Enantioselective Synthesis of Bioactive Molecules *via* Asymmetric Reductions, Dihydroxylations of Olefins and Synthetic Methodologies Involving Reduction of Esters, Halogenation of Ketones and Hydroarylation of Arenes

A THESIS

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IN

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By

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UNDER THE GUIDENCE OF

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June 2008


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CERTIFICATE

Certified that the work incorporated in the thesis entitled "**Enantioselective Synthesis of Bioactive Molecules *via* Asymmetric Reductions, Dihydroxylations of Olefins and Synthetic Methodologies Involving Reduction of Esters, Halogenation of Ketones and Hydroarylation of Arenes**" was carried out by the candidate under my supervision. Such material as had been obtained from other sources has been duly acknowledged in the thesis.

June 2008 **(Dr. A. Sudalai)**

Pune Research Supervisor

NATIONAL CHEMICAL LABORATORY

DECLARATION

I here by declare that the thesis entitled **"Enantioselective Synthesis of Bioactive Molecules *via* Asymmetric Reductions, Dihydroxylations of Olefins and Synthetic Methodologies Involving Reduction of Esters, Halogenation of Ketones and Hydroarylation of Arenes"** 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.

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CONTENTS

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ABBREVATIONS

Ac	Acetyl
Ar	Aryl
Bn	Benzyl
n-Bu	n-Butyl
n-BuLi	n-Butyl Lithium
CAN	Cerric ammonium nitrate
Cbz	Benzyloxy carbonyl
CH_2Cl_2	Methylene chloride
$CHCl_3$	Chloroform
CH_3CN	Acetonitrile
$CuSO_4$	Copper(II) sulfate
DBAD	Dibenzyl azodicarboxylate
DBU	1,8-Diazabicyclo[5.4.0]undecene-7
DIBAL-H	Diisobutyl alulinum hydride
DET	Diethyl Tartarate
DMF	Dimethyl formamide
DMSO	Dimethyl sulphoxide
DMAP	N,N-dimethyl-4-aminopyridine
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
IR	Infra red
IBX	2-Iodoxybenzoic acid
K_2CO_3	Potassium carbonate
KOH	Potassium hydroxide
$LiAlH_4$	Lithium aluminum hydride
LDA	Lithium diisopropyl amide
M+	Molecular ion
Me	Methyl
MeOH	Methyl alcohol
min	Minutes
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
NIS	*N*-iodosuccinimide
NMR	Nuclear Magnetic Resonance
NMO	*N*-Methyl morpholine *N*-oxide
Pd/C	Palladium on activated charcoal
Pet. ether	Petroleum ether
Ph	Phenyl
p-TSA	*p*-Toluene sulfonic acid
PhNO	Nitrosobenzene
Py	Pyridine
TBS	*tert*-Butyldimethylsilyl
TBHP	*tert*-Butyl hydroperoxide
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
TMSCN	Trimethylsilyl cyanide
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 (60-120 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 and MSL-300 MHz instruments using TMS as an internal standard. The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet, dd = doublet of doublet, dt = doublet of triplet and ddd = doublet of doublet of doublet.

8. Mass spectra (MS) were recorded on an automated finnigan MAT 1020C mass spectrometer using ionization energy of 70eV.

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

10. HPLC analyses were performed on Waters Alliance separation module-2695; equipped with 2487 UV-Visible detector.

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.

14. All the ligands [$(DHQ)_2$-PHAL, $(DHQD)_2$-PHAL, oxazolidine] were purchased from Aldrich.

ABSTRACT

The title of the thesis "**Enantioselective Synthesis of Bioactive Molecules *via* Asymmetric Reductions, Dihydroxylations of Olefins and Synthetic Methodologies Involving Reduction of Esters, Halogenation of Ketones and Hydroarylation of Arenes**" clearly reflects the objective, which is to synthesize enantiomerically pure bioactive molecules and also to develop useful synthetic methodologies. **Chapter 1** deals with the $CoCl_2$-catalyzed reductive cyclization of nitro cyclic sulphites using $NaBH_4$ to give the corresponding tetrahydroquinolin-3-ol and its application in the asymmetric synthesis of sumanirole maleate (PNU 95666-E) and 1-[(*S*)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1-(2*H*)-yl]propan-1-one (*S*-903). **Chapter 2** presents the synthesis of two anti-depressant drugs namely (±)-paroxetine and (±)-femoxetine using Suzuki coupling of enol tosylate with boronic acids as the key reaction. **Chapter 3** describes the development of an improved methodology involving $CoCl_2$-catalysed chemoselective reduction of esters and its application in the asymmetric synthesis of (*R*)-tolterodine. **Chapter 4** describes a novel methodology involving *p*-TSA-mediated hydroarylation of cinnamic acids with substituted phenols and anisoles and $Cu(OTf)_2$-catalyzed α-halogenation of ketones with 1,3-dichloro-5,5-dimethylhydantoin and *N*-bromosuccinimide as halogen sources.

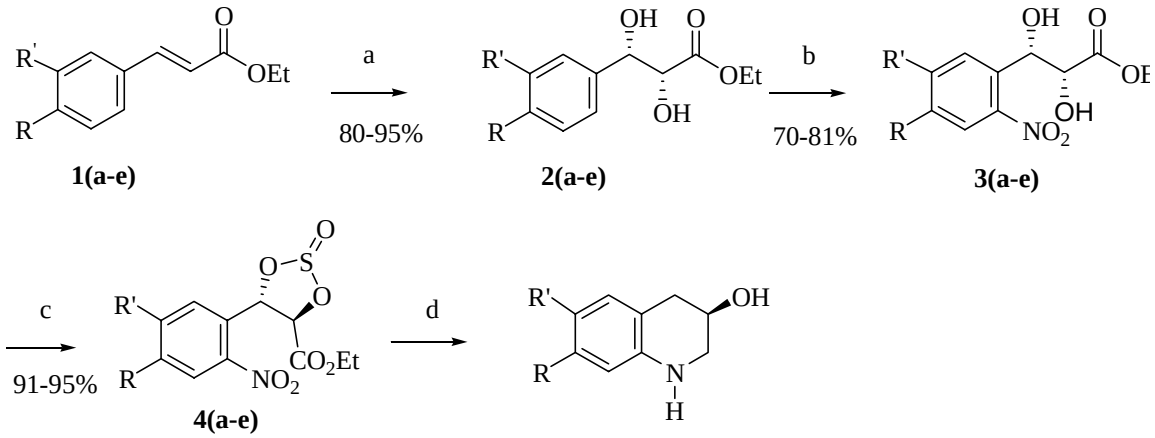
Chapter1

A new concise method of synthesis of tetrahydroquinolin-3-ol, sumanirole maleate (PNU 95666-E) and 1-((*S*)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1-(2*H*)-yl)propan-1-one

Sharpless asymmetric dihydroxylation (ADH) is one of the most effective methods for the preparation of chiral diols, which are important intermediates for the synthesis of various bioactive compounds. This chapter deals with development of a novel method for the synthesis of tetrahydroquinolin-3-ol (**5a-e**) *via* $CoCl_2$-catalyzed reductive cyclization of nitro cyclic sulphites followed by its application to the synthesis of sumanirole maleate (PNU 95666-E) and 1-[(*S*)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1-(2*H*)-yl]propan-1-one (*S*-903), and is divided into three sections.

Section I: A new route for the synthesis of *(R)*-tetrahydroquinolin-3-ol *via* Os-catalyzed asymmetric dihydroxylation coupled with $CoCl_2$-catalyzed reduction of cyclic sulphites with $NaBH_4$

Substituted tetrahydroquinolines display a wide range of physiological activities[1] such as analgesic, antiarrhythmic, cardiovascular, immuno-suppresent, antitumor, antiallergenic, anticonvulsant and antifertility and NMDA antagonist activities.[2] This section describes a novel methodology for the synthesis of substituted tetrahydroquinolin-3-ols (**5a-e**) *via* $CoCl_2$-catalyzed one-pot reduction of nitro cyclic sulphites **4a-e** using $NaBH_4$ as reducing agent. *α,β*-Unsaturated esters **1a-e,** prepared readily from Wittig olefination of the corresponding benzaldehydes, were subjected to Os-catalyzed asymmetric dihydroxylation (ADH) using $(DHQ)_2$-PHAL as ligand to give the corresponding *α*-diols **2a-e,** which on nitration using conc. HNO_3 in CH_2Cl_2 at 25 ºC gave the nitro diols **3a-e** in high yields. Nitrodiols **3a-e** were smoothly converted into the corresponding cyclic sulphites **4a-e** ($SOCl_2$, Et_3N in CH_2Cl_2) in excellent yields. These cyclic sulphites (**4a-e),** when subjected to $CoCl_2$-catalyzed reduction with $NaBH_4$, the corresponding tetrahydroquinoline derivatives **5a-e** were obtained in 78-83% yields (**Scheme 1**).



