-4-(Naphthalen-2-yl)-6-tosyl hexahydropyrrolo[3,4-e][1,3]oxazin-2(3H)-one (135e)

Yield: 63%; colorless solid; **mp** 153-156 ^oC; $[\alpha]^D_{25}$ +14.7 (*c* 0.3, $CHCl_3$); 98% ee from **HPLC analysis**; Column: Chiracel OD-H (250 x 4.6 mm), mobile phase:

isopropyl alcohol/n-hexane (10/90), wavelength: 254 nm, flow rate: 0.5 mL/ min, conc.: 1.5 mg/mL, injection vol.: 10µL, retention time: 34.50 min (-)-isomer, 39.89 min (+)-isomer; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 740, 1154, 1268, 1718, 2286, 2390, 3010, 3053, 3290; **^{1}H NMR** (400 MHz, $CDCl_3$): 2.45 (s, 3H), 2.58-2.64 (m, 1H), 3.31-3.36 (m, 1H), 3.51-3.56 (m, 1H), 3.60-3.63 (m, 1H), 3.70-3.75 (m, 1H), 4.58-4.60 (m, 1H), 4.72-4.73 (m, 1H), 5.78 (s, 1H), 7.26-7.29 (m, 2H), 7.34-7.36 (m, 2H), 7.52-7.54 (m, 2H), 7.66 (s, 1H), 7.71-7.74 (m, 2H), 7.80-7.89 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.5, 42.2, 48.4, 53.9, 54.1, 60.3, 75.8, 123.1, 124.9, 126.7, 127.0, 127.4, 127.7, 127.9, 129.5, 129.9, 133.1, 133.4, 137.4, 144.1, 151.9; **HRMS** (ESI) calcd for $C_{23}H_{22}N_2O_4S$ $[M+H]^+$ 423.1379; found: 423.1385.

(4*R*, 4*aR*, 7*aS*)-4-(4-Bromophenyl)-6-tosylhexahydropyrrolo [3,4-e][1,3]oxazin-2(3H)-one (135f)

Yield: 61%; colorless solid; **mp** 210-213 ^oC; $[\alpha]^D_{25}$ +12.3 (*c* 0.3, $CHCl_3$); 98% ee from **HPLC analysis**; Column: Chiracel OD-H (250 x 4.6 mm), mobile phase: isopropyl alcohol/n-hexane (10/90), wavelength: 254 nm, flow rate: 0.5 mL/ min, conc.: 1.5 mg/mL, injection vol.: 10µL, retention time: 40.07 min (-)-isomer, 43.89 min (+)-isomer; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 742, 1160, 1271, 1705, 2286, 2350, 2999, 3290; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.31 (s, 3H), 2.34-2.43 (m, 1H), 3.14 (t, *J* = 9.7 Hz, 1H), 3.31-3.39 (dd, *J* = 4.0, 11.7 Hz, 1H), 3.46-3.62 (m, 2H), 4.31 (d, *J* = 2.7 Hz, 1H), 4.52-4.57 (m, 1H), 6.98 (d, *J* = 8.6 Hz, 2H), 7.23 (d, *J* = 7.5 Hz, 2H), 7.38 (d, *J* = 7.5 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.4, 42.0, 42.4, 52.7, 54.4, 75.8, 122.4, 127.5, 130.1, 132.3, 133.1, 139.8, 144.5, 152.7; **HRMS** (ESI) calcd for $C_{19}H_{19}BrN_2O_4S$ $[M+H]^+$ 451.0278; found: 451.0333.

(4*R*, 4*aR*, 7*aS*)-4-(4-Fluorophenyl)-6-tosyl hexahydropyrrolo [3, 4-e][1,3]oxazin-2(3H)-one (135g)

Yield: 66%; colorless solid; **mp** 207-211 ^{o}C; $[\alpha]^{D}_{25}$ +12.3 (*c* 1, $CHCl_3$); 96% ee from **HPLC analysis**; Column: Chiracel OD-H (250 x 4.6 mm), mobile phase: isopropyl alcohol/n-hexane (10/90), wavelength: 254 nm, flow rate: 0.5 mL/ min, conc.: 1.5 mg/mL, injection vol.: 10µL, retention time: 33.07 min (-)-isomer, 38.89 min (+)-isomer; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 740, 1158, 1267, 1713, 2293, 2356, 3059, 3282; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.45 (s, 3H), 2.47-2.52 (m, 1H), 3.26 (t, *J* = 8.7 Hz, 1H), 3.52-3.61 (m, 2H), 3.62-3.67 (dd, *J* = 7.8, 9.6 Hz, 1H), 4.43 (t, *J* = 3.7 Hz, 1H), 4.68-4.71 (m, 1H), 5.82 (br s, 1H), 7.08 (d, *J* = 8.7 Hz, 1H), 7.20 (d, *J* = 8.7 Hz, 1H), 7.21 (d, *J* = 8.7 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.7, 42.7, 48.4, 53.4, 54.1, 75.8, 116.4 (d, *J* = 22 Hz), 127.5, 127.7 (d, *J* = 8.6 Hz), 130.0, 136.1, 144.1, 151.8, 162.8 (d, *J* = 250 Hz); Analysis: $C_{19}H_{19}FN_2O_4S$ requires C, 58.45; H, 4.91; N, 7.18; S, 8.21; found C, 58.60; H, 4.98; N, 7.51; S, 8.05%.

***tert*-Butyl ((*R*)-(4-cyanophenyl)((3*R*, 4*S*)-4-hydroxy-1-tosylpyrrolidin-3-yl)methyl) carbamate (135h)**

Yield: 71%; colorless solid; **mp** 195-198; $[\alpha]^{D}_{25}$ +3.0 (*c* 0.3, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 888, 1096, 1342, 1371, 1470, 1512, 1562, 1659, 1681, 2223, 2978, 3364; **^{1}H NMR** (500 MHz, $CDCl_3$): 1.39 (s, 9H), 2.45 (s, 3H), 2.86-2.98 (m, 1H), 3.32-3.44 (m, 3H), 3.68 (t, *J*= 8.5 Hz, 1H), 3.73 (s, 1H), 4.86 (s, 1H), 5.24 (s, 1H), 7.34 (d, *J*= 7.6 Hz, 2H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.72 (d, *J* = 7.9 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 21.6, 28.2, 49.0, 49.6, 56.9, 70.1, 111.5, 118.5, 127.4, 127.6, 129.6, 132.5, 133.8, 143.8, 155.0; **HRMS** (ESI) calcd for $C_{24}H_{29}N_3O_5S$ $[M+Na]^+$; 494.1725 found: 494.1728.

***tert*-Butyl ((*R*)-((3*R*, 4*S*)-4-hydroxy-1-tosylpyrrolidin-3-yl)(4-(methylthio) phenyl)methyl)carbamate (135i)**

Yield: 65%; colorless solid; **mp** 209-211 ^{o}C; $[\alpha]^{D}_{25}$ +1.6 (*c* 0.1, $CHCl_3$); 93% ee from **HPLC analysis**; Column: Chiracel AS-H (250 x 4.6 mm), mobile phase: isopropyl alcohol/n-hexane (10/90), wavelength: 254 nm, flow rate: 0.5 mL/ min, conc.: 1.5 mg/mL, injection vol.: 10µL, retention time: 27.07 min (-)-isomer, 39.89 min (+)-isomer; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 886, 1096, 1339, 1371, 1467, 1512, 1559, 1658, 1684, 2969, 3366; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.41 (s, 9H), 2.19-2.40 (m, 1H), 2.45 (s, 3H), 2.51 (s, 3H), 2.75-2.85 (dd, *J* = 9.6, 11.8 Hz, 1H),), 2.94-3.02 (dd, *J* = 7. 5, 9.1 Hz, 1H), 3.43 (d, *J* = 11.4 Hz, 1H), 3.55-3.64 (m, 1H), 4.20-4.26 (m, 1H), 4.46-4.55 (dd, *J* = 7.9, 10.7 Hz, 1H), 4.66 (br s, 1H), 4.79(d, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 8.5 Hz, 2H), 7.21 (d, *J* = 8.7 Hz, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 7.66 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 15.7, 21.6, 28.3, 48.3, 52.2, 52.8, 56.0, 70.0, 81.1, 127.2, 127.3, 127.6, 129.5, 134.4, 135.8, 139.7, 143.1, 156.6; **HRMS** (ESI) calcd for $C_{24}H_{32}N_2O_5S_2$ $[M+Na]^+$ 515.1650; found: 515.1651.

***tert*-Butyl ((*R*)-((*3R, 4S*)-4-hydroxy-1-tosylpyrrolidin-3-yl)(thiophen-2-yl)methyl) carbamate (135j)**

Yield: 68% (major); colorless crystal (recrystallized in MeOH); **mp** 186-189 ^{o}C; $[\alpha]^{D}_{25}$ +37.3 (*c* 0.3, $CHCl_3$); 92% ee from **HPLC analysis**; Column: Chiracel AS-H (250 x 4.6 mm), mobile phase: isopropyl alcohol/n-hexane (10/90), wavelength: 254 nm, flow rate: 0.5 mL/ min, conc.: 1.5 mg/mL, injection vol.: 10µL, retention time: 13.7 min (-)-isomer, 18.2 min (+)-isomer; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1345, 1370, 1472, 1521, 1565, 1655, 1685, 3369; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.32 (br s, 1H), 2.45 (s, 3H), 2.53 (brs,1H), 3.23 (d, *J* = 10.1 Hz, 1H), 3.32 (t, *J* = 9.8 Hz, 1H), 3.49 (d, *J* = 10.1 Hz, 1H), 3.60 (t, *J* = 9.2, 1H), 4.04 (s, 1H), 4.87 (d, *J* = 7.4 Hz, 1H), 5.13 (br s, 1H), 6.93-6.97 (m, 2H), 7.20 (d, *J* = 4.9 Hz, 2H), 7.32 (d, *J* = 7.6 Hz, 2H), 7.72 (d, *J* = 7.9 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.6, 28.4, 48.6, 48.9, 50.3,

56.0, 70.0, 80.5, 124.6, 124.9, 127.0, 127.5, 129.8, 134.1, 143.4, 144.4, 155.2; **HRMS** (ESI) calcd for $C_{21}H_{28}N_2O_5S_2$ $[M+Na]^+$ 475.1337; found: 475.1339.

***tert*-Butyl ((*R*)-((*3R, 4R*)-4-hydroxy-1-tosylpyrrolidin-3-yl)(thiophen-2-yl)methyl) carbamate (135j)**

Yield: 6.7% (minor); colorless solid; **mp** 180-182 $[\alpha]^{D}_{25}$ -4.9 (*c* 0.05, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 888, 1341, 1367, 1466, 1516, 1558, 1655, 1683, 3367; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.42 (s, 9H), 2.32-2.38 (m, 1H), 2.45 (s, 3H), 2.89 (t, *J* = 10.7 Hz, 1H), 3.17 (t, *J* = 8.5 Hz, 1H), 3.45 (d, *J* = 11.3 Hz, 1H), 3.54-3.58 (m, 1H), 4.20 (s, 1H), 4.60 (s, 1H), 4.82-4.90 (m, 2H), 6.97-6.99 (m, 2H), 7.28 (d, *J* = 6.1 Hz, 1H), 7.32 (d, *J* = 7.6 Hz, 2H), 7.68 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.6, 28.3, 48.5, 53.5, 55.9, 69.9, 81.3, 125.4, 125.6, 127.2, 127.6, 129.5, 134.4, 142.0, 143.1, 156.3; Analysis: $C_{21}H_{28}N_2O_5S_2$ requires C, 55.73; H, 6.24; N, 17.68; S, 14.17; found C, 55.60; H, 6.17; N, 6.45; S, 14.32%.

***tert*-Butyl ((*R*)-furan-2-yl((*3R, 4S*)-4-hydroxy-1-tosylpyrrolidin-3-yl) methyl) carbamate (135k)**

Yield: 64%; colorless solid; **mp** 136-139 ^oC; $[\alpha]^{D}_{25}$ -16.3 (*c* 0.5, $CHCl_3$); 91% ee from **HPLC analysis**; Column: Chiracel AS-H (250 x 4.6 mm), mobile phase: isopropyl alcohol/n-hexane (10/90), wavelength: 254 nm, flow rate: 0.5 mL/ min, conc.: 1.5 mg/mL, injection vol.: 10µL, retention time: 17.8 min (-)-isomer, 26.89 min (+)-isomer; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 887, 1341, 1366, 1467, 1514, 1558, 1654, 1682, 3365; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.27-2.31 (m, 1H), 2.44 (s, 4H), 2.98-3.02 (t, *J* = 8.0 Hz, 1H), 3.11-3.16 (t, *J* = 10.0 Hz, 1H), 3.37-3.42 (t, *J* = 8.0 Hz, 1H), 3.58-3.62 (t, *J* = 8.0 Hz, 1H), 3.93 (d, *J* = 6.8 Hz, 1H), 4.93-5.02 (m, 2H), 6.16 (d, *J* = 3.3 Hz, 1H), 6.31-6.32 (dd, *J* = 1. 7, 3.0 Hz, 1H), 7.30-7.34 (m, 3H), 7.69 (d, *J* = 8.1 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.6, 28.2, 47.0, 50.5, 52.2, 70.9, 80.8, 106.7, 110.5, 126.5, 127.6, 129.8, 142.3, 143.6, 156..3; Analysis: $C_{21}H_{28}N_2O_6S$

requires C, 57.78; H, 6.47; N, 6.42; S, 7.34; found C, 57.95; H, 6.64; N, 6.52; S, 7.49%.

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26 Refer experimental section (2.1.5) for general experimental procedure of Sequential α-amination/Corey-Chaykovsky reaction of aldehydes.

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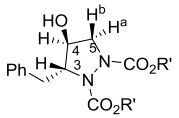

Fig. 6

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64 Refer experimental section (2.2.5) for general experimental procedure of formal [4+1]-annulation (Sequential *syn*-Mannich/Corey-Chaykovsky) reaction.

65 The acidity of Ts-N**H** is greater than Boc-N**H**, hence the former readily transfer the proton to alkoxide which facilitate the formation of substituted pyrrolidines. (see **Scheme 39**).

Chapter III

Asymmetric Synthesis of 2-Substituted Indolines and 3-Substituted Cinnolines *via* Cu-Catalyzed Intramolecular N-Arylation of Chiral Hydrazine Derivatives, Derived from Proline-catalyzed α-Amination of *o*-Bromohydro cinnamaldehydes

Section I

Asymmetric Synthesis of 2-Substituted Indolines *via* "One-Pot" N-Alkylation/E1cB/Intramolecular N-Arylation of Chiral Hydrazines, Derived from Proline-Catalyzed α-Amination of *o*-Bromohydrocinnamaldehyes

3.1.1 Introduction

Chiral indoline frameworks are found as sub-structure in many naturally occurring alkaloids[1] and biologically active molecules[2] (**Fig. 1**). It exhibits wide spread application not only as chiral auxillary and building blocks in total synthesis of bioactive natural products,[3] but also as a common motif in the design of new biologically significant compounds. In particular, enantioenriched 2-substituted indolines are considered as the privileged structures due to their diverse pharmacological activities[4] as found in many compounds such as benzastatin E (**1**), pentopril (**5**) etc (**Fig. 1**). This has stimulated several research groups to have a great deal of research in the asymmetric synthesis of 2-substituted indolines.[5]

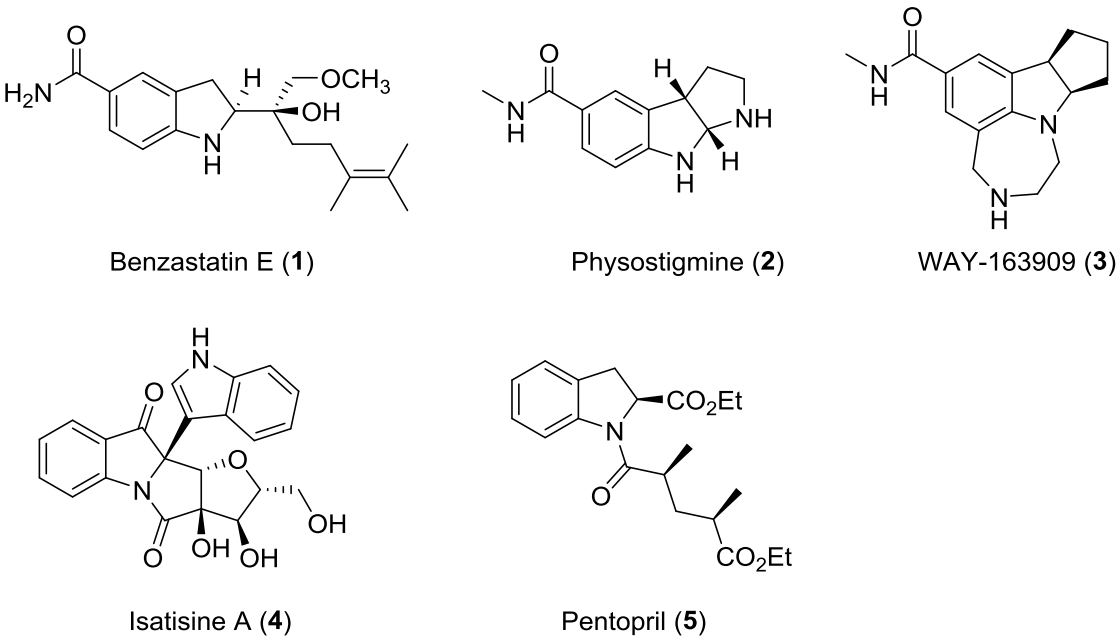


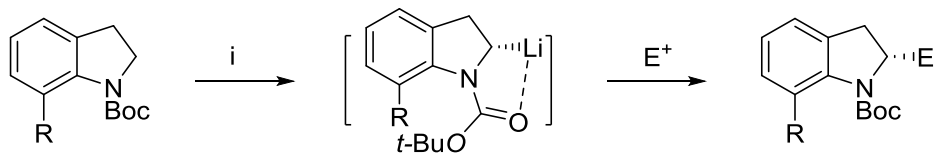
Fig. 1: Natural products and bioactive molecules with indoline motif

3.1.2 Review of literature

Literature search revealed that there are number of strategies developed for the asymmetric synthesis of 2-substituted indolines. The strategies include, not limited to, kinetic resolution techniques, chiral auxiliary approaches and the other chiral transition metal complexes catalyzed processes; some of which are described briefly below.

Beak's approach (1997)[6]

Beak *et al*. have demonstrated a stoichiometric approach for the preparation of enantiopure 2-substituted indolines **8**. It was found that *N*-Boc indoline **6** could be deprotonated regioselectively in the 2-position with *s*-BuLi/(-)-sparteine and the anion allowed to react with electrophiles to afford 2-substituted *N*-Boc indolines in variable yields and excellent ees. Mechanistic investigation established that the enantioselectivities arose from an initial asymmetric deprotonation to provide the enantioenriched and configurationally stable organolithium intermediates **7**, which react stereoselectively with electrophiles to afford indolines **8 (Scheme 1)**.



6 **7** **8**

R = H, Cl

$E^+ = CO_2$, Ph_2CO, Me_3SnCl, C_3H_5Br, TMSCl

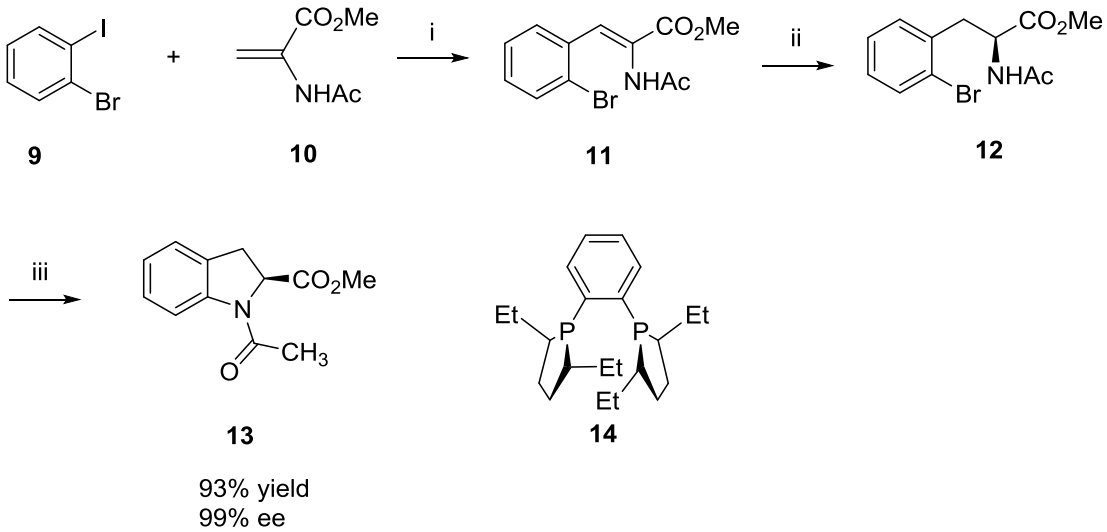
37-90% yield
50-80%ee

Scheme 1: (i) *s*-BuLi/(-)-sparteine, -78 ^oC, 6 h, cumene, then E^+, -78 ^oC, 2 h.

Buchwald's approach (1997)[7]

Buchwald *et al.* have described the catalytic asymmetric hydrogenation as the key reaction for the synthesis of chiral-2-substituted indolines **13**. (*S*)-N-Acetylindoline-

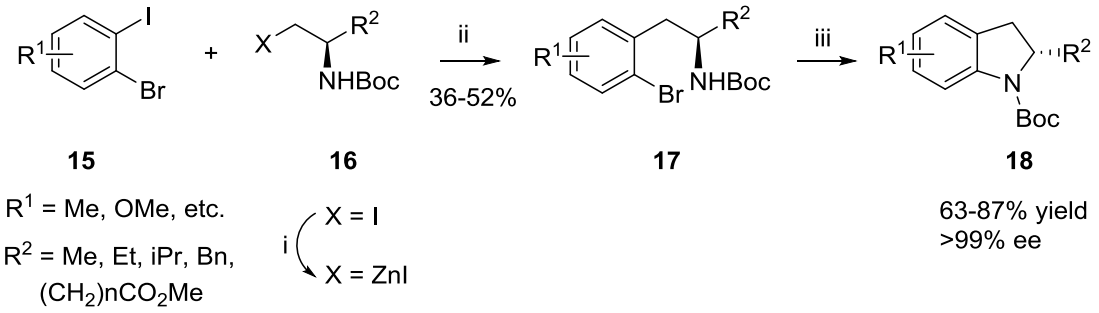
2-carboxylate methyl ester **13** was prepared in 99% ee by a Heck coupling reaction of *o*-bromoiodobenzene (**9**) with methyl-2-acetamido acrylate (**10)** to produce eneamide **11**. Asymmetric hydrogenation of the resulting eneamide **11** in the presence of chiral ligand **14** gave the corresponding amino ester **12**. Further, ester **12** was subjected to Pd-catalyzed intramolecular coupling to give enantiomerically enriched 2-substituted indoline **13** (**Scheme 2**).



Scheme 2: (i) $Pd(OAc)_2$, NEt_3, 100 ^oC, 2.5 h (74%); (ii) $[(COD)_2Rh]OTf$, (*S, S*)-Et DuPHOS (**14**), H_2 (2 atm), MeOH, 25 ^oC, 2 h, 90% yield, 99% ee; (iii) $Pd_2(dba)_3$, P(*o*-tolyl)$_3$, Cs_2CO_3, toluene, 100 ^oC, 4 h.

Jackson's approach (2002)[8]

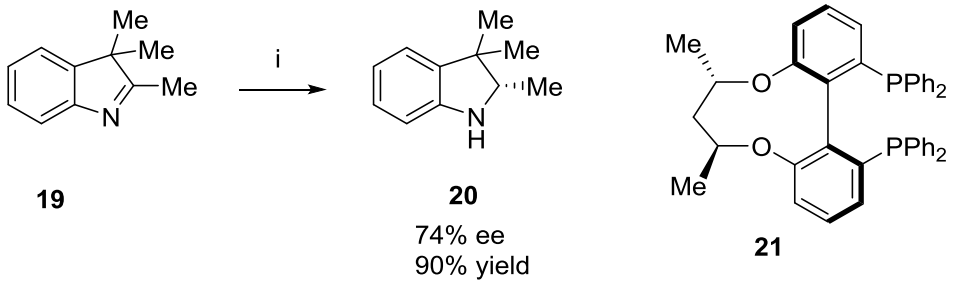
Jackson *et al.* have developed a simple and effective method to access enantiomerically pure 2-substituted indolines **18** using sequential Pd-catalyzed processes (**Scheme 3**). The chemistry involved in this protocol was the application of the Pd-catalyzed coupling of a chiral amino organozinc reagent **16** with 2-bromoiodobenzene **15**, followed by Buchwald's Pd-catalyzed intramolecular amination of the amine ester **17**.



Scheme 3: (i) Zn, DMF, 0 °C; (ii) $Pd_2(dba)_3$, P(o-tolyl)$_3$, 25 ^oC, 4 h; (iii) $Pd_2(dba)_3$,P(*o*-tolyl)$_3$, Cs_2CO_3, toluene, 100 °C, 15 h.

Chan's approach (2006)[9]

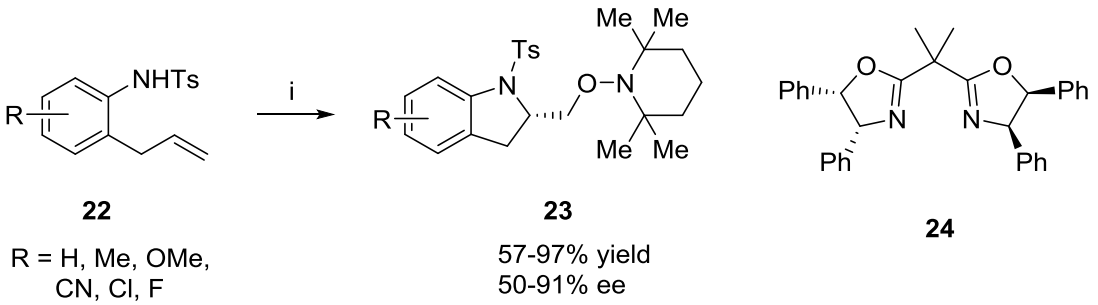
Chan *et al.* have reported the preparation of chiral 2,3,3-indoline **20** by an Ir-catalyzed asymmetric hydrogenation of 2,3,3-trimethylindolenine **19** in the presence of chiral phosphine ligand **21**. The product **20** was obtained in high yield with moderate enantioselectivity (**Scheme 4**).



Scheme 4: (i) [Ir(COD)Cl] (0.6 mol%), ligand **21**, CH_2Cl_2, 25 ^oC, H_2 (34 atm), 28-100 h.

Chelmer's approach (2008)[10]

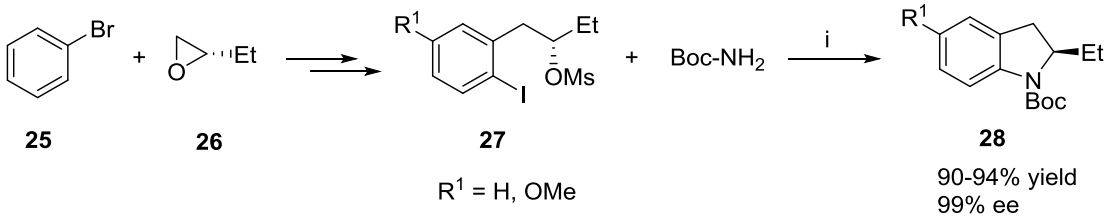
Chelmer *et al.* have reported a novel and mechanistically distinct Cu-catalyzed enantioselective intramolecular aminooxygenation of olefins **22** in the presence of TEMPO leading to the synthesis of chiral 2-indolines **23**. After a detailed ligand screening study for the asymmetric induction, it was found that ligand **24** was optimal for this transformation. Under these conditions, N-tosyl-2-allyl aniline **22** cyclized giving 2-substituted indoline **23** in 97% yield with 91% ee (**Scheme 5)**.



Scheme 5: (i) $Cu(OTf)_3$ (2 mol%), ligand **24** (2.4 mol%), K_2CO_3, TEMPO, $PhCF_3$, 110 ^oC, 24 h.

Buchwald's approach (2008)[11]

Buchwald *et al*, in yet another approach, have reported an efficient one-pot procedure for the synthesis of chiral 2-ethylindolines **28** based on a domino Cu-catalyzed amidation/nucleophilic substitution reaction. The Cu-catalyzed reaction of (*2S*)-iodophenethyl mesylate **27** with Boc amide in THF resulted in the formation of (*2S*)-ethyl indoline **28** in excellent yield. The enantiomerically pure mesylate **27** was obtained by *n*-BuLi mediated-ring opening of (*S*)-1,2-epoxybutane **26** with bromobenzene **25** in the presence of $BF_3.Et_2O$, followed by the subsequent treatment with $AgCO_2CF_3$ and powdered iodine (**Scheme 6**).

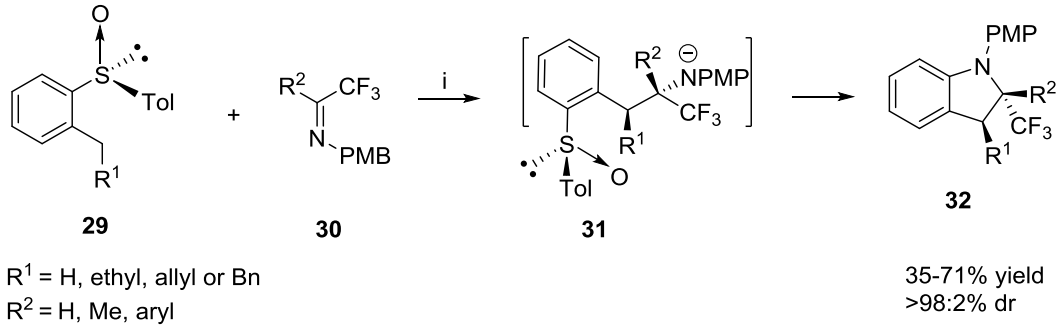


Scheme 6: CuI (8 mol%), DMEDA, THF, 80 ^oC, 16 h, 94%.

Ruano's approach (2008) [12]

Ruano *et al*. have developed an anionic–anionic asymmetric tandem reaction for the preparation of enantiopure fluorinated indolines **32** from 2-*p*-tolylsulfinyl alkyl benzenes **29.** This approach involved the direct reaction of N-PMP-fluorinated imine **30** with 2-(*p*-toluenesulfinyl) alkyl benzene **29** in the presence of LDA. High

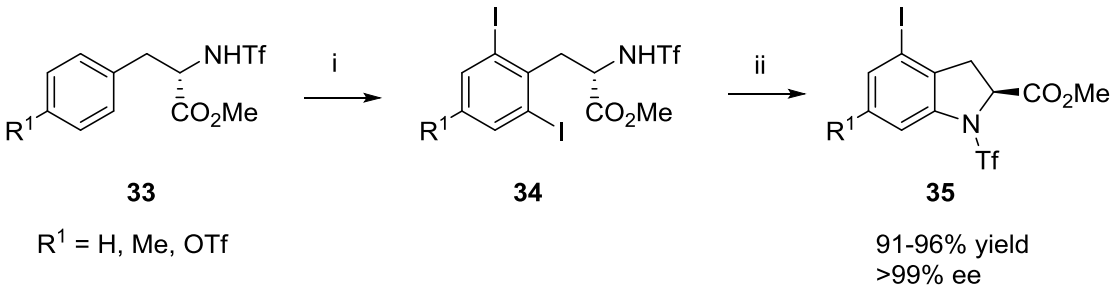
stereoselectivity and mild conditions are the key features of this tandem process, which included the unusual intramolecular nucleophilic aromatic substitution of a *p*-tolylsulfinyl group by the amide anion in **31** as the key reaction (**Scheme 7**).



Scheme 7: (i) LDA, THF, 25 °C, 30 min.

Yu's approach (2008)[13]

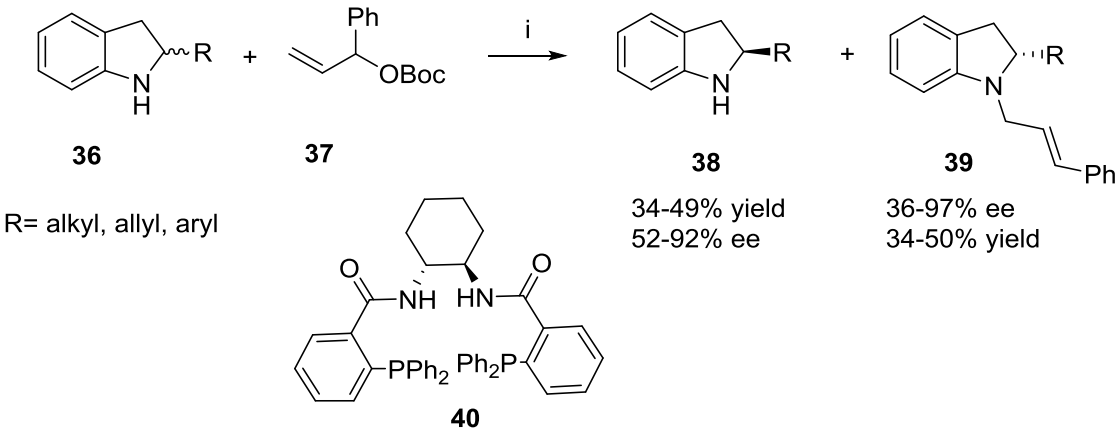
Yu *et al*. have developed a novel C–H bond iodination/ intramolecular amination route for the synthesis of enantiopure indoline-2-carboxylic esters **35** from natural amino acids such as phenyl alanine and tyrosine. The Pd(II)-catalyzed iodination of the amino acid derivative **33** in presence of $PhI(OAc)_2$ and I_2 followed by CuI-mediated intramolecular amination of the diiodo product **34** resulted in the formation of indoline-2-carboxylic acid derivative **35** in excellent yields (**Scheme 8**).



Scheme 8: (i) $Pd(OAc)_2$, $PhI(OAc)_2$, I_2, $NaHCO_3$, DMF, 130 °C, 72 h (31-91% yield); (ii) CuI (10 mol%), $NaHCO_3$, DMF, 130 °C, 24 h.

Zheng's approach (2009)[14]

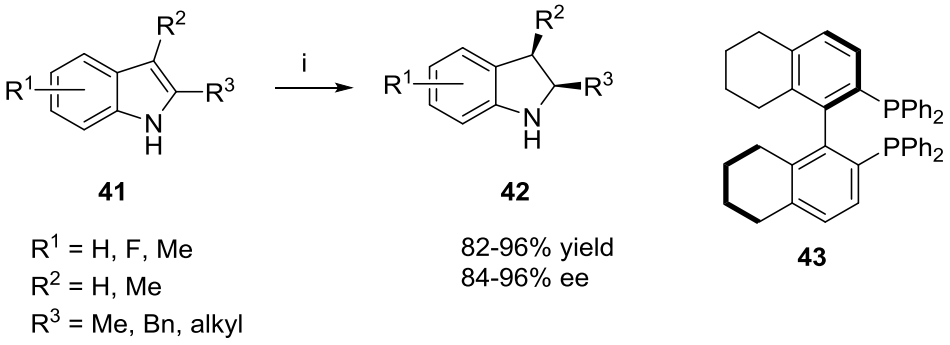
Zheng *et al.* have employed the kinetic resolution of racemic indolines **36** *via* a Pd-catalyzed allylic substitution reaction with the use of Trost's chiral ligand **40**, that afforded optically active indolines **38** and N-allylated indolines **39** in high yields and high enantioselectivities with an *S* factor up to 59. It provided for the first example of the kinetic resolution of nucleophiles *via* a transition metal-catalyzed allylic substitution reaction (**Scheme 9**).



Scheme 9: (i) $Pd(CH_3CN)_2$ (2 mol%), ligand **40** (2 mol%) , toluene, 25 ^oC.

Zhang's approach (2010)[15]

Zhang *et al*. have developed a highly enantioselective hydrogenation of simple indoles **41** using $Pd(OCOCF_3)_2$/(*R*)-H_8-BINAP **43** with a Brønsted acid as an activator.

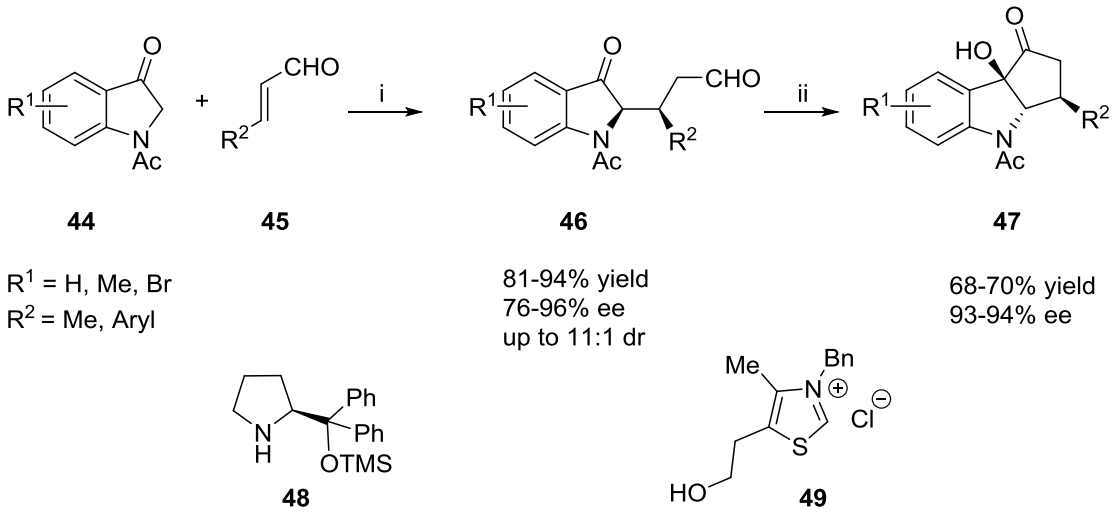


Scheme 10: (i) $Pd(OCOCF_3)_2$ (2 mol%), ligand **43** (2.4 mol%), *L*-CSA, H_2 (700 psi), CH_2Cl_2/TFE (1:1).