5a R = R' = OMe, 78%
5b R, R' = OCH_2O, 81%
5c R = OBn, R' = OMe, 83%
5d R = OBn, R' = OBn, 85%
5c R = Ocyclopentyl, R' = OMe, 82%

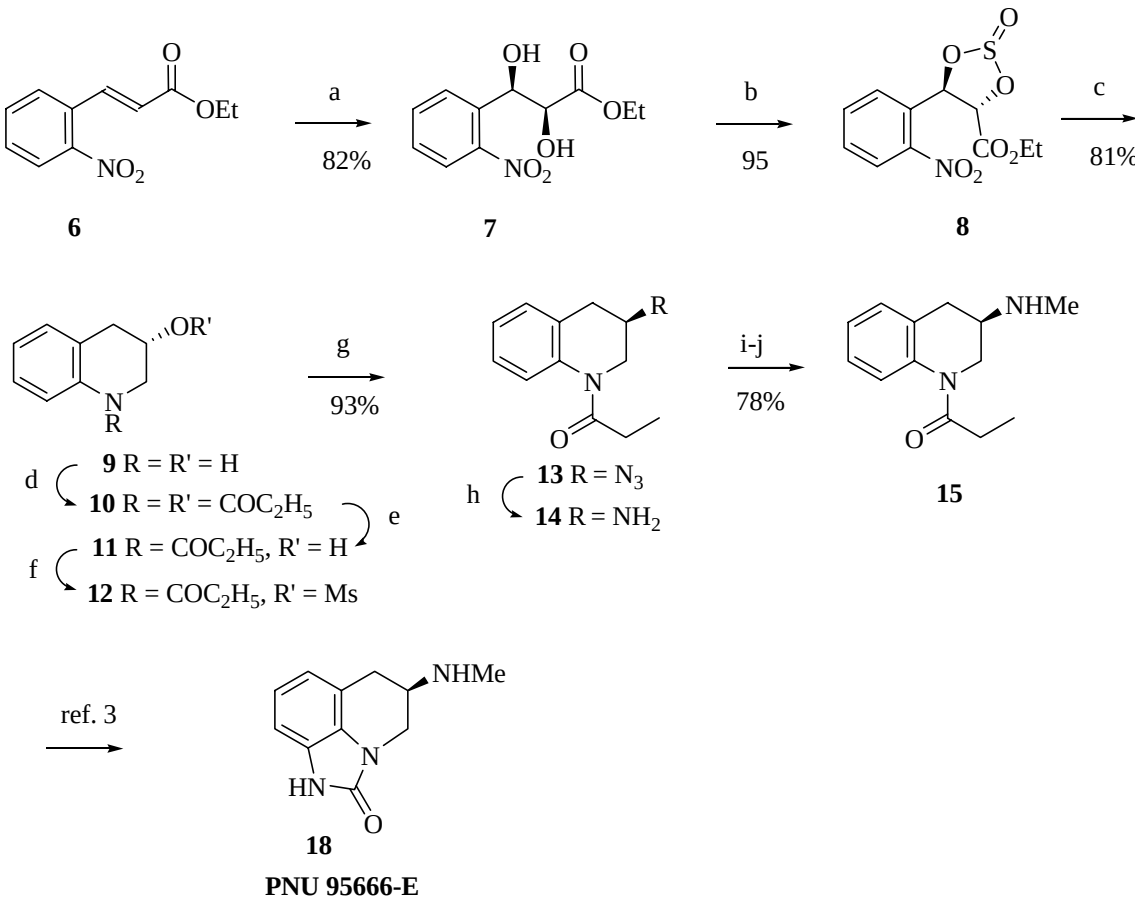
Scheme 1: (a) OsO_4, $(DHQ)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, *tert*-BuOH:H_2O, 25 °C, 24 h; (b) conc. HNO_3,CH_2Cl_2, 1 h, 25 °C; (c) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C; (d) $CoCl_2 \cdot 6H_2O$(1 mol%), $NaBH_4$, EtOH, 0 -25 °C.

During the course of this reaction, surprisingly we observed the reduction of multifunctional groups, all occurring in a single step.

Section II: Formal asymmetric synthesis of sumanirole maleate (PNU 95666-E)

Sumanirole maleate (PNU95666-E) (**18)** is a selective and high-affinity agonist at the dopamine D_2 receptor subtype and is of interest as a potential agent for the treatment of Parkinson's disease.[3] In this section, we describe a short synthesis of sumanirole maleate **18**, by employing $CoCl_2$-catalyzed one-pot reduction of the corresponding cyclic sulphite **8** as the key step.

Unsaturated nitroester **6** was subjected to Os-catalyzed asymmetric dihydroxylation using $(DHQD)_2$-PHAL as ligand to give the chiral diol **7** in 82% yield, which was readily converted into the corresponding cyclic sulphite **8** ($SOCl_2$, Et_3N in CH_2Cl_2). Catalytic one-pot reduction of cyclic sulphite **8** using $CoCl_2 \cdot 6H_2O$ (1 mol %) and $NaBH_4$ (5 equiv.)**,** gave the tetrahydroquinoline derivative **9** in 81% yield. Selective amine protection in **9** was achieved with propionic anhydride in two steps to give amide **11** in 92% yield. Chiral amido alcohol **11** was mesylated (MsCl, Et_3N in CH_2Cl_2) and subsequent displacement of the mesylate with azide anion (NaN_3, DMF) gave azide **13,** which on reduction [H_2 (1atm), 10% Pd/C] gave amine **14**. Formation of imine from amine **14** (HCHO, $MgSO_4$ in CH_2Cl_2) followed by its reduction (H_2, 10% Pd/C) gave the monomethylated amine **15** in 78% yield. Synthesis of PNU 95666-E (**18)** from **15** has already been reported[3] in the literature (**Scheme 2**).

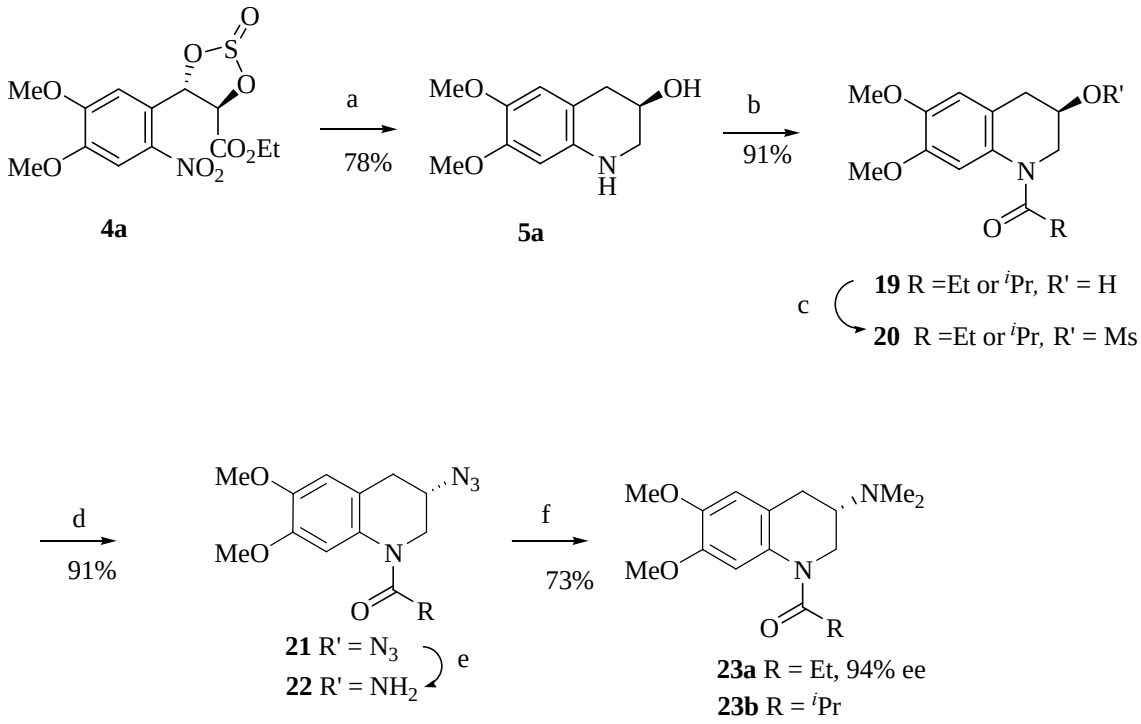


Scheme 2: (a) OsO_4, $(DHQD)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, *tert*-BuOH:H_2O, 25 °C, 24 h, 82%; (b) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 1 h, 95%; (c) $CoCl_2 \cdot 6H_2O$ (1 mol%), $NaBH_4$, EtOH, 0-25 °C, 6 h, 81%; (d) $(C_2H_5CO)_2O$, Et_3N, CH_2Cl_2, 25 °C; (e) K_2CO_3, MeOH:H_2O, 25 °C, 92% over two steps; (f) MsCl, Et_3N, CH_2Cl_2, 0 °C , 10 min; (g) NaN_3, DMF, 80 °C, 1 h, 93% over two steps; (h) H_2 (1 atm), 10% Pd/C, MeOH, 25 °C, 12 h; (i) HCHO, $MgSO_4$, CH_2Cl_2; (j) H_2 (1 atm), 10% Pd/C, MeOH, 25 °C, 5 h, 78%.

Section III: Asymmetric synthesis of 1-[(*S*)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1-(2*H*)-yl]propan-1-one

Asymmetric synthesis of 1-[(*S*)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1-(2*H*)-yl]propan-1-one (**23a-b),** a positive inotropic agent,[4] is described in this section. Tetrahydroquinolinol **5a,** prepared by the $CoCl_2$-catalyzed reduction of the corresponding cyclic sulphite **4a,** was treated with propionic anhydride to give amido alcohol **19** in 93% yield and 95.5% ee (determined by chiral HPLC). Alcohol **19** on mesylation (MsCl, Et_3N in CH_2Cl_2) followed by its displacement with azide ion (NaN_3 in DMF) gave azide **21** in 91% yield**.** Finally, azide **21** was reduced to amine [H_2 (1 atm), 10% Pd/C] (**Scheme 3**).

The *N, N'*- dimethylation of amine **22** was achieved by treating **22** with formic acid and formaldehyde solution under reflux condition to afford **23a** in 73% yield and 94% ee.



Scheme 3: (a) $CoCl_2 \cdot 6H_2O$ (1 mol%), $NaBH_4$, EtOH, 0-25 °C, 78%; (b) $(RCO)_2O$, Et_3N, CH_2Cl_2, 0 °C, 91%; (c) MsCl, Et_3N, CH_2Cl_2, 0 °C, 10 min; (d) NaN_3, DMF, 80 °C, 12 h, 91% (two steps); (e) H_2 (1 atm) 10% Pd/C, MeOH, 25 °C, 12 h; (f) HCHO (40 % aq. solution), HCO_2H, 80 °C, 3 h, 73% over two steps.