This method provides for an efficient route to make chiral indolines **42** from unprotected indolines **41** in excellent enantioselectivities (up to 96% ee) (**Scheme 10**).

Xu's approach (2011)[16]

Xu *et al*. have developed an asymmetric Michael addition of 1-acetylindolin-3-ones **44** to α, β-unsaturated aldehydes **45** to afford 2-substituted indolin-3-one derivatives **46** in high yields (up to 94%) with good stereoselectivities (up to 11:1 dr and 96% ee). The Michael adducts were further transformed conveniently without racemization into substituted cyclopentyl[b]indoline **47** using NHC **49** intramolecularly (**Scheme 11**).

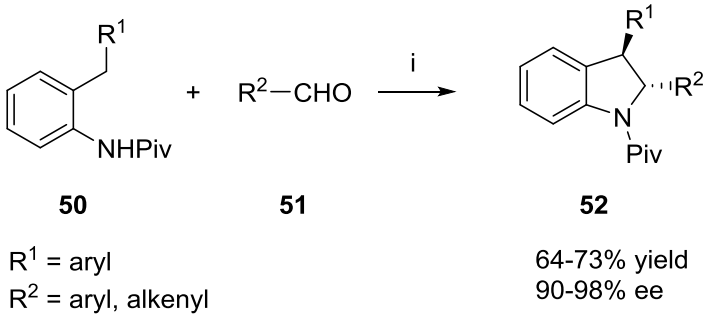


Scheme 11: (i) indanone (0.2 mmol), aldehyde (0.4 mmol), H_2O (0.4 mmol) and prolinol derivative **48** (20 mol%), THF -10 °C; (ii) NHC **49** (10 mol%), NEt_3, $CHCl_3$, reflux, 4 h.

Park's approach (2012)[17a]

Park *et al.* have developed a novel method for the asymmetric synthesis of *trans*-2,3-disubstituted indolines **52**. This strategy involved the (−)-sparteine-mediated electrophilic substitution of 2-benzyl N-pivaloylaniline **50** with aromatic or α, β-unsaturated aldehydes **51** followed by subsequent intramolecular nucleophilic substitution or Mitsunobu cyclodehydration[17b] (**Scheme 12**).

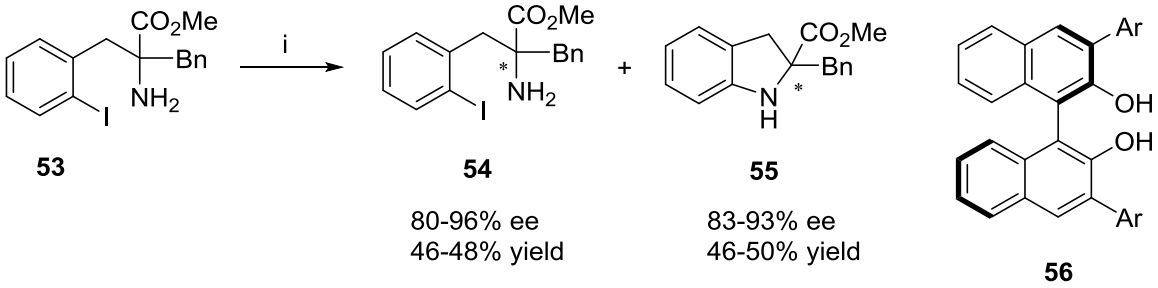
.



Scheme 12: (i) (a) *n*-BuLi, (-) sparteine, MTBE, -25 °C, 1 h; (b) aldehyde, -78 °C, 10 min; (ii) conc. HCl, H_2O/1,4-dioxane, 80 °C, 1 h.

Cai's approach (2013)[18]

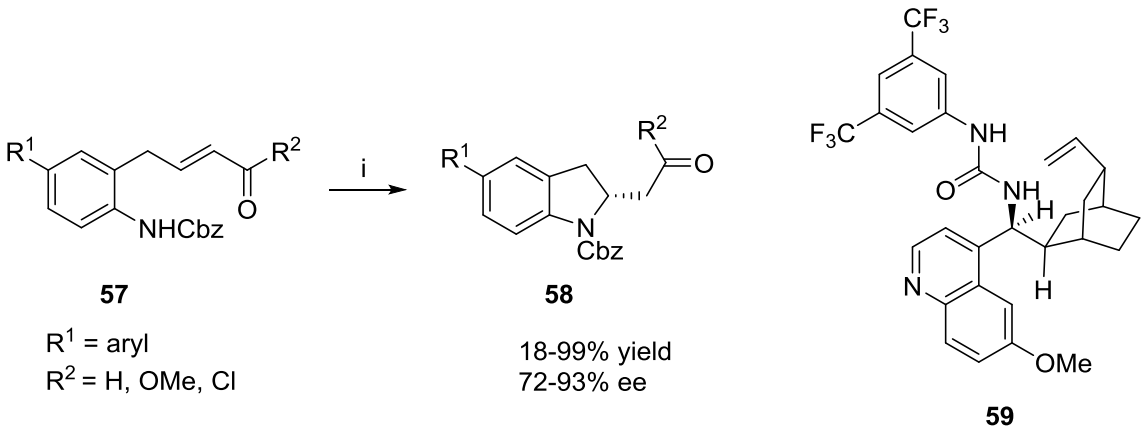
Cai *et al.* have developed a kinetic resolution approach using Cu-catalyzed N-arylation of the *rac*-2-amino-3-(2-iodoaryl)propionate **53** that led to the formation of the coupled chiral indoline product **55** in good yields and high ee and the recovered starting materials **54** are also obtained in high ees (**Scheme 13**).



Scheme 13: (i) : **53** (0.2 mmol, 1.0 equiv), CuI (5 mol %), **56** (6 mol %), Cs_2CO_3, (1.0 equiv), 1,4-dioxane (1.5 mL), 25 °C.

Seijiro Matsubara's approach (2013)[19]

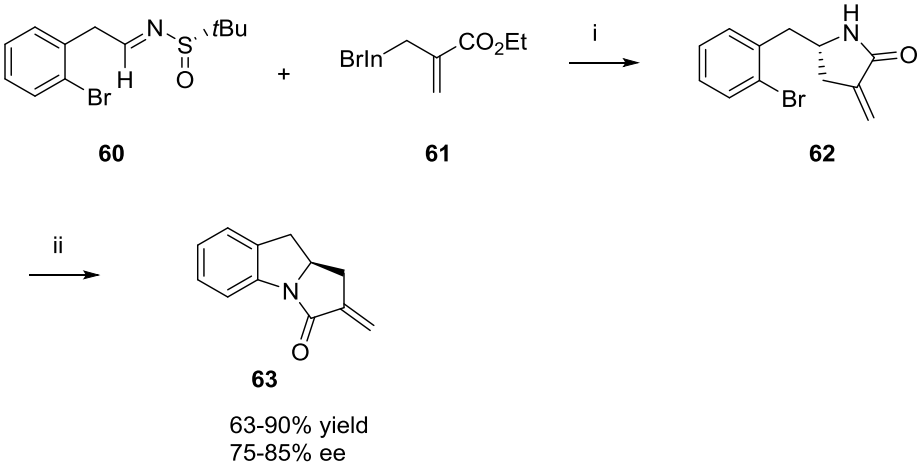
Seijiro Matsubara *et al.* have demonstrated a novel asymmetric synthesis of 2-substituted indolines **58** *via* intramolecular aza-Michael addition of **57** by employing **59** as a bifunctional organocatalyst. The reaction proceeded by activation *via* hydrogen bonding, enabling a flexible catalytic mechanism that was widely applicable to a range of substrates with α,β-unsaturated carboxylic acid derivatives (**Scheme 14**).



Scheme 14: (i) catalyst **59** (10 mol%), mesitylene, 25 °C, 24 h.

Foubelo's approach (2014)[20]

Foubelo *et al.* have demonstrated a diastereoselective addition of an allylic indium intermediate **61** to chiral *o*-bromophenyl sulfinyl imine **60** which gave lactam **62** in two additional steps with good levels of diastereoselectivity. Cu-mediated intramolecular N-arylation of lactam **62** led to the formation of chiral indolines **63**.



Scheme 15: (i) (a) **61** (4 equiv) NaBr-H_2O (sat), 23 ^oC, 72 h; (b) 4M HCl-dioxane, MeOH, 0 to 23 ^oC, 1 h; (c) 2M NaOMe-MeOH, 0 to 23 ^oC, 30 min; (ii) CuI (8 mol %), DMEDA (16 mol %), K_2CO_3 (2 equiv), 1,4-dioxane, 100 °C, 20 h.

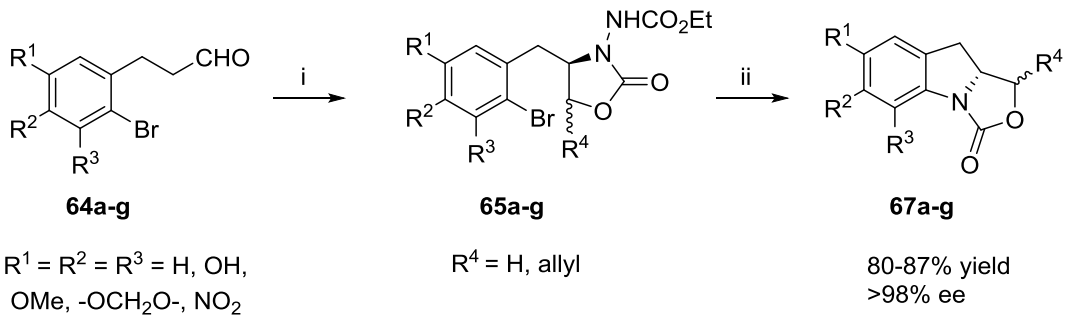
3.1.3 Present Work

3.1.3.1 Objective

The literature survey reveals that a number of strategies are available for the synthesis of 2-substituted indolines; most of which are however based on kinetic resolution of racemic indolines, asymmetric hydrogenation of indoles, intramolecular hydroaminations of olefins including multistep reaction sequence involving chiral pool approaches. Although these methods are quite effective, there are certain short-comings associated with them such as: (a) dependence on chiral pool resources; (b) expensive chiral ligands and catalysts; (c) harsh reaction conditions; (d) low yields and enantioselectivities, and (e) multi-step reaction sequences. Hence, a general method, which overcomes the above limitations for their asymmetric synthesis is of interest to synthetic organic chemists.

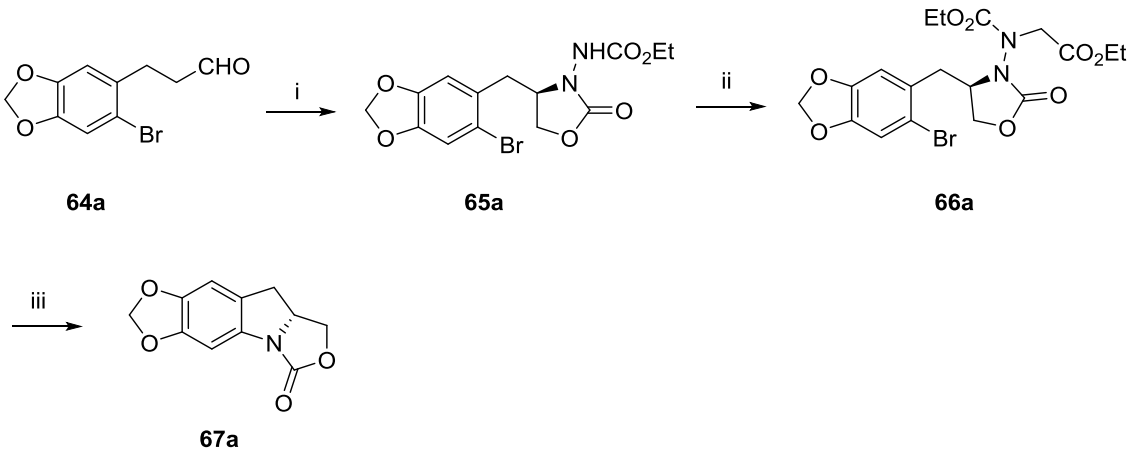
3.1.3.2 Results and Discussion

Organocatalyzed α-amination of carbonyl compounds has emerged as a reliable method for the enantioselective synthesis of α-amino acid derivatives.[21] In continuation of our research work on proline-catalyzed α-amination of aldehydes for the asymmetric synthesis of bioactive compounds and natural products,[22] we were interested in expanding the utility of this organocatalytic route for the enantioselective synthesis of indolines. Recently, Magnus and co workers have developed an efficient method for the N-N' bond cleavage that finds wide applications in the conversion of hydrazines into amines.[23] Also, there are reports that uses Cu-catalysts for the intramolecular coupling of aryl bromides with enantiomerically enriched amines with stereogenic centers α to the nitrogen giving cyclized products without loss of stereochemical integrity.[7, 24]



Scheme 16: (i) (a) DEAD, L-proline, CH_3CN, 0 ^oC, 3 h then MeOH, $NaBH_4$, 0 ^oC, 45 min or allyl bromide, Zn, aq. NH_4Cl, 0 ^oC, 2 h b) K_2CO_3, EtOH, 70 ^oC, 12 h or NaOH, EtOH: H_2O (4:1), 0-25 ^oC, 6 h; (ii) $BrCH_2CO_2Et$ (1.2 equiv), Cs_2CO_3 (2.0 equiv), CH_3CN, 50 ^oC, 5 h; then CuI (10 mol%), DMEDA (10 mol%) Cs_2CO_3 (1.5 equiv), 95 ^oC, 12 h.

With this in mind, we envisaged that, a 'one-pot' 3-step reaction involving N-alkylation, E1cB[23] and intramolecular N-arylation of chiral hydrazines **65a-g**, obtained from *o*-bromohydrocinnamaldehydes **64a-e**, should provide the corresponding indoline derivatives **67a-g.** This section discloses an elegant method that provides for the asymmetric synthesis of 2-substituted indolines **67a-g** directly from chiral hydrazine derivatives **65a-g** *via* N-alkylation-E1cB-N-arylation cascade (**Scheme 16**).



Scheme 17: (i) (a) L-Proline (10 mol%), DEAD, CH_3CN, 0 ^oC, 3 h then MeOH, $NaBH_4$; after work up K_2CO_3, MeOH, 70 ^0C, 6 h, 85% yield, >99% ee; (ii) $BrCH_2CO_2Et$, Cs_2CO_3, CH_3CN, 50 ^oC, 5 h, 92%; (iii) CuI (10 mol%), DMEDA (10 mol%), Cs_2CO_3 (1.5 equiv), 95 ^oC, 12 h 85%.

In a preliminary study, *o*-bromohydrocinnamaldehyde **64a** was subjected to L-proline (10 mol%)-catalyzed asymmetric α-amination, followed by *in situ* reduction of aldehyde with $NaBH_4$ in MeOH to furnish the crude amino alcohol. Conversion of crude amino alcohol to the corresponding oxazolidinone **65a** proceeded smoothly using K_2CO_3 in 85% yield and >99% ee {$[\alpha]^{D}_{25}$ -33.2 (*c* 1.8, $CHCl_3$)} (**Scheme 16**). The formation of chiral hydrazine **65a** was confirmed from its ^{1}H NMR spectrum, which showed two doublet of doublets at δ 2.85-2.90 (dd, *J* = 7.3, 13.8 Hz, 1H) and δ 3.22-3.26 (dd, *J* = 3.7, 13.3 Hz, 1H) corresponding to the diastereotopic benzylic

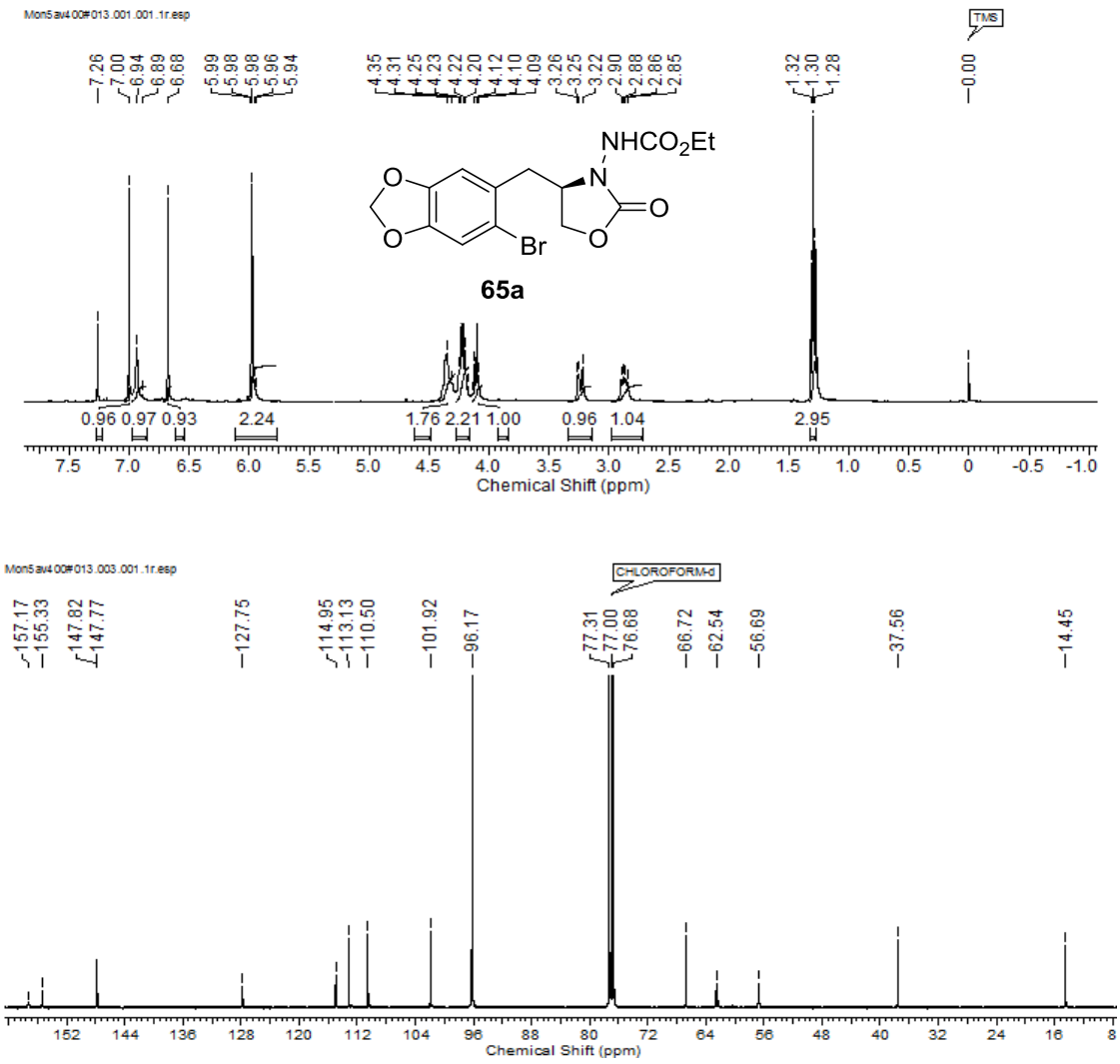
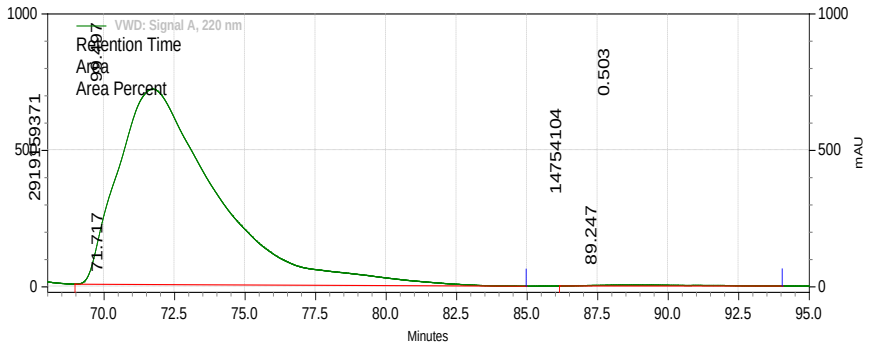


Fig. 2: ^{1}H and ^{13}C NMR spectra of oxazolidinone **65a**

protons. A multiplet at δ 4.09-4.14 (1H) indicated the presence of one of the diastereotopic methylene protons (-C**H**$_2$-O) of the oxazolidinone ring. Further, a broad multiplet at δ 4.31-4.35 (2H) corresponds to the methine (-C**H**-NR$_2$) and one of the methylene (-C**H**$_2$-O) protons of the 5-membered heterocycle. Its ^{13}C NMR spectrum displayed a typical carbon signal at δ 56.6 due to the chiral methine (-**C**H-NR$_2$) carbon of the oxazolidinone ring. Also, other carbon signals at δ 62.5 and 66.7 are due to the methylene (-**C**H$_2$-OR and –O**C**H$_2$CH$_3$) carbons of oxazolidinone ring and ester moiety respectively, which confirms the formation of **65a** (**Fig. 2**). The optical purity of chiral hydrazine **65a** was determined from chiral HPLC anaylsis; chiracel OD-H column (**Fig.3**).



Ret. Time	Area	Area %	Height	Height %
71.717	2919159371	99.50	12010666	99.56
89.247	14754104	0.50	52957	0.44
Total	2933913475	100.00	12063623	100.00

Fig. 3: HPLC chromatogram of oxazolidinone **65a**

Further, treatment of **65a** with bromoethyl acetate (Cs_2CO_3, CH_3CN, 50 ^oC, 5 h) gave N-alkylated product **66a** in 92% yield {$[\alpha]^D_{25}$ -33.2 (*c* 1.8, $CHCl_3$)} (**Scheme 16**). Formation of N-alkylated hydrazine **66a** was confirmed from its ^{1}H NMR spectrum, which showed typical proton signals at δ 1.26-1.38 (m, 6H) corresponding to the methyl (-CO_2CH_2**C**H$_3$) protons of the carbamate ester functionality. Absence of a ^{1}H NMR signal at δ 6.89 (1H) corresponding to the –N**H**R proton confirmed the

occurrence of N-alkylation. Its ^{13}C NMR spectrum showed a typical carbon signal at δ 168.7 corresponding the ester carbonyl group, thus establisihing the formation of N-alkylated hydrazine **66a** (**Fig. 4**).[25]

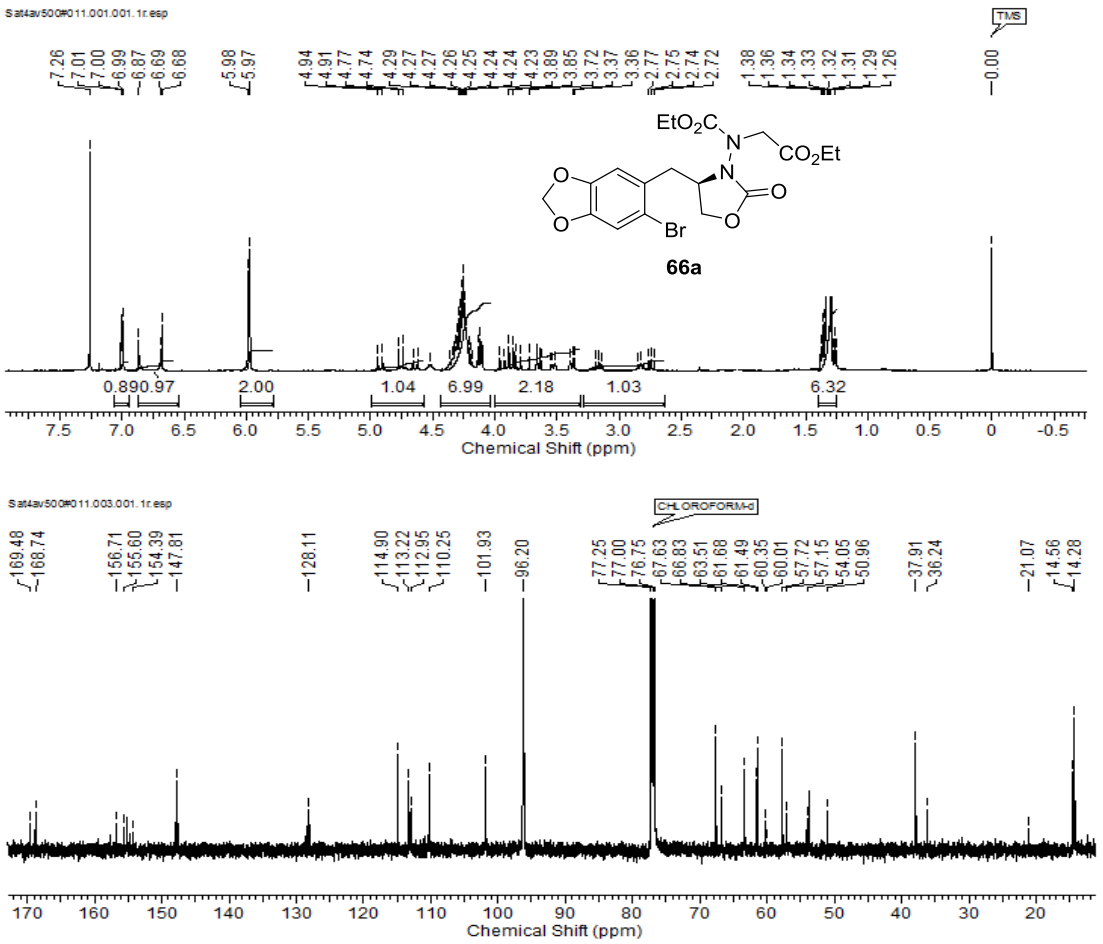
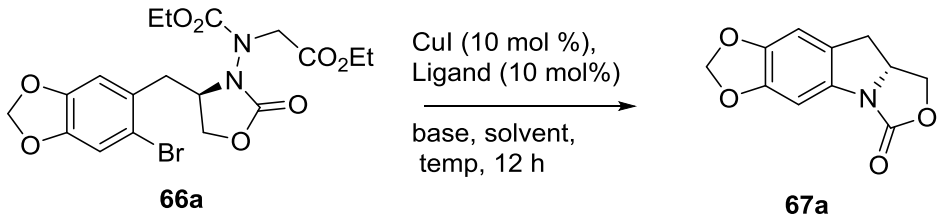


Fig. 4: ^{1}H and ^{13}C NMR spectra of N-alkylated hydrazine **66a**

N-Alkylated hydrazine derivative **66a** was then subjected to several optimization studies to identify the best condition for E1cB-intramolecular N-arylation cascade to deliver the corresponding chiral indoline **67a**; the results of which are presented in Table 1. Firstly, N-alkylated hydrazine **66a** was subjected to E1cB elimination/N-arylation cascade with catalytic amount of CuI/L-proline combination in DMSO using

K_2CO_3 as base. No reaction took place even after 12 h of stirring at 100 ^oC, probably due to relatively less basicity of K_2CO_3 (entry 1).

Table 1. Optimization studies for E1cB elimination/N-arylation cascade[a]



entry	solvent	ligand	temp (^oC)	base	Yield **67a** (%)[b]
1	DMSO	L-proline	100	K_2CO_3	-
2	DMSO	L-proline	100	Cs_2CO_3	60
3	DMF	L-proline	100	Cs_2CO_3	45
4	CH_3CN	L-proline	100	Cs_2CO_3	56
5	**CH_3CN**	**DMEDA**	**95**	**Cs_2CO_3**	**85**
6	CH_3CN	DMEDA	65	Cs_2CO_3	35

[a] **66a** (1 mmol), CuI (10 mol%), ligand (10 mol%), base (2 equiv), solvent (10 mL), [b]isolated yield after chromatographic purification. DMEDA: N,N'-dimethylethylenediamine.

To our surprise, 2-substituted indoline **67a** was obtained in moderate yield (60%), when Cs_2CO_3 was used as base (entry 2). A sluggish reaction, with low yields (45 and 56%) was observed by changing the solvent system of the cascade reaction (entry 3 and 4). However, a dramatic improvement in yield of **67a** (85%) was realized by performing the reaction using CuI/DMEDA catalyst combination in CH_3CN with Cs_2CO_3 as base at 95 °C for 12 h. Further, lowering of temperature of the cascade protocol to 65°C had deleterious effect in yield. With this result in hand, we then turned our attention to convert chiral hydrazine **65a** directly to 2-substituted indoline **67a** in a "one-pot" sequential manner without isolating the intermediate **66a** (**Scheme**

17). Accordingly, N-alkyaltion of **65a** was carried out with bromoethyl acetate, which gave N-alkylated product **66a** (Cs_2CO_3, CH_3CN, 50 ^oC, 5 h). Further, *in situ* generated **66a** was reacted with CuI/DMEDA catalyst and Cs_2CO_3 at 95 ^oC for 12 h, which gave the corresponding indoline derivative **67a** in excellent yield (83%) (entry 1,**Table 2**).

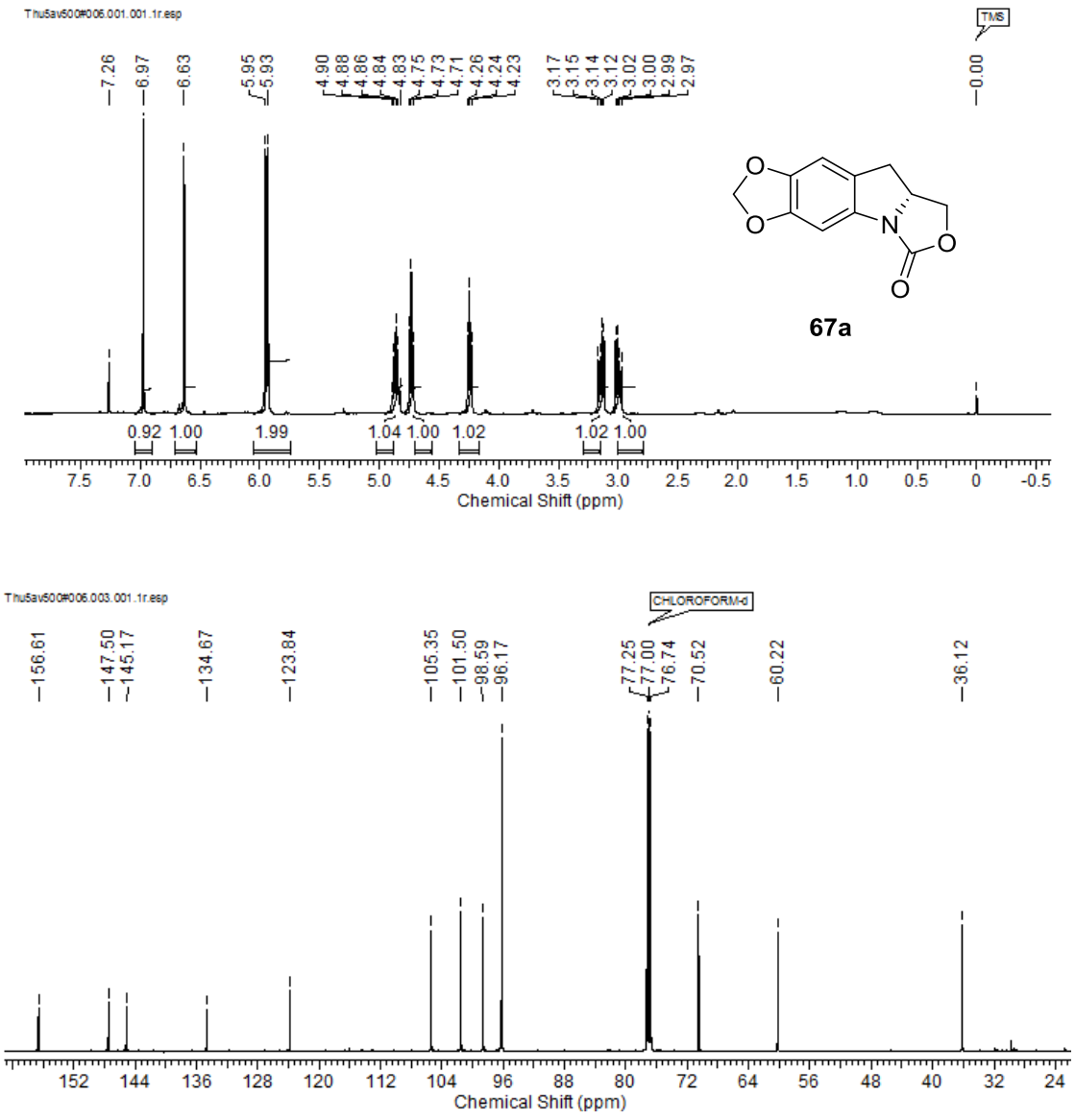
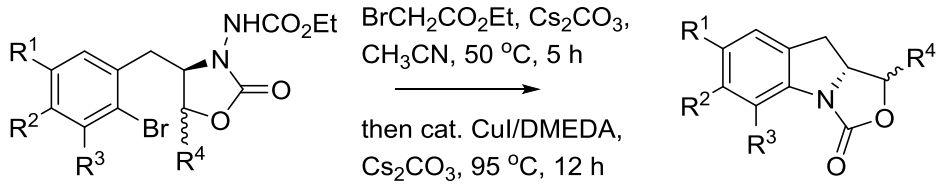


Fig. 5: ^1H and ^{13}C NMR spectra of indoline derivative **67a**

The formation of 2-substituted indoline **67a** was confirmed from its ^1H NMR spectrum**,** which showed two triplets at δ 4.24 (t, *J* = 8.2 Hz, 1H) and δ 4.73 (t, *J* = 8.5 Hz, 1H) corresponding to diastereotopic methylene (-**CH$_2$**-OR) protons of the

oxazolidinone moiety, while a proton signal at δ 4.83-4.90 (m, 1H) indicated the presence of methine (-**CH**-NR_2) proton**.** Further it was ascertained by the absence of proton signals corresponding to N-alkyl group (**Et**CO_2N-C**H**$_2$CO**Et**). Its ^{13}C NMR spectrum displayed two typical typical carbon signals at δ 60.2 and 70.5 corresponding to methine CH-NR_2 and methylene -**C**H_2OR carbons respectively of the oxazolidinone ring, while a downfield shift of aromatic carbon signal from δ 114.9 (C-Br) to 123.8 (C-N) indicated the N-arylation, which in turn confirmed the formation of **67a** (**Fig. 5**). Further, its formation was substantiated by **HRMS** (ESI+, *m/z*): calcd for $(C_{11}H_9NO_4)^+$ [$(M+H)^+$] 220.0604; found: 220.0610. Encouraged by the outcome of "one-pot" 3-step process, we next investigated the scope of the reaction

Table 2. Asymmetric synthesis of 2-substituted indolines [a]



65a-g **67a-g**

entry	substrates **65a-g**				indolines **67a-g**
	R^1	R^2	R^3	R^4	Yield (%)[b]
1	-OCH_2O-		H	H	83
2	OMe	OH	H	H	87
3	OMe	H	OMe	H	81
4	OMe	OMe	OMe	H	80
5[c]	H	H	H	H	88
6	OMe	OMe	H	$CH_2CH=CH_2$	87
7[c]	H	NO_2	H	H	86

[a] **65a-g** (1 mmol), $BrCH_2CO_2Et$ (1.2 equiv), Cs_2CO_3 (2.0 equiv), CH_3CN (7mL), 50 °C, 4 h; then CuI (10 mol%), DMEDA (10 mol%), Cs_2CO_3 (1.5 equiv), 95 °C, 12 h; [b]isolated yield after chromatographic purification. DMEDA: N,N'-dimethylethylenediamine;[c] chiral hydrazino alcohol was used as indoline precursor.

by subjecting several chiral hydrazines (**65b-g**) to this cascade reaction. It was found that, this cascade protocol took place smoothly to provide indoline derivatives **67a-g** in a "one-pot" reaction, which comprised of several sequential reactions taking place in single step. As can be seen, chiral hydrazines bearing electron-releasing groups such as hydroxy,[26] methoxy and methylenedioxy and electron-withdrawing substituent like nitro group on the aromatic nucleus underwent this cascade reaction smoothly to give the corresponding 2-substituted indolines in good yields (**Table 2**). Substrates with differently substituted methoxy groups which alter the electronic environment of the aromatic ring, were also well-tolerated for the cascade reaction (entries 1,3 and 5, **Table 2**). Additionally, more sterically hindered hydrazines with two chiral centres could also be employed successfully for this reaction (**67g**). For all the cases studied, indolines **67a-g** were indeed obtained in high yields (80-87%).

The formation of all the final products i.e. indolines **67a-g** was established unambiguously from their corresponding ^{1}H & ^{13}C NMR, IR, CHNS analysis and HRMS spectral data. Their optical purity was determined from chiral HPLC analysis.

Example 1: The formation of indoline **67c** was confirmed from its ^{1}H NMR spectrum, which showed a doublet of doublet at δ 4.31-4.36 (dd, J = 3.2, 8.3 Hz, 1H) corresponding to one of the diastereotopic methylene (-**C**$\mathbf{H_2}$-OR) protons of the oxazolidinone moiety. A downfield multiplet signal at δ 4.63-4.83 (m, 2H) indicated the presence of the other diastereotopic methylene (-**C**$\mathbf{H_2}$-OR) and methine (-C**H**-NArR) protons. Its ^{13}C NMR spectrum displayed two typical carbon signals at δ 62.3 and 67.7 corresponding to methine **C**H-NR_2 and methylene -**C**H_2OR carbons respectively of the oxazolidinone ring. The carbon signal at δ 123.2 is due to the aromatic carbon attached to nitrogen atom. Additionally, an upfield shift of aromatic carbon signal at δ 151.2 from 156.5 attached to methoxy group is due to mesomeric

(+M) effect of anilinic nitrogen at the *ortho* position, thus confirming the formation of **67c** (**Fig. 6**).

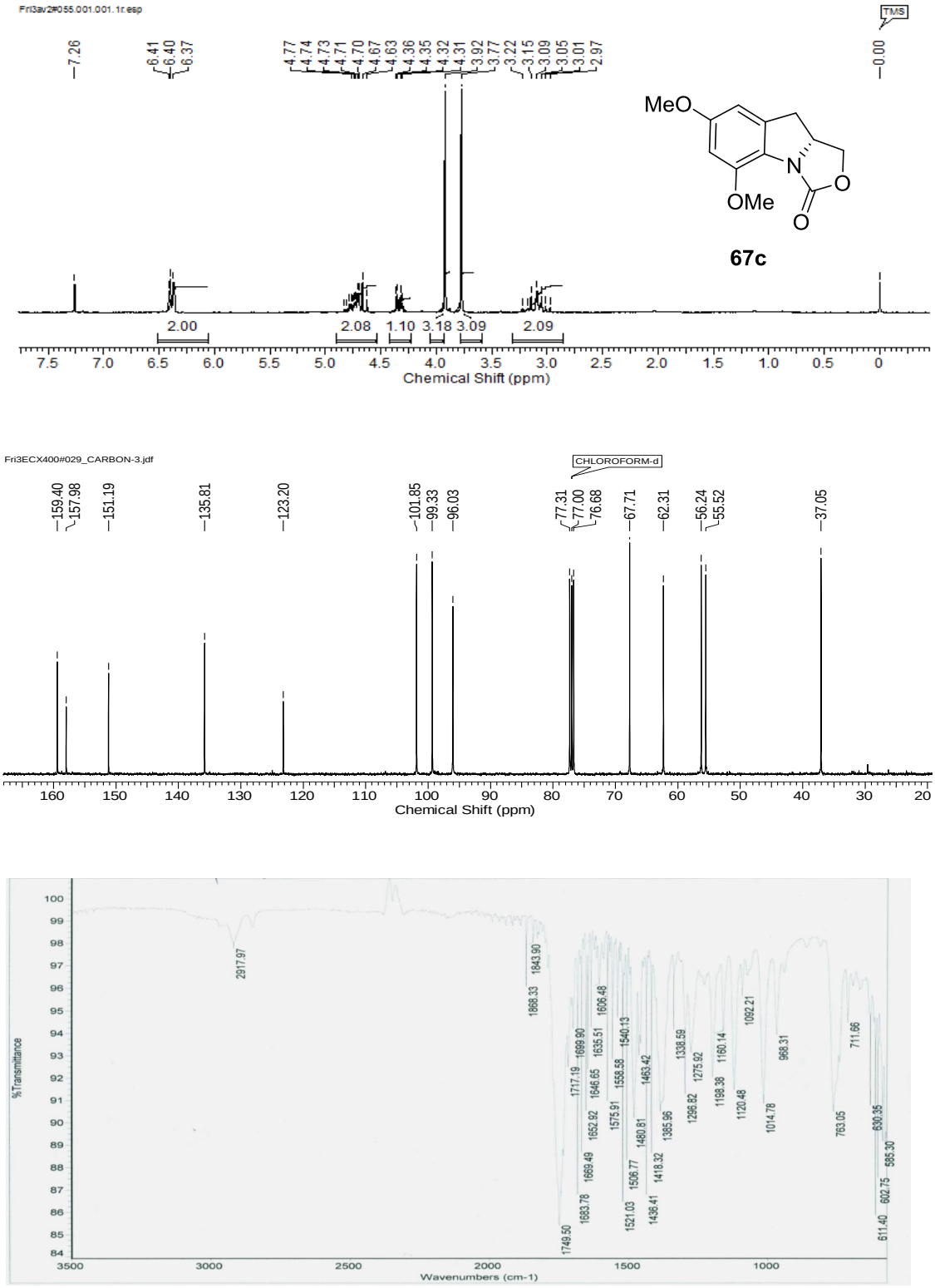


Fig. 6: ^{1}H, ^{13}C NMR and IR spectra of indoline derivative **67c**

Further, the formation of **67c** was clearly demonstrated by a strong IR absorption band at 1749 cm^{-1} due to the C=O stretching of the carbamate moiety (**Fig. 6**).

Example 2: The ^{1}H NMR spectrum of **67f** showed a triplet at δ 4.34 (t, *J* = 8.8 Hz, 1H) corresponding to one of the diastereotopic methylene (-**CH_2**-OR) protons of the oxazolidinone moiety. Another triplet at δ 4.87 (t, *J* = 8.8 Hz, 1H) and a downfield multiplet at δ 4.98-5.07 (m, 1H) indicated the presence of the other diastereotopic methylene (-**CH_2**-OR) and methine (-C**H**-NArR) protons of the heterocyclic ring respectively.

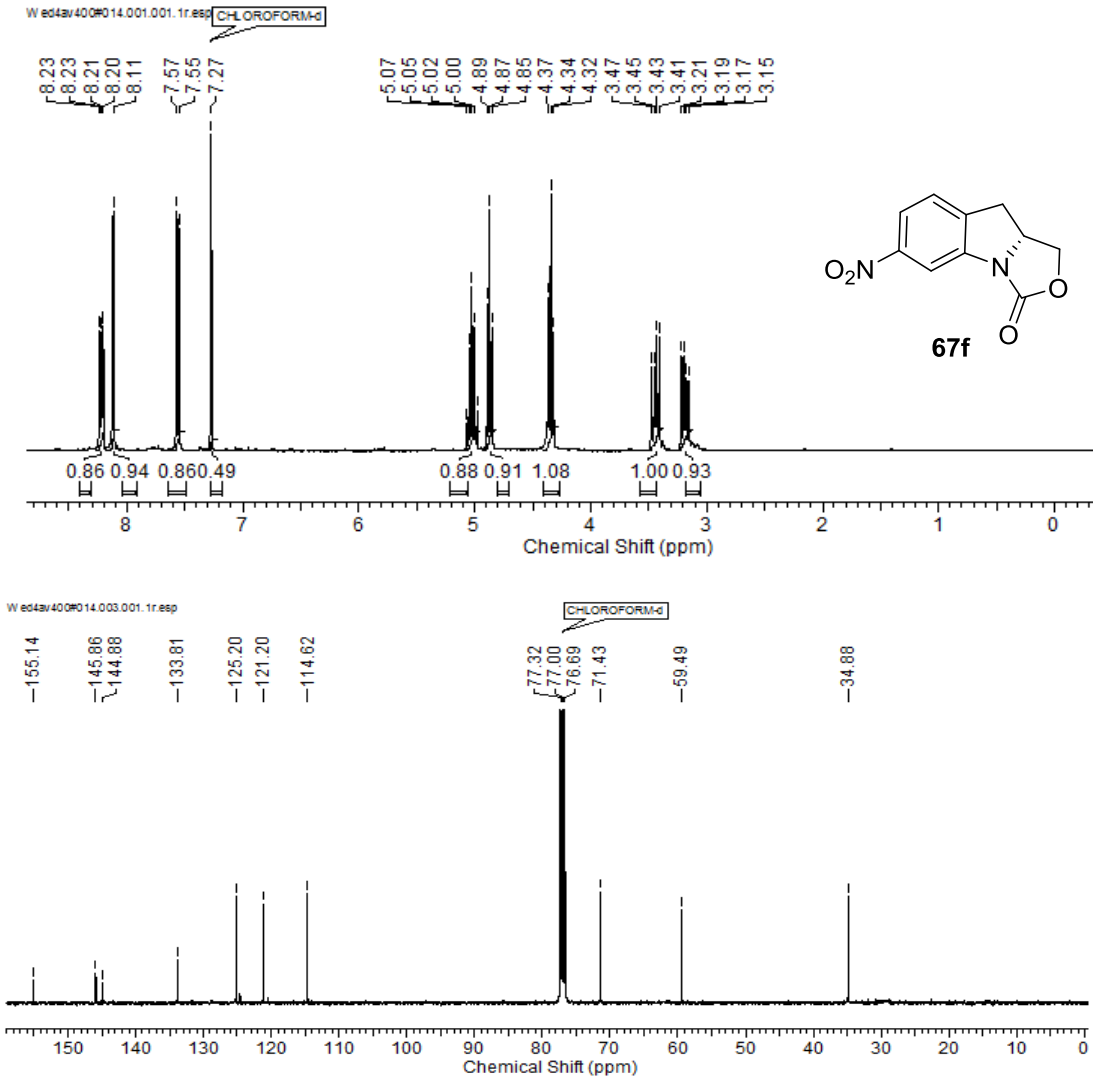
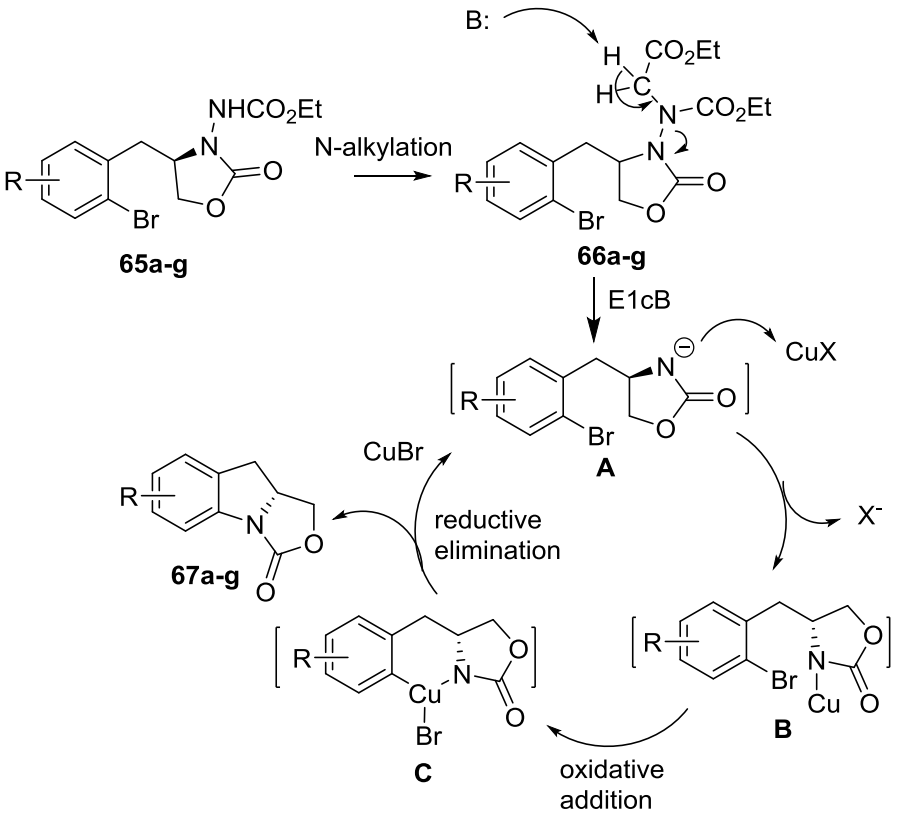


Fig. 7: 1H and 13C NMR spectra of indoline derivative **67f**

Its ^{13}C NMR spectrum displayed two typical carbon signals at δ 59.5 and 71.4 corresponding to chiral methine **C**H-NR_2 and methylene -**C**H_2OR carbons respectively, while the other carbon signal at δ 34.9 indicated the presence of benzylic (Ar**C**H_2-) carbon. Additionally, the carbon signals at δ 133.8 and145.9 are due to the aromatic carbons attached to anilinic nitrogen and nitro group respectively, thus confirming the formation of **67c** (**Fig. 7**).



Scheme 18: Catalytic cycle for indoline formation

A probable mechanistic pathway for the formation of indolines **67a-g** is proposed **Scheme 18**. It begins with the formation of oxazolidinone anion **A,** formed *in situ* from N-alkylation-E1cB of **65a-g** under basic condition, which reacts with CuI/DMEDA catalyst to generate the intermediate species **B**. This in turn leads to intramolecular oxidative addition of Cu(I) into the C-Br bond of aryl bromide to produce the organocopper species **C**. The organocopper species **C** subsequently

undergoes reductive elimination to produce the optically enriched indolines **67a-g** with the regeneration of Cu(I) catalyst.

3.1.4 Conclusion

In conclusion, a novel one-pot procedure of N-alkylation-E1cB-N-arylation cascade has been described, for the first time, in which chiral hydrazines **65a-g** were transformed into enantioenriched 2-substituted indolines **67a-g** in good yields. Chiral hydrazines **65a-g** were prepared by proline-catalyzed α-amination of o-bromohydro cinnamaldehydes in high yields (80-88%) and excellent enantioselectivity (>98% ee). Easily accessible starting materials, milder reaction conditions, high yields, excellent enantioselectivity, functional group tolerance and availability of proline in both enantiomeric forms are the salient features of the methodology.

3.1.5 Experimental Section:

General Experimental Procedure:

(a) **Preparation of chiral hydrazines (65a-d):**

To a cooled solution of diethyl azadicarboxylate (2.5 mmol) and L-proline (10 mol%) in dry CH_3CN (20 ml) at 0 ^oC was added o-bromohydrocinnamaldehydes (**64a-d**, 3.0 mmol) and the mixture was stirred at 0 ^oC for 3 h. After the reaction turned colorless, it was cooled to 0 ºC again and then treated with MeOH (15 mL) and $NaBH_4$ (6.0 mmol, 240 mg) for 10 min at 0 ºC. After completion of reaction, it was quenched by adding saturated aq. NH_4Cl and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude hydrazino alcohols. This crude alcohol was taken up for the next step without purification. A solution of crude hydrazino alcohols in absolute ethanol (20 ml) was refluxed for 6 h. Removal of solvent under reduced pressure followed by flash chromatographic purification gave hydrazines **65a-d**.

Ethyl (*R*)-(4-((6-bromobenzo[d][1,3]dioxol-5-yl)methyl)-2-oxooxazolidin-3-yl)carbamate (65a)

Yield: 85%; colourless solid; **mp** 131-133 ^{o}C; >98% ee from HPLC analysis; Chiracel OD-H column (2-propanol:*n*-hexane = 10:90, flow rate 0.5 mL/min, λ = 254 nm). Retention time (min): 71.7 (major) and 89.1 (minor), $[\alpha]^{25}_{D}$: -33.1 (*c* 0.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max}756,1034, 1112, 1410, 1479, 1508, 1732, 1777, 2912, 2981, 3291; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.30 (t, *J* = 7.0 Hz, 3H), 2.85-2.90 (dd, *J* = 7.5, 13.8 Hz, 1H), 3.22-3.26 (dd, *J* = 3.8, 13.3 Hz, 1H), 4.09-4.14 (m, 1H), 4.31-4.35 (m, 2H), 5.94-5.99 (m, 2H), 6.68 (s, 1H), 6.94 (br s, 1H), 7.00 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.4, 37.6, 56.7, 62.5, 66.7, 101.9, 110.5, 113.1, 114.9, 127.5, 147.7, 147.8, 155.3, 157.3; **Analysis**: $C_{14}H_{15}BrN_2O_6$ requires; C, 43.43; H, 3.91; N, 7.24; Found: C, 43.59; H, 3.67; N, 7.69%.

Ethyl (*R*)-(4-(2-bromo-4-hydroxy-5-methoxybenzyl)-2-oxooxazolidin-3-yl) carbamate (65b)

Yield: 82%; gum; $[\alpha]^{25}_{D}$: +18.8 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 746,1053, 1111, 1425, 1479, 1518, 1732, 1797, 2956, 3051; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.31 (t, *J* = 7.3 Hz, 3H), 2.86-2.95 (dd, *J* = 7.8, 13.8 Hz, 1H), 3.21-3.31 (dd, *J* = 3.6, 12.9 Hz, 1H), 3.9 (s, 3H), 4.14-4.24 (m, 3H), 4.33-4.37 (m, 2H), 5.65 (s, 1H), 6.58 (s, 1H), 6.67 (br s, 1H), 7.13 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.4, 37.6, 56.3, 56.8, 62.5, 66.7, 114.4, 115.1, 120.6, 132.3, 145.5, 147.9, 155.4, 156.7; **Analysis**: $C_{14}H_{17}BrN_2O_6$ requires; C, 43.20; H, 4.40; N, 7.20; Found: C, 43.45; H, 4.18; N, 7.10%.

Ethyl (*R*)-(4-(2-bromo-3,5-dimethoxybenzyl)-2-oxooxazolidin-3-yl)carbamate (65c)

Yield: 88%; gum; $[\alpha]^{25}_{D}$: -16.2 (*c* 0.9, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 752,932, 1415, 1485, 1508, 1737, 1779, 2915, 3293; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.29 (t, *J* = 6.9 Hz, 3H), 2.84-2.89 (dd, *J* = 7.4, 13.5 Hz, 1H), 3.27-3.30 (dd, *J* = 3.2, 13.4 Hz, 1H),

3.74 (s, 3H), 3.89 (s, 3H), 4.14-4.24 (m, 3H), 4.32-4.37 (m, 2H), 6.37 (d, *J* = 1.9 Hz, 1H), 6.42 (d, *J* = 1.9 Hz, 1H), 6.59 (br s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.2, 36.1, 55.7, 56.3, 56.9, 62.5, 66.8, 99.0, 104.7, 107.5, 120.1, 137.6, 156.5, 157.2, 159.8, 160.1; **Analysis**: $C_{15}H_{19}BrN_2O_6$ requires; C, 44.68; H, 4.75; N, 6.95; Found: C, 44.73; H, 4.57; N, 6.71%

Ethyl (4-(2-bromo-3,4,5-trimethoxybenzyl)-oxooxazolidin3-yl)carbamate (65d)

Yield: 84%; gum; 98% ee from HPLC analysis; Chiracel OD-H column (2-propanol:*n*-hexane = 10:90, flow rate 0.5 mL/min, λ = 254 nm). Retention time (min): 38.7 (major) and 59.1 (minor), $[\alpha]^{25}_D$: -21.2 (*c* 0.4, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 756, 1060, 1177, 1377, 1797, 2985, 3299 ; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.28 (t, *J* = 6.9 Hz, 3H), 2.91-2.96 (dd, *J* = 6.9, 16.3 Hz, 1H), 3.29-3.32 (dd, *J* = 3.2, 13.7 Hz, 1H), 3.85 (s, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 4.10-4.24 (m, 3H), 4.34-4.46 (m, 2H), 6.60 (s, 1H), 7.17 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.4, 38.1, 56.3, 60.9, 61.0, 62.5, 66.8, 109.9, 111.0, 130.5, 142.4, 151.3, 152.9, 155.4; **Analysis**: $C_{16}H_{21}BrN_2O_7$ requires; C, 44.36; H, 4.89; N, 6.47; Found: C, 44.54; H, 4.56; N, 6.82%.

(b) **Preparation of chiral hydrazines (65e,g):**

To a cooled solution of azadicarboxylate (2.5 mmol) and L-proline (10 mol%) in dry CH_3CN (20 ml) at 0 ^oC was added o-bromohydrcinnamaldehydes (**64e,g** 3.0 mmol) and the mixture was stirred at 0 - 20 ^oC for 3 h. After the reaction mixture became colorless, it was cooled to 0 ºC again and then treated with MeOH (15 mL) and $NaBH_4$ (6.0 mmol, 240 mg) for 10 min at 0 ºC. After completion of reaction, it was quenched by adding saturated aq. NH_4Cl and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried (anhydrous Na_2SO_4), filtered and concentrated under reduced pressure to give the crude hydrazino alcohols which were

purified by silica gel column chromatography with petroleum ether/EtOAc as colorless crystalline solids as given below.

Diethyl (*S*)-1-(1-(2-bromophenyl)-3-hydroxypropan-2-yl)hydrazine-1,2-dicarboxylate (65e)

Yield: 87%; colorless solid; **mp** 123-125 ^{o}C; 98% ee from HPLC analysis; Chiracel OD-H column (2-propanol:*n*-hexane = 10:90, flow rate 0.5 mL/min, λ = 254 nm). Retention time (min): 40.6 (major) and 46.1 (minor), $[\alpha]^{25}_{D}$: +43.8 (*c* 2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1026, 1058, 1255, 1410, 1520, 1715, 2981, 3262; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.00-1.36 (m, 6H), 2.74-2.78 (d, *J* = 6.7 Hz, 2H), 3.58 (t, *J* = 6.9 Hz, 1H), 3.91 (t, *J* = 6.3 Hz, 1H), 4.06-4.17 (q, *J* = 7.2 Hz, 1H), 4.20-4.31 (q, *J* = 7.2 Hz, 2H) , 4.39 (brs, 1H), 4.70 (t, *J* = 6.7 Hz, 1H), 6.76 (br s, 1H), 7.03-7.26 (m, 3H), 7.51-7.54 (d, *J* = 7.8, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.1, 14.2, 14.3, 20.9, 34.5, 34.9, 59.4, 60.3, 61.7, 62.6, 62.9, 124.6, 127.6, 128.3, 132.9, 137.2, 155.6, 156.7, 159.6 ; **Analysis**: $C_{15}H_{21}BrN_2O_5$ requires; C, 46.29; H, 5.44; N, 7.20; Found: C, 46.47; H, 5.26; N, 7.08 %.

Diethyl (*S*)-1-(1-(2-bromo-4-nitrophenyl)-3-hydroxypropan-2-yl)hydrazine-1,2-dicarboxylate (65g)

Yield: 88%; colorless solid; **mp** 127-128 ^{o}C; >98% ee from HPLC analysis; Chiracel OD-H column (2-propanol:*n*-hexane = 10:90, flow rate 0.5 mL/min, λ = 254 nm). Retention time (min): 61.8 (major) and 71.1 (minor), $[\alpha]^{25}_{D}$: +29.1 (*c* 0.5, $CHCl_3$, cm^{-1}); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1030, 1063, 1255, 1344, 1524, 1715, 2924, 3265; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.12 (t, *J* = 6.9 Hz, 3H), 1.34 (t, *J* = 7.3 Hz, 3H), 2.82-2.97 (m, 2H), 3.61-3.63 (m, 2H), 3.95-4.15 (m, 2H), 4.22-4.34 (m, 2H), 4.41 (br s, 1H), 4.77 (brs, 1H), 6.52-6.56 (d, *J* = 16.0 Hz, 1H), 7.74 (d, *J* = 8.7 Hz, 1H), 7.96 (d, *J* = 8.2 Hz, 1H), 8.10 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.2, 14.4, 35.0, 60.1, 61.8, 63.1, 63.3, 123.0, 125.3, 131.9, 133.9, 139.4, 147.3, 156.4, 159.6; **Analysis**:

$C_{15}H_{20}BrN_3O_7$ requires; C, 41.49; H, 4.64; N, 9.68; Found: C, 41.46; H, 4.67; N, 9.69%.

(a) **Preparation of chiral hydrazine 65f:**

To a cooled solution of diethyl azadicarboxylate (2.5 mmol) and L-proline (10 mol%) in dry CH_3CN (20 ml) at 0 ^oC was added o-bromohydrcinnamaldehydes (**64f**, 3.0 mmol) and the mixture was stirred at 0 ^oC for 2 h and further at 10 ^oC for 1 h. This was followed by the addition of allyl bromide (540 mg, 4.5 mmol), activated Zn (295 mg, 4.5 mmol) and 5 mL of aq. NH_4Cl (saturated) in that sequence and the whole mixture was stirred at 0 ^oC for 1 h. It was then filtered through a pad of Celite and extracted with ethyl acetate (3x20 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude hydrazine alcohol. The crude alcohol was taken up for the next step without purification. To a ice cooled solution of crude hydrazino alcohols in ethanol/H_2O (15:5 ml) was added NaOH (80 mg, 2 mmol), and the mixture was allowed to stir at 25 ^oC for 6 h. Ethanol was removed under reduced pressure and aqueous layer extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried (anhydrous Na_2SO_4), filtered and concentrated under reduced pressure to give the crude product which was followed by flash chromatographic purification to give chiral oxazolidinone **65f** as inseparable diastereomers (dr = 1:1, determined by ^1H NMR analysis).

Ethyl ((4*R*)-5-allyl-4-(2-bromo-4,5-dimethoxybenzyl)-2-oxooxazolidin-3-yl) carbamate (65f)

Yield: 81%; gum; $[\alpha]^{25}_D$: +1.33 (*c* 0.9, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1040, 1061, 1177, 1377, 1732, 1777, 2918, 2982, 3050, 3126; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.16-1.32 (m, 3H), 2.44-2.88 (m, 2H), 3.10-3.31 (m, 1H), 3.51-3.68 (m, 1H), 3.77 (s, 3H), 3.84 (s, 3H), 4.05-4.22 (m, 2H), 4.34-4.76 (m, 2H), 4.96-5.33 (m, 2H), 5.58-5.96

(m, 1H), 6.37-6.48 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.5, 36.0, 38.3, 55.6, 62.9, 80.0, 98.9, 104.9, 107.4, 119.5, 131.3, 137.0, 156.3, 157.1, 159.7, 159.9; **Analysis**: $C_{18}H_{23}BrN_2O_6$ requires; C, 48.77; H, 5.23; N, 6.32; Found: C, 48.70; H, 5.28; N, 6.36;%.

General Procedure for the Synthesis of 2-substituted indolines *via* N-alkylation/E1cB/N-arylation cascade:

To a suspension of **65a-g** (1.0 mmol) and Cs_2CO_3 (652 mg, 2 mmol) in CH_3CN (10 mL), was added ethyl bromoacetate (200 mg, 1.2 mmol). The mixture was heated to 50 °C and stirred under N_2 atmosphere until the complete consumption of starting materials (5 h) took place, as indicated by tlc. This was followed by the sequential addition of CuI (20 mg, 0.1 mmol), DMEDA (10 mg, 0.1 mmol) and Cs_2CO_3 (488 mg, 1.5 mmol) in that sequence and the whole mixture was stirred at 95 ^oC for 12 h. The reaction was quenched with saturated aq. NH_4Cl, and extracted with ethyl acetate (3x10 mL). The combined extracts were washed with brine, dried over Na_2SO4 and concentrated in vacuum. The crude products were purified by flash column chromatography to give **67a-g** in pure form.

(*R*)-8a,9-Dihydro-6H,8H-[1,3]dioxolo[4,5-f]oxazolo[3,4-a]indol-6-one (67a)

Yield: 83%; colorless solid; **mp** 143-146 ^oC**;** $[\alpha]^{25}_D$: +129.2 (*c* 0.9, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 585, 630, 763, 968, 1092, 1198, 1275, 1355, 1521, 1575, 1652, 1749, 2850, 2917; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.97-3.02 (dd, *J* = 9.5, 9.1 Hz, 1H), 3.12-3.17 (dd, *J* = 8.9, 15.9 Hz, 1H), 4.24 (t, *J* = 8.2 Hz, 1H), 4.73 (t, *J* = 8.5 Hz, 1H), 4.83-4.90 (m, 1H), 5.94 (d, *J* = 10.1 Hz, 1H), 6.63 (s, 1H), 6.97 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 36.1, 60.2, 70.5, 98.6, 101.5, 105.4, 123.8, 134.7, 145.2, 156.6; **HRMS** (ESI+, *m/z*): calcd for $(C_{11}H_9NO_4)^+$ [$(M+H)^+$] 220.0604; found: 220.0610; **Analysis**: $C_{11}H_9NO_4$ requires C, 60.28; H, 4.14; N, 6.39; Found: C, 60.45; H, 4.27; N, 6.17 %.

Ethyl (*R*)-2-((7-methoxy-3-oxo-9,9a-dihydro-1H,3H-oxazolo[3,4-a]indol-6-yl)oxy)acetate (67b)

Yield: 87%; colorless oil; $[\alpha]^{25}_{D}$: +41.8 (*c* 0.9, $CHCl_3$); **IR** ($CHCl_3$,cm^{-1}): υ_{max} 630, 778, 1092, 1203, 1289, 1346, 1521, 1575, 1652, 1750, 2850, 2917; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.32 (t, *J* = 7.2 Hz, 3H), 2.97-3.09 (dd, *J* = 8.9, 8.6 Hz, 1H), 3.13-3.25 (dd, *J* = 8.7, 15.5 Hz, 1H), 3.85 (s, 3H), 4.21-4.32 (q, *J* = 7.2 Hz, 2H), 4.69 (s, 2H), 6.76 (s, 1H), 6.97 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.1, 35.9, 56.6, 59.9, 61.2, 62.3, 70.6, 102.5, 109.6, 124.5, 134.0, 147.2, 147.4, 156.6, 168.3; **Analysis**: $C_{15}H_{17}NO_6$ requires C, 58.63; H, 5.58; N, 4.56; Found: C, 58.34; H, 5.75; N, 4.38%.

(*R*)-5,7-Dimethoxy-9,9a-dihydro-1H,3H-oxazolo[3,4-a]indol-3-one (67c)

Yield: 81%; gum; $[\alpha]^{25}_{D}$: +128.7 (*c* 1.8, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1060, 1177, 1377, 1521, 1580, 1652, 1756, 2844, 2924, 3050; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.97-3.22 (m, 2H), 3.77 (s, 3H), 3.92 (s, 3H), 4.31-4.36 (dd, *J* = 3.2, 8.4 Hz, 1H), 4.67 (t, *J* = 8.9 Hz, 1H), 4.71-4.83 (m, 1H), 6.36-6.37 (d, *J* = 1.9 Hz, 1H), 6.40-6.41 (d, *J* = 1.9 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 37.1, 55.5, 56.2, 62.3, 67.7, 96.0, 99.3, 101.9, 123.2, 135.8, 151.2, 158.0, 159.4; **Analysis**: $C_{12}H_{13}NO_4$ requires C, 61.27; H, 5.57; N, 5.95; Found: C, 61.15; H, 5.79; N, 5.82%.

(*R*)-5,6,7-Trimethoxy-9,9a-dihydro-1H,3H-oxazolo[3,4-a]indol-3-one (67d)

Yield: 80%; gum; $[\alpha]^{25}_{D}$: -79.6 (*c* 0.8, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 763, 1013, 1198, 1275, 1355, 1521, 1575, 1652, 1749, 2845, 2925; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.02-3.15 (m, 2H), 3.82 (s, 3H), 3.85 (s, 3H), 4.05 (s, 3H), 4.30-4.33 (dd, *J* = 4.0 Hz, 9.5 Hz, 1H), 4.67 (t, *J* = 8.9 Hz, 1H), 4.72-4.78 (m, 1H), 6.51 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 37.0, 56.4, 60.1, 60.9, 62.1, 67.9, 103.6, 126.9, 128.7, 142.1, 145.4, 152.3, 157.7; **Analysis**: $C_{13}H_{15}NO_5$ requires C, 58.86; H, 5.70; N, 5.28; Found: C, 58.72; H, 5.92; N, 5.45 %.

(*R*)-9,9a-Dihydro-1H,3H-oxazolo[3,4-a]indol-3-one (67e)

Yield: 88%; colorless oil; $[\alpha]^{25}_{D}$: +16.9 (*c* 0.9, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 630, 711, 968, 1014, 1296, 1385, 1558, 1669, 1749, 2928; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.04-3.09 (dd, *J* = 9.2, 15.9 Hz, 1H), 3.24-3.28 (dd, *J* = 8.9, 15.6 Hz, 1H), 4.24 (t, *J* = 8.5 Hz, 1H), 4.76 (t, *J* = 8.5 Hz, 1H), 4.82-4.89 (m, 1H), 7.08 (t, *J* = 7.3 Hz, 1H), 7.18-7.20 (d, *J* = 7.3 Hz, 1H), 7.24 (t, *J* = 7.3 Hz, 1H), 7.42-7.43 (d, *J* = 7.9 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 35.7, 59.3, 71.9, 115.3, 124.7, 125.1, 128.0, 132.2, 140.4, 156.4; **Analysis**: $C_{10}H_9NO_2$ requires C, 68.56; H, 5.18; N, 8.00; Found: C, 68.48; H, 5.25; N, 8.25%.

(9a*R*)-1-Allyl-6,7-dimethoxy-9,9a-dihydro-1H,3H-oxazolo[3,4-a]indol-3-one (67f)

Yield: 87%; colorless oil; $[\alpha]^{25}_{D}$: +77.5 (*c* 0.8, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 715, 971, 1014, 1296, 1385, 1558, 1669, 1754, 2926, 3045; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.49-2.78 (m, 2H), 2.95-3.55 (m, 2H), 3.77 (s, 3H), 3.91 (s, 3H), 4.00-4.92 (m, 2H), 5.18-5.46 (m, 2H), 5.73-5.93 (m, 1H), 6.35-6.47 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14. 8, 31.0, 36.8, 55.5, 56.2, 66.3, 74.9, , 99.5, 101.9, 118.9, 123.6, 131.1, , 135.3, 135.9, 156.9, 159.2, 159.5; **HRMS** (ESI+, *m/z*): calcd for $(C_{15}H_{17}NO_4)^+$ $[(M+H)^+]$ 276.1236; found: 276.1238; **Analysis**: $C_{15}H_{17}NO_4$ requires; C, 65.44; H, 6.22; N, 5.09; Found: C, 65.41; H, 6.24; N, 5.10 %.

(*R*)-6-Nitro-9,9a-dihydro-1H,3H-oxazolo[3,4-a]indol-3-one (67g)

Yield: 86%; colorless oil; $[\alpha]^{25}_{D}$: -136.5 (*c* 0.3, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 666, 756, 797, 870, 939, 1004, 1519, 1581, 1616, 1731, 2852, 2983; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.14-3.20 (dd, *J* = 9.1, 16.1 Hz, 1H), 3.40-3.46 (dd, *J* = 9.1, 16.4 Hz, 1H), 4.33 (t, *J* = 8.8 Hz, 1H), 4.86 (t, *J* = 8.8, 1H), 4.97-5.06 (m, 1H), 7.55 (d, *J* = 8.6 Hz, 1H), 8.10 (s, 1H), 8.19-8.22 (dd, *J* = 8.8, 2.0 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 34.9, 59.5, 71.4, 114.6, 121.2, 125.2, 133.8, 144.9, 145.9, 155.1; **Analysis**:

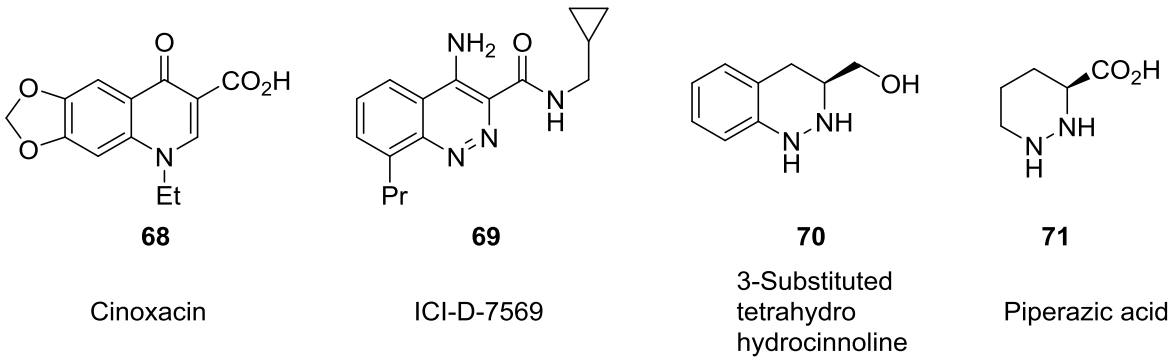
$C_{10}H_8N_2O_4$ requires; C, 54.55; H, 3.66; N, 12.72 Found: C, 54.67; H, 3.44; N, 12.94 %.

Section II

Asymmetric Synthesis of 3-Substituted Dihydrocinnoline Derivatives *via* Cu-Catalyzed Intramolecular N-Arylation of Chiral Hydrazines derived from Proline-Catalyzed *α*-Amination of *o*-Bromohydro cinnamaldehyes

3.2.1 Introduction

The cinnoline scaffold is considered as a previleged structural motif in agriculture, biology, and medicine.[27] For example, cinoxacine **68** is a cinnoline analogue of quinoline antibacterials used for urinary tract infection, while ICI-D-7569 **71** is an anxiolytic agent. Significant commercial interest in the development of cinnoline derivatives is evidenced by the large number of patents filed in this area.[28] Chiral 3-substituted cinnolines **70,** which are not only structural analogs of cinnolines but also resemble chiral piperazic acid derivative **71** (**Fig. 8**). Hence, chiral cinnolines can be an attractive target for pharmaceuticals, since piperazic acids are components of several naturally-occurring cyclodepsipeptides with remarkable biological activities.[29] Therefore, an operationally simple method for the construction of such important nitrogen-containing heterocycles in enantioenriched manner from easily accessible starting materials is of interest.



68 Cinoxacin

69 ICI-D-7569

70 3-Substituted tetrahydro hydrocinnoline

71 Piperazic acid

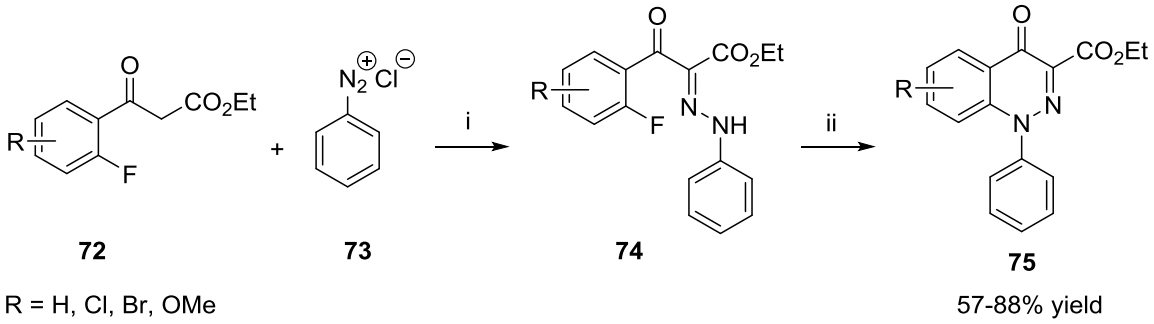
Fig. 8: Bioactive molecules with cinnoline motif

3.2.2 Review of literature

Literature search revealed that there are number of strategies developed for the synthesis of cinnoline derivatives involving arenediazonium salts,[30] arylhydrazones,[31] arylhydrazines,[32] nitriles,[33] and transition metal catalyzed coupling; some of which are described briefly below.