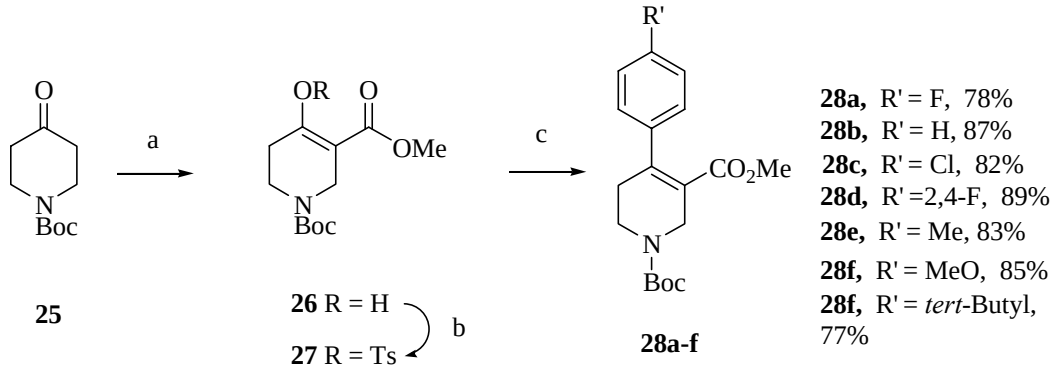
Chapter 2

Pd-catalyzed Suzuki-Miyaura coupling of enol tosylate with boronic acids: A short synthesis of (±)-paroxetine and (±)-femoxetine, potent anti-depressant drugs

Suzuki-Miyaura coupling is one of the most effective reactions for the construction of C-C bonds in organic synthesis.[5] This chapter describes a new route for the synthesis of arylheterocyclic derivatives **28a-e** wherein Pd-catalyzed Suzuki-Miyaura coupling of enol tosylate **27**, derived from piperdine-4-one, with a variety of boronic acids was carried out. Synthesis of (±)-paroxetine **34** and (±)-femoxetine **35**, two potentially proven anti-depressant drugs, *via* Suzuki coupling, have also been described in this chapter.

Section I: Pd-catalyzed Suzuki coupling of enol tosylate with boronic acids

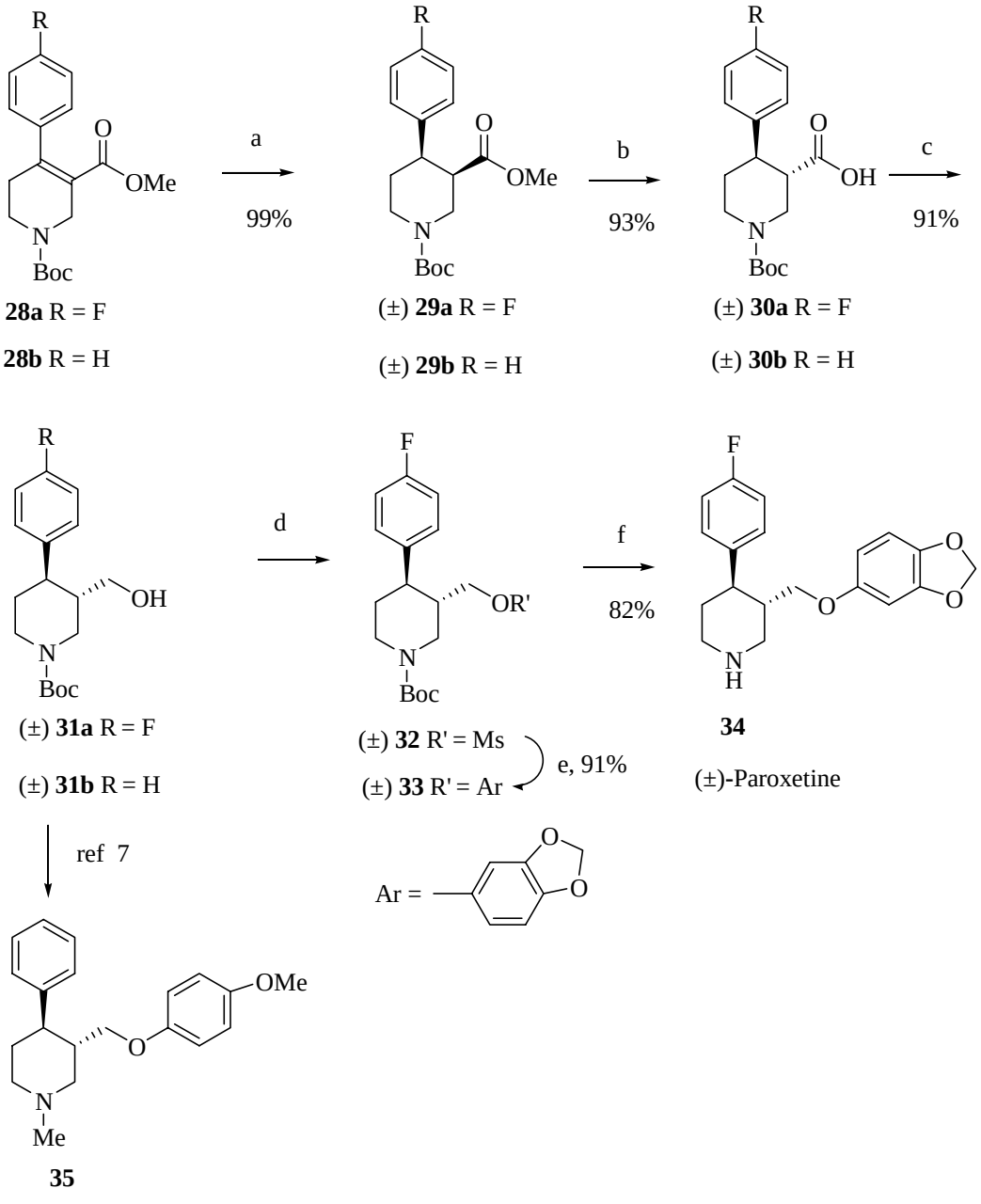
This section provides a new route for the synthesis of tetrahydropyridine derivatives **28a-e** in three steps with substitutions at C_3 and C_4 positions (in three steps), starting from 4-piperidone (**25)**. Boc-protected 4-piperidinone **25** was carbomethoxylated (NaH, $(MeO)_2CO$ in DMF) to give enol ester **26** in 89% yield, which on tosylation **(**TsCl, Et_3N in CH_2Cl_2) gave enol tosylate **27** in 93% yield. Enol tosylate **27** was then subjected to Pd-catalyzed Suzuki coupling with several aryl boronic acids to give tetrahydropyridine derivatives **28a-e** in 77-89% yields (**Scheme 4**).



Scheme 4: (a) NaH, $(MeO)_2CO$, DMF, 25 °C, 12 h, 89%; (b) TsCl, Et_3N, CH_2Cl_2, 25 °C, 12 h, 93%; (c) $ArB(OH)_2$, $PdCl_2(PPh_3)_2$ (5 mol%), aq. Na_2CO_3, THF, 60 °C, 6 h, 71-81%.

Section II: A short synthesis of (±)-paroxetine and (±)-femoxetine, potent anti-depressant drugs

(±)-Paroxetine **34** and (±)-femoxetine **35** are selective serotonin reuptake inhibitors used in the treatment of depression, obsessive compulsive disorder and panic.[6] *α,β*-Unsaturated ester **28a,** prepared *via* Suzuki coupling, on reduction with H_2 (1 atm) over 10% Pd/C) gave the corresponding saturated ester **29a** with *syn* fashion in 99% yield. Both epimerization of ester **29a** at C_3-position, coupled with hydrolysis of ester, was achieved with ^{t}BuOK in methanol to give the *anti* acid **30a** in 85% yield, which on reduction with $BH_3 \cdot SMe_2$ gave alcohol **31a** in 93 % yield. Etherification of alcohol **31a** with sesamol was carried out in two steps: by mesylation of alcohol **31a**, followed by its displacement with sesamol gave *N*-Boc protected paroxetine **33** in 91% yield over two steps (**Scheme 5)**.



Scheme 5: (a) 10% Pd/C (10 wt %), H_2 (1 atm), MeOH, 25 °C, 24 h, 99%; (b) ^{t}BuOK, MeOH, 65 °C, 12 h, 93%; (c) $BH_3{\cdot}SMe_2$, THF, 0 °C, 12 h, 91%; (d) MsCl, Et_3N, CH_2Cl_2, 25 °C, 3 h; (e) sesamol, NaH, DMF, 110 °C, 2 h then 25 ° C,16 h, 91%; (f) TFA, CH_2Cl_2 0-25 °C, 6 h, 82 %.

Finally, Boc- deprotection in **33** with TFA gave (±)-paroxetine **34** in 82% yield. For the formal synthesis of (±)-femoxetine **35**, a similar sequence of reactions as that of (±)-paroxetine **34** was carried out.[7]

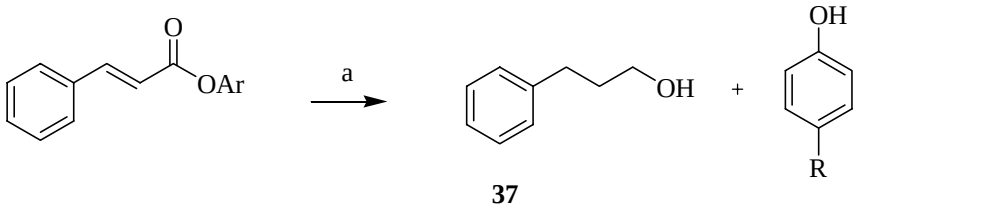
Chapter 3

$CoCl_2$-catalyzed chemoselective reduction of carboxylic esters with $NaBH_4$: asymmetric synthesis of (*R*)-tolterodine

This chapter describes a new, milder and efficient methodology for the chemoselective reduction of carboxylic esters catalyzed by $CoCl_2$. The use of this methodology is exemplified by its application in the asymmetric synthesis of (*R*)-tolterodine (**43**), a potent and competitive muscarinic antagonist.

Section I: $CoCl_2$-catalyzed chemoselective reduction of carboxylic esters with $NaBH_4$

We have developed a simple and efficient procedure for the reduction of phenolic esters **36** and **39**, using catalytic amount of $CoCl_2 \cdot 6H_2O$with $NaBH_4$ (**Schemes 6** and **7**). For example C=C double bond in aryl acrylates **36** was reduced to give the corresponding saturated alcohol **37** along with phenols **38a-b** in excellent yields.



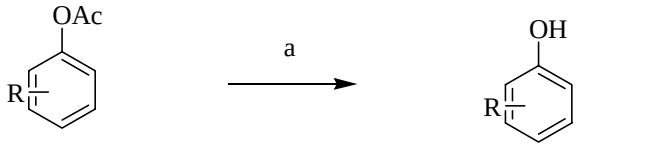
37

36a Ar = Ph
36b Ar = 4-O_2N-C_6H_4-

38a R = H, 95%
38b R = 4-O_2N, 98%

Scheme 6: (a) $CoCl_2 \cdot 6H_2O$ (1 mol%), $NaBH_4$ (3 equiv.), EtOH, 25 °C, 2 h.

Surprisingly, phenolic acetates **39** were reductively deacylated under the same reaction conditions provides the corresponding phenols **40** in high yields. Several reducible groups such as NO_2, CN and halogens were not affected. Good chemoselectivity, excellent yields, milder reaction conditions and use of $NaBH_4$ are some of the distinct features of this methodology.

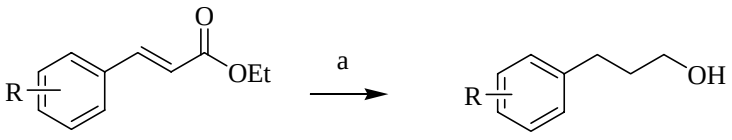


39 **40**

R = Cl, Br, I, NO_2, CN, CO_2Et, Yield = upto 99%

Scheme 7: (a) $CoCl_2 \cdot 6H_2O$ (1 mol%), $NaBH_4$ (2 equiv.), EtOH, 0-25 °C, 2 h.

In continuation of this investigation, we found surprisingly that addition of catalytic amount of diisopropyl amine enhances the reactivity of $CoCl_2 \cdot 6H_2O/NaBH_4$ system towords the reduction of carboxylic esters.

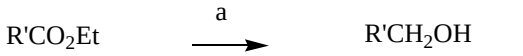


41 **42**

R= OMe, Cl, NO_2 Yield = 75- 92%

Scheme 8: (a) $CoCl_2 \cdot 6H_2O$ (10 mol%), $^{i}Pr_2NH$(20 mol%), $NaBH_4$ (4 equiv.), EtOH, 50-60 °C, 24 h.

Several carboxylic esters such as **41** and **43** underwent reduction smoothly with $NaBH_4$ using catalytic amount of $CoCl_2 \cdot 6H_2O/^{i}Pr_2NH$ to give the corresponding saturated alcohols **42** and **44** in excellent yields (**Schemes 8** and **9**).



43 **44**

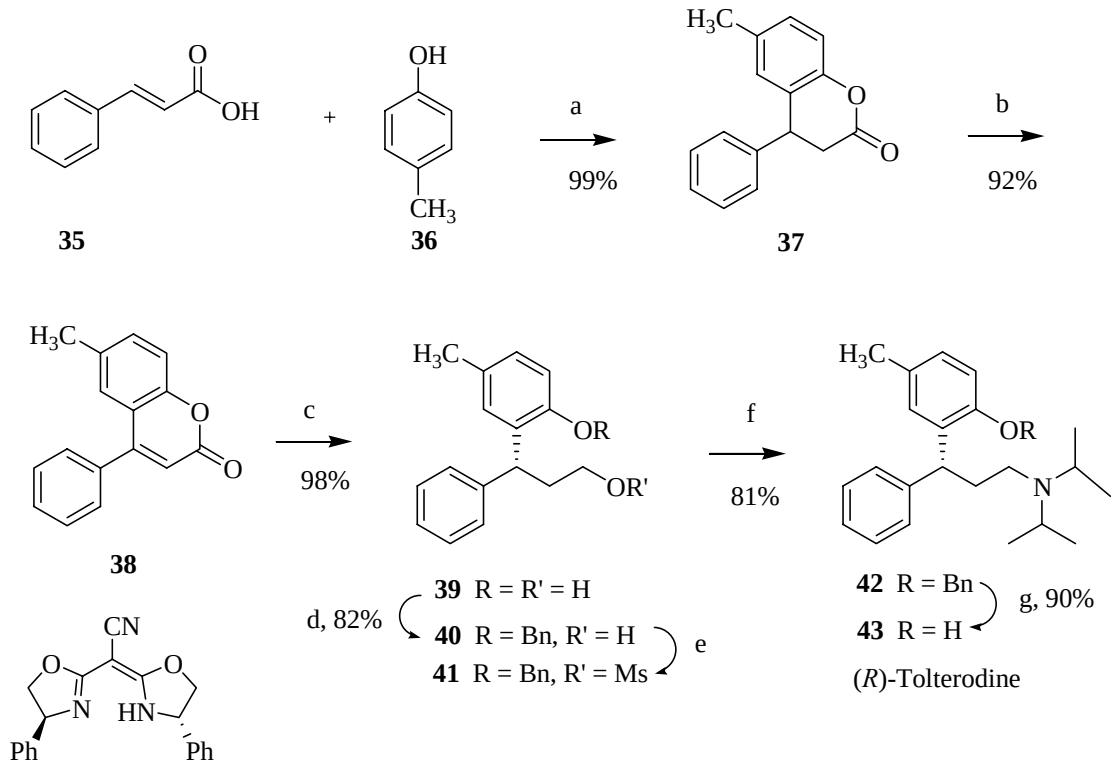
R' = Bn, Ar, alkyl Yield = 72-90%

Scheme 9: (a) $CoCl_2 \cdot 6H_2O$ (10 mol%), $^{i}Pr_2NH$ (20 mol%), $NaBH_4$ (4 equiv.), EtOH, 50-60 °C, 24 h.

Section II: Asymmetric Synthesis of (*R*)-tolterodine

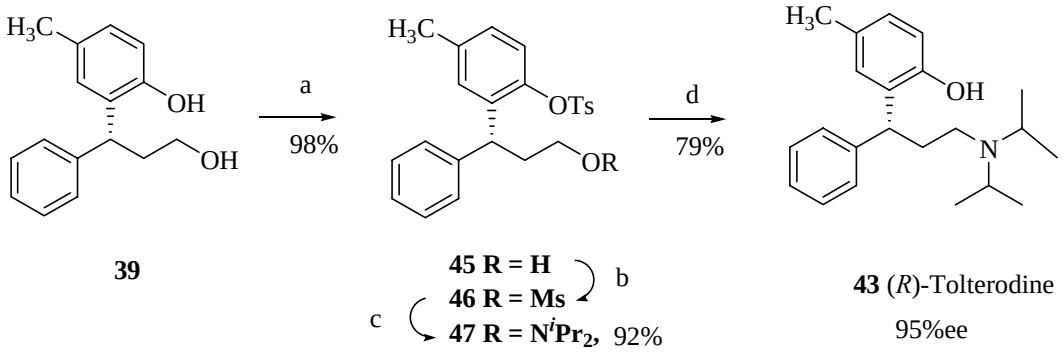
(*R*)-Tolterodine, a potent and competitive muscarinic antagonist, is used in the treatment of urinary urge incontinence and other overactive bladder disorders, whereas (*S*)-tolterodine exhibits a non-cholinergic spasmolytic activity as well as weak sedative effect.[8] This section deals with a short asymmetric synthesis of (*R*)-tolterodine **43**.

The *p*-TSA-mediated hydroarylation of cinnamic acid **35** with *p*-cresol gave dihydrocoumarin **37** in 99% yield in a single step, which on aromatization with DDQ produced the corresponding coumarin **38** in 92% yield. Asymmetric reduction of coumarin **38** with catalytic $CoCl_2 \cdot 6H_2O$ and oxazolidine ligand **44** in catalytic amounts with $NaBH_4$ gave the saturated alcohol **39** in 98 % yield. Further selective protection of phenolic function in **39** with BnBr in the presence of K_2CO_3 in acetone gave the protected phenolic ether **40** in 82% yield. Alcohol moiety in **40** was transformed to mesylate **41** (MsCl, Et_3N in CH_2Cl_2) and its displacement with diisopropyl amine ($^iPr_2NH$, NaI and Na_2CO_3 in DMF) gave the protected tolterodine **42** in 81% yield and 95% ee.[9] Finally, deprotection of benzyl group was carried out under reductive conditions with H_2 (1 atm) over 10% Pd/C to give (*R*)-tolteridone in 95% yield and 95% ee (**Scheme 10**).



Scheme 10: (a) *p*-TSA, 130 °C, 3 h, 99%; (b) DDQ, dioxane, 110 °C, 12h, 92%; (c) $CoCl_2 \cdot 6H_2O$ (1 mol%, ligand **44** (1.1 mol%), $NaBH_4$ (3 equiv.), EtOH, DMF, 0 °C, 36 h, 98%; (d) BnBr, K_2CO_3, acetone, 60 °C, 12 h, 82%; (e) MsCl, Et_3N, CH_2Cl_2, 25 ºC, 30 min; (f) $^iPr_2NH$ (5 equiv.), NaI (20 mol%), Na_2CO_3 (20 mol%), CH_3CN, 80 ºC, 6 h, 81%; (g) H_2 (1 atm), 10% Pd/C, MeOH, 12 h, 90%;

To improve the yield, we protected phenolic OH with OTs (TsCl, aq. NaOH in CH_2Cl_2) at reflux conditions to give the tosylate **45** in 98% yield and 95% ee (determined by Mosher's ester analysis). Alcohol **45** was transformed to mesylate **46,** which was displaced with diisopropyl amine to give **47**. Finally, OTs was deprotected with aq. NaOH under reflux condition to give (*R*)-tolterodine in 76% yield (**Scheme 11**).