Ames's approach (1983)[34]

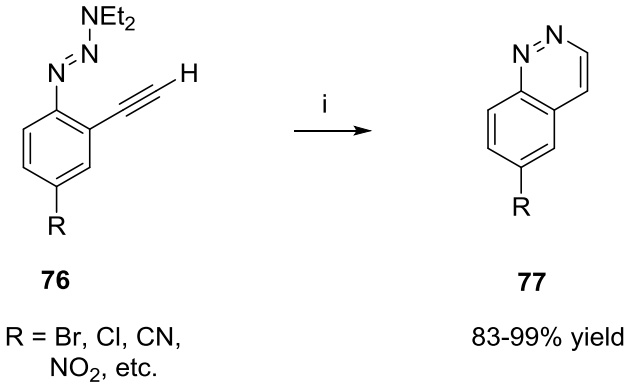
Ames *et al* have developed an efficient method, which involved the reaction of diazonium salt **73** with ethyl 2-fluorobenzoyl acetate derivatives **72** under basic conditions to afford cinnoline-3-carboxylic esters **75** *via* the isolable intermediate **74.** The strongly electron-attracting fluoride acts as a good leaving group while steric hindrance to the reaction is minimized (**Scheme 19**).



Scheme 19: (i) Na_2CO_3, EtOH, 0 ^oC, 2 h; (ii) K_2CO_3, 2-butanone, 110 ^oC, 6 h.

Haley's approach (2000)[35]

Haley *et al.* have reported an efficient synthesis of 6-substituted cinnolines **77** directly

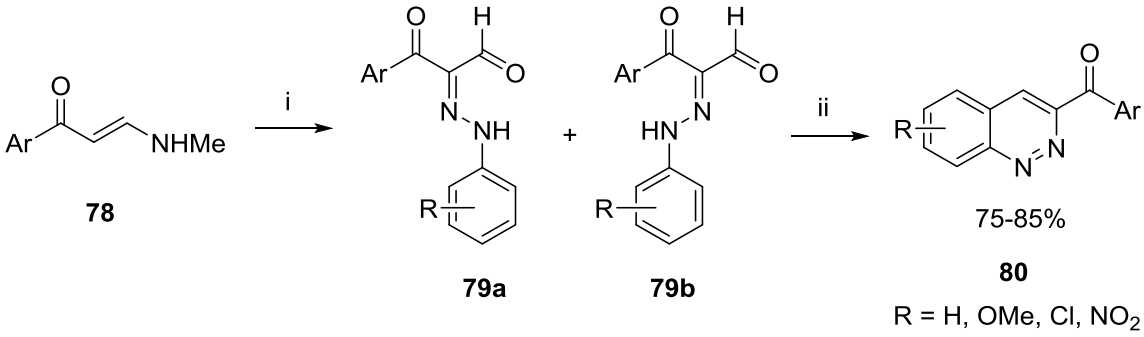


Scheme 20: (i) *o*-Cl_2Ph, 200 ^oC.

from (4-substituted-2-ethynylphenyl)triazenes **76** *via* intramolecular cyclization of **76** when carried out under neutral conditions at 200 ^{o}C (**Scheme 20**).

Al-Awadi's approach (2001)[36]

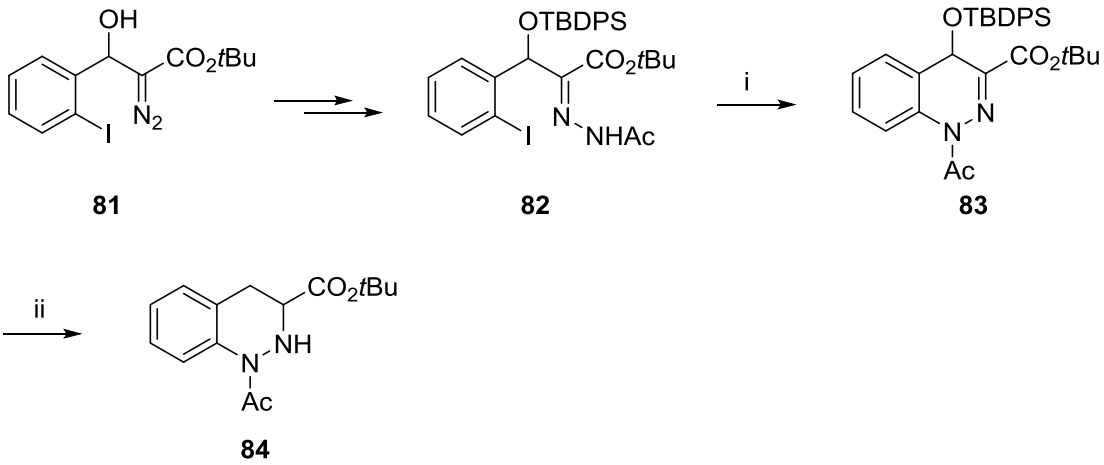
Al-Awadi *et al.* have reported an efficient synthesis of 3-aroylcinnolines **80** starting from the appropriate enamine **78**. The enamine **78** on reaction with aryl diazonium chloride gave the corresponding 3-oxo-3-aryl-2-arylhydrazonopropanals **79**, which upon acid-catalyzed cyclization in conc. H_2SO_4 led to the isolation of 3-aroylcinnolines **80** in high yields (**Scheme 21**).



Scheme 21: (i) $RC_6H_4N_2Cl$, NaOH, EtOH; (ii) conc. H_2SO_4, 100 ^{o}C, 3-5 min.

Nishida's approach (2008)[37]

Nishida *et al*. have demonstrated that iodo hydrazones **82** are useful precursors for the

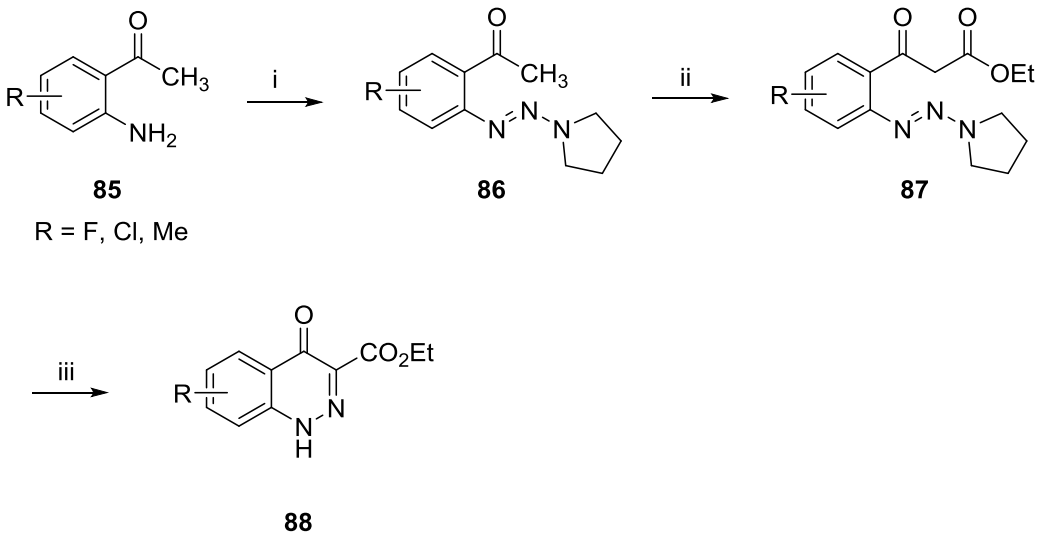


Scheme 22: (i) CuI (10 mol%), DMEDA (10 mol%), Cs_2CO_3 (2 equiv), DMSO, 25 ^{o}C, 10 min, 89%; (ii) H_2 (1 atm), 5% Pd/C , MeOH, 6 h, 55%.

facile synthesis of cinnoline **83**, dihydrocinnoline derivatives **84** by Cu-catalyzed intramolecular N-arylation. The hydrazones as cyclization precursors are obtained from 3-haloaryl-3-hydroxy-2-diazopropanoates **81** in 4 steps (**Scheme 22**).

Scott's approach (2011)[38]

Scott *et al*. have reported a diazotization strategy in which *o*-aminoacetophenone **85** is reacted with pyrrolidine for the synthesis of dihydrocinnoline ester **88** in high yields. In this reaction *in situ* generated diazonium salt of **85** was trapped with pyrrolidine to give **86**, which on reaction with diethyl carbonate gave **87**, isolated as its sodium salt. The cyclization of **87** in TFA gave the corresponding dihydrocinnoline ester **88** (**Scheme 23**).



85

R = F, Cl, Me

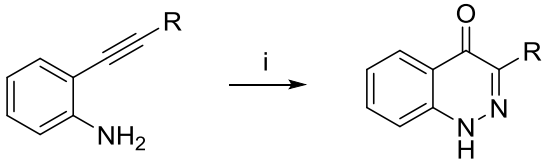
86 **87**

88

Scheme 23: (i) conc. HCl, $NaNO_2$, H_2O, 0 ^oC then pyrrolidine, 0.4 N aq NaOH; (ii) $CO(OEt)_2$, NaH, THF, reflux; (ii) TFA, 0 ^oC.

Ranu's approach (2011)[39]

Ranu *et al* have developed a general and green protocol for the synthesis of cinnolines **90** starting from commercially available 2-alkylethynyl aniline **89** through diazotization strategy (**Scheme 24**). The yields were found to be excellent so that the protocol can be applied for the large scale synthesis.



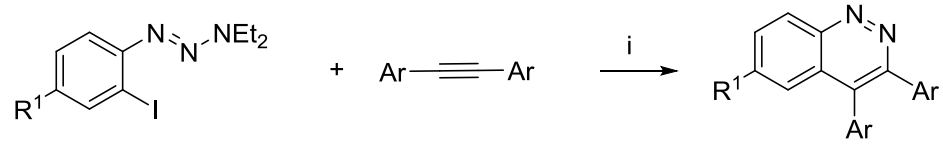
89 **90**

R = aryl, alkyl 80-92% yield

Scheme 24: (i) $NaNO_2$/HCl, H_2O, 0-5 ^oC, 5 min.

Yamane's approach (2011)[40]

Yamane *et al.* have developed a useful method for the synthesis of 3,4-disubstituted cinnolines **93** *via* Pd-catalyzed annulation of 2-iodophenyltriazenes **91** with an internal alkyne **92** in moderate to good yields. Several internal alkynes are applicable to this reaction and the method is compatible with a number of functional groups as well (**Scheme 25**).



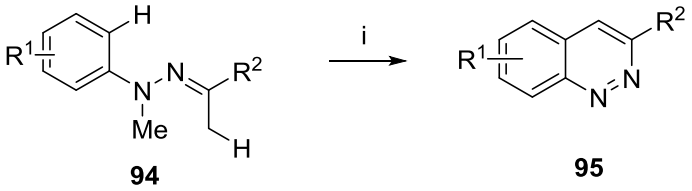
91 **92** **93**

R_1 = NO_2, Cl, CN, OMe, etc 35-84% yield

Scheme 25: (i) $PdCl_2$ (8 mol%), P(o-tolyl)$_3$ (16 mol%), *n*-Bu_3N (50 mol%), DMF, 90 ^oC,

Ge's approach (2012)[41]

Ge *et al.* have developed an efficient Cu-catalyzed aerobic intramolecular dehydrogenative cyclization reaction of N-methyl-N-phenylhydrazones **94** through sequential Csp^3-H oxidation, cyclization, and aromatization processes. This transformation is the first example of Cu-catalyzed coupling reactions of hydrazones through a Csp^3-H bond functionalization pathway. This novel method provides an efficient route to produce cinnoline derivatives **95** (**Scheme 26**).



94 **95**

R^1 = Cl, Br, CN, OMe, etc
R^2 = Aryl, Br, CN,OMe, etc

47-96% yield

Scheme 26: (i) $CuSO_4$ (1.5 mol%), CuI (7.5 mol%), pyridine (3.5 equiv), CF_3SO_3H (1 equiv), O_2 (1 atm), DMF, 110 ^oC.

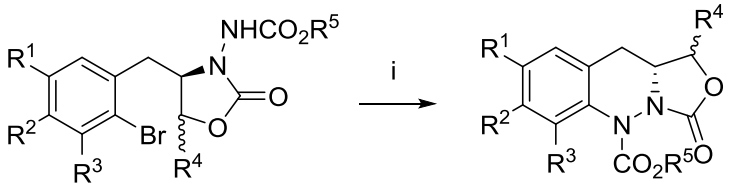
3.2.3 Present Work

3.2.3.1 Objective

The literature survey reveals that there are number of strategies available for the synthesis of substituted aromatic cinnolines. However, no literature reports are available for the asymmetric synthesis of 3-substituted dihydrocinnolines.

3.2.3.2 Results and Discussion

In continuation of our research program on proline-catalyzed α-amination of aldehydes for the asymmetric synthesis of nitrogen containing bioactive heterocycles,[22] it was of our interest to demonstrate the applicability of chiral hydrazines **65** (see Section I of this Chapter) for the enantioselective synthesis of 3-substituted cinnolines using Cu-catalyzed intramolecular N-arylation.[7, 24]



65a-f

R^1 = R^2 = R^3 = H, OH, OMe, $-OCH_2O-$
R^4 = H, allyl, R^5 = *i*Pr, ethyl

96a-f

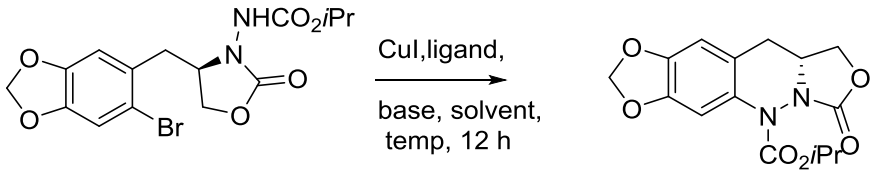
63-74% yield
>98% ee

Scheme 27: CuI (10 mol%), DMEDA (10 mol%), Cs_2CO_3 (2 equiv), 95 ^oC, 12 h.

The CuI-catalyzed intramolecular N-arylation of chiral amines has been shown to be an efficient method for the synthesis of a variety of aniline heterocycles without loss of enantiomeric purity.[24] This section describes CuI/DMEDA-catalyzed intramolecular N-arylation of chiral hydrazine derivatives **65a-f** that led to the asymmetric synthesis of 3-substituted dihydrocinnolines **96a-f** in high yields (**Scheme 27**).

A systematic study of intramolecular N-arylation of chiral hydrazine **65a** was conducted to identify the optimized condition for the synthesis of cinnoline derivatives (**Table 3**). Initially, chiral hydrazine **65a** was subjected to N-arylation with catalytic amount of CuI/L-proline (10 mol%) in DMSO using K_2CO_3 as base. After 12 h of stirring at 120 ^oC, 3-substituted dihydrocinnoline **96a** was indeed obtained in 36% yield (entry 1).

Table 3. Optimization studies for cinnoline synthesis[a]



65a **96a**

entry	solvent	ligand	temp (^oC)	base	yield (%)[b]
1	DMSO	L-proline	120	K_2CO_3	36
2	DMF	L-proline	120	K_2CO_3	30
3	**CH_3CN**	**DMEDA**	**100**	**Cs_2CO_3**	**72**
4	DMSO	DMEDA	100	Cs_2CO_3	35

[a]**65a** (1 mmol), CuI (10 mol%), ligand (10 mol%), base (1 equiv.), solvent (7mL), [b]isolated yield after chromatographic purification. DMEDA: N,N'-dimethylethylenediamine.

Further, DMF as solvent was found to be less effective for the N-arylation protocol. However, a high yield of cinnoline derivate **96a** (72%) was realized in CH_3CN as solvent when CuI/DMEDA was used as catalyst with Cs_2CO_3 as base stirring at 100 ^oC for 12 h. Subsequently, it was found that lowering the temperature of the reaction resulted in low yield of **96a**. The formation of chiral cinnoline derivative **96a** was confirmed from its ^1H NMR spectrum, which indicated the absence of a proton signal at δ 6.94 corresponding to hydrazine R_2N-N**H**R due to N-arylation.

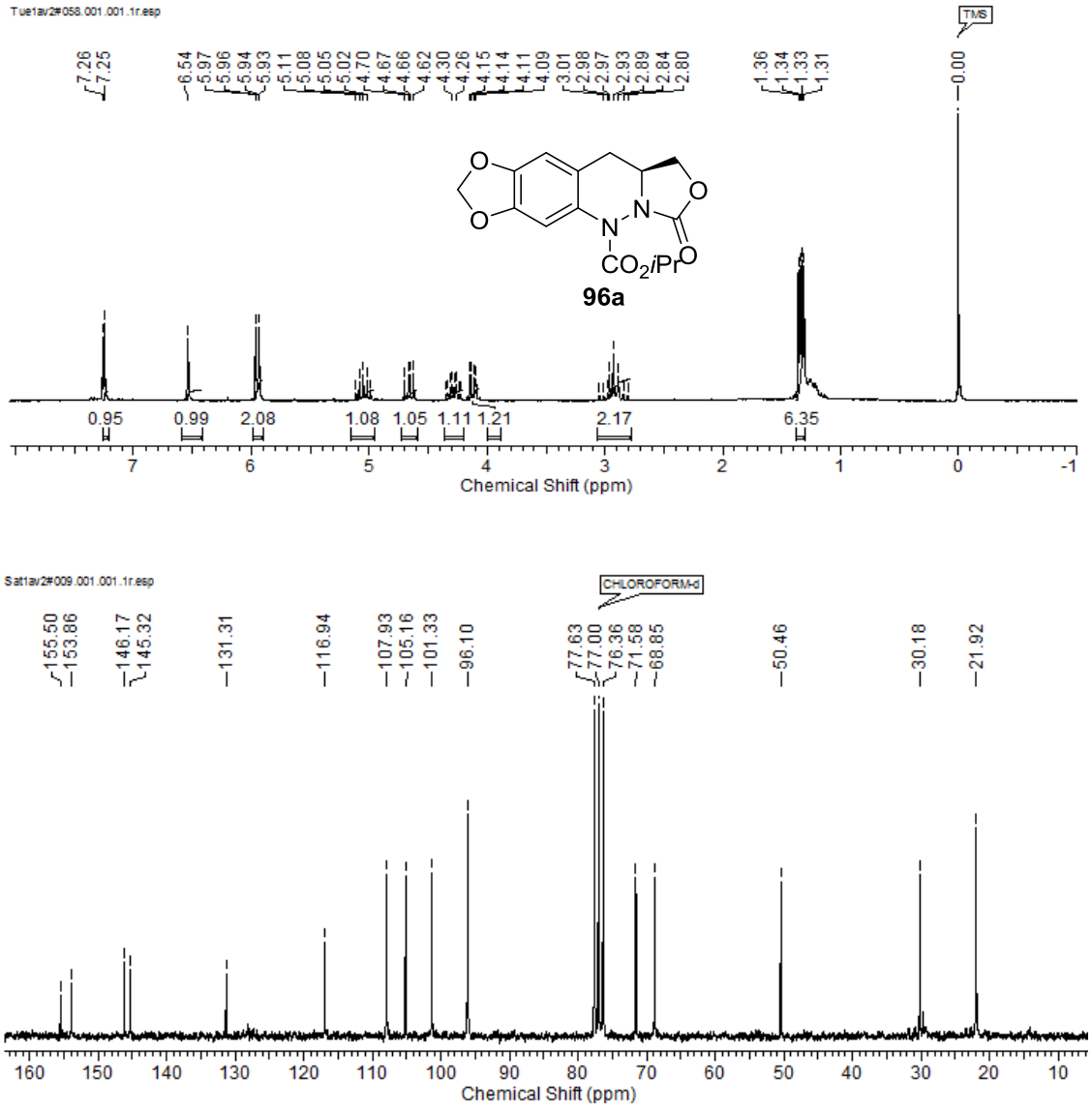


Fig. 9: ^1H and ^{13}C NMR spectra of cinnoline derivative **96a**

Further, multiplets at δ 4.22-4.34 (m, 1H) and 4.99-5.11 (m, 1H) indicated the presence of methine -C**H**NR_2 and $RNCO_2C$**H(**$CH_3)_2$ protons respectively. Its ^{13}C NMR spectrum displayed two typical carbon signals at δ 153.9 and 155.5 due to the carbonyl (C=O) carbons of the oxazolidinone and carbamate moieties respectively, confirming the formation of cinnoline derivative **96a (Fig. 9)**. Also, other carbon signals at δ 50.5 and 68.9 indicated the presence of methine -**C**H-NR_2 and methylene -**C**H_2-OR carbons respectively. Further, a resonance signal at δ 131.3 is due to the quarternary aromatic carbon attached to hydrazinic nitrogen atom (**Fig. 9**). It was further evidenced from its HRMS data; HRMS (ESI+, *m/z*): calcd for $(C_{15}H_{16}N_2O_6)^+$ $[(M+H)^+]$ 321.1087; found: 321.1083. With the optimized reaction conditions in hand (entry 3, **Table 3**), we then investigated the scope of the reaction by subjecting several chiral hydrazines **65a-f** to this intramolecular N-arylation protocol.

Table 4 : Asymmetric synthesis of 3-substituted cinnolines *via* N-arylation of chiral hydrazine derivatives[a]

entry	substrates (**65a-f**)				cinnolines (**96a-f**)
	R^1	R^2	R^3	R^4	Yield (%)[b]
1	-OCH_2O-		H	H	72
2[c]	OMe	OH	H	H	70
3	OMe	H	OMe	H	72
4[c]	OMe	OMe	OMe	H	65
5	H	H	H	H	70
6	OMe	OMe	H	$CH_2CH=CH_2$	63

65a-f (1 mmol), CuI (10 mol%), DMEDA (10 mol%), Cs_2CO_3 (1.5 equiv), CH_3CN (8 mL). [b]isolated yield after chromatographic purification.[c] hydrazinoalcohol was used directly as cinnoline precursor with Cs_2CO_3 (2.2 equiv). DMEDA = N,N'-dimethylethylenediamine.

For instance, chiral hydrazines bearing electron-releasing substituents on the aryl nucleus such as methylenedioxy, (entry 1, **Table 4**) as well as methoxy groups

(entries 2, 3 and 4) underwent this cascade reaction smoothly to give the corresponding 3-substituted dihydrocinnolines in good yields. Interestingly, hydroxy substituent on the aromatic ring was also well-tolerated under the reaction condition giving the corresponding cinnoline **96b** in 70% yield (entry 2). As can be seen, this N-arylation reaction took place smoothly with other aromatic substrates having different electronic environments to provide the corresponding chiral cinnolines **96a-f** in good yields (63-72%).

The formation of all the intermediates and final products such as cinnolines **96a-f** were established unambiguously from their corresponding ^{1}H & ^{13}C NMR, IR, CHNS analysis and HRMS spectral data. Their optical purity was established from the chiral HPLC analysis.

Example 1: The ^{1}H NMR spectrum of hydrazine **65e** showed a multiplet at δ 4.31-4.67 (m, 1H) corresponding to the methine (-**C**H-NR_2) proton, while a proton signal at δ 3.55-3.62 (m, 2H) indicated the methylene (-CH_2OH) protons attached to the hydroxyl group. In addition, a broad singlet at δ 6.76 (br s, 1H) indicated the presence of hydrazine proton (R_2N-N**H**R), thus confirming the formation of **65e**. Its ^{13}C NMR spectrum displayed a two typical carbon signals at δ 156.7 and 159.6 corresponding to C=O carbons of the carbamate functionality, while the other signals at δ 34.9 and 60.1 were indicative of the benzylic (Ph**C**H_2-) and methine (-**C**H-NR_2) carbons respectively. The carbon resonance signal at δ 124.6 indicated the presence of aromatic carbon attached to bromine atom (**Fig. 10**).

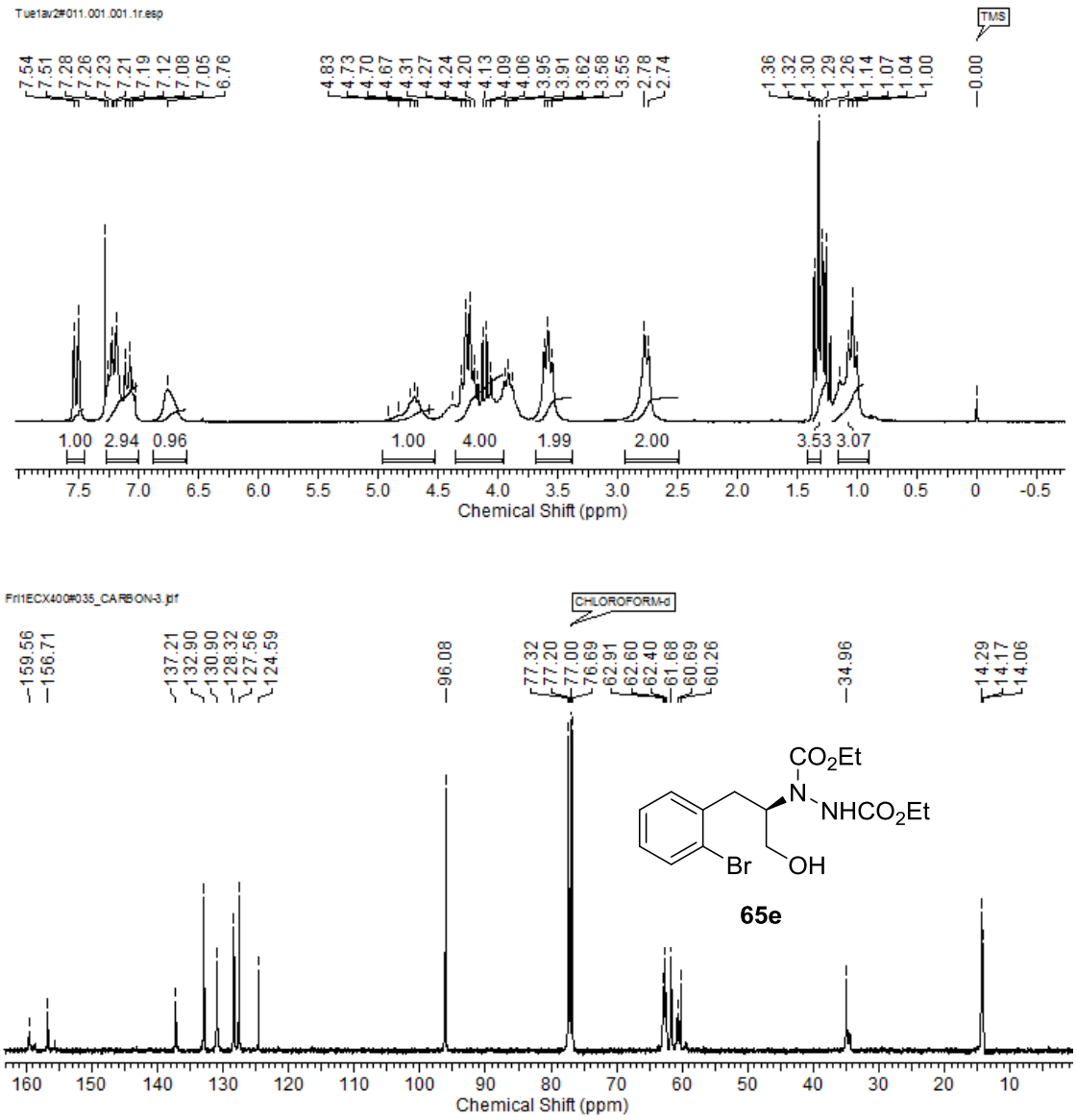
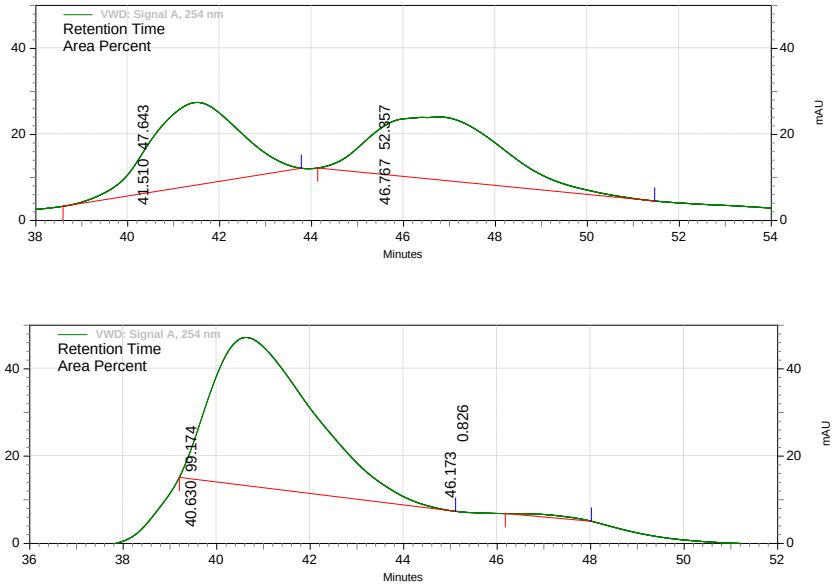


Fig. 10: ^{1}H and ^{13}C NMR spectra of hydrazino alcohol **65e**

Further, the formation of hydrazino alcohol **65e** was clearly demonstrated by a strong IR absorption bands at 1715 and 3282 cm^{-1} due to the C=O and OH stretching frequencies of the carbamate and primary alcohol groups respectively (**Fig. 11**).The enantiomeric excess of hydrazine alcohol **65e** (>98% ee**)** was determined from chiral HPLC analysis (**Fig. 11**); column chiracel OD-H (n-hexane/isopropanol, 95:5).



Ret. Time	Area	Area %	Height	Height %
40.630	86872264	99.17	569409	100.00
46.173	723101	0.83	0	0.00
Totals	87595365	100.00	569409	100.00

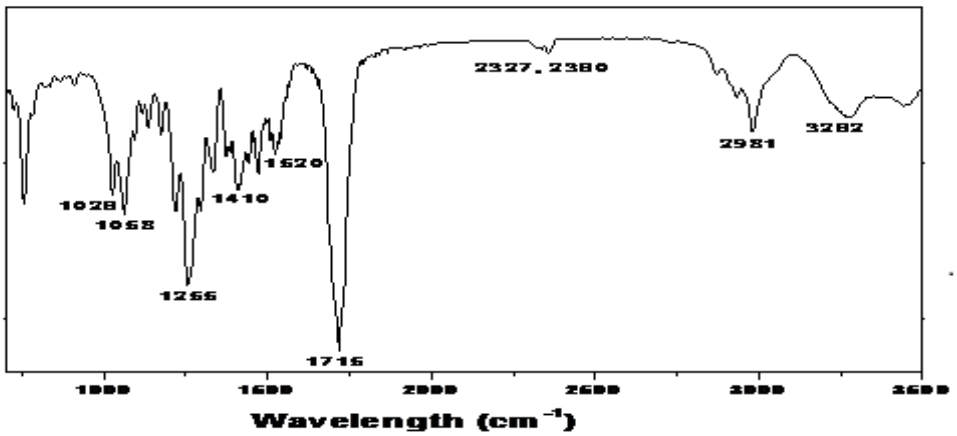


Fig. 11: HPLC chromatogram and IR spectrum of hydrazine alcohol **65e**

Example 2: The formation of 3-substituted cinnoline **96e** from the intramolecular N-arylation of **65e** was confirmed by its ^{1}H NMR spectrum, which showed two doublet of doublets at δ 4.16-4.18 (dd, *J* = 1.8, 8.9 Hz, 1H) and δ 4.67 - 4.70 (dd, *J* = 7.0, 8.9 Hz, 1H) corresponding to the diastereotopic methylene -CH_2O- protons of the 5-membered oxazolidinone ring (**Fig 12**). Another multiplet at δ 4.27-4.35 (m, 3H)

indicated the presence of methylene (-$NCO_2C\mathbf{H_2}CH_3$) and methine (-C**H**-NR_2) protons. It was further supported by the absence of a proton signal at δ 6.76 corresponding to hydrazine R_2N-N**H**R proton.

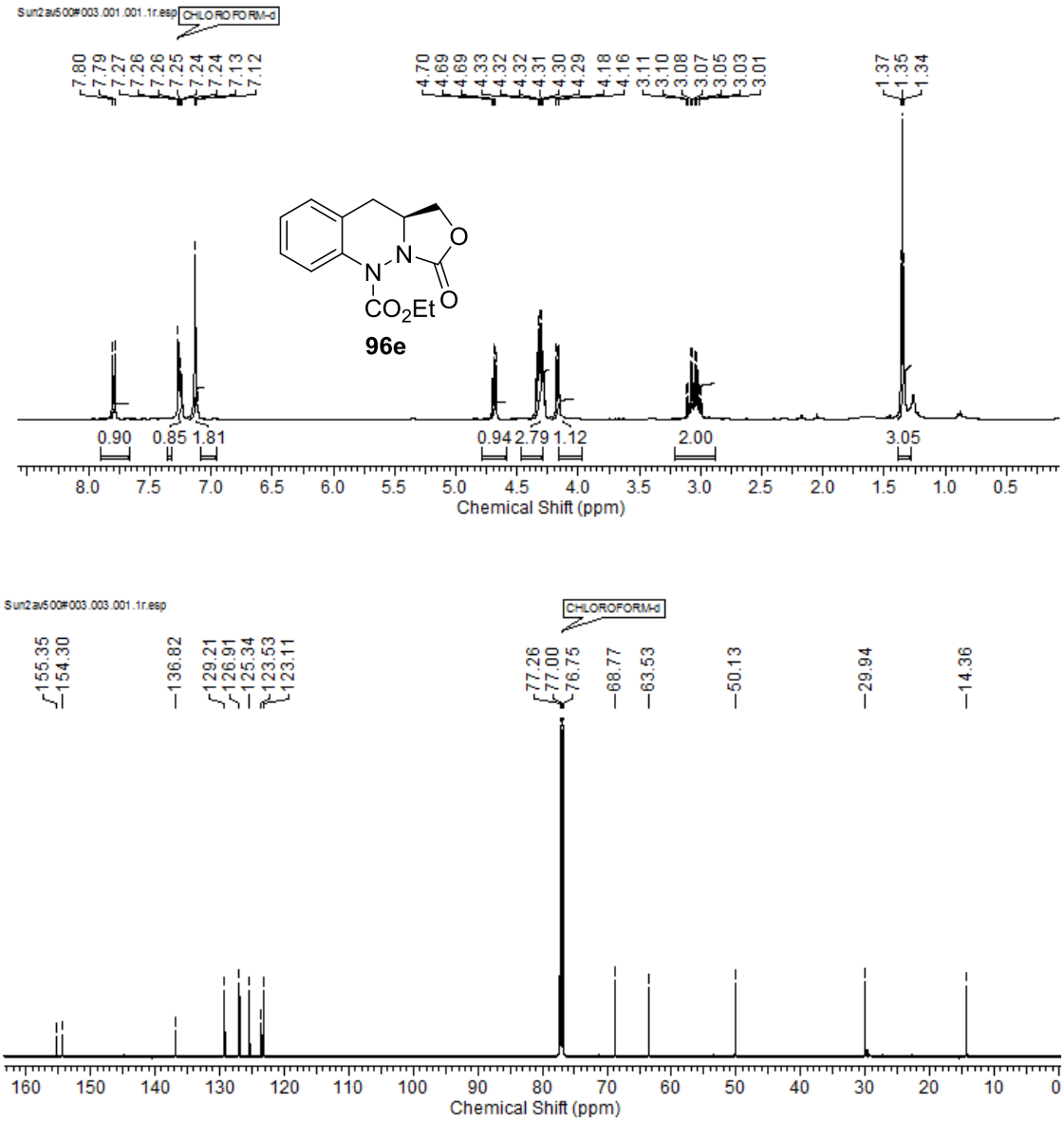


Fig.12: ^{1}H and ^{13}C NMR spectra of cinnoline derivative **96e**

Its ^{13}C NMR spectrum displayed two carbon signals at δ 154.3 and 155.3 due to the carbonyl (C=O) carbons of the carbamate and oxazolidinone moieties**.** Also, carbon signals at δ 50.1 and 68.7 indicated the presence of methine (-**C**HNR_2) and methylene

(-**C**H_2-OR) carbons respectively. An upfield shift in the quarternary aromatic carbon at δ 123.1 from 137.2 i.e. *ortho* to anilinic carbon confirmed the N-arylation process (**Fig. 12)**.

Further, an interesting and challenging substrate of the methodology having two chiral centres (dr = 1:1) was cinnoline derivative **96f** which was obtained from hydrazine **65f.** Its ^{1}H NMR spectrum showed two multiplets at δ 2.44-2.71 (m, 2H) and δ 2.76 - 3.12 (m, 2H) corresponding to the diastereotopic allylic and benzylic methylene protons respectively. Another multiplet at δ 4.19-4.34 (m, 3H) indicated the presence of methylene (-NCO_2C**H_2**CH_3) and methine (-C**H**-NR_2) protons **(Fig. 13)**.[25]

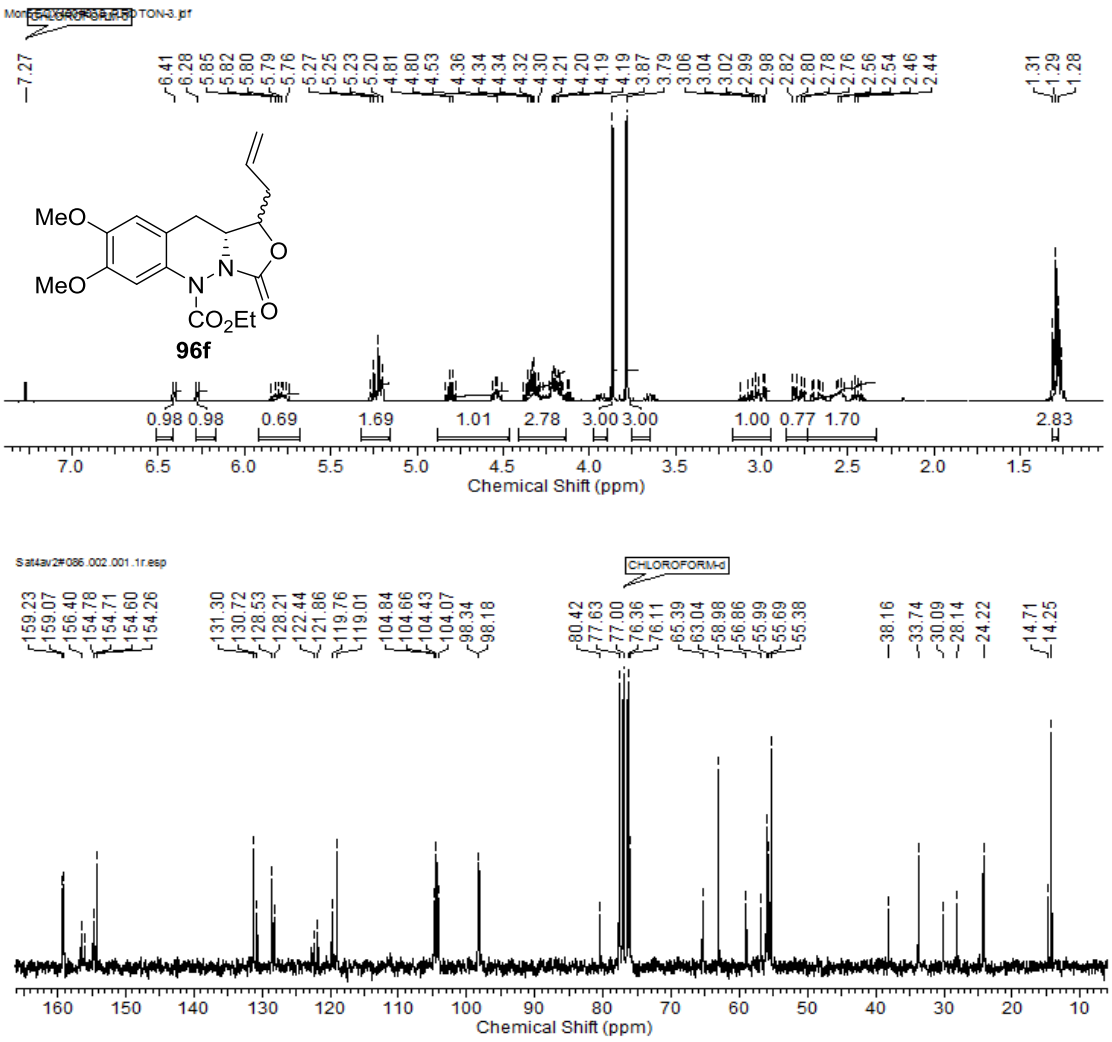
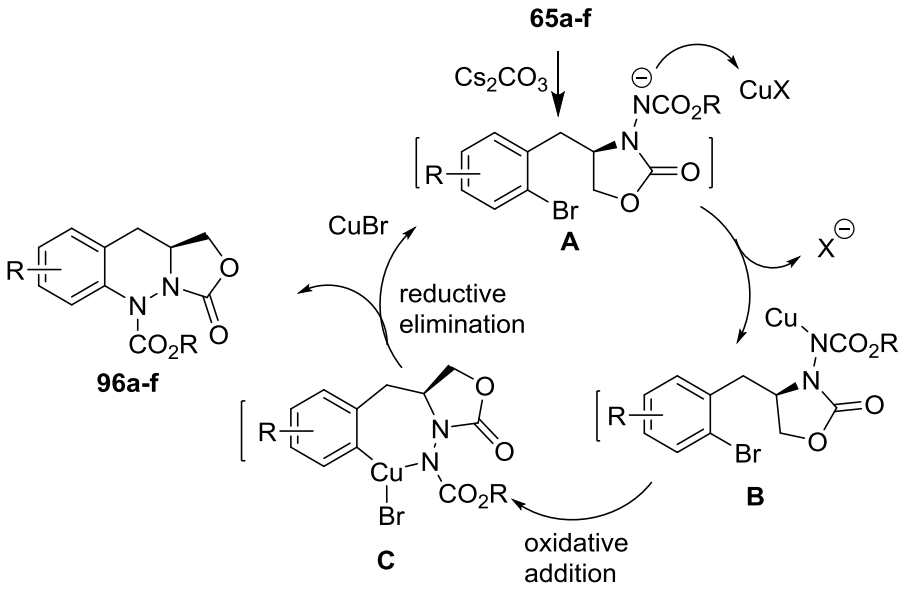


Fig. 13: ^{1}H and ^{13}C NMR spectra of cinnoline derivative **96f**

The absence of a proton signal at δ 6.56 (brs, 1H) corresponding to hydrazine R_2N-N**H**R confirmed the formation of **96f** *via* N-arylation (**Fig. 13**). The other proton signals at 5.20-5.27 (m, 2H) and 5.74-5.85 (m, 1H) were due to the terminal and internal olefinic protons respectively. The ^{13}C NMR spectrum displayed two typical carbon signals at δ 154.3 and 156.4 due to the carbonyl (C=O) carbons of the oxazolidinone and carbamate moieties. Also, an upfield shift in the aromatic methine carbons at δ 98.2 and 104.6 indicated the occurrence of intramolecular N-arylation. The other carbon signals at δ 159.1 and 159.2 were due to the presence of aromatic quarternary carbons attached to methoxy groups (**Fig. 13**).

A probable catalytic cycle for the formation of cinnoline derivatives **96a-g** is shown in **Scheme 28**. Firstly, base abstracts hydrazinic proton of **65a-f** to form the hydrazine carbamate anion **A,** which reacts with CuI/DMEDA catalyst to generate the Cu-coordinated intermediate **B**.



Scheme 28: Catalytic cycle for cinnoline formation

This in turn is followed by an intramolecular oxidative addition of Cu(I) into the C-Br bond of aryl bromide to produce the 7-membered organocopper species **C**.

Subsequent reductive elimination of organocopper species C results in N-arylation to deliver cinnolines **96a-f** with the release of CuBr back into the catalytic cycle.

3.2.4 Conclusion

In conclusion, we have described, for the first time, that chiral hydrazines **65a-f** can be successfully transformed into 3-substituted dihydrocinnoline derivatives **96a-f** in high yields, *via* Cu-catalyzed intramolecular N-arylation. The salient features of the methodology are as follows: (a) chiral cinnolines have been prepared, for the first time under milder reaction conditions in high yields with excellent enantioselectivity; (b) intramolecular N-arylation reaction has shown good functional group tolerance, and (c) proline is available in both enantiomeric forms to obtain the desired enantiomers.

3.2.5 Experimental Section:

Preparation of cinnolines 96a-f:

To a suspension of **65a-f** (1.0 mmol) and Cs_2CO_3 (714 mg, 2.2 mmol) in CH_3CN (10 mL), was added CuI (20 mg, 0.1 mmol), DMEDA (10 mg, 0.1 mmol) and the whole mixture was stirred at 100 ^oC for 12 h. The reaction was quenched with saturated aq. NH_4Cl, and extracted with EtOAc (3x10 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude products were purified by flash column chromatography to give cinnolines **96a-f** in pure form.

Isopropyl (*R*)-7-oxo-9a,10-dihydro-7H-[1,3]dioxolo[4,5-g]oxazolo[3,4-b]cinnoline-5(9H)-carboxylate (96a)

Yield: 72%; pale yellowish gum; $[\alpha]^{25}_D$: +48.7 (*c* 0.2, $CHCl_3$, cm^{-1}); **IR** ($CHCl_3$,cm^{-1}): υ_{max} 1060, 1177, 1377,1726, 1784, 2900, 3050; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.30-1.36 (m, 6H), 2.80-3.05 (m, 2H), 4.09-4.15 (dd, *J* = 2.5, 8.7 Hz, 1H), 4.22-4.34 (m, 1H), 4.62-4.74 (dd, *J* = 6.9, 8.7 Hz, 1H), 4.99-5.11 (m, 1H), 5.93-5.97 (dd, *J* = 1.4,

5.4 Hz, 2H), 6.54 (s, 1H), 7.25 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.9, 30.2, 50.5, 68.9, 71.6, 101.3, 105.2, 107.9, 116.9, 131.3, 145.3, 146.2, 153.9, 155.5; **HRMS** data; HRMS (ESI+, *m/z*): calcd for $(C_{15}H_{16}N_2O_6)^+$ $[(M+H)^+]$ 321.1087; found: 321.1083; **Analysis**: $C_{15}H_{16}N_2O_6$ requires; C, 56.25; H, 5.04; N, 8.75; Found: C, 56.58; H, 5.12; N, 8.67 %.

Diethyl (*R*)-7-hydroxy-3-(hydroxymethyl)-6-methoxy-3,4-dihydrocinnoline-1,2-dicarboxylate (96b)

Yield: 70%; colorless gum; $[\alpha]^{25}_D$: +72.7 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1037, 1095, 1299, 1750, 1785, 2950, 3400; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.35 (t, *J* = 7.0 Hz, 3H), 1.46 (t, *J* = 7.0 Hz, 3H), 2.93-3.00 (m, 2H), 3.82 (s, 3H), 4.08-4.12 (q, *J* =7.0 Hz, 2H), 4.14-4.15 (d, *J* = 8.5 Hz, 1H), 4.21-4.26 (q, *J* = 8.2 Hz, 1H), 4.27-4.32 (q, *J* = 7.0 Hz, 2H), 4.66 (t, *J* = 7.0 Hz, 1H), 6.55 (s, 1H), 7.39 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.4, 14.6, 29.5, 50.1, 56.1, 63.3, 64.4, 68.8, 108.2, 111.4, 114.9, 130.0, 146.8, 146.9, 154.4, 155.3; **Analysis**: $C_{16}H_{22}N_2O_7$ requires; C, 54.23; H, 6.26; N, 7.91; Found: C, 54.11; H, 6.37; N, 7.99 %.

Ethyl (*R*)-6,8-dimethoxy-3-oxo-10,10a-dihydro-3H-oxazolo[3,4-b]cinnoline-5(1H)-carboxylate (96c)

Yield: 72%; colorless gum; $[\alpha]^{25}_D$: -16.9 (*c* 0.9, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 700, 1037, 1056, 1095, 1726, 1775, 2900, 3050; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.29 (t, *J* = 7.0 Hz, 3H), 2.73-2.77 (dd, *J* = 3.4, 16.8 Hz, 1H), 3.05-3.10 (dd, *J* = 7.9, 16.5 Hz, 1H), 3.76 (s, 3H), 3.86 (s, 3H), 4.04-4.08 (m, 1H), 4.15-4.22 (m, 1H), 4.30-4.37 (m, 1H), 4.59-4.65 (m, 2H), 6.27-6.28 (d, *J* = 1.8 Hz, 1H), 6.40-6.41 (d, *J* = 2.1 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.4, 30.4, 52.5, 55.5, 56.1, 63.2, 69.2, 98.4, 104.8, 122.3, 128.4, 154.4, 154.9, 157.0, 159.3; **Analysis**: $C_{15}H_{18}N_2O_6$ requires; C, 55.90; H, 5.63; N, 8.69; Found: C, 55.82; H, 5.50; N, 8.51 %.

Ethyl (*R*)-6,7,8-trimethoxy-3-oxo-10,10a-dihydro-3H-oxazolo[3,4-b]cinnoline-5(1H)-carboxylate (96d)

Yield: 65%; colorless gum; $[\alpha]^{25}_{D}$: -3.32 (*c* 2.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1056, 1098, 1154, 1380, 1495, 1736, 1780, 2920, 3050, 3115; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.23 (t, *J* = 7.2 Hz, 3H), 2.63-2.73 (dd, *J* = 3.8, 16.8 Hz, 1H), 2.92-3.04 (dd, *J* = 7.6, 16.6 Hz, 1H), 3.76 (s, 3H), 3.81 (s, 3H), 3.91 (s, 3H), 3.98-4.07 (m, 1H), 4.11-4.34 (m, 2H), 4.46-4.62 (m, 2H), 6.38 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 29.6, 52.2, 55.9, 60.8, 60.9, 63.2, 69.2, 106.7, 121.9, 126.0, 141.2, 147.9, 152.4, 154.7, 156.7; **Analysis**: $C_{16}H_{20}N_2O_7$ requires; C, 54.54; H, 5.72; N, 7.95; Found: C, 54.76; H, 5.64; N, 7.77%.

Ethyl (*R*)-3-oxo-10,10a-dihydro-3H-oxazolo[3,4-b]cinnoline-5(1H)-carboxylate (96e)

Yield: 70%; colorless solid; **mp** 143-146 ^{o}C; $[\alpha]^{25}_{D}$: +113.3 (*c* 0.9, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1060, 1177, 1377, 1735, 1797, 2950, 3120; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.34 (t, *J* = 7.0 Hz, 3H), 2.96-3.10 (m, 2H), 4.15-4.17 (dd, *J* = 1.8, 8.9 Hz, 1H), 4.26-4.36 (m, 3H), 4.66-4.69 (dd, *J* = 7.0, 8.9 Hz, 1H), 7.10-7.12 (m, 2H), 7.23-7.25-4.22 (m, 1H), 7.78-7.79 (d, *J* = 7.9 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.4, 29.9, 50.1, 63.5, 68.8, 123.1, 123.5, 125.3, 126.9, 129.2, 136.8, 154.3, 155.4; **Analysis**: $C_{13}H_{14}N_2O_4$ requires; C, 59.54; H, 5.38; N, 10.68; Found: C, 59.36; H, 5.49; N, 10.78%.

Ethyl (10a*R*)-1-allyl-7,8-dimethoxy-3-oxo-10,10a-dihydro-3H-oxazolo[3,4-b]cinnoline-5(1H)-carboxylate (96f)

Yield: 63%; yellowish gum; $[\alpha]^{25}_{D}$: +8.1 (*c* 1.6, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1040, 1177, 1377, 1740, 1790, 2900, 3050, 3126; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.27 (t, *J* = 7.0 Hz, 3H), 2.38-2.69 (m, 2H), 2.74-2.80 (dd, *J* = 7.8, 17.8 Hz, 1H), 2.96-3.10 (m, 1H), 3.77 (s, 3H), 3.85 (s, 3H), 4.10-4.36 (m, 3H), 4.49-4.81 (m, 1H), 5.18-5.25 (m, 2H), 5.73-5.84 (m, 1H), 6.26 (s, 1H), 6.39 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ

14.3, 28.1, 33.7, 55.4, 56.0, 59.1, 63.2, 76.3, 98.2, 104.5, 119.7, 122.7, 128.5, 131.3, 154.3, 156.4, 159.0, 159.2; **HRMS** data; HRMS (ESI+, *m/z*): calcd for $(C_{15}H_{16}N_2O_6)^+$ $[(M+H)^+]$ 363.1556 and found 363.1550; **Analysis**: $C_{18}H_{22}N_2O_6$ requires; C, 59.66; H, 6.12; N, 7.73; Found: C, 59.45; H, 6.33; N, 7.50%.

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26 Phenolic OH of **65b** was also underwent O-alkylation to give the corresponding product **67b** (therefore, 2.2 equiv of ethylbromo acetate was used for that substrate).

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CHAPTER IV

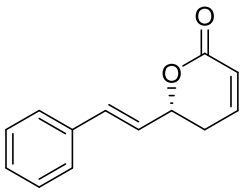
A Concise Enantioselective Synthesis of *R*-(+)-Goniothalamin oxide and Tandem Azidation, Intramolecular [3+2]-Cycloaddition of Acrylates for the Regioselective Synthesis of Triazole Derivatives

Section I:

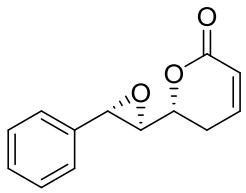
A Concise Enantioselective Synthesis of *R*-(+)-Goniothalamin Oxide, A Trypanocidal Active Agent *via* Organocatalyzed Asymmetric Epoxidation and Diastereoselective Allylation of Aldehydes

4.1.1 Introduction

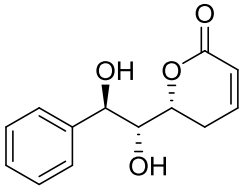
Chiral six-membered lactones are common subunits present in a variety of natural products and bioactive molecules. For example, styryl lactones (**Fig. 1**) are a group of secondary metabolites commonly isolated from the genus *Goniothalamus*.[1] These bioactive natural products (**1-4**) with relatively small and densely functionalized molecules are found to exhibit cytotoxicity on a variety of cells lines including: MCF-7, T47D, and MDA-MB-231 (breast carcinoma); HeLa (human cervical carcinoma); HL-60 (leukemia carcinoma); Caov-3 (ovarian carcinoma).[2] In particular, *R*-(+)-goniothalamin oxide (**2**) shows significant trypanocidal activity against free trypomastigotes forms of *trypanosome cruzi*.[3]



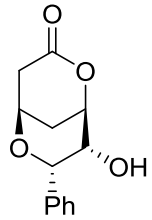
R-(+)-Goniothalamin (**1**)



R-(+)-Goniothalamin oxide (**2**)



(+)- Goniodiol (**3**)



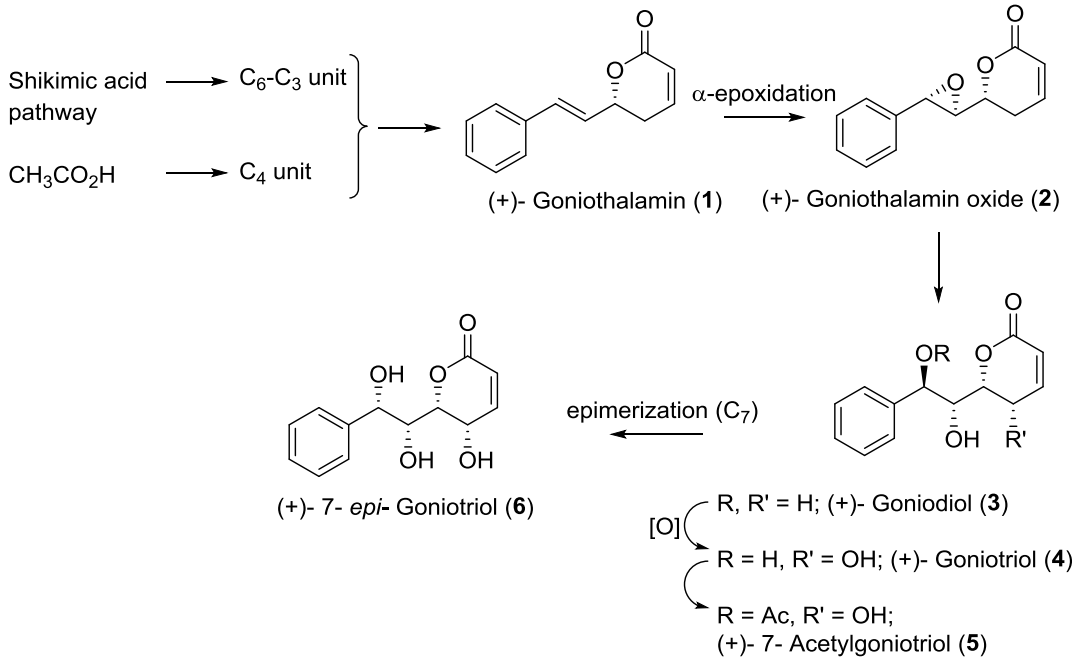
(+)-9-Deoxygoniopyrone (**4**)

Fig. 1: Structures of bioactive styryllactones (**1-4**)

Its unique structural features coupled with potent biological activities make (**2**) an ideal target for testing new synthetic methodology. Consequently, there have been consistent efforts toward the total synthesis of *R*-(+)-goniothalamin oxide (**2**).[5-9]

4.1.2 Pharmacology and mode of action

Natural products containing this lactone unit also possess a wide range of biological activity such as insect antifeedants, antifungal, plant growth inhibitors, etc.



Scheme 1: Proposed biosynthetic pathways for styryllactones

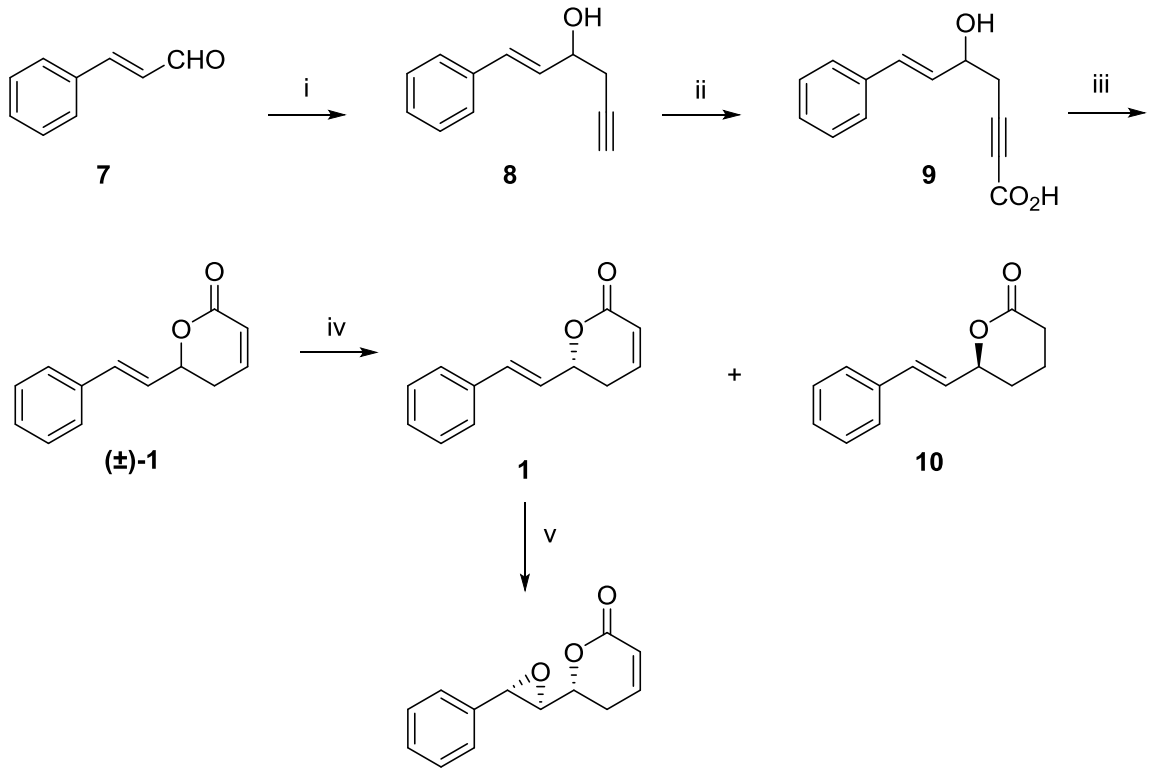
The α, β- unsaturated δ- lactone functionality is presumed to be responsible for the biological activities due to its ability to act as a Michael acceptor, enabling these molecules to bind to a target enzyme. Literature report reveals that *R*-(+)-goniothalamin oxide (**2**) is considered to be the biosynthetic precursor to other styryllactones as well. Thus, *R*-(+)-goniothalamin oxide (**2**) may be more important and can be an immediate precursor to many higher-order functionalized styryllactones **3**-**6** (**Scheme 1**).[4]

4.1.3 Review of literature

Literature search revealed that there are only few reports are available for the synthesis of *R*-(+)-goniothalamin oxide (**2**). These include chiral pool, chemo-enzymatic approach or enantioselective syntheses, which are described below.

Stefano's approach (1994)[5]

Stefano *et al.* have reported the synthesis of *R*-(+)-goniothalamin oxide (**2**) by employing the enzymatic reduction of α, β-unsaturated δ-lactone, (±)-**1** as the key reaction.

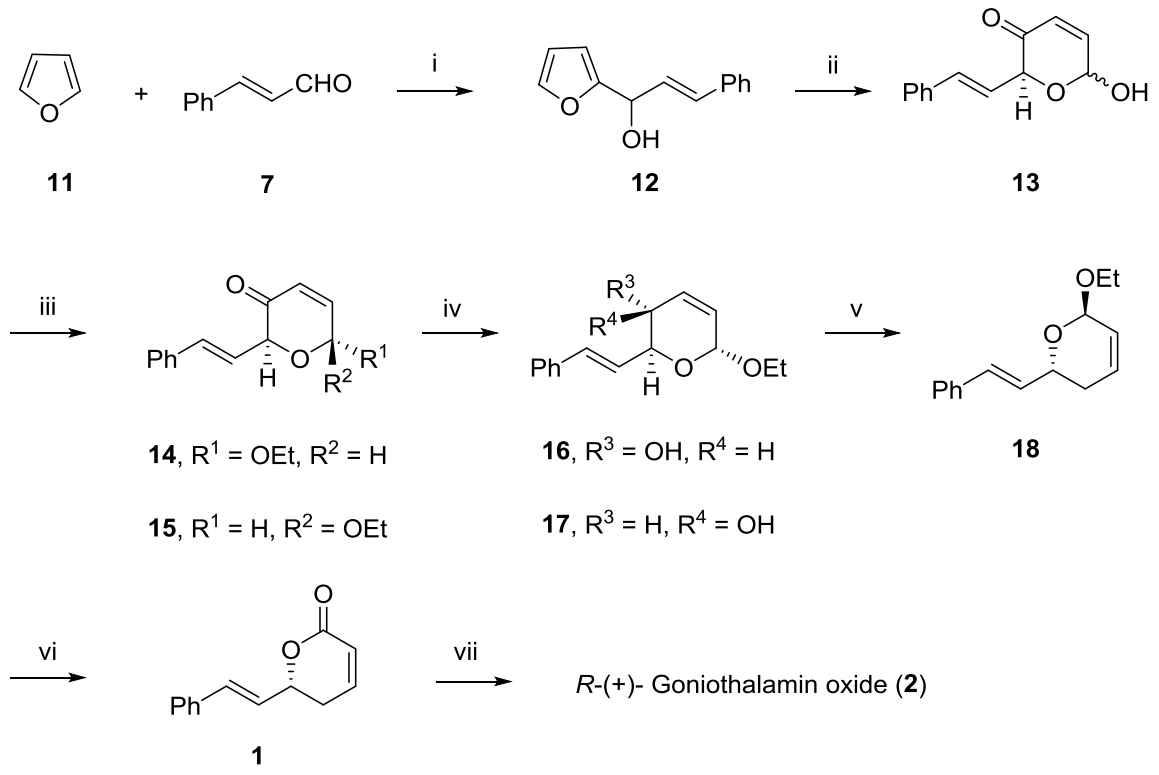


R-(+)- Goniothalamin oxide (**2**)

Scheme 2: (i) propargyl magnesium bromide, THF, 25 ^{o}C, 2 h, 60%; (ii) *n*-BuLi, solid CO_2, THF, -40 ^{o}C, 1 h, 87.5%; (iii) Lindlar catalyst, H_2 (1 atm), EtOAc, 4 h, 71%; (iv) Baker's yeast, D-glucose, DMSO, 36 °C, 6 h, 36%; (v) *m*-CPBA, CH_2Cl_2, 40 ^{o}C, 8 h, 90%.

Thus, cinnamaldehyde **7** was subjected to Grignard reaction with propargyl magnesium bromide, giving alcohol **8** in 60% yield. Carboxylation of terminal alkyne **8** with solid CO_2 in presence of *n*-BuLi gave acetylenic carboxylic acid **9**, which on subsequent *cis*-reduction with Lindlar catalyst furnished racemic α, β-unsaturated δ-lactone (±)-**1** in 80% yield (for 2 steps). The racemic lactone (±)-**1** was then subjected to enzymatic reduction with Baker's yeast to furnish chiral α, β-unsaturated δ-lactone **1** (99% ee) and saturated lactone **10**. Finally, diastereoselective epoxidation of **1** with *m*-CPBA gave *R*-(+)-goniothalamin oxide (**2**) in 90% (**Scheme 2**).

Pan's approach (2002)[6]



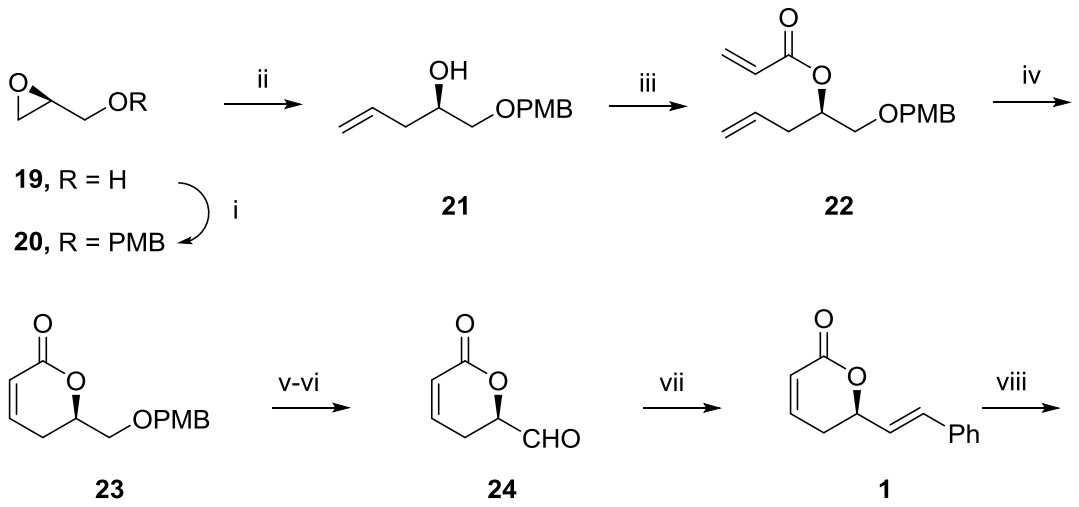
Scheme 3: (i) *n*-BuLi, THF, –78 °C, 1 h, 90%; (ii) (+)-DIPT, Ti(O-*i*Pr)$_4$, TBHP, CH_2Cl_2, -25 °C, 6 h, 35%; (iii) ethyl vinyl ether, PPTS, CH_2Cl_2, 25 ^oC, 2 h, (**14**, 74%), (**15**, 10%); (iv) $NaBH_4$, $CeCl_3$. $7H_2O$, MeOH, –30 to –40 °C, 4 h, (**16,** 78%), (**17**, 4%); (v) (a) Et_3N, DMAP, CH_3SO_2Cl, CH_2Cl_2, 0 °C, 1 h, 90%; (b) $LiAlH_4$, THF, 50 °C, 3 h, 74%; (vi) CrO_3/AcOH, 25 ^oC, 3 h; (vii) *m*-CPBA, CH_2Cl_2, 25 ^oC, 6 h, 96%.

Pan *et al.* have employed Sharpless kinetic resolution of racemic secondary 2-furylmethanol **12** as the key reaction. The kinetic resolution of compound **12** was performed to afford pyranone **13** in 35% yield with 95% ee. Protection of the lactol **13** with ethyl vinyl ether gave the corresponding α- and β-ethoxyethyl ethers **14** (74%) and **15** (10%) respectively. Reduction of major diastereomer **14** with $NaBH_4$ in the presence of $CeCl_3.7H_2O$ furnished the allyl alcohols **16** and **17** in 78% and 4.0% yield respectively. The alcohol **16** was deoxygenated by successive methanesulfonylation followed by lithium aluminium hydride reduction of the mesylate to afford compound **18**. Finally, oxidation of **18** with Jones' reagent gave **1**, which on subsequent olefinic epoxidation provided the natural product **2** in 96% yield **(Scheme 3)**.

Marko's approach (2006)[7]

Marko *et al*. have commenced their synthesis from commercially available (*R*)-glycidol (**19**), which was protected with PMB yielding the corresponding epoxy ether **20.** Cu-catalyzed regioselective opening of epoxide **20** with vinyl magnesium bromide furnished the optically enriched homoallylic alcohol **21** in excellent yield and purity. Homoallylic alcohol **21** on smooth acylation, with acrylic acid, afforded the metathesis precursor **22**. Treatment of **22** with Grubbs' IInd generation catalyst in presence of $Ti(OPr^i)_4$ as additive resulted in the formation of the desired lactone **23** in 92% yield. Removal of the PMB group was efficiently accomplished, in the presence of the activated olefin, on treatment of **23** with DDQ. Swern oxidation of the corresponding alcohol yielded the unstable aldehyde **24**, which was subsequently subjected to standard sulfoxide-modified Julia olefination sequence, producing (*R*)-(+)-goniothalamin **1** in 78% yield with excellent

E/Z- selectivity. Finally, the target molecule (*R*)-(+)-goniothalamin oxide (**2**) was obtained in excellent yields by diastereoselective epoxidation of **1** (**Scheme 4**).



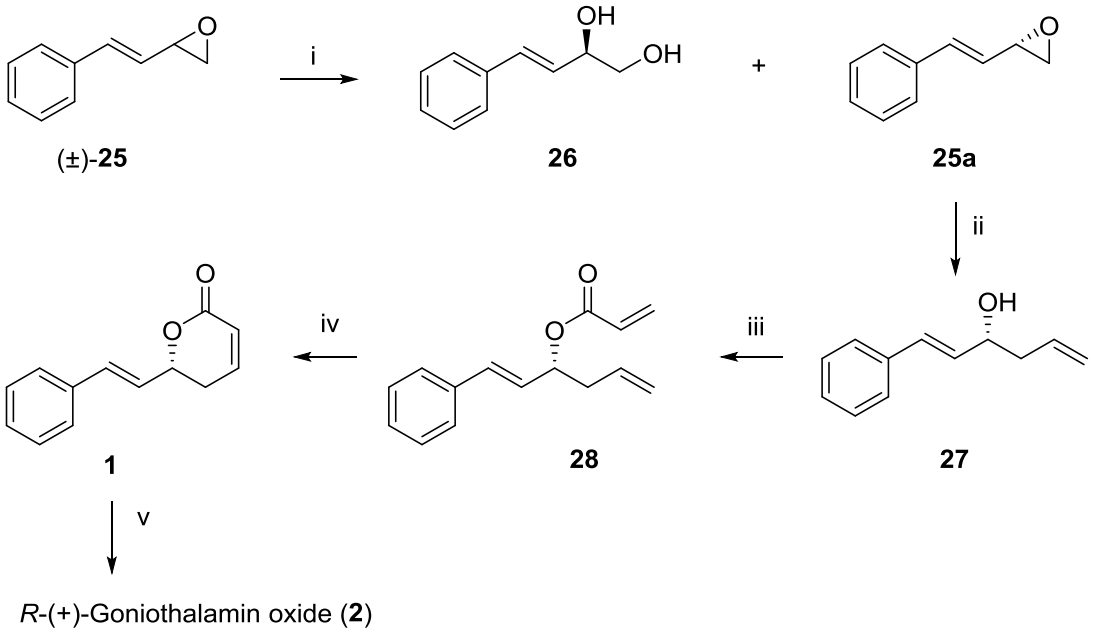
R-(+)- Gonoiothalamin oxide (**2**)

Scheme 4: (i) PMBCl, NaH, DMF, 0 ^{o}C, 2 h, 86%; (ii) CH_2=CH-MgBr, CuCN (20 mol%), THF, -20 ^{o}C, 3 h, 99%; (iii) acrylic acid, DCC, CH_2Cl_2, 25 ^{o}C, 8 h, 91%; (iv) cat. Grubbs' IInd generation catalyst, Ti(OPr^{i})$_4$, CH_2Cl_2, 40 ^{o}C, 15 h, 99%; (v) DDQ, CH_2Cl_2, 25 ^{o}C, 2.5 h, 92%; (vi) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, -78 ^{o}C, 1 h; (vii) (a) LDA, BnS(O)Ph, THF, -78 ^{o}C, 30 min; (b) BzCl, -78 ^{o}C to 25 ^{o}C; (c) $Me_2N(CH_2)_3NH_2$, SmI_2, HMPA, THF, -78 °C, 30 min, 78% (2 steps) *E/Z* = >98:1; (viii) *m*-CPBA, CH_2Cl_2, 0 ^{o}C, 24 h, 98%, dr = 19:1.

Bose's approach (2008)[8]

Bose *et al*. have achieved the synthesis of *R*-(+)-goniothalamin oxide (**2**) by employing Jacobsen's hydrolytic kinetic resolution protocol. The racemic epoxide (±)-**25** was subjected to Jacobsen's HKR resolution strategy {(*S*,*S*)-salen–Co(III)OAc (0.5 mol%), H_2O (0.55 equiv, 25 ^{o}C} to afford the (*S*)- epoxide **25a** (48% yield, 99% ee) and (*R*)-diol **26** (46% yield, 97% ee). The Cu-catalyzed regioselective opening of (*S*)- epoxide **25a**

with vinyl magnesium bromide followed by its acylation with acrylic acid afforded the metathesis precursor **28** in 78% yield. Ring-closing metathesis of **28** with the Grubbs' Ist generation catalyst furnished the lactone **1** in 98% yield. Diastereoselective epoxidation of internal olefin of **1** using (+)- (*R*, *R*)- salen–Mn(III) catalyst with oxone as an oxidant gave **2** in 90% yield (dr = 98:2) (**Scheme 5**).