Scheme 11: (a) TsCl in CH_2Cl_2 then aq NaOH, 45 ºC, 3 h, 98%; (b) MsCl, Et_3N, CH_2Cl_2, 0 ºC, 30 min; (c) $^iPr_2NH$ (5 equiv.), NaI (20 mol%), Na_2CO_3 (20 mol%), CH_3CN, 80 ºC, 6 h, 92%; (d) aq. NaOH, MeOH reflux, 4 h, 79%.

Chapter 4

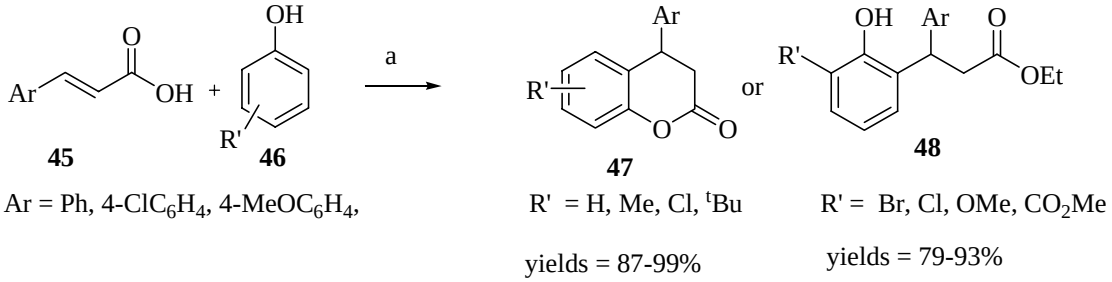
p-Toluenesulfonic acid (*p*-TSA)-mediated hydroarylation of cinnamic acids with anisoles and phenols under metal- and solvent-free conditions and $Cu(OTf)_2$-catalyzed α-halogenation of ketones

Section I describes the development of a novel synthetic methodology involving *p*-TSA-mediated hydroarylation of cinnamic acids with substituted anisoles and phenols. Section II presents the results of $Cu(OTf)_2$-catalyzed α-halogenations of ketones with 1,3-dichloro-5,5-dimethylhydantoin and *N*- bromosuccinimide as halogen sources.

Section I: *p*-Toluenesulfonic acid (*p*-TSA)-mediated hydroarylation of cinnamic acids with anisoles and phenols under metal- and solvent-free conditions

4-Aryl 3,4-dihydrocoumarins **47** are of synthetic target as they are present in a number of natural products, such as neoflavonoids and complex flavonoids.[10] This section describes a novel single-step procedure for the synthesis of 4-aryl 3,4-dihydrocoumarins **47** in high yields and excellent selectivity *via* hydroarylation of cinnamic acids with phenols

mediated by *p*-toluenesulfonic acid (*p*-TSA) under metal- and solvent-free conditions.[11] In case of phenolic substrates with *ortho* substitutents such as Cl, Br, OMe and CO_2Me, the dihydrocoumarins formed initially, were labile and underwent transesterification with ethyl acetate to give the respective phenolic esters **48** in good yields (**Scheme12**).



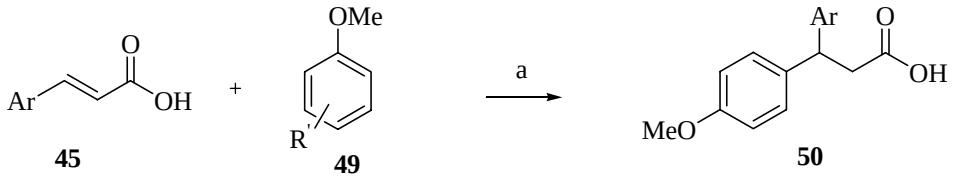
45 **46** **47** **48**

Ar = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, R' = H, Me, Cl, ^tBu yields = 87-99%

R' = Br, Cl, OMe, CO_2Me yields = 79-93%

Scheme 12: (a) *p*-TSA, 125 °C, 3 h, No solvent.

In continuation of this work, we have also developed an elegant methodology in which hydroarylation of cinnamic acids such as **45** with substituted anisoles **49** mediated by *p*-toluenesulfonic acid (*p*-TSA) under metal- and solvent-free conditions gave 3-(4-methoxyphenyl)-3-phenylpropanoic acids **50** in high yields and excellent selectivity, thus anisoles **49** undergoing a Michael-type addition with cinnamic acids **45** (**Scheme 13**). Compounds **50** show excellent activity as G protein-coupled receptor 40 agonists.[12]



45 **49** **50**

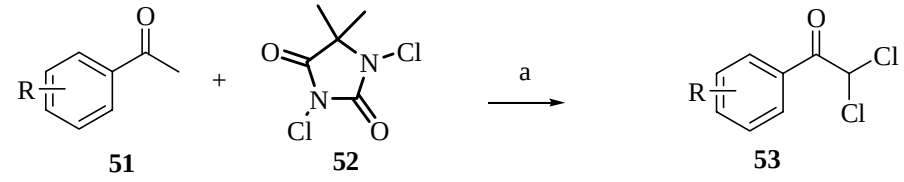
Ar = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, R' = H, Br, Cl, MeO yield = 65-95%

Scheme 13: (a) *p*-TSA, 125 °C, 3 h, No solvent.

Section II: $Cu(OTf)_2$-catalyzed *α*-halogenation of ketones with 1,3-dichloro-5,5-dimethylhydantoin and *N*-bromosuccinimide.

α-Halo ketones are valuable intermediates for the synthesis of several organic compounds.[13] This section describes $Cu(OTf)_2$-catalyzed *α*-halogenation of ketones. We have found that $Cu(OTf)_2$-catalyzes *α,α*-dichlorination of aromatic ketones **51** with 1,3-

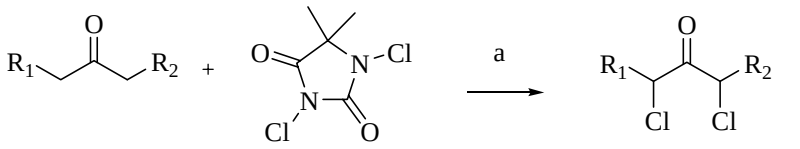
dichloro-5,5-dimethylhydantoin (**52**) as chlorine source to give *α,α*-dichloroketones **53** (**Scheme 14**). Under the same reaction conditions aliphatic ketones **54** gave *α,α'*-dichloroketones **55** (**Scheme 15**)..



51 **52** **53**

R = H, Cl, Br, OMe, NO_2 yield = 62-95%

Scheme 14: (a) $Cu(OTf)_2$ (5 mol%), $CHCl_3$, 80 °C, 6-12 h.

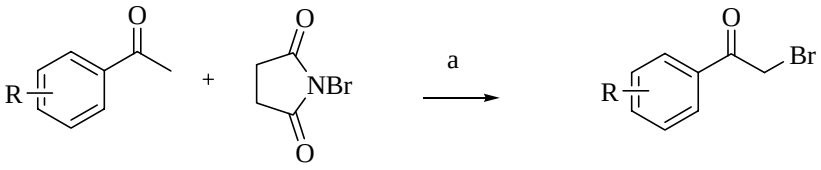


54 **52** **55**

R_1 = Et, Me, R_2 = Me, H yield = 70- 92%

Scheme 15: (a) $Cu(OTf)_2$ (5 mol%), $CHCl_3$, 80 °C, 6-12 h.

In continuation of this work, we have subjected several aromatic ketones **51** to $Cu(OTf)_2$ catalyzed *α*-bromination with *N*-bromosuccinamide (**Scheme 16**), wherein we found that *α*-bromoketones **57** were formed as the major product along with *α,α*-dibromoacetophenones formed in small quantities.



51 **56** **57**

R = alkyl , OMe, NO_2, halogen Yield 61 - 92%

Scheme 16: (a) $Cu(OTf)_2$ (5 mol%), $CHCl_3$, 80 °C, 6-12 h.

Aromatic ketones with electron-rich as well as electron-withdrawing substituents underwent *α*-halogenation with good yield and chemoselectivity. Other ketones such as aromatic, aliphatic, cyclic and acyclic ketones underwent halogenation under milder and catalytic conditions. Use of a catalytic amount of $Cu(OTf)_2$ and a stable halogen sources

such as 1,3-dichloro-5,5-dimethylhydantoin (**52**) or NBS (**56**) make this procedure an attractive one.

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Chapter I

A new concise method of synthesis of tetrahydroquinolin-3-ol, Sumanirole maleate (PNU 95666-E) and 1-[(S)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1-(2H)-yl]propan-1-one

Section I:

A novel method for the synthesis of *(R)*-tetrahydroquinolin-3-ols *via* Os-catalyzed asymmetric dihydroxylation coupled with $CoCl_2$-catalyzed reduction of cyclic sulphites with $NaBH_4$

1.1.1 Introduction

The greatest interest in the synthesis of 1,2,3,4-tetrahydroquinolines is due to their biological activities.[1] Simplest example is 2-methyl-1,2,3,4-tetrahydroquinoline (**1**) present in human brain(**Fig. 1**). Tetrahydroquinoline L-689560 (**2**) is one of the most potent NMDA antagonists yet found.[2] Virantmycin (**3**) shows antibiotic activity.[3] (+)-Duocarmycin D_1 (**4**), having chiral 3-hydroxytetrahydroquinoline system in their structure shows potential cytotoxic activity.[4] Anechalin-H (**5**) is a complex tetrahydroquinoline and exhibits antibiotic activity against *Moraxella catarrhalis*.[5]

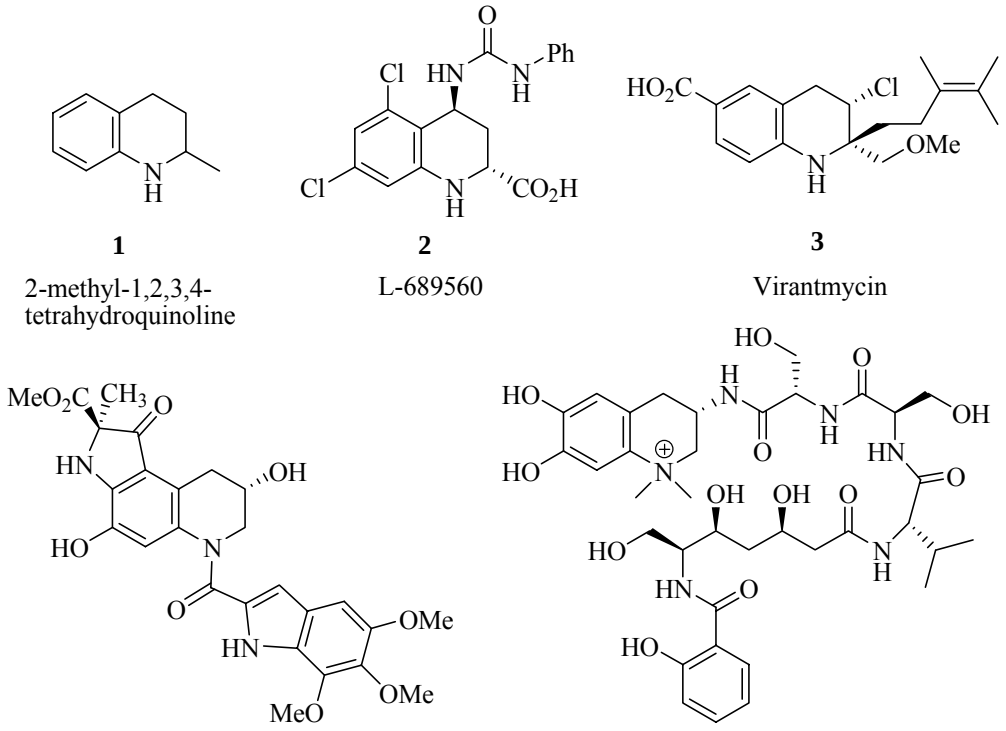


Fig. 1 Some of the examples of tetrahydroquinoline derivatives

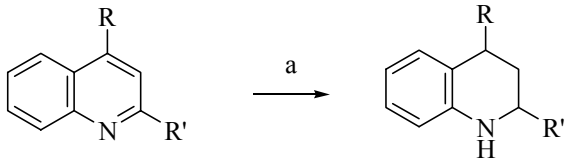
Many relatively simple synthesized 1,2,3,4-tetrahydroquinolines are already proven as potential drugs.[6] Moreover, besides pharmaceutical applications, tetrahydroquinoline derivatives are useful as pesticides,[7] antioxidants,[8] and corrosion inhibitors,[9] Also tetrahydroquinolines are widely used as active components of dyes[10] and photosensitizers in photography.[11]

1.1.2 Review of literature

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

Murahashi's Approach (1987)[12]

Murahashi *et al*. have described the synthesis of tetrahydroquinolines **6a-d** *via* hexarhodiumhexadecacarbonyl complex catalyzed selective reduction of pyridine nucleus in quinolines **7a-d** using carbon monoxide and water as efficient reducing agent (**Scheme 1**).



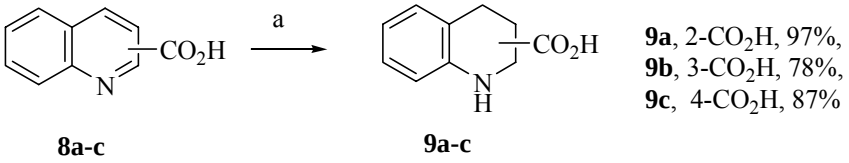
6a-d **7a-d**

7a, R, R' = H, 97%
7b, R, R' = CH_3, 89%
7c, R = CH_3, R' = H, 91%
7d, R = H, R' = CH_3, 87%

Scheme 1: (a) Catalytic $Rh_6(CO)_{16}$, CO, H_2O.

Gracheva's Approach (1988)[13]

Gracheva *et al.* have reported the use of Ni-Al alloy for the reduction of quinolinecarboxylic acid **8a-c** to obtain tetrahydroquinolinecarboxylic acid **9a-c** in high yields (**Scheme 2**).

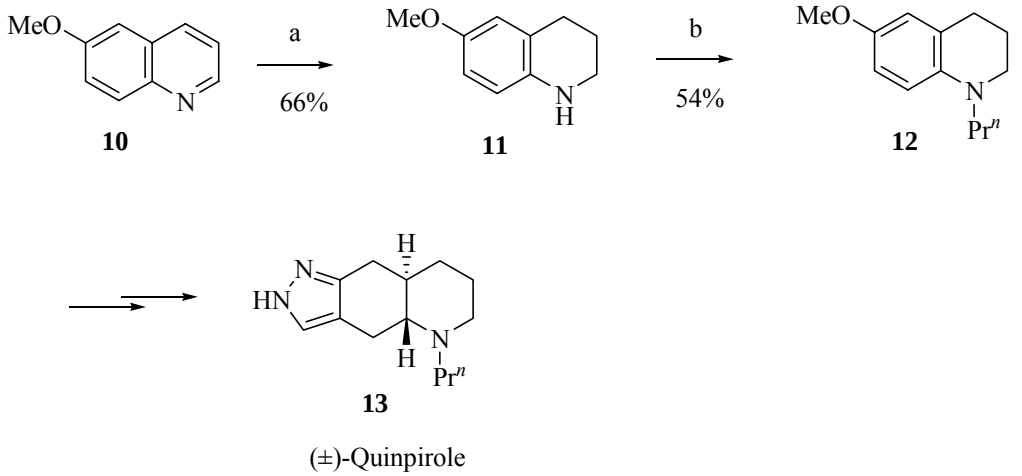


8a-c **9a-c**

Scheme 2: (a) Ni-Al, aq. NaOH, 50 °C, 12 h,

Schaus's Approach (1990)[14]

Schaus *et al.* have reported the synthesis of (±)-quinpirole (**13**) using hydrogenation [catalytic PtO_2, H_2 (60 psig)] of 6-methoxyquinoline (**10**) which afforded 6-methoxy-l,2,3,4-tetrahydroquinoline (**11**). Reductive alkylation of **11** [propanaldehyde, 15% Pd/C, H_2 (60 psig)] furnished tetrahydroquinoline **12** in 36 % yield over two steps. Further **12** was converted into (±)-quinpirole (**13**) employing a sequence of reactions (**Scheme 3**).



10 **11** **12**

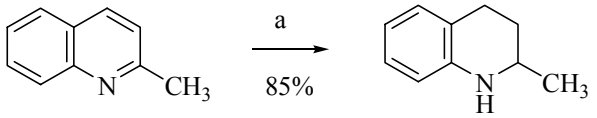
13

(±)-Quinpirole

Scheme 3: (a) PtO_2 (10 wt%), H_2 (60 psig), 50 °C, 12 h, MeOH; (b) 15% Pd/C, H_2 (60 psig), EtCHO, EtOH, 50 °C, 12 h.

Bouyssou's Approach (1992)[15]

Bouyssou *et al.* had employed transfer hydrogenation (10% Pd/C, HCO_2H/Et_3N) as a method for reducing quinoline **6d** to afford the corresponding tetrahydroquinoline **7d** in 85 % yield (**Scheme 4**).

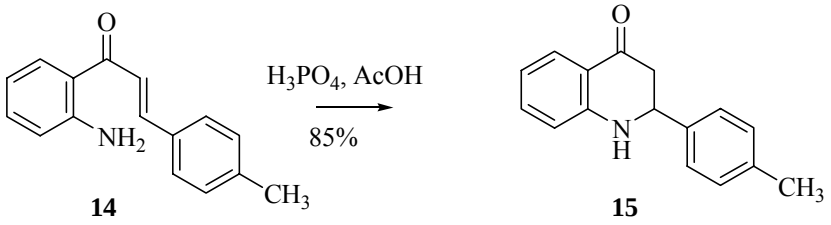


6d **7d**

Scheme 4: (a) 10% Pd/C, HCOOH (5 equiv.), Et_3N (2 equiv.), 50 °C, 12 h.

Szilagyi's approach (1992)[16]

Szilagyi *et al.* have reported an intramolecular Michael addition of amine functionality onto a *α,β*-unsaturated ketone **14** catalyzed by phosphoric acid to give 2-aryl-4-oxo-1,2,3,4-tetrahydroquinoline **15** in 85% yield (**Scheme 5**).