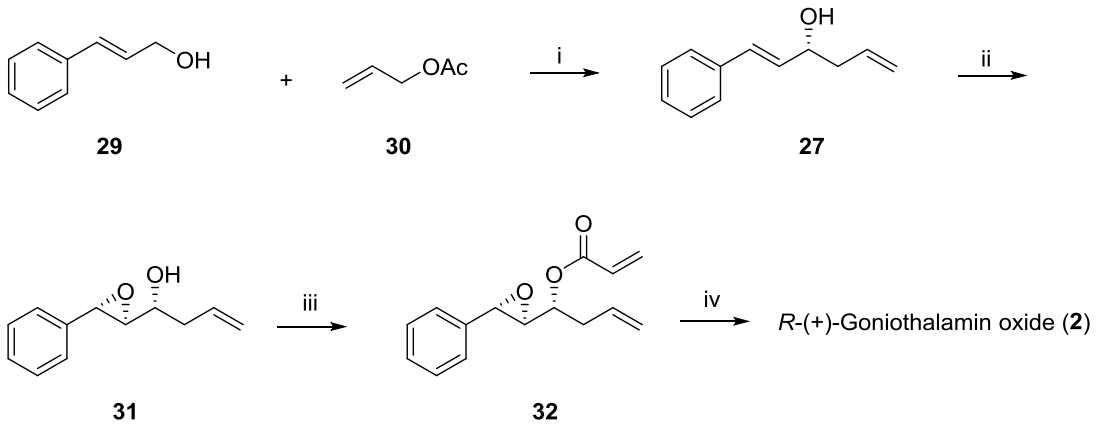


Scheme 5: (i) {Co^{III}(OAc)[(*S*, *S*)-salen]} (0.5 mol%), H_2O (0.55 equiv), 25 ^oC, 72 h, 48%, 99% ee; (ii) CH_2=CH-MgBr, CuCN (20 mol%), THF, -20 ^oC, 3 h, 99%; (iii) acrylic acid, DCC, CH_2Cl_2, 0 ^oC, 12 h, 78%; (iv) Grubbs' Ist generation catalyst (1 mol%), CH_2Cl_2 40 ^oC, 4 h, 98%; (v) (*S*, *S*)-salen–Mn(III), hexafluoroacetone, oxone, 5 h, 90%, dr = 98:2.

O'Doherty's approach (2009)[9]

O'Doherty *et al* have reported a useful method of synthesis of *R*-(+)-goniothalamin oxide (**2**) using a highly stereoselective asymmetric Krische allylation of *trans*-cinnamyl alcohol **29** as the key step. The asymmetric allylation of cinnamyl alcohol **29** using the Ir/(*R*)-Cl,MeO-BIPHEP catalytic system provided the homoallylic alcohol **27** in 68%

yield with good enantiomeric excess (90% ee). Chemo- and stereoselective epoxidation of the internal double bond in **27** with *m*-CPBA furnished **31** as inseparable diastereomers (*syn/anti* = 1.5:1).



Scheme 6: (i) cat. $[Ir(cod)Cl]_2$, cat. (*R*)-Cl,MeOBIPHEP, Cs_2CO_3, *m*-NO_2BzOH, THF, 100 ^oC, 24 h, 68%, 90% ee; (ii) *m*-CPBA, CH_2Cl_2, 0 ^oC, 3 h, 70%, dr = 1.5:1; (iii) acrylic acid, DMAP, DCC, CH_2Cl_2, 25 ^oC, 6 h, 70%; (iv) Grubbs' Ist generation catalyst (1 mol%), CH_2Cl_2 40 ^oC, 4 h, 77%.

The diastereomeric mixture **31** was acylated with acrylic acid, DMAP and DCC in CH_2Cl_2 to provide a mixture of acylated products **32** (70% yield), which were then separated by flash chromatography to give two pure diastereomers. Finally, ring closing metathesis of the desired *syn*-diastereomer using Grubbs' Ist generation catalyst furnished goniothalamin oxide (**2**) in 75% yield (**Scheme 6**).

4.1.4 Present Work:

4.1.4.1 Objective:

Review of literature reveals that only limited reports are available for the synthesis of (*R*)-(+)-goniothalamin oxide (**2**).[5-9] Additionally, use of chiral building blocks, exotic reagents, involvement of longer reaction sequences, expensive and hazardous reagents, low overall yields, low diastereomeric ratios, etc make the existing methods

uneconomical. In this section, a more practical method of synthesis of *R*-(+)-goniothalamin oxide (**2**) has been described employing organocatalyzed asymmetric epoxidation as the key reaction. Retrosynthetic analysis of reveals that homoallylic alcohol **31** could be visualized as the key intermediate.

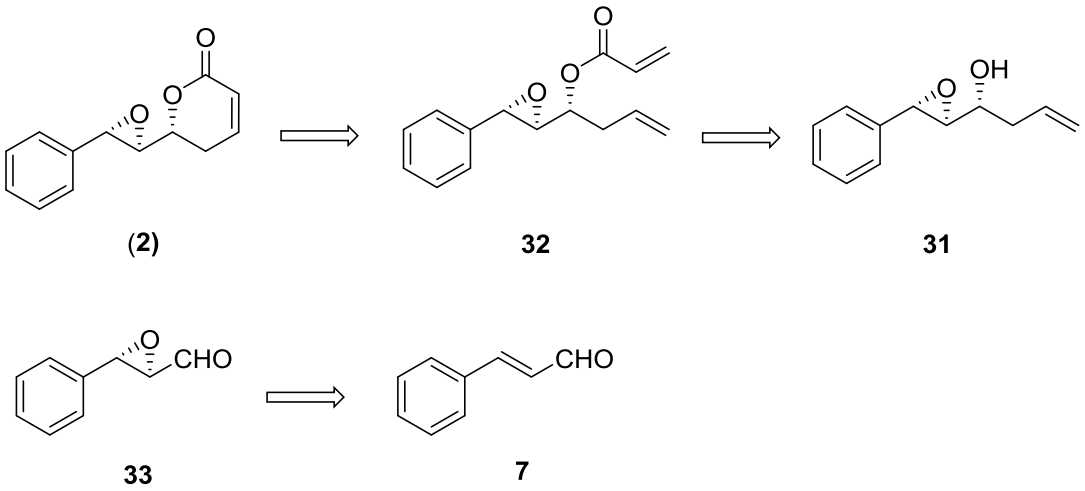


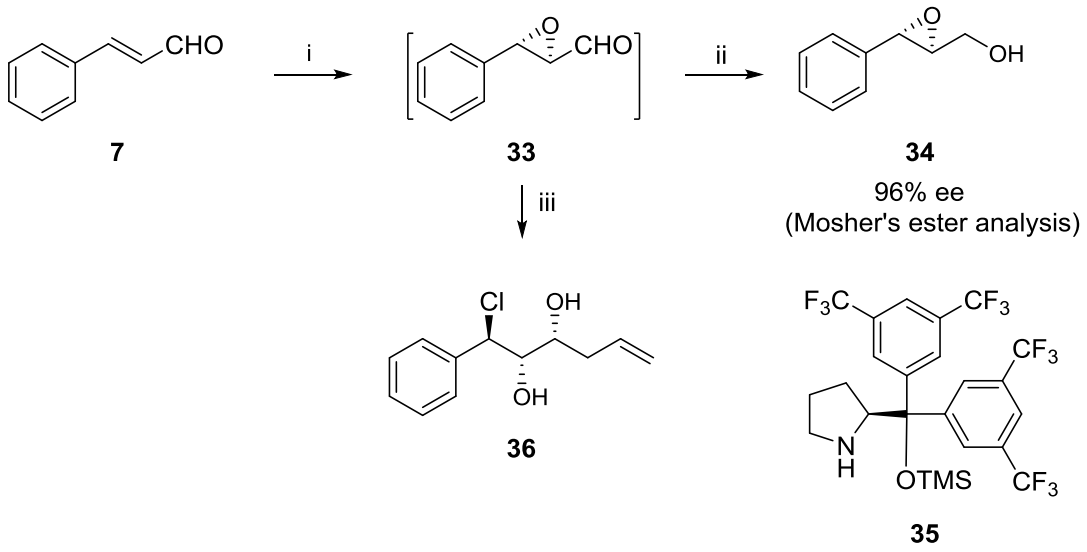
Fig. 2: Retrosynthetic analysis of *R*-(+)-goniothalamin oxide (**2**)

The homoallylic alcohol **31** could be prepared by means of Lewis acid - mediated diastereoselective allylation of epoxy aldehyde **33**, which inturn could be obtained from cinnamaldehyde **7** *via* Jorgensen's asymmetric epoxidation strategy[10] (**Fig. 2**).

4.1.4.2 Results and Discussion

In continuation of our research work on organocatalyzed reactions as applied in the asymmetric synthesis of bioactive molecules and natural products,[11] we undertook the synthesis of *R*-(+)-goniothalamin oxide (**2**) employing organocatalyzed epoxidation of cinnamaldehyde **7** followed by Lewis acid - mediated diastereoselective allylation of epoxy aldehyde **33** as the key reactions.

The synthesis of *R*-(+)-goniothalamin oxide (**2**) commenced from commercially available cinnamaldehyde **7**, which on asymmetric epoxidation with Jorgensen protocol[10] using aq. H_2O_2 in the presence of prolinol derivative **35** as the catalyst resulted in the formation of the labile epoxy aldehdye **33**. The *in situ* generated chiral epoxy aldehyde **33** was filtered through a pad of silica and subjected to reduction with $NaBH_4$ in methanol that afforded epoxy alcohol **34** as a pale yellow solid {m.p. 53.5–54 °C and $\mathbf{[\alpha]^{25}_D}$ = -48.4 (*c* 1, $CHCl_3$)} in 78% yield (**Scheme 7**).



Scheme 7: (i) 35% H_2O_2 (w/w) in water, prolinol derivative **35** (10 mol%), CH_2Cl_2, 25 ^oC, 5 h; (ii) $NaBH_4$, MeOH, 0 ^oC, 30 min, 78% (2 steps), 96% ee; (iii) $TiCl_4$, tributyl allyl stannane, CH_2Cl_2, -78 °C, 30 min, 60%, dr = >99%.

The formation of epoxy alcohol **34** was confirmed from its ^1H NMR spectrum, which showed a doublet at δ 3.90 (d, *J* = 2.2 Hz, 1H) and a multiplet at δ 3.17-3.22 (m, 1H) corresponding to methine protons of epoxide functionality. Its ^{13}C NMR spectrum showed two typical carbon signals at δ 55.4 and 62.4 indicative of the methine carbons of epoxide function, thus confirming the formation of epoxy alcohol **34** (**Fig. 3**).

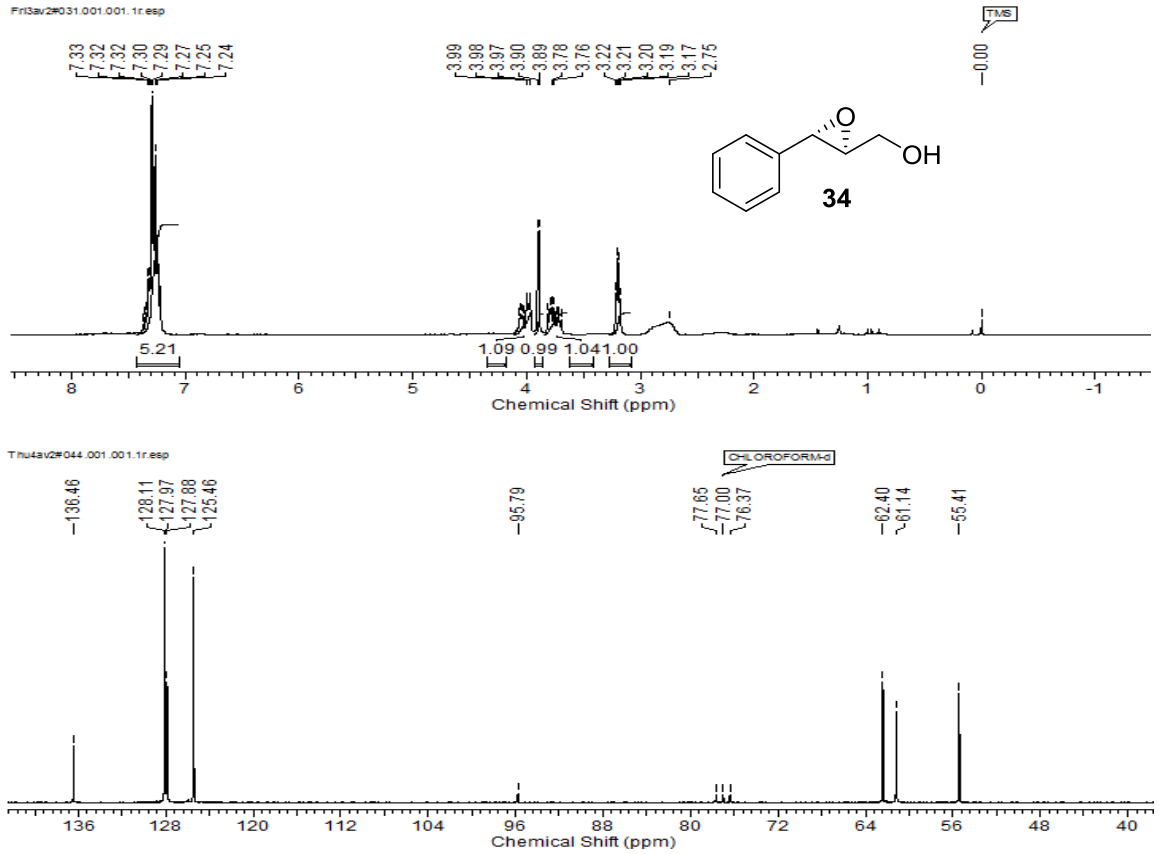


Fig. 3: ^{1}H and ^{13}C NMR spectra of epoxy alcohol **34**

The enantiomeric excess of epoxy alcohol **34** (96% ee) was determined from ^{1}H NMR analysis of the corresponding Mosher's ester **34b** (**Fig. 4**).

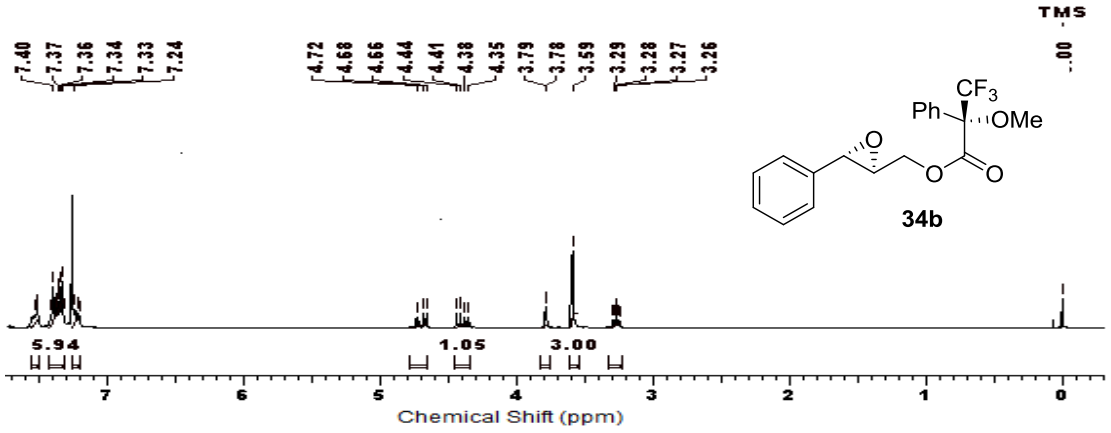
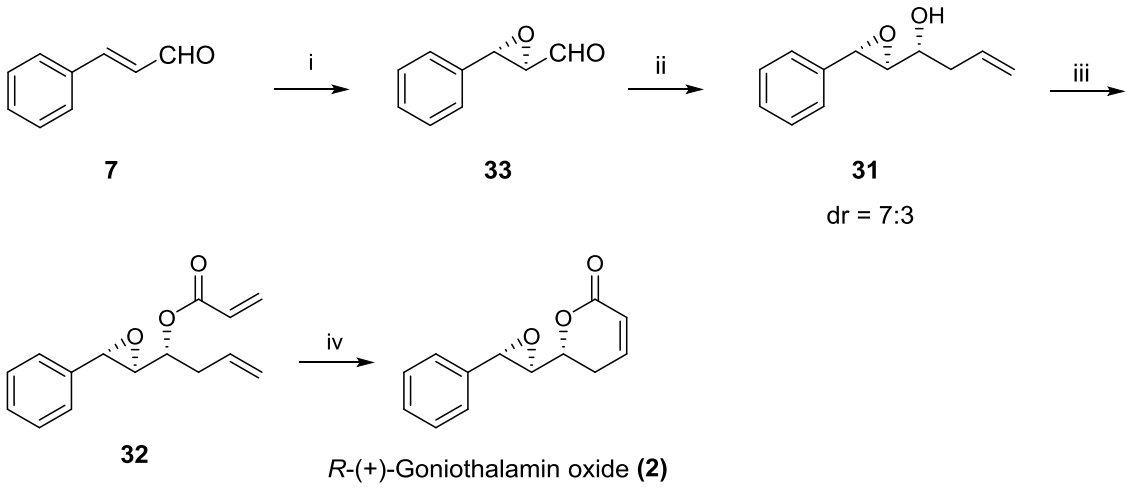


Fig. 4: ^{1}H NMR spectrum of Mosher's ester **34b**

Our next task was to prepare homoallylic alcohol **31** from epoxy aldehyde **33.** To achieve this, the *in situ* generated chiral epoxy aldehdye **33** was subjected to Ti-mediated diastereoselective allylation ($TiCl_4$, tri-*n*-butyl allyl stannane, CH_2Cl_2, -78 ^oC) with a view to obtain the key intermediate homoallylic alcohol **31**. Unexpectedly, it resulted in the formation of chlorodiol **36** (60 % yield, dr > 99%) probably due to the stronger Lewis acidity of $TiCl_4$ (**Scheme 7**).

Accordingly, we believed that a milder Lewis acid such as $LiClO_4$ could selectively facilitate the allylation of epoxy aldehyde **33** without affecting the epoxide functionality. Indeed, the desired homoallylic alcohol **31** was obtained in 70% yield with dr = 7:3 (determined from ^1H NMR analysis of **31**, see **Fig. 5**) as an inseparable mixture (**Scheme 8**).[12]



Scheme 8: (i) 35% H_2O_2 (w/w) in water, **35** (10 mol%), CH_2Cl_2, 25 ^oC, 5 h; (ii) tributyl allyl stannane, $LiClO_4$, diethylether, 25 ^oC, 7 h, 70% (2 steps), dr = 7:3; (iii) acrylic acid, DMAP, DCC, CH_2Cl_2, 0 ^oC-25 ^oC, 8 h, 91%; (iv) Grubbs' IInd generation catalyst (10 mol %), CH_2Cl_2, 45 ^oC, 8 h, 85%.

The formation of homoallylic alcohol **31** was confirmed from its ^{1}H NMR spectrum, which showed a triplet at δ 2.44 (t, *J* = 6.7 Hz, 2H) and a multiplet at δ 3.68-3.81 (m, 1H) corresponding to allylic -C**H**$_2$ and methine (-C**H**OH) protons respectively. Further, a multiplet at δ 5.77-5.99 (m, 1H) indicated the presence of an olefinic proton. Its ^{13}C NMR spectrum displayed two typical carbon signals at δ 118.4 and 133.4 indicative of the terminal and internal olefinic carbons respectively **(Fig. 5).**

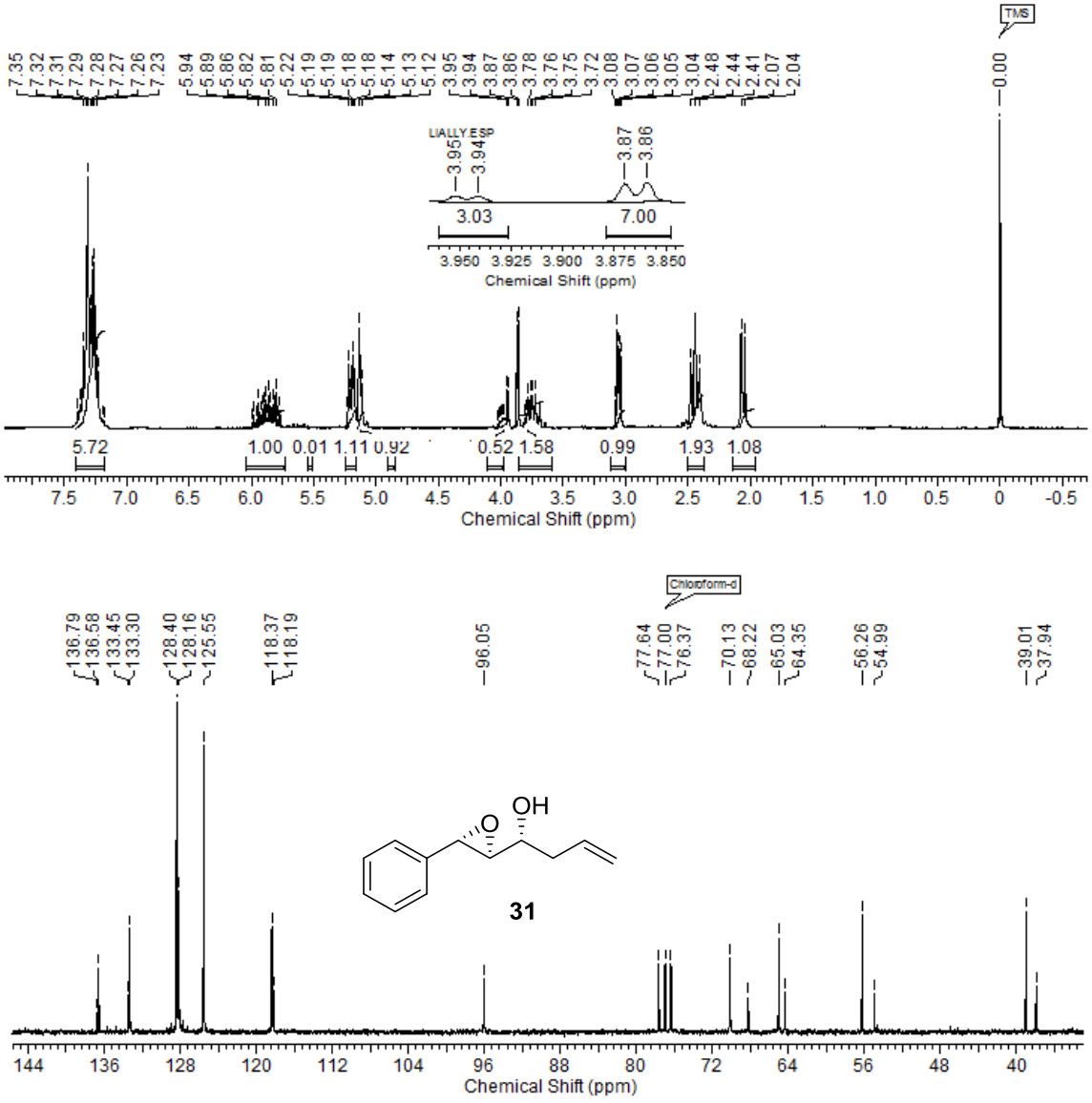


Fig. 5: ^{1}H and ^{13}C NMR spectra of homoallylic alcohol **31**

However, the Steglich esterification of homoallylic alcohol **31** with acrylic acid, (DCC, DMAP, CH_2Cl_2) gave the acrylate ester **32** {$[\alpha]^{25}_{D}$ = -26.7 (*c* 1.2, $CHCl_3$)} as a separable diastereomers, which were readily seperated *via* flash column chromatography. The formation of acrylate ester **32** (major diastereomer) was confirmed from its ^{1}H NMR spectrum, which displayed two doublet of doublets at δ 5.86-5.92 (dd, *J* = 1.6, 10.2 Hz, 1H) and 6.43-6.53 (dd, *J* = 1.6, 17.2 Hz, 1H) corresponding to terminal olefinic protons of the acrylate moiety. It was further substantiated from its ^{13}C NMR spectrum, which displayed a characteristic signal at δ 165.2 due to carbonyl carbon group **(Fig. 6)**.

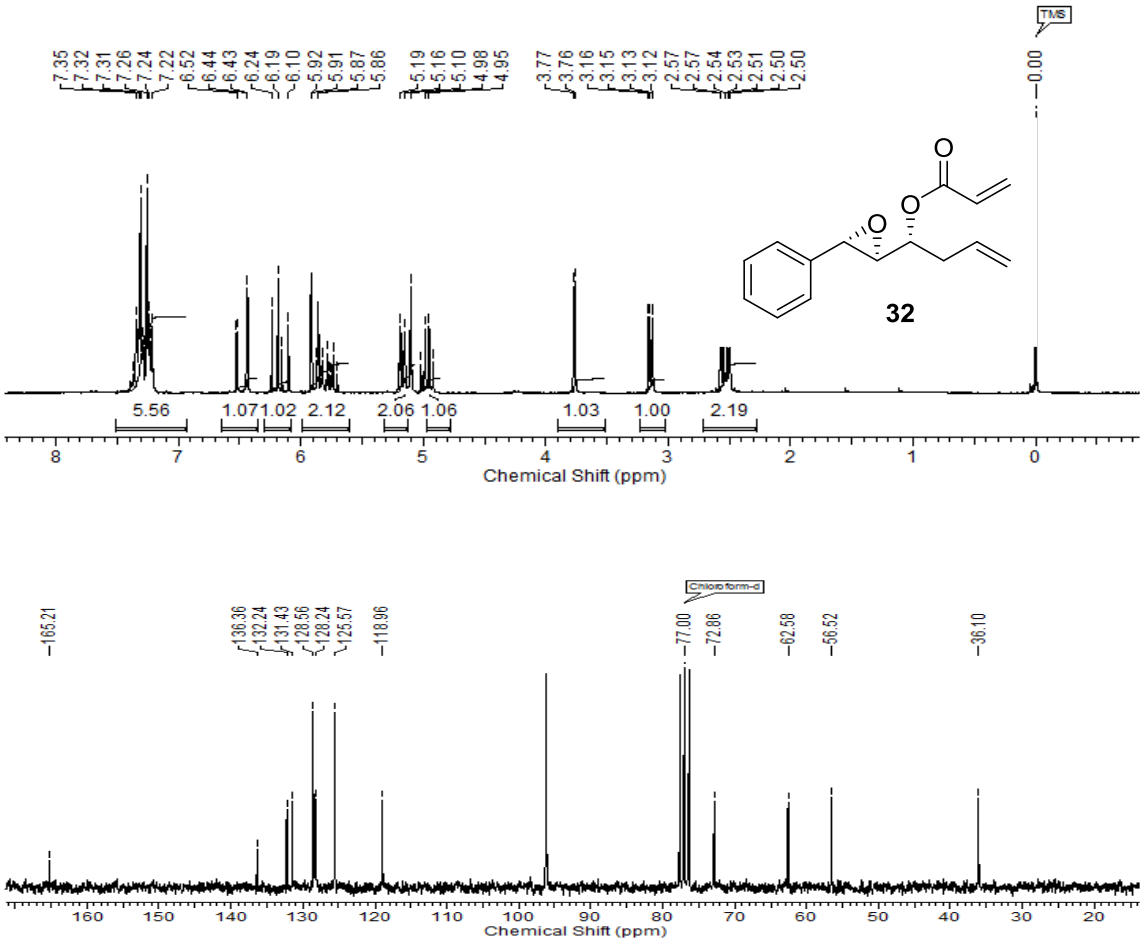


Fig.6: ^{1}H and ^{13}C NMR spectra of acrylate ester **32**

Finally, the ring closing metathesis of acrylate ester **32** with Grubbs' II[nd] generation catalyst afforded *R*-(+)-goniothalamin oxide in 76% yield. The ^{1}H NMR spectrum of **2** showed two typical multiplets at δ 6.03-6.10 (m, 1H) and 6.87-6.96 (m, 1H) due to the olefinic protons of the α, β-unsaturated δ-lactone moiety. The other proton signal at δ 2.47-2.65 (m, 2H) was attributed to allylic methylene (-C**H**$_2$CH=CH) protons of the lactone moiety (**Fig. 7**).

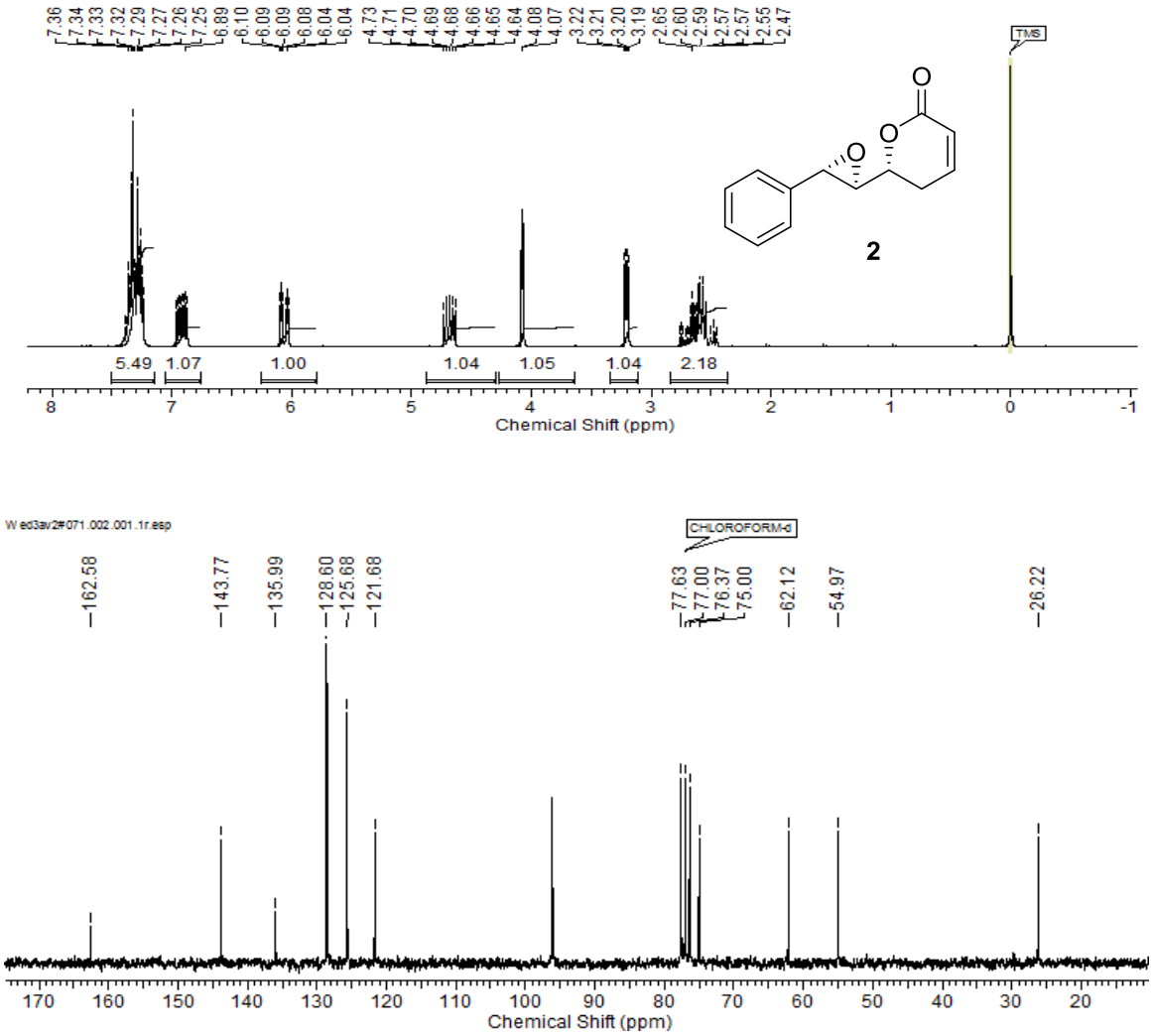


Fig. 7: ^{1}H and ^{13}C NMR spectra of *R*-(+)-goniothalamin oxide (**2**)

Its ^{13}C NMR spectrum displayed two typical carbon signals at δ 121.6 and 143.8 due to olefinic carbons of the lactone moiety, while a carbon signal at δ 162.6 indicated the presence of lactone carbonyl functionality (**Fig. 7**). Further, the formation of **2** was substantiated from its IR spectrum, which showed a strong absorption band at 1720 cm^{-1} due to the carbonyl vibration of lactone moiety (**Fig. 8**).

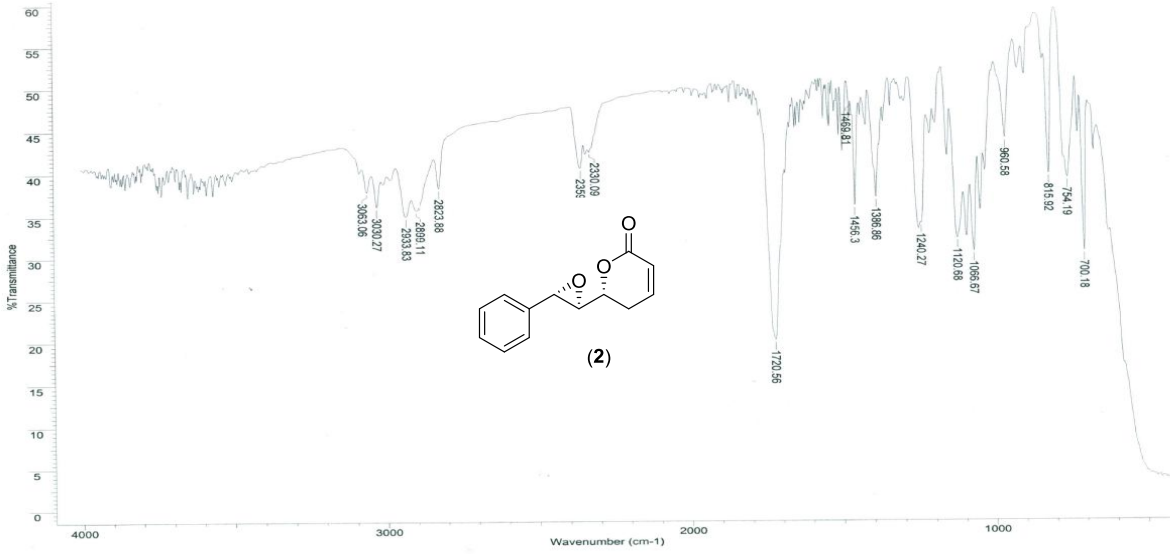


Fig. 8: IR spectrum of *R*-(+)-goniothalamin oxide (**2**)

The ee of *R*-(+)-goniothalamin oxide (**2**) was found to be 96% based on comparison of its optical rotation with the reported value[6] {$[\alpha]^{D}_{25}$ = + 99.5 (*c* 0.24, $CHCl_3$); lit. $[\alpha]^{D}_{25}$ = +100.7 (c 0.3, $CHCl_3$)}. The spectral data of (+)-goniothalamin oxide (**2**) were in good agreement with the reported values.[6]

4.1.5 Conclusion

In conclusion, an efficient and straight-forward enantioselective synthesis of (+)-goniothalamin oxide (**2**) has been achieved with an overall yield of 24.8% and 96% ee. The approach involved an organocatalyzed asymmetric epoxidation of cinnamaldehyde

followed by Lewis acid-mediated diastereoselective allylation of epoxy aldehyde as the key chiral-inducing steps. This methodology is also amenable to the synthesis of other diastereomers of styryllactone family if other antipode of the prolinol catalyst is employed.

4.1.6 Experimental section

((2*S*, 3*S*)-3-Phenyloxiran-2-yl)methanol (34)

To a stirred solution of cinnamaldehyde **7** (132 mg, 1 mmol) in CH_2Cl_2 (5 mL) at 25 °C was added prolinol derivative **35** (60 mg, 1 mmol) followed by the addition of 35% aq. H_2O_2 (44.2 mg, 1.3 mmol). After being stirred for 5 h at the same temperature, the crude reaction mixture was passed through a pad of silica gel (EtOAc/pet ether) and the filtrate concentrated under reduced pressure to give crude oxirane-2-carbaldehyde. The crude epoxy aldehyde was diluted with MeOH (5 mL) and cooled to 0 °C followed by the addition of $NaBH_4$ (75 mg, 2 mmol) to it. The mixture was then stirred for 30 min, quenched with sat. NH_4Cl and extracted with EtOAc. The organic layer was separated, dried over anhyd. Na_2SO_4 and concentrated to give the crude material, which was then purified by column chromatography over silica gel with pet. ether/EtOAc (85:15) to give the epoxy alcohol **34** (117 mg, 78%).

Yield: 78%; pale yellow solid; **mp** 53.5–54 °C; **$[\alpha]^{25}_{D}$**: -48.4 (*c* 1, $CHCl_3$) {lit.[32] $[\alpha]_D^{25}$ -49.6, (*c* 2.4, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 758, 840, 863, 881, 1027, 1068, 1108, 1256, 1392, 1462, 1606, 2871, 2927, 3017, 3428; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.75 (br s, 1H), 3.17–3.22 (m, 1H), 3.72–3.79 (m, 1H), 3.90 (d, *J* = 2.2 Hz, 1H), 3.97–4.06 (m, 1H), 7.23–7.34 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.4, 61.1, 62.4, 125.5,

127.8, 128.1, 136.4; **Anal.** Calcd for $C_9H_{10}O_2$ requires C, 71.98; H, 6.71; found: C, 71.62; H, 6.86%.

(1*R*, 2*S*, 3*R*)-1-Chloro-1-phenylhex-5-ene-2,3-diol (36)

To a stirred solution of cinnamaldehyde **7** (660 mg, 5 mmol) in CH_2Cl_2 (20 mL) at 25 °C was added prolinol derivative **35** (300 mg, 0.5 mmol) followed by the addition of 35% aq. H_2O_2 (220 mg, 6.5 mmol). After being stirred for 5 h at the same temperature, the crude reaction mixture was passed through a pad of silica gel (EtOAc/pet ether) and the filtrate concentrated under reduced pressure to give crude epoxy aldehyde, which was directly used for the next step without purification. To a stirred epoxy aldehyde solution in dry CH_2Cl_2 (30 mL) was added $TiCl_4$ (6.8 mL, 1M solution in CH_2Cl_2) at -78 ^oC. After stirring for 10 min, tributyl allyl stannane (2.3 g) was added. The reaction mixture was stirred at -78 ^oC for 30 min, quenched with $NaHCO_3$, extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated to give the crude material, which was then purified by column chromatography over silica gel with pet. ether/EtOAc (75:25) to give the alcohol **36** (678 mg, 60%).

Yield: 60%; colorless liquid; $[\alpha]^D_{25}$ = - 61.5 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 700, 754, 1115, 1220, 1396, 1496, 1649, 1985, 3030, 3063, 3480; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.02-2.11 (m, 2H), 2.30-2.51 (m, 2H), 3.82-3.89 (m, 1H), 4.12-4.26 (m, 1H), 4.94 (d, *J* = 8.8 Hz, 1H), 5.08-5.14 (m, 1H), 5.19-5.22 (m, 1H), 5.76-5.97 (m, 1H), 7.29-7.46 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 38.7, 61.7, 69.0, 75.9, 118.3, 128.2, 128.7, 134.2, 138.5; **Analysis** for $C_{12}H_{15}ClO_2$ requires: C, 63.58; H, 6.67;; found: C, C, 63.88; H, 6.45;%.

(*R*)-1-((2*S*, 3*S*)-3-Phenyloxiran-2-yl)but-3-en-1-ol (31)

To a stirred solution of cinnamaldehyde **7** (660 mg, 5 mmol) in CH_2Cl_2 (20 mL) at 25 °C was added prolinol derivative **35** (300 mg, 0.5 mmol) followed by the addition of 35% aq. H_2O_2 (220 mg, 6.5 mmol). After being stirred for 5 h at the same temperature, the crude reaction mixture was passed through a pad of silica gel (EtOAc/pet ether) and the filtrate concentrated under reduced pressure to give crude oxirane-2-carbaldehyde, which was directly used for the next step without purification. To a stirred crude epoxy aldehyde solution in dry diethyl ether (30 mL) was added $LiClO_4$ (638 mg, 6 mmol) at 0 ^oC. After stirring for 10 min, tributyl allyl stannane (1.99 g, 6 mmol) was added. The reaction mixture was stirred at 0 ^oC for 1 h and the reaction was brought to 25 ^oC and stirred for 6 h, quenched with $NaHCO_3$, extracted with diethyl ether (3x20 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated to give the crude material, which was then purified by column chromatography over silica gel with pet. ether/EtOAc (90:10) to give the homoallylic alcohol **31** (665 mg, 70%).

Yield: 70%; thick oily liquid; **$[\alpha]^{25}_D$**: -33.7 (*c* 1.6, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 700, 756, 1109, 1209, 1396, 1496, 1650, 1980, 3020, 3063, 3479; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.05 (d, *J* = 6.7 Hz, 1H), 2.32-2.54 (m, 2H), 3.04-3.08 (m, 1H), 3.65-3.81 (m, 1H), 3.86 (d, *J* = 2.2 Hz, 1H), 5.11-5.14 (m, 1H), 5.16-5.23 (m, 1H), 5.77-5.99 (m, 1H), 7.18-7.39 (m, 5H) ; **^{13}C NMR** (50 MHz, $CDCl_3$): δ 39.0, 56.3, 65.0, 70.1, 118.4, 125.6, 128.2, 133.5, 136.8; **Analysis**: $C_{12}H_{14}O_2$ requires C, 75.76; H, 7.42; Found: C, 75.43; H, 7.85 %.

(*R*)-1-((2*S*, 3*S*)-3-Phenyloxiran-2-yl)but-3-en-1-yl acrylate (32)

A stirred solution of alcohol **31** (400 mg, 2.1 mmol) in dry CH_2Cl_2 (20 mL) was cooled to 0 ^oC followed by the addition of acrylic acid (302 mg, 4.2 mmol), DCC (865 mg, 4.2 mmol) and 4-dimethylaminopyridine (25 mg, 0.21 mmol). The entire reaction mixture was then warmed to 25 ^oC and stirred for 8 h. Solvent was removed under vacuum to give the crude product, which was then purified by column chromatography over silica gel with pet. ether/EtOAc (95:5) to give acrylate ester **32** (466 mg, 91%).

Yield: 91%; colorless gum; $[\alpha]^D_{25}$ = -26.7 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 700, 767, 1118, 1203, 1309, 1454, 1637, 1714, 2885, 3030, 3063; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.49-2.57 (m, 2H), 2.32-2.54 (m, 2H), 3.12-3.16 (dd, *J* = 2.2, 5.9 Hz, 1H), 4.92-5.02 (q, *J* = 6.8 Hz, 1H), 5.10 (s, 1H), 5.15-5.20 (m, 1H), 5.16-5.23 (m, 1H), 5.70-5.84 (m, 1H), 5.86-5.94 (dd, *J* = 1.6, 10.2 Hz, 1H), 6.10-6.24 (dd, *J* = 10.2, 17.2 Hz, 1H), 6.43-6.53 (dd, *J* = 1.6, 17.2 Hz, 1H), 7.21-7.37 (m, 5H) ; **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.1, 56.5, 62.6, 72.9, 119.0, 125.6, 128.2, 128.6, 131.4, 132.2, 136.4, 165.2; **Analysis**: $C_{15}H_{16}O_3$ requires C, 73.75; H, 6.60; Found: C, 73.98; H, 6.44%.

(*R*)-6-((2*S*, 3*S*)-3-Phenyloxiran-2-yl)-5,6-dihydro-2H-pyran-2-one: *R*-(+)-goniothalamin oxide (2)

A solution of Grubbs' IInd generation catalyst [$RuCl_2$(=CHPh)(Pcy_3)(*bis*mesitylimidazolidinylidene)] (18 mg, 2.5 mol%) in dry CH_2Cl_2 (5 mL) was added dropwise to a refluxing solution of acrylate ester **32** (200 mg, 0.82 mmol) in CH_2Cl_2 (10 mL). Heating to reflux was continued for 8 h till all the starting material was consumed completely (TLC). Solvent was distilled off under reduced pressure and the crude product purified by column chromatography over silica gel with pet. ether/EtOAc (70:30) to give *R*-(+)-goniothalamin oxide (**2**) (150 mg, 85%).

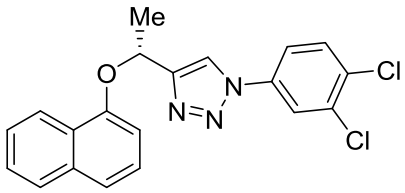
Yield: 85%; colorless solid; **mp** 92-95 ^{o}C; $[\alpha]^{D}_{25}$ = + 99.5 (*c* 0.8, $CHCl_3$) {lit.[32] $[\alpha]_{D}^{25}$ 100.7, (*c* 0.4, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 815, 1066, 1456, 1720, 2933, 3030, 3063; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.45-2.76 (m, 2H), 3.19-3.22 (dd, *J* = 2.0, 3.5 Hz, 1H), 4.08 (d, *J* = 2.0 Hz, 1H), 4.64-4.73 (m, 1H), 5.30 (s, 1H), 6.03-6.10 (m, 1H), 6.87-6.96 (m, 1H), 7.26-7.36 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 26.2, 54.9, 62.1, 75.0, 121.7, 125.7, 128.6, 139.1, 143.8, 162.1; **Analysis**: $C_{13}H_{12}O_3$ requires C, 72.21; H, 5.59; Found: C, 72.45; H, 5.35%.

Section II:

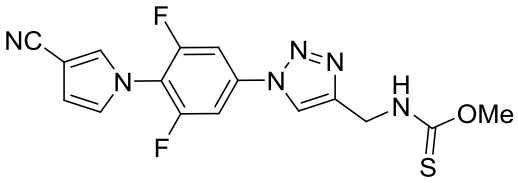
Tandem Azidation, Intramolecular [3+2]-Cycloaddition and Aromatization of Substituted Ethyl Acrylates: A "One-Pot" Sequential Process for the Regioselective Synthesis of Substituted 1,2,3-Triazoles

4.2.1 Introduction

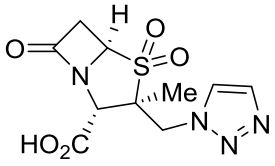
Substituted 1,2,3-triazoles have received considerable interest because of their useful applications in organic synthesis, chemical biology, and materials science.[13] Not present in natural products, however, there are large number of synthetic molecules that contain these substituted 1,2,3-triazole moieties with a wide range of biological activities such as, anti-HIV,[14] anti-allergic,[15] anti-fungal,[16] anti-viral[17] and anti-microbial activities[18] (**Fig. 9**). Moreover, besides pharmaceutical uses, these substituted triazole moieties also exhibit a wide range of industrial applications such as dyestuffs, anticorrosive agents, photostabilizers, photographic materials, agrochemicals, etc.[19]



antiparasitic (**37**)



antibacterial (**38**)



antibiotic (**39**)

Fig. 9: Bioactive molecules with 1,2,3-triazole motif

Due to the significance of these scaffolds in drug discovery, medicinal chemistry, and material chemistry the development of new methodologies for the synthesis of

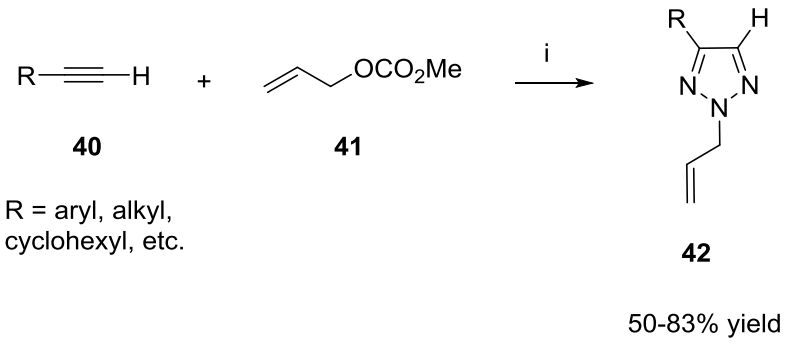
substituted 1,2,3-triazole derivatives under "metal-free" conditions is of interest in recent years.

4.2.2 Review of literature

Literature search suggested that a number of strategies have been developed for the synthesis of substituted 1,2,3-triazole derivatives. The strategies include, not limited to, thermal[20] and transition metal (Cu, Ru) catalyzed[21] [3+2]-cycloaddition of azides with various alkynes; some of the recent reports for the synthesis of substituted 1,2,3-triazole derivatives are described briefly below.

Yamamoto's approach (2003)[22]

Yamamoto *et al*. have developed a useful method for the synthesis of substituted 1,2,3-triazoles **42** from nonactivated terminal alkynes **40**, allyl methyl carbonate **41**, and $TMSN_3$ *via* the three-component coupling reaction using a Pd(0)-Cu(I) bimetallic catalyst. A key for this transformation is the utilization of Pd(0)-Cu(I) bimetallic catalytic system for the coupling reaction (**Scheme 9**).

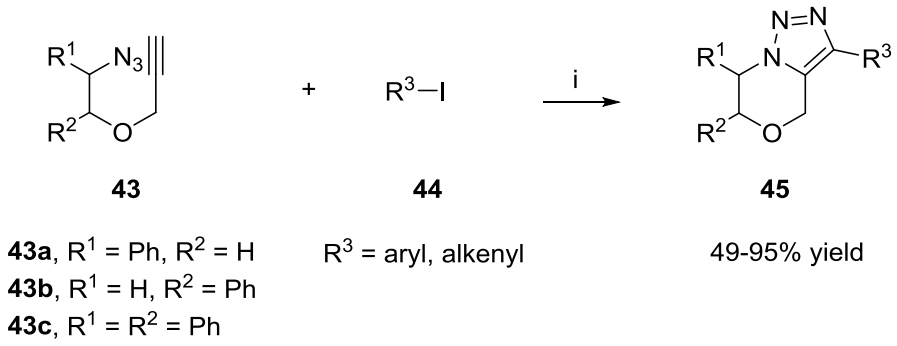


Scheme 9: (i) $TMSN_3$, $Pd_2(dba)_3.CHCl_3$ (2.5 mol %), $P(OPh)_3$ (20 mol %), $CuCl(PPh_3)_3$ (10 mol %), EtOAc, 4-24 h, 100 °C.

Chowdhury's approach (2009)[23]

Chowdhury *et al.* have employed a "one-pot" two-step process which involves: (a) Pd(0)-catalyzed coupling reaction of alkynes **43** with aryl or alkenyl iodide **44**, followed by (b) Cu(I)-catalyzed intramolecular cycloaddition between azide and

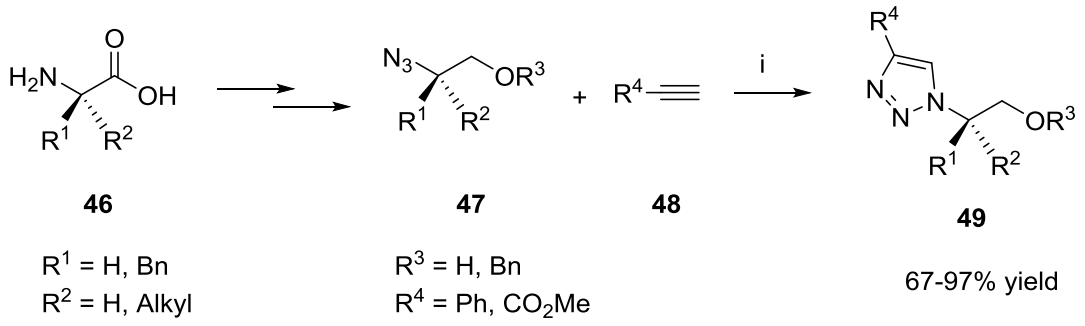
internal alkyne, leading to the synthesis of 1,2,3-triazolo[5,1-*c*]morpholines **45**. Good regioselectivity, mild reaction conditions, high yields and short reaction time are the salient features of this protocol (**Scheme 10**).



Scheme 10: (i) $Pd(OAc)_2$ (5 mol%), PPh_3 (20 mol%), CuI (10 mol%), *n*-Bu_4NBr, K_2CO_3, DMF, 100 ^oC, 2 h.

Grotli's approach (2009)[24]

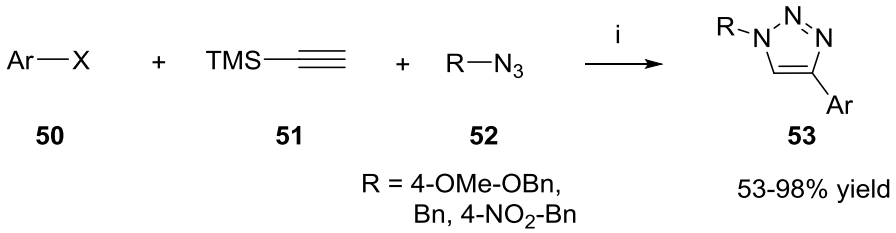
Grotli *et al*. have demonstrated a versatile method for the synthesis of chiral 1,4-disubstituted-1,2,3-triazole derivatives **49** starting from easily accessible naturally occurring amino acids **46** as chiral synthons. The amino acids were converted into corresponding azido alcohols **47**, followed by its Cu-catalyzed [3+2]-cycloaddition reactions with alkynes **48** furnished the substituted triazoles **49**, in excellent yields without racemization (**Scheme 11**).



Scheme 11: (i) sodium ascorbate (10 mol%), $CuSO_4$ (1 mol%) , H_2O:*t*-BuOH (1:1), 15 h, 25 ^oC.

Boon's approach (2010) [25]

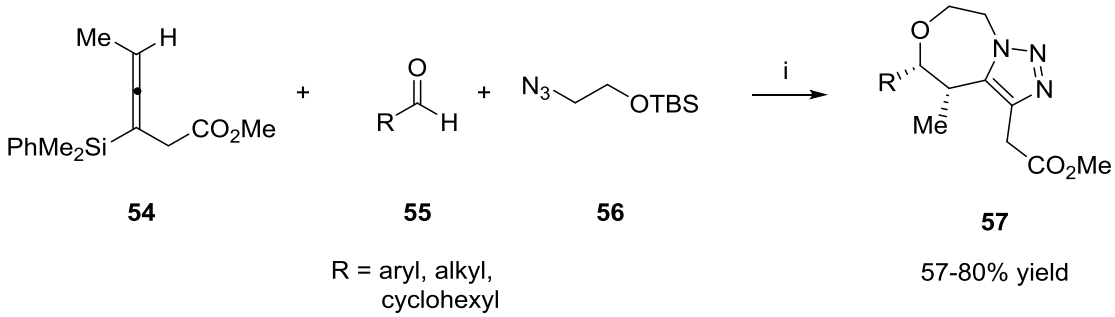
Boon *et al.* have described a microwave-assisted, "one-pot" three-step sequences of reaction i.e. Sonogashira cross-coupling-desilylation-cycloaddition strategy for the convenient preparation of 1,4-disubstituted 1,2,3-triazoles **53** starting from a range of aryl halides **50**, ethynyltrimethylsilane **51**, and organic azides **52** (**Scheme 12**).



Scheme 12: (i) TBAF (1 equiv), CuI (10 mol %), DIPEA, MeOH, 120 ^{o}C, MW, 20 min.

Panek's approach (2010)[26]

Panek *et al.* have developed a tandem propargylation/dipolar cycloaddition sequence to rapidly construct structurally and stereochemically diverse fused ring systems containing 1,2,3-triazoles **57**.



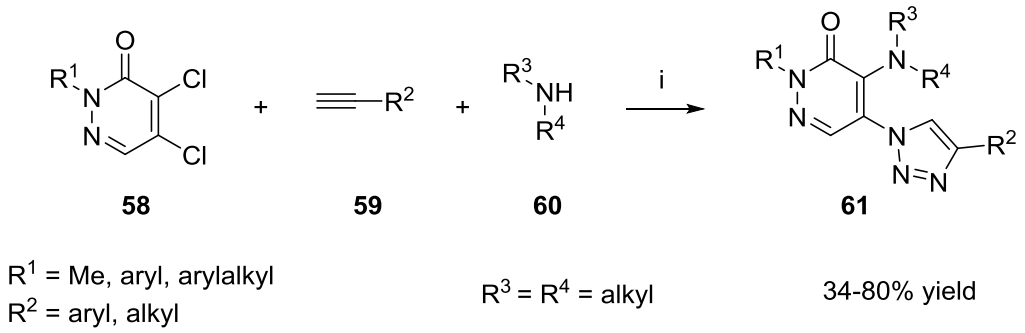
Scheme 13: (i) (a) TMSOTf, EtCN, -78 ^{o}C; (b) toluene, 130 ^{o}C.

The tandem protocol involved the reaction of enantioenriched allenylsilanes **54** with aldehydes **55** and azido silyl ethers **56** to obtain *syn*-homopropargylic ethers that contained an imbedded azide. These materials then further underwent thermally

induced intramolecular 1,3-dipolar cycloaddition reactions, resulting in unique fused ring systems containing 1,2,3-triazoles **57** (**Scheme 13**).

Qian's approach (2011)[27]

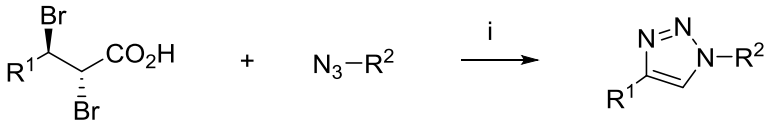
In this approach, a "click and activate" strategy was designed and executed in a 4-component, stepwise condensation that led to a trisubstituted triazolylpyridazinone library **61**. This "one-pot" process included regioselective azide substitution at 2-substituted-4,5-dichloropyridazinones **58**, followed by a Cu(I)-catalyzed triazole formation with alkynes **59,** which triggered subsequent nucleophilic substitution with various secondary amines **60** at the neighbouring position to achieve three points of diversity (**Scheme 14**).



Scheme 14: (i) (a) NaN_3, DMF; (b) *i*Pr_2NEt, CH_3CN, CuI (5 mol%); (b) secondary amines (**60**).

Yang's approach (2011)[28]

Yang *et al.* have demonstrated a simple and efficient "one-pot" method for the preparation of 1,4-disubstituted 1,2,3-triazoles **64** from *anti*-3-aryl-2,3-dibromo-propanoic acids **62** and organic azides **63** with CuI as catalyst, in moderate-to-excellent yields. The process has considerable advantages in terms of its use of easily available substrates, its product diversity, and its mild reaction conditions (**Scheme 15**).



62 **63** **64**

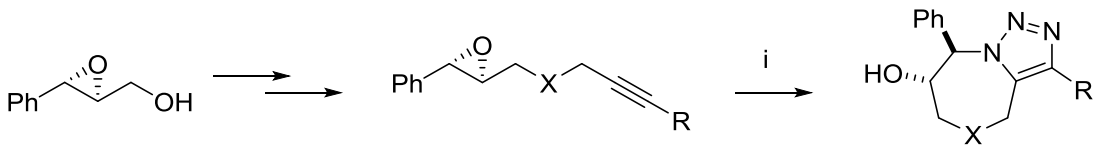
R^1, R^2 = alkyl, aryl

62-85% yield

Scheme 15: (i) DBU, CuI (20 mol%), sodium ascorbate (40 mol%), DMSO, 3-12 h.

Pericas's approach (2011)[29]

Pericas *et al.* have reported a straightforward procedure for the generation of bicyclic systems featuring a 1,2,3-triazole ring fused to a seven-membered heterocycle (oxepane, azepane, or thiepane) **67** in enantiopure form through a cascade process. The reaction involved regioselective and stereospecific epoxide ring opening of alk-2-ynyl derivatives **66,** obtained from enantiopure phenylglycidol **65** with azide followed by intramolecular azide-alkyne cycloaddition under metal-free conditions (**Scheme 16**).



65 **66** **67**

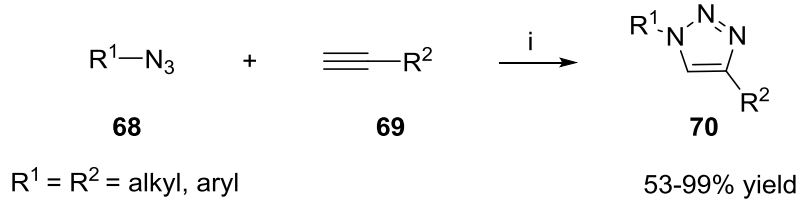
R= H, Ph
X = O, NR, S

53-80% yield

Scheme 16: (i) NaN_3, *t*-BuOH/H_2O (1:1), 110-140 ^oC.

Silvia's approach (2011)[30]

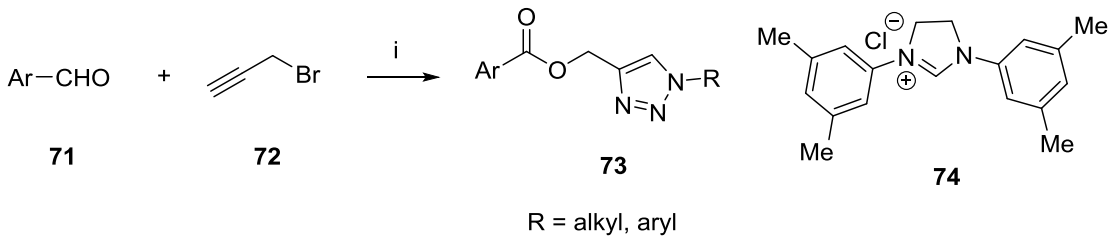
Silvia *et al*. have demonstrated a click catalytic system based on commercially available [$CuBr(PPh_3)_3$] for the synthesis of 1,4-disubstituted 1,2,3-triazoles **70** directly from organic azides **68** and terminal alkynes **69**. This system is active at room temperature, with 0.5 mol % [Cu] (or less), in the absence of any additive, and it does not require any purification step to isolate pure triazoles **(Scheme 17)**.



Scheme 17: $CuBr(PPh_3)$ (0.5 mol%), neat, 25 ^oC.

Anand's approach (2013)[31]

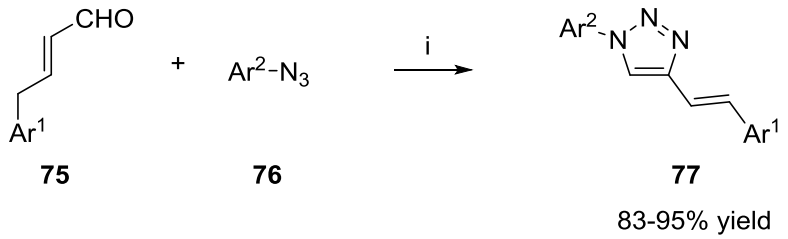
Anand *et al.* have reported a new synthesis of 1,2,3-triazole derivatives **73** in a "one-pot" procedure by combining oxidative N-heterocyclic carbene catalysis with click chemistry. This method was utilized for the synthesis of a diverse range of 1,2,3-triazoles **73** from aromatic aldehydes **71**, propargyl bromide **72** and NHC **74** under mild reaction conditions in high yields (**Scheme 18**).



Scheme 18: (i) (a) DBU, NHC **74** (15 mol%), THF, 25 ^oC; (b) Cu_2O (20 mol%), RN_3, 25 ^oC.

Wang's approach (2013)[32]

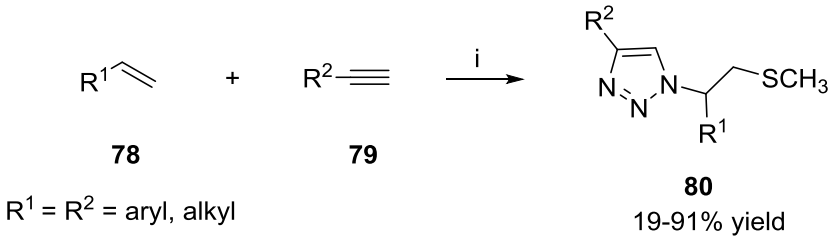
Wang *et al* have reported an organocatalytic approach for the synthesis of substituted 1,2,3-triazoles **77** involving inverse-electron-demand 1,3-dipolar cycloaddition reaction between various azides **76** with unsaturated aldehydes **75**. In this reaction, the *in situ* formed dienamines acting as HOMO-raising dipolarophiles react with aryl azides to afford the corresponding triazoles **77** in good to excellent yields (**Scheme 19**).



Scheme 19: (i) Et_2NH (10 mol%), DBU (10 mol%), DMSO, 50 ^oC, 2 h.

Alanso's approach (2013) [33]

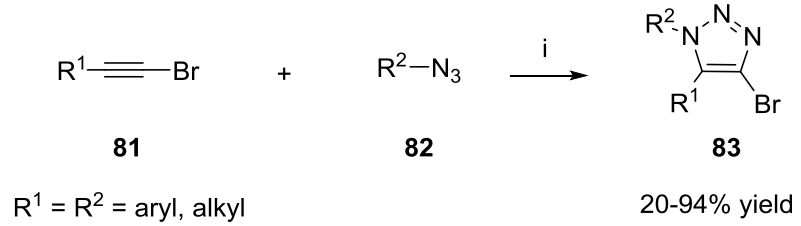
Alanso *et al*., for the first time, have described a "one-pot" synthesis of 1,2,3-triazoles **80** from inactivated alkenes through a sequence including two "click" steps catalyzed by CuNPs/C: (a) the azidosulfenylation of olefin **78** and (b) the reaction of the *in situ* generated organic azide with the terminal alkyne **79**. The β-methylsulfanyl triazoles **80**, potential ligands, are obtained in high regio- and diastereoselective fashion (**Scheme 20**).



Scheme 20: (i) (a) NaN_3, DMTSF, CuNPs/C (0.5 mol %), CH_3CN 25 ^oC,1 h; (b) alkynes, 70°C, 14-24 h.

Taran's approach (2013)[34]

Taran *et al*. have developed an unprecedented Ir-catalyzed [3 + 2]-cycloaddition of bromoalkynes **81** with organic azides **82**, offering a direct and regioselective route to 4-bromo-1,5-triazoles **83** in moderate to high yields. This method also offers a direct route to the synthesis of novel 1,4,5-trisubstituted 1,2,3-triazoles *via* metal-catalyzed coupling reaction of bromotriazoles with aryl boronic acids **83** (**Scheme 21**).



Scheme 21: (i) $[Ir(cod)OMe]_2$ (10 mol%), CH_2Cl_2, -25 ^oC, 15 h.

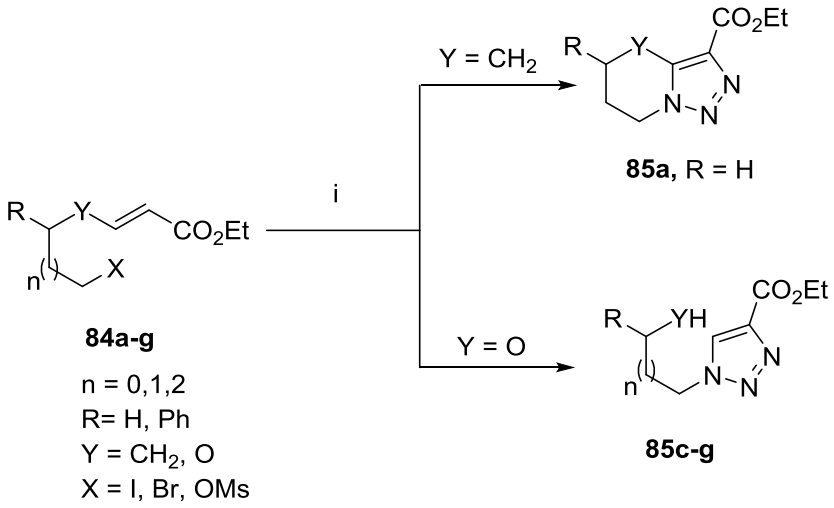
4.2.3 Present Work

4.2.3.1 Objective

The literature survey reveals that although a number of strategies are available for the synthesis of substituted 1,2,3-triazole derivatives, many are based on [3+2]-cycloaddition reaction between organic azides and akynes with or without transition metal catalyst. In addition, there are certain limitations associated with these available reports which include: (a) use of transition metals as catalyst, (b) lack of regioselectivity, (c) harsh reaction conditions, (d) sensitivity to air and moisture, etc. Furthermore, there are only a few reports on the use of olefinic compounds over alkynes for the synthesis of 1,2,3-triazoles. The under-utilization of olefins for the synthesis 1,2,3-triazole derivatives may be attributed to the fact that an overwhelming number of olefins generate triazolines, which require an additional step of acid/base treatment or oxidation to afford 1,2,3-triazoles in moderate to poor overall yields.[35] In this section, a metal-free, "one-pot" method of regioselective synthesis of substituted 1,2,3-triazoles proceeding through tandem azidation, intramolecular [3+2]-cycloaddition and aromatization of substituted acrylates all occurring in that sequence is described (**Scheme 22**).

4.2.3.2 Results and Discussion

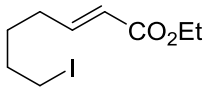
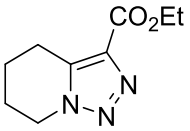
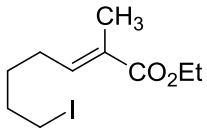
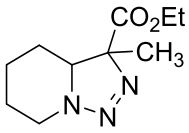
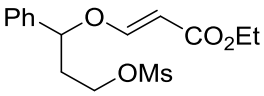
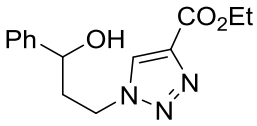
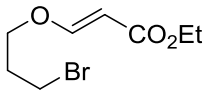
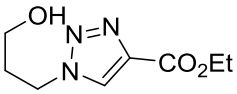
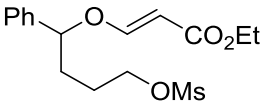
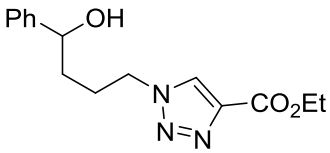
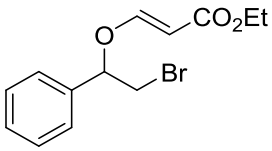
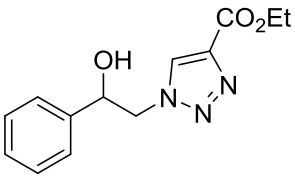
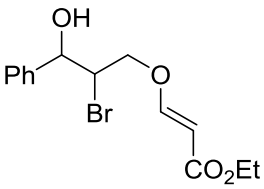
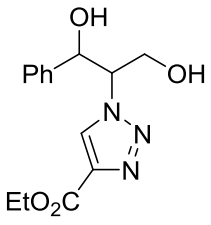
In continuation of our research work on the synthesis of bioactive nitrogen-containing heterocycles,[11] we envisaged a new synthesis of substituted 1,2,3-triazole derivatives **85a-g** *via* tandem azidation, intramolecular [3+2]-cycloaddition, and aromatization of acrylates **84a-g (Scheme 22)**. Substituted acrylates **84a-g,** triazole precursors for the tandem protocol was prepared, employing the literature procedures[36] from readily available starting materials.



Scheme 22: (i) NaN_3 (1.5 equiv), DMF, 80 ^oC, 12 h, 15-88%.

Initially, azidation of β-alkyl substituted ethyl acrylate **84a** (n = 1, R = H, Y = CH_2, X = I) was carried out with NaN_3 in DMF at 80 ^oC for 12 h. Surprisingly, it resulted in the formation of substituted 1,2,3-triazole **85a** in 82% yield (**Table 1**). We believed that, the formation of triazole **85a** could be reasoned from sequential reactions involving azidation followed by intramolecular [3+2]-cycloaddition and dehydrogenative aromatization respectively (**Table 1**, entry a).

Table 1. Tandem azidation, intramolecular [3+2]-cycloaddition and aromatization[a]

entry	substrates (**84a-g**)	products (**85a-g**)	yields (%)[b]
a			82
b			78
c			84
d			81
e			88
f			85
g			15

[a]**84a-g** (5 mmol), NaN_3 (7.5 mmol), DMF (20 mL), 80 ^oC, 12 h. [b] isolated yield after chromatographic purification.

The formation of substituted triazole **85a** was confirmed from its ^{1}H NMR spectrum, which showed a triplet at δ 3.10 (d, *J* = 6.4 Hz, 2H) corresponding to allylic (-C=C-C**H$_2$**) protons of the piperidine moiety. A multiplet at δ 4.35-4.46 (m, 4H) indicated the presence of methylene protons (-C**H$_2$**-NR$_2$, OC**H$_2$**CH$_3$) attached to nitrogen and oxygen atoms respectively.

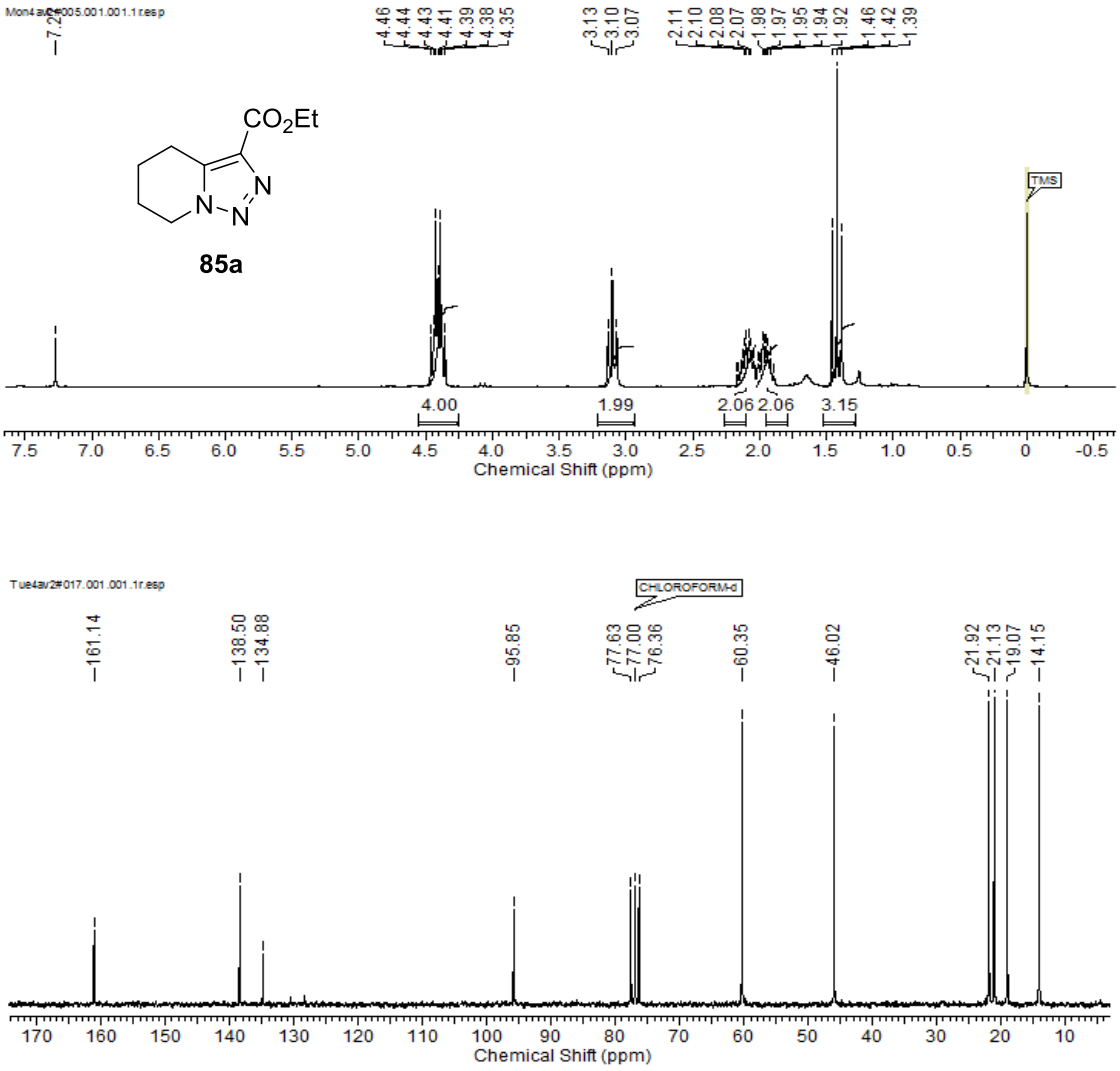


Fig. 10: ^{1}H and ^{13}C NMR spectra of 1,2,3-triazole derivative **85a**

Its ^{13}C NMR spectrum showed two typical carbon signals at δ 134.9 and 138.5 indicative of the α and β carbon of the triazole ring, thus confirming the formation of

substituted 1,2,3-triazole **85a** (**Fig. 10**). Further, the formation of **85a** was clearly demonstrated from its mass spectrum (**Fig. 11**).