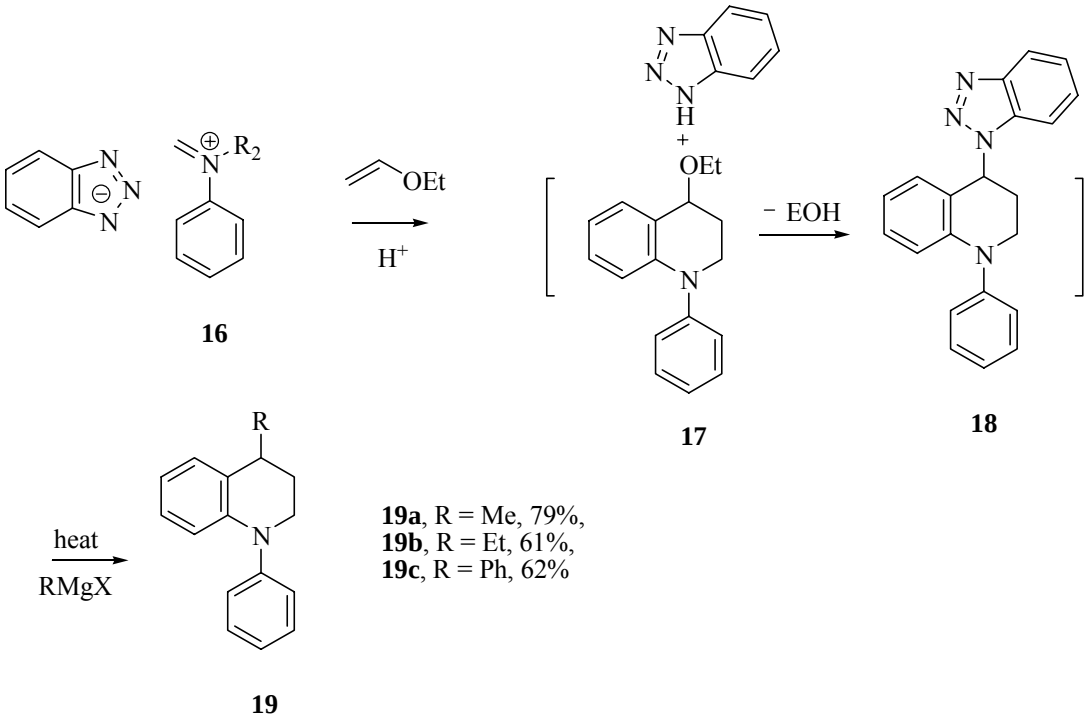


14 **15**

Scheme 5 : H_3PO_4, AcOH, 80 ºC, 1 h.

Katritzky's approach (1995)[17]

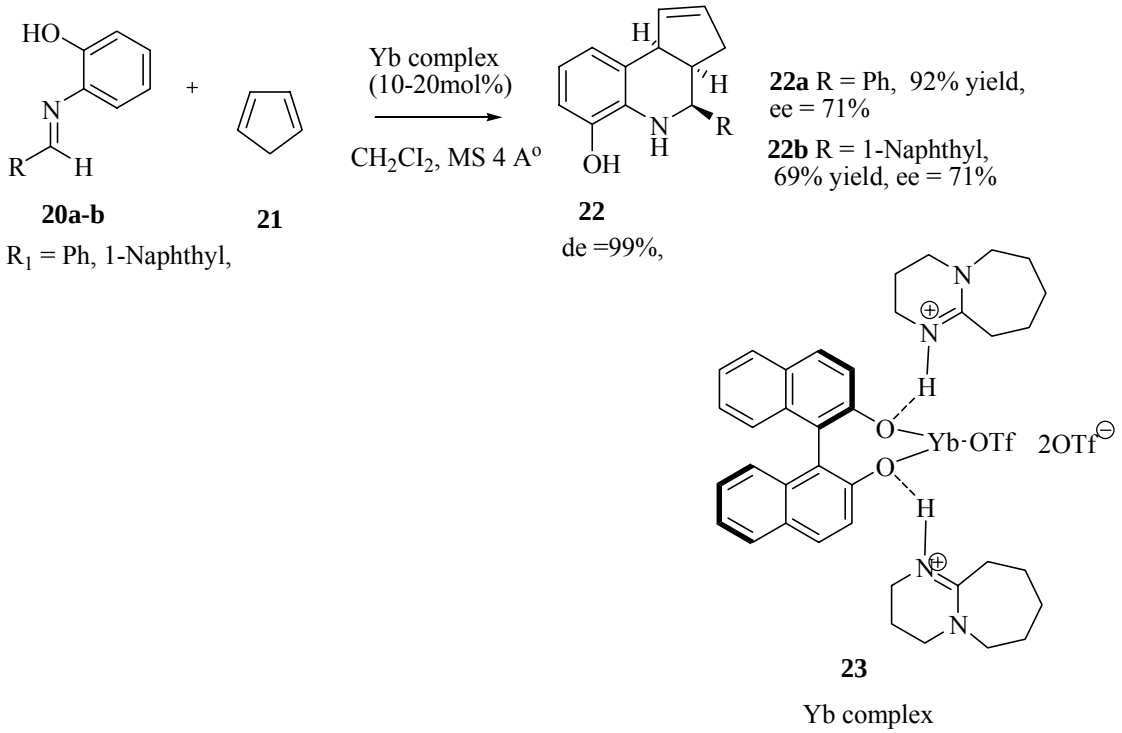
Katritzky *et al.* have reported acid catalyzed Diels-Alder reaction of *N*-methylaniline derivative **16** with ethyl vinyl ether to give reactive intermediate 4-ethoxy-1,2,3,4-tetrahydroquinoline (**17**) which underwent *in situ* substitution by benzotriazol to provide 4-(benzotriazolyl)-1,2,3,4-tetrahydroquinoline (**18**) in 48% yield. At elevated temperatures, ionization of **18** gives immonium cation which can be trapped *insitu* by Grignard reagent to provide 4-substituted tetrahydroquinolines **19** in good yields (**Scheme 6**).



Scheme 6: (a) **16** (10 mmol), ethyl vinyl ether (1.2 mL, 12 mmol), *p*-toluenesulfonic acid monohydrate (10 mg), 22 ºC, 30 min. then 120 ºC, 10 min; (b) RMgX (25 mmol, Et_2O (25mL) reflux, 1 h.

Kobayashi'Approach (1996)[18]

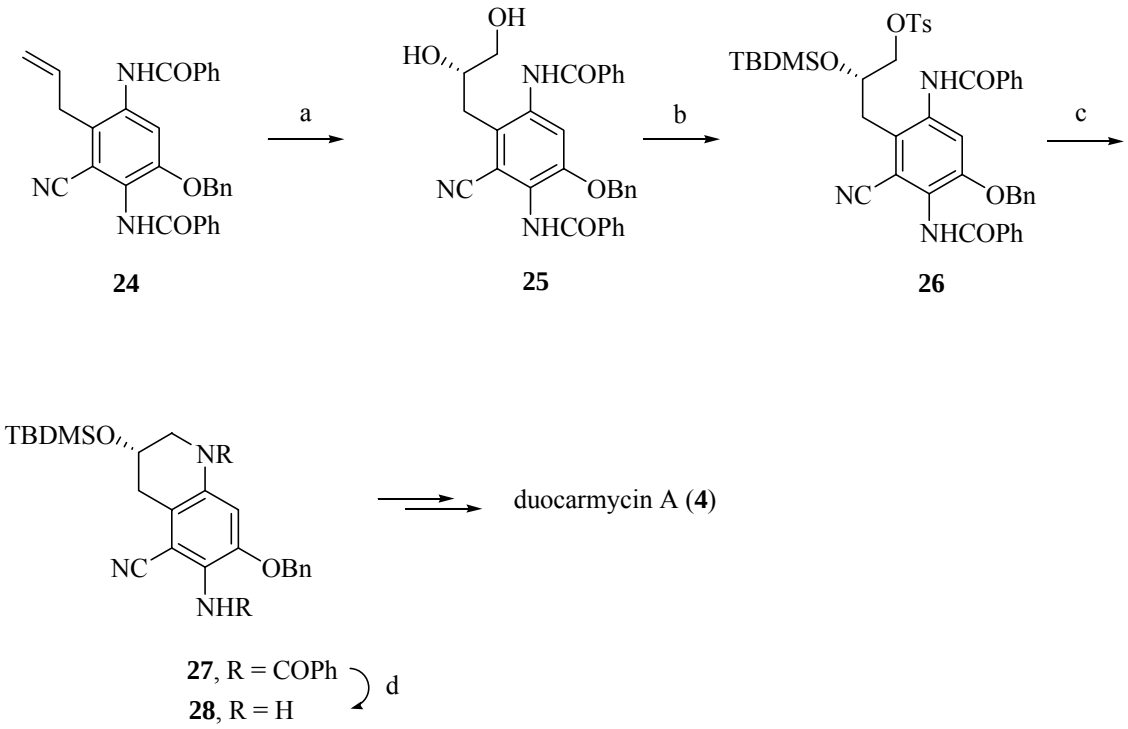
Kobayashi *et al*. have used asymmetric Aza Diels-Alder reactions of imine **20a-b** and cyclopentadiene (**19a)** catalysed by $Yb(OTf)_3$·(*R*)-BINOL (**23**) complex to provide tetrahydroquinoline derivatives **20a-b** in 69-92% yields and 71% ee (**Scheme 7**).



Scheme 7: (a) $Yb(OTf)_3$:(*R*)-BINOL:DBU (20 mol%) **23**, 2,6-Di-^{t}butylpyridine (1 equiv.), CH_2Cl_2, MS 4 A^o, -15-0 ºC, 20 h.