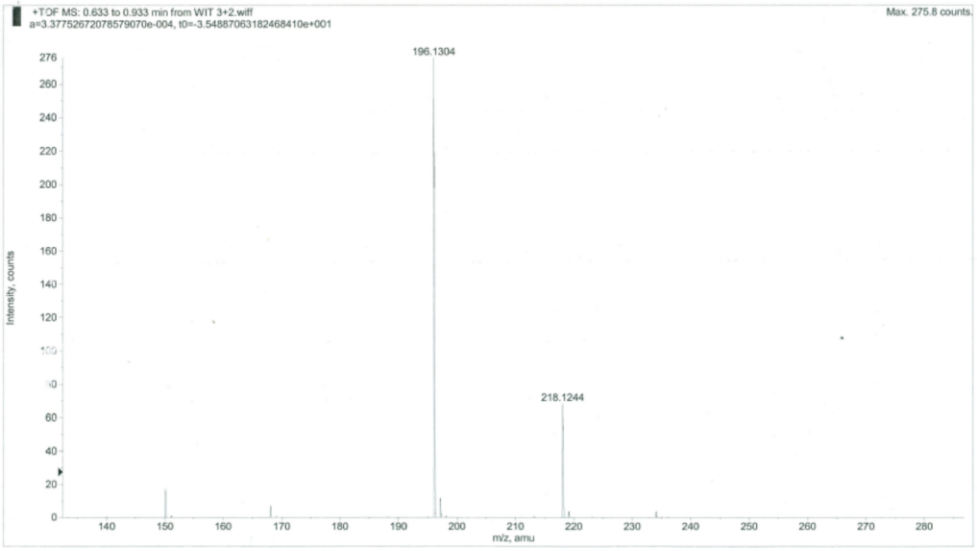


Fig. 11: Mass spectra of 1,2,3-triazole derivative **85a**

Also, α-methyl substituted β-alkylethyl acrylate **84b** produced the corresponding dipolar cycloaddition adduct **85b** in 78% under the same reaction condition (**Table 1**, entry b).[37] Encouraged by the above results, we explored this reaction by employing various alkoxy ethyl acrylates **84c-h** as substrates, the results of which are summarized in Table 1. Firstly, alkoxy ethyl acrylate **84c** was subjected to this tandem protocol under the same reaction condition. Unexpectedly, it resulted in the formation of substituted 1,2,3-triazole **85c** with a free hydroxy group, in 84% yield. Substrates **84d-f** with variations in carbon chains similarly underwent this tandem protocol to afford the corresponding 1,2,3-triazole derivatives **85d-f** as a single regioisomer in high yields (81-88%). However, the triazole precursor **84g** under the reaction condition gave the corresponding substituted triazole **85g** in poor yield (15%), probably due to more steric hindrance associated with the compound **84g** (**Table 1**). The formation of all the substituted 1,2,3-triazoles **85a-g** was established

unambiguously from their respective ^{1}H & ^{13}C NMR, IR, ESIMS spectral data and CHNS analysis.

Example 1: The formation of substituted triazole derivative **85c** was confirmed from its ^{1}H NMR spectrum, which showed a singlet at δ 8.12 (s, 1H) corresponding to aromatic -C**H**=CNR proton of the triazole moiety, while a multiplet at δ 4.50-4.73 (m, 3H) indicated the presence of benzylic (PhC**H**-OH) and methylene (-C$\mathbf{H_2}$-NR_2) protons respectively.

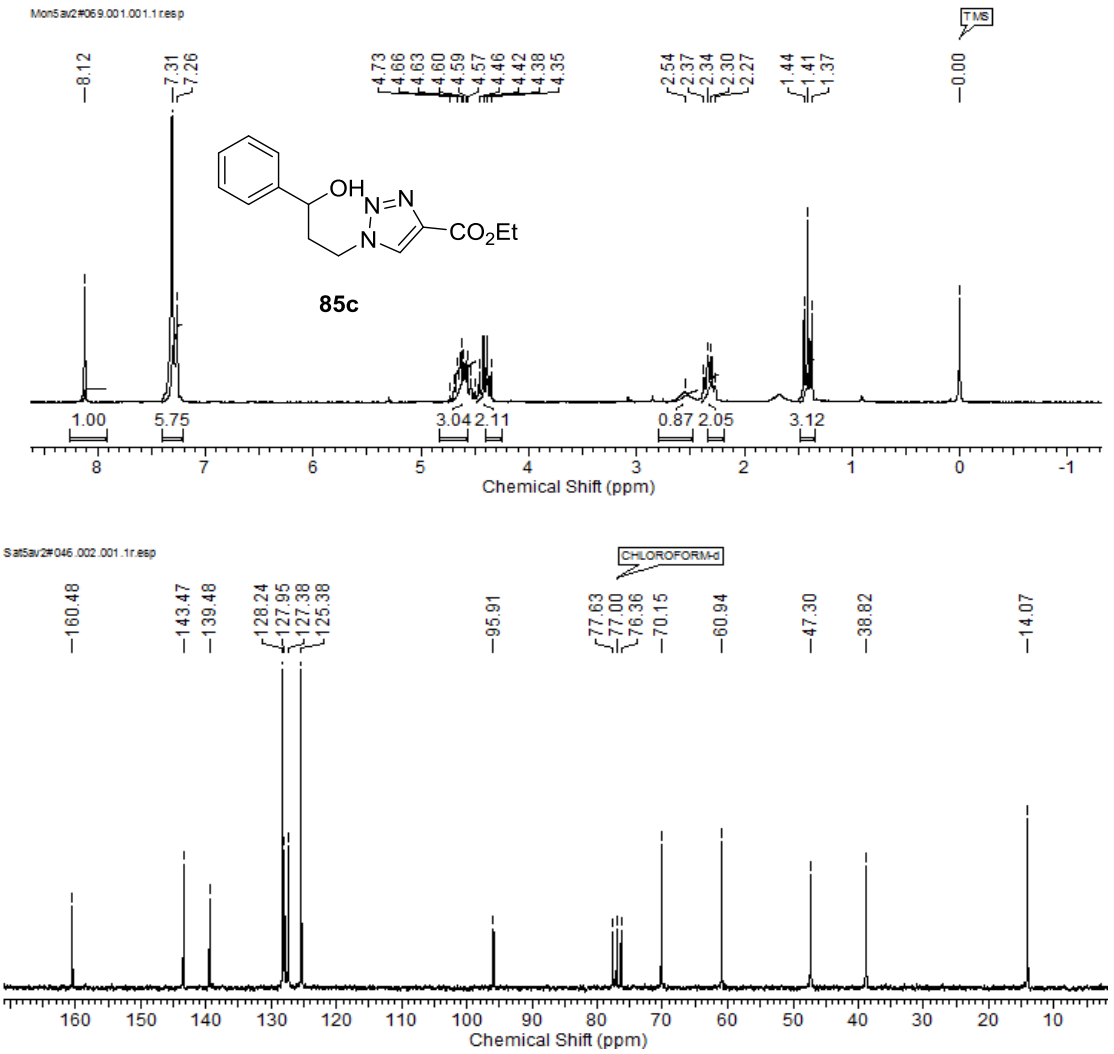


Fig. 12: ^{1}H and ^{13}C NMR spectra of substituted triazole derivative **85c**

Its ^{13}C NMR spectrum displayed two typical carbon signals at δ 127.4 and 139.5 indicative of the α and β carbon of the triazole moiety, thus confirming the formation

of substituted 1,2,3-triazole derivative **85c** (**Fig. 12**). Further the formation of **85c** was ascertained from its mass spectrum, which showed mass of 276.1936 correspondind to $[C_{14}H_{17}N_3O_3 + H]^+$ species.

Example 2: The ^{1}H NMR spectrum of **85f** showed a singlet at δ 8.17 (s, 1H) corresponding to aromatic (-C**H**=CNR) proton of the triazole moiety, while a multiplet at δ 5.16-5.24 (m, 1H) indicated the presence of benzylic (PhC**H**-OH) proton. Further, a doublet of doublet at δ 4.65-4.74 (dd, *J* = 3.0, 13.9 Hz, 1H) corresponds to one of the diastereotopic protons of the methylene carbon bonded with triazole moiety.

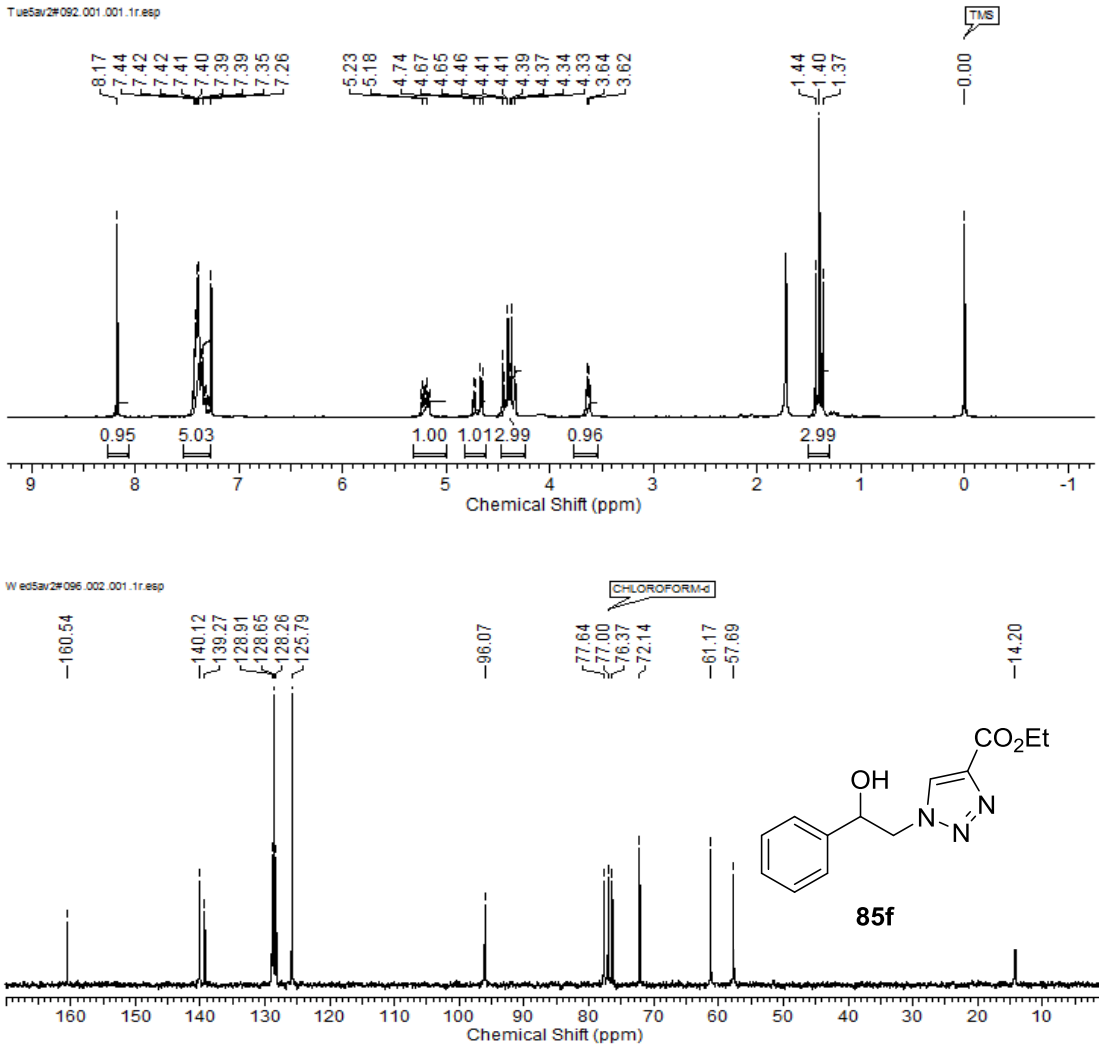


Fig. 13: ^{1}H and ^{13}C NMR spectra of 1,2,3-triazole derivative **85f**

Its ^{13}C NMR spectrum showed two typical carbon signals at δ 128.3 and 139.3 indicative of the α and β carbon of the triazole ring, while a carbon signal at δ 72.1 corresponding to the benzylic (Ph**C**HOH) carbon confirmed the formation of substituted 1,2,3-triazole derivative **85f** (**Fig. 13**). It was further substantiated from its IR spectrum, which showed two strong absorption bands at 1731 and 3383 cm^{-1} corresponding to the carbonyl and hydroxyl groups present in **85f** (**Fig. 14**).

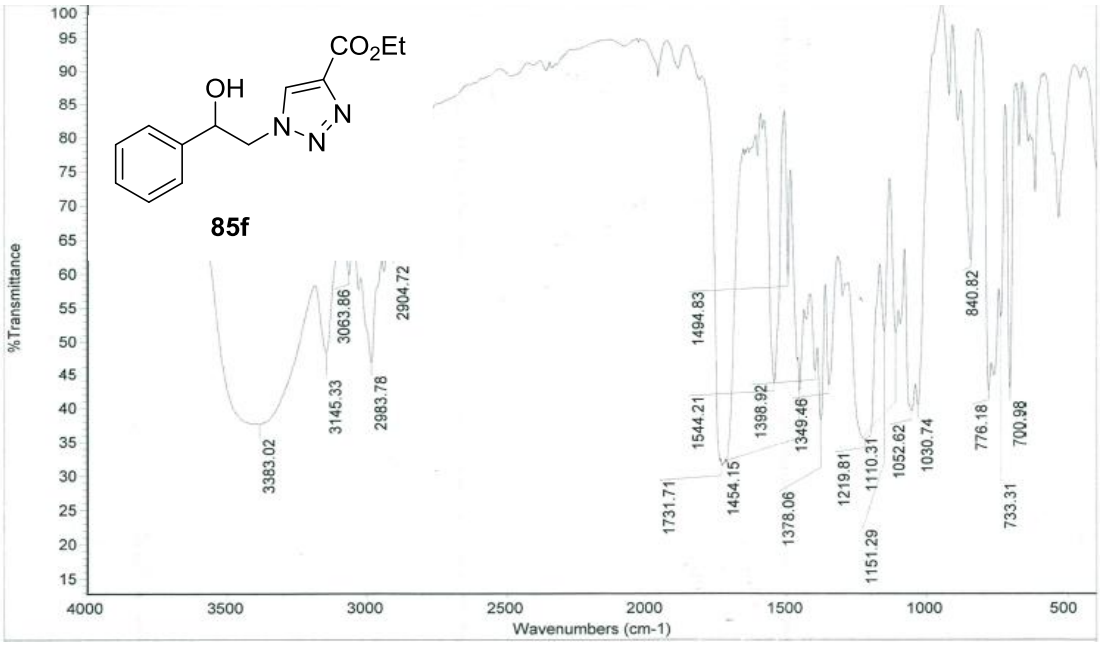
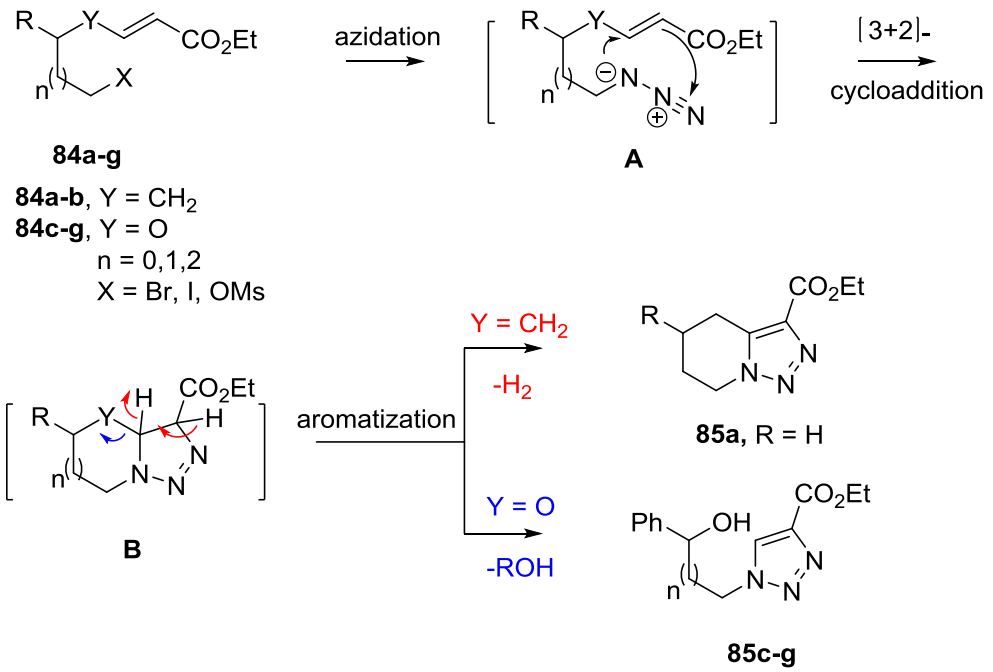


Fig. 14: IR spectrum of substituted triazole derivative **85f**

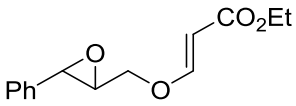
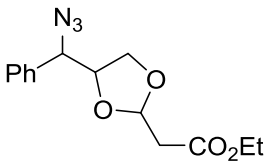
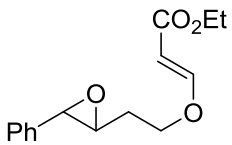
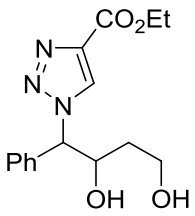
A probable mechanistic pathway for the formation of substituted 1,2,3-triazole derivatives **85a-g** is proposed in **Scheme 23**. Firstly, S_N2 displacement of leaving groups (X, OMs) in **84** with azide ion produces the intermediate azido species **A**. This in turn is followed by the intramolecular [3+2]-cycloaddition of N_3 with olefin to generate intermediate species **B.** The cycloadduct **B** instantaneously undergoes elimination either *via* dehydrogenation (when Y = CH_2) or dehydroxylation (when Y = O) to give the corresponding 1,2,3-triazole derivatives **84a-g**.



Scheme 23: Probable mechanistic pathway for 1,2,3-triazole derivatives **85a-g**

With the above obtained results, it was of our interest to extend the scope of the reaction with epoxide functionality associated with acrylates. Thus, epoxy acrylate **84h** was subjected to triazole formation using NaN_3 (1.5 equiv) in MeOH/H_2O (4:1) at 80 ^oC for 12 h.

Table 2. Tandem epoxide opening, intramolecular [3+2]-cycloaddition and aromatization[a] of epoxy acrylates

entry	substrates (**84h-i)**	products (**85h-i)**	yield (%)[b]
1			90 (dr = 3:2)
2			82

[a]**84h-i** (5 mmol), NaN_3 (7.5 mmol), MeOH/H_2O (16/4 ml), 80 ^oC, 12 h; [b]isolated yield after chromatographic purification

Unexpectedly, oxa-Michael adduct **85h** was obtained in 90% yield with dr = 3:2 (determined from ^{1}H NMR analysis), probably due to more favourable 5-membered acetal formation over cycloaddition (**Table 2**, entry 1). However, the reaction of one-carbon homologated epoxy acrylate **84i** under the same reaction conditions, gave the desired triazole derivative **85i** in 82% *via* the tandem protocol. The formation of substituted triazole derivative **85i** was confirmed from its ^{1}H NMR spectrum, which showed a singlet at δ 8.19 (s, 1H) corresponding to aromatic (-C**H**=CNR) proton of the triazole moiety, while two multiplets at δ 3.15-3.20 (m, 1H) and 3.47-3.51 (m, 1H) indicated the presence of diastereotopic methylene (-C**H$_2$**-OH) protons.

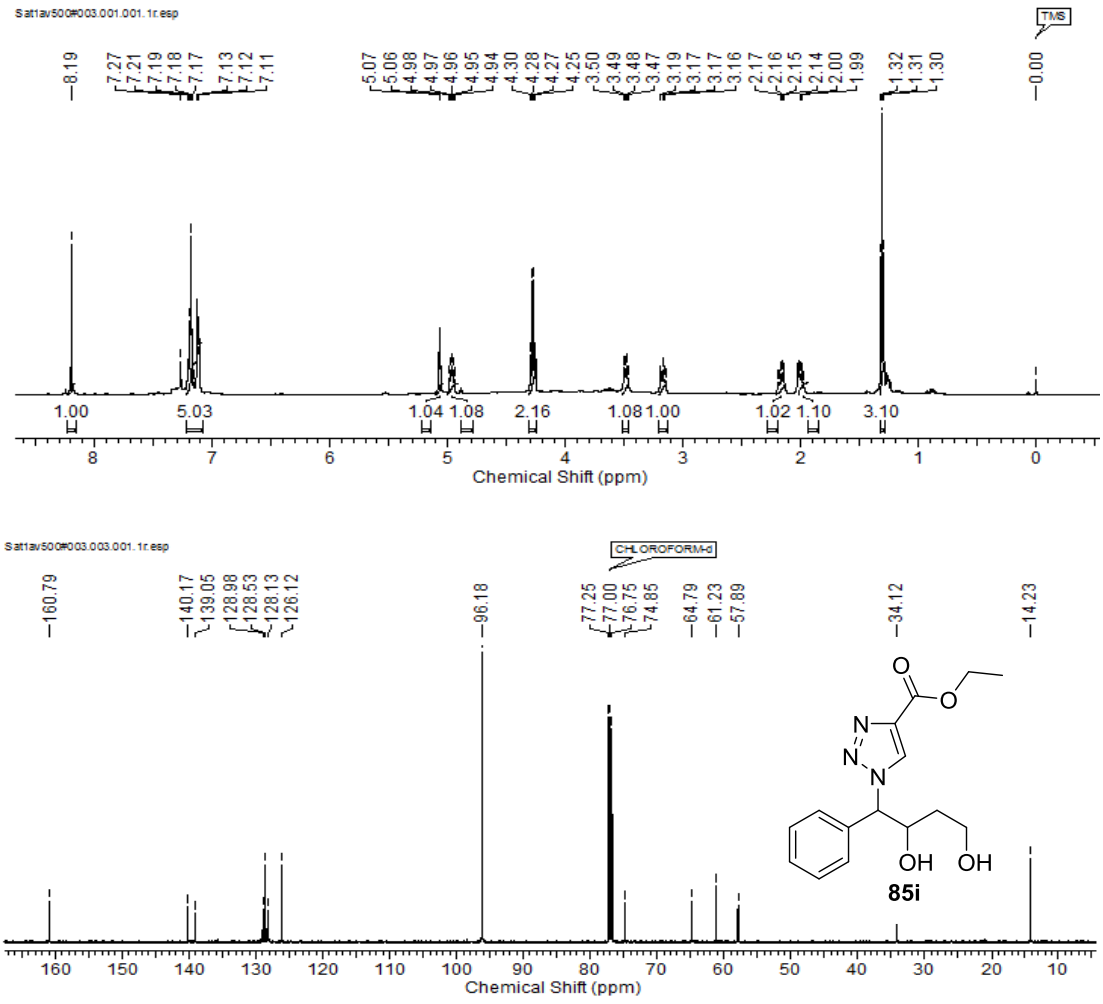


Fig. 15: ^{1}H and ^{13}C NMR spectra of 1,2,3-triazole derivative **85i**

The other proton signal at δ 5.07 (d, *J* = 5.5 Hz, 1H) corresponded to the benzylic (PhC**H**-NR_2) proton. Its ^{13}C NMR spectrum showed two typical carbon signals at δ 128.1 and 139.1 indicative of the α and β carbon of the triazole ring, while the carbon signal at δ 74.9 corresponded to the benzylic (Ph**C**H-NR_2) carbon. The other carbon signals at δ 57.9 and 64.8 were indicative of the methylene (-**C**H_2-OH) and methine (-**C**H-OH) carbons respectively attached to hydroxyl group, thus confirming the formation of substituted triazole derivative **85i** (**Fig. 15**).

4.2.4 Conclusion

In conclusion, we have described, a *novel* "one-pot" procedure of tandem azidation, intramolecular [3+2]-cycloaddition and aromatization of acrylates that leads to an efficient synthesis of substituted 1,2,3-triazole derivatives **85a-i** as single regioisomer in excellent yields. The salient features of the methodology are: (1) triazole derivatives are obtained directly from olefins without the need of an additional step; (2) metal-free synthesis; (3) milder reaction conditions; (4) high yields with complete regioselectivity.

4.2.5 Experimental section

(a) General experimental procedure for the synthesis of 1,2,3-triazoles 85a-g.

To a stirred solution of acrylates **84a-g** (5 mmol) in dry DMF (20 mL), NaN_3 (500 mg, 7.5 mmol) was added. The reaction mixture was stirred for 12 h at 80 ^oC. After completion of reaction (monitored by TLC), it was poured into 30 mL of ice cold water and extracted with ethyl acetate (3 x 25 mL). The combined organic layers were washed with brine (2 x 15 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude products **85a-g**. Chromatographic purification of the crude product using silica gel (100-200 mesh) and pet. ether: ethyl acetate (70:30) gave pure 1,2,3-triazole derivatives **85a-g**.

Ethyl 4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-3-carboxylate (85a)

Yield: 82%; pale yellow solid; **mp** 90-92 ^{o}C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1555, 1755, 2904, 2993, 3376; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.42 (t, *J* = 7.2 Hz, 3H), 1.89-2.01 (m, 2H), 2.04-2.17 (m, 2H), 3.10 (t, *J* = 6.4 Hz, 2H), 4.35-4.46 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 19.1, 21.1, 21.9, 46.0, 60.4, 134.9, 138.5, 161.2; **LCMS** calcd for $[C_9H_{13}N_3O_2+H]^+$ 196.1081, Found 196.1304; **Analysis**: $C_9H_{13}N_3O_2$ requires C, 55.37; H, 6.71; N, 21.52; Found: C, 55.49; H, 6.96; N, 21.35%.

Ethyl 3-methyl-3,3a,4,5,6,7-hexahydro-[1,2,3]triazolo[1,5-a]pyridine-3-carboxylate (85b)

Yield: 78%; viscous liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1365, 1549, 1736, 2904, 2983, 3356; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.32 (t, *J* = 7.1 Hz, 3H), 1.38 (s, 3H), 1.45-1.79 (m, 5H), 1.88-1.99 (m, 1H), 3.14-3.28 (m, 1H), 3.43-3.50 (dd, *J* = 3.5, 11.6 Hz, 1H), 4.16-4.36 (m, 3H) ; **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.9, 15.1, 23.1, 23.8, 24.9, 47.5, 61.5, 61.6, 83.3, 171.5; **LCMS** calcd. for $[C_{10}H_{17}N_3O_2+H]^+$ 212.1394, Found 212.1856; **Analysis**: $C_{10}H_{17}N_3O_2$ requires C, 56.85; H, 8.11; N, 19.89; Found: C, 56.57; H, 8.00; N, 19.57 %.

Ethyl 1-(3-hydroxy-3-phenylpropyl)-1H-1,2,3-triazole-4-carboxylate (85c)

Yield: 88%; colorless solid; **mp** 78-80 ^{o}C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1454, 1377, 1544, 1735, 2904, 2983, 3380; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.41 (t, *J* = 7.2 Hz, 3H), 2.27-2.37 (m, 2H), 2.55 (brs, 1H), 4.41 (q, *J* = 7.2 Hz, 2H), 4.50-4.73 (m, 3H), 7.31 (br s, 5H), 8.12 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 38.8, 47.3, 60.9, 70.2, 125.4, 127.4, 128.0, 128.2, 139.5, 145.5, 160.5; **LCMS** calcd for $[C_{14}H_{17}N_3O_3+H]^+$ 276.3155, Found 276.1936**; Analysis**: $C_{14}H_{17}N_3O_3$ requires C, 61.08; H, 6.22; N, 15.26; Found: C, 61.10; H, 6.23; N, 15.24%.

Ethyl 1-(3-hydroxypropyl)-1H-1,2,3-triazole-4-carboxylate (85d)

Yield: 84%; viscous liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1060, 1187, 1377, 1726, 2904, 2983, 3380; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.41 (t, *J* = 7.2 Hz, 3H), 2.11-2.24 (m, 2H), 2.72 (br s, 1H), 3.67 (t, *J* = 5.7 Hz, 2H), 4.41 (q, *J* = 7.2 Hz, 2H), 4.61 (t, *J* = 6.8 Hz, 2H), 8.18 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.2, 32.5, 47.5, 58.0, 61.1, 128.2, 139.6, 160.6; **LCMS** calcd for $[C_8H_{13}N_3O_3 + Na]^+$ 222.0855, Found 222.5760 **Analysis**: $C_8H_{13}N_3O_3$ requires 48.23; H, 6.58; N, 21.09; Found: C, 48.11; H, 6.79; N, 21.22%.

Ethyl 1-(4-hydroxy-4-phenylbutyl)-1H-1,2,3-triazole-4-carboxylate (85e)

Yield: 85%; gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1060, 1177, 1377, 1740, 2980, 3380; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.41 (t, *J* = 7.2 Hz, 3H), 1.63-1.84 (m, 2H), 1.92-2.18 (m, 2H), 2.26 (br s, 1H), 4.35-4.52 (m, 4H), 4.70-4.76 (dd, *J* = 5.4, 7.2 Hz, 1H), 7.22-7.37 m, 5H), 8.05 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.2, 26.5, 35.3, 50.3, 61.1, 73.3, 125.6, 127.4, 127.5, 128.4, 139.9, 144.2, 160.7; **Analysis**: $C_{15}H_{19}N_3O_3$ requires C, 62.27; H, 6.62; N, 14.52; Found: C, 62.25; H, 6.60; N, 14.50%.

ethyl 1-(2-hydroxy-2-phenylethyl)-1H-1,2,3-triazole-4-carboxylate (85f)

Yield: 85%; gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1454, 1494, 1544, 1731, 2904, 2983, 3383; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.40 (t, *J* = 7.2 Hz, 3H), 3.63 (d, *J* = 3.9 Hz, 1H), 4.33-4.46 (m, 3H), 4.65-4.74 (dd, *J* = 3.0, 13.4 Hz, 1H), 5.16-5.24 (m, 1H), 7.28-7.45 (m, 5H), 8.17 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.2, 57.7, 61.2, 72.1, 125.8, 128.3, 128.7, 128.9, 139.3, 140.1, 160.5; **Analysis**: $C_{13}H_{15}N_3O_3$ requires C, 59.76; H, 5.79; N, 16.08 Found: C, 59.95; H, 5.98; N, 16.22%.

Ethyl 1-(3-(benzyloxy)-1-hydroxy-1-phenylpropan-2-yl)-1H-1,2,3-triazole-4-carboxylate (85g)

Yield: 15%; viscous liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1484, 1554, 1746, 2905, 2976, 3389; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.38 (t, *J* = 7.0 Hz, 3H), 3.75 (br s, 1H), 4.36-

4.44 (m, 5H), 4.93 (q, *J* = 5.5 Hz, 1H), 5.27 (d, *J* = 6.4 Hz, 1H), 7.14-7.28 (m, 10H), 8.28 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 14.3, 61.1, 67.3, 69.2, 72.8, 72.9, 73.5, 73.6, 126.1, 127.8, 128.0, 128.5, 128.7, 136.9, 139.5, 139.6, 160.8; **Analysis**: $C_{21}H_{23}N_3O_4$ requires 66.13; H, 6.08; N, 11.02; Found: 66.31; H, 5.80; N, 11.36%.

(b) General experimental procedure for the synthesis of 85h-i.

To a stirred solution of epoxy acrylates **84h-i** (5 mmol) in MeOH/H_2O (16:4 mL), NaN_3 (500 mg, 7.5 mmol) was added. The reaction mixture was stirred for 12 h at 80 ^oC. After completion of reaction (monitored by TLC), MeOH was removed under reduced pressure and aqueous layer was extracted with ethyl acetate (3 x 25 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude products **85h-i**. Chromatographic purification of crude product using silica gel (100-200 mesh) and pet. ether: ethyl acetate gave pure products **85h-i**.

Ethyl 2-(4-(azido(phenyl)methyl)-1,3-dioxolan-2-yl)acetate (85h)

Yield: 90%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1136, 1255, 1453, 1494, 1736, 2105, 2899, 2983; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.26 (t, *J* = 7.1 Hz, 3H), 2.63 (d, *J* = 5.2 Hz, 2H), 3.79-4.08 (m, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.25-4.37 (m, 1H), 4.78 (d, *J* = 5.7 Hz, 1H), 5.47 (t, *J* = 5.2 Hz, 1H), 7.27-7.43 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.0, 39.8, 60.5, 66.1, 66.6, 78.4, 101.7, 126.9, 128.5, 128.7, 135.5, 168.7; **Analysis**: $C_{14}H_{17}N_3O_4$ requires C, 57.72; H, 5.88; N, 14.42; Found: C, 57.85; H, 5.99; N, 14.25%.

Ethyl 1-(2,4-dihydroxy-1-phenylbutyl)-1H-1,2,3-triazole-4-carboxylate (85i)

Yield: 82%; gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1554, 1746, 2904, 2975, 3386; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.31 (t, *J* = 7.3 Hz, 3H), 1.97-2.04 (m, 1H), 2.12-2.20 (m, 1H), 3.15-3.20 (m, 1H), 3.47-3.51 (m, 1H), 4.28 (q, *J* = 7.0 Hz, 2H), 4.94-4.98 (m, 1H),5.07 (d, *J* = 5.5 Hz, 1H) 7.11-7.21 (m, 5H), 8.19 (s, 1H); **^{13}C NMR** (125 MHz,

$CDCl_3$): δ 14.2, 34.1, 57.9, 61.2, 64.8, 74.9, 126.1, 128.1, 128.5, 129.0, 139.1, 140.2, 160.8; **Analysis**: $C_{15}H_{19}N_3O_4$ requires 59.01; H, 6.27; N, 13.76; Found: 59.35; H, 6.10; N, 13.54%.

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37 1,2,3-Triazoline derivative **85b** was obtained as single regioisomer, due to the presence of α-methyl group in acrylate **84b** (see **Table 1**).

LIST OF PUBLICATIONS

1. Organocatalytic Sequential α-Amination/Core-Chaykovsky Reaction of Aldehydes: A High Yield Synthesis of 4-Hydroxypyrazolidine Derivatives; **Kumar, B. S**.; Venkataramasubramanian, V.; Sudalai, A. *Org. Lett.*, **2012**, *14*, 2468.
2. One-Pot Asymmetric Synthesis of 4-Hydroxypyrazolidines from Aldehydes; **Kumar, B. S**.; Venkataramasubramanian, V.; Sudalai, A. *Synfacts*, **2012**, *8*, 1191.
3. Proline-catalyzed sequential α-aminooxylation or -amination/ reductive cyclization of o-nitrohydrocinnamaldehydes: A high yield synthesis of chiral 3-substituted tetrahydroquinolines; Rawat, V.; **Kumar, B. S.**; Sudalai, A.* *Org. Biomol. Chem.*, **2013**, *10*, 3988.
4. "One-pot" synthesis of cyclic carbonates from aldehydes, sulphur ylide and CO_2; Aher. R. D.; **Kumar, B. S**.; Sudalai, A. *Synlett*, **2014**, *25*,97.
5. Proline-catalyzed *syn*-Mannich/Corey-Chaykovsky Reaction or N-alkylation-Michael Addition *via* [4+1]-Annulation Cascade: A High Yield Synthesis of Densely Functionalized Pyrrolidine Derivatives; **Kumar, B. S.**; Aher, R. D.; Sudalai, A. (Patent filed, *Manuscript to be communicated*).
6. Asymmetric Synthesis of 2-Substituted Indolines and 3-Substituted Cinnolines *via* Cu-Catalyzed Intramolecular N-Arylation of Chiral Hydrazine Derivatives, Derived from Proline-catalyzed α-Amination of *o*-Bromohydro cinnamaldehydes; **Kumar, B. S**.; Sudalai, A. (*to be communicated*).
7. Tandem Azidation, Intramolecular [3+2]-Cycloaddition and Aromatization of Substituted Ethyl Acrylates: A "One-Pot" Sequential Process for the Regioselective Synthesis of Substituted 1,2,3-Triazoles; **Kumar, B. S**.; Sudalai, A. (*Manuscript under preparation*)
8. One-pot Sequential α-Amination/Olefination/Corey-Chaykovsky Reaction Cascade: A Highly enantio- and Diastereoselective Synthesis of 4-Substituted Pyrazolidine Derivatives *via* Formal [4+1]-Annulation; Lalwani, K. G.; **Kumar, B. S.**; Sudalai, A. (Patent filed, *Manuscript under preparation*).
9. A New Organocatalytic Synthesis of Chiral Pyrazolidines and Their Analogues; **Kumar, B. S**.; Venkataramasubramanian, V.; Sudalai, A. **2012**, **WO2013088456 (A1).**
10. A new Process for the Synthesis of Chiral 3-Substituted Tetrahydroquinolines; Rawat, V.; **Kumar, B. S**.; Sudalai, A. **2013**, **WO2013140419** (**A1**).
11. New Process Route to Cyclic Carbonates Directly From Aldehydes and CO_2; Aher, R. D.; **Kumar, B. S**.; Sudalai, A. **PCT/IN2013/000610**.