Boger's approach (1997)[19]

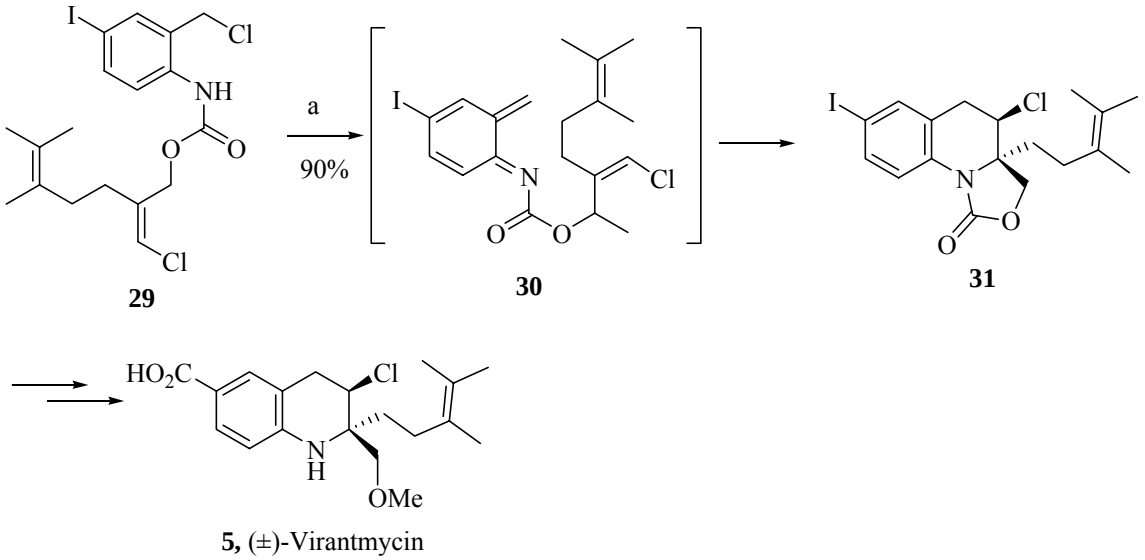
Boger *et al.* have used asymmetric dihydroxylation as key step for the synthesis of duocarmycin-A (**4**). Asymmetric dihydroxylation of olefin **24** gave diol **25** in 95 % yield. Tosylation of primary alcohol and protection of secondary alcohol as silyl ether in **25** gave **26**. Intramolecular nucleophilic displacement of tosylate **26** with amide anion provided key intermediate **27** which on hydrolysis (N_2H_4, sealed tube, 140 ºC) gave diamine **28**. By sequential transformations, **28** was further converted to duocarmycin A (**4**) (**Scheme 8**).



Scheme 8 : (a) OsO_4 (1 mol%), $(DHQD)_2$-PHAL (10 mol%), $K_3Fe(CN)_6$ (3 equiv.), K_2CO_3 (3 equiv.), $MeSO_2NH_2$ (40 mol%), THF:H_2O (4:1), 0-25 °C, 24 h, 92%; (b) (i) Bu_2SnO, toluene-THF (10:1), reflux, 6 h; (ii) 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%; (c) NaH, THF, 0 °C, 2 h, 92%; (d) NH_2NH_2, EtOH, 140 ºC, 12 h, sealed tube, 85%.

Corey's approach (1999)[20]

Corey *et al.* have reported the synthesis of (±)-virantmycin (**5**) via intramolecular Diels-Alder reaction of *o*-azaxylylene **30** which was prepared by elimination reaction of chloro carbamate **29** and underwent intramolecular [4+2] cycloaddition reaction in high stereoselectivity to furnish tetrahydroquinoline derivative **31** in 90% yield. Further (±)-virantmycin (**5**) was synthesized by sequential reactions (**Scheme 9**).



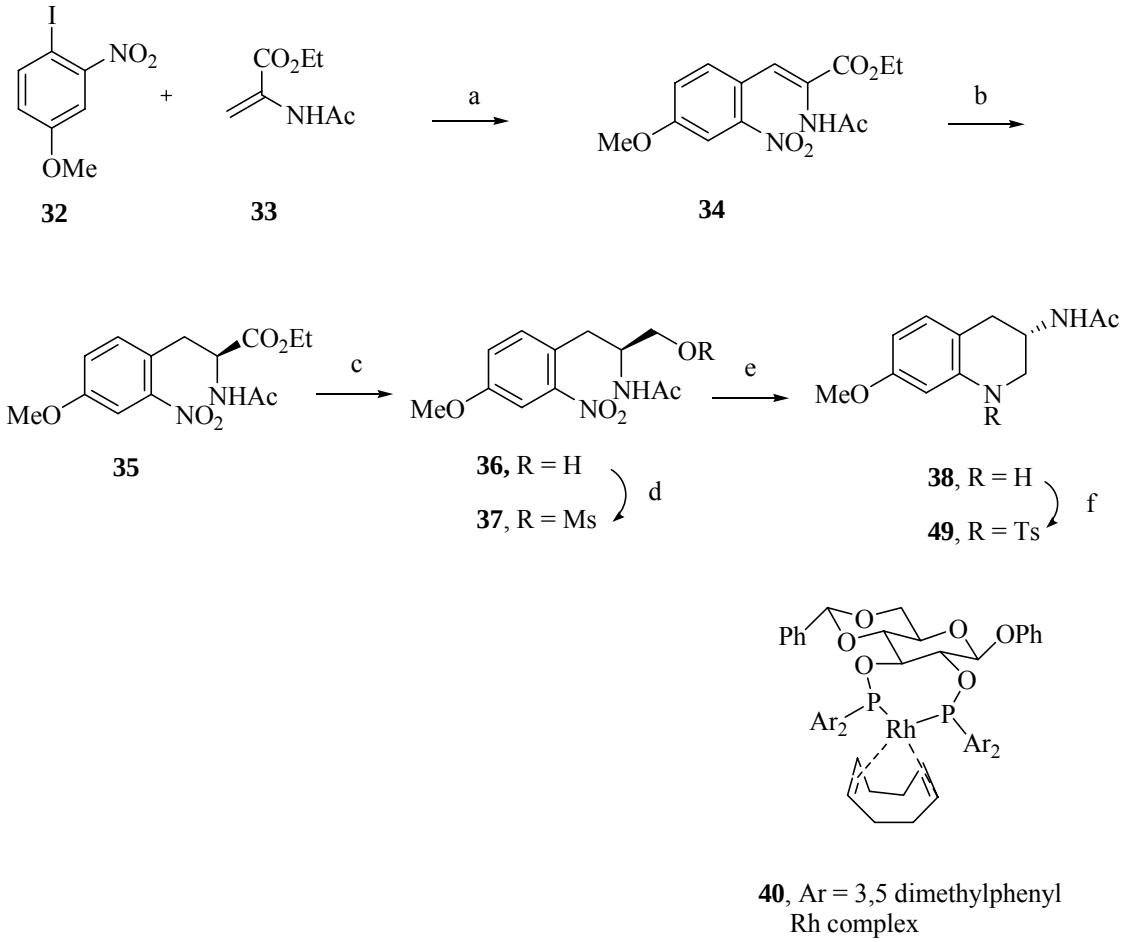
29 **30** **31**

5, (±)-Virantmycin

Scheme 9: (a) $CsCO_3$ (5equiv.), CH_2Cl_2, 23 ºC, 48 h.

Rajan Babu's approach (2001)[21]

Rajan Babu *et al.* have used Rh-catalyzed asymmetric hydrogenation as a key reaction for the synthesis of aminotetrahydroquinoline **40**. Rh-catalyzed asymmetric hydrogenation of α-acetamido-2 nitrocinnamate ester (**35**) gave α-acetamido ester **36** in 96% yield and 98% ee. Further reduction of ester functionality with super hydride afforded the corresponding alcohol **37** which was subsequently transformed into its mesylate **38**. Reduction (H_2, 10% Pd/C) of nitro in **38** to amine followed by cyclization provided 3-aminotetrahydroquinoline **39** which was transformed (TsCl/ Et_3N) as its tosylamide **40** (**Scheme 10**).

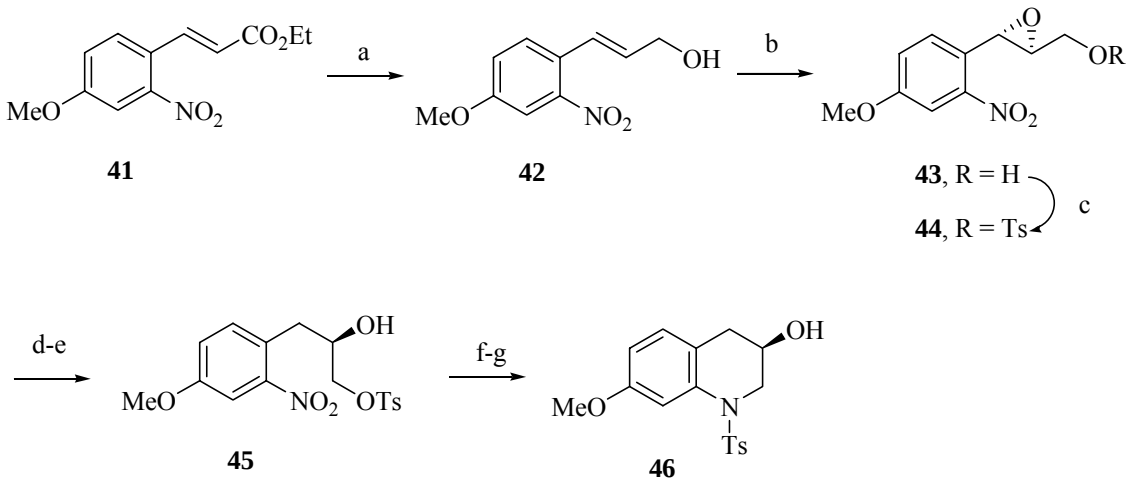


40, Ar = 3,5 dimethylphenyl Rh complex

Scheme 10: (a) $Pd(OAc)_2$, Bu_4NCl, $NaHCO_3$, sealed tube, 80 ºC, 24 h, 80%; (b) Rh catalyst **40**, H_2 (40 psig.), THF, 96%, 98%ee; (c) super hydride, 0 ºC; (d) MsCl, Et_3N, CH_2Cl_2, 0 ºC, 30 min; (e) H_2, Pd/C, 1 h, 25 ºC; (f) TsCl, Et_3N, CH_2Cl_2, 0 ºC.

In another approach, 2-nitrocinnamate **41** was reduced to the corresponding allyl alcohol **42** using DIBAL-H. Sharplesss asymmetric epoxidation of allyl alcohol **42** gave the chiral epoxy alcohol **43,** which was further transformed into tosylate **44.** Reductive opening of epoxide **44** over PtO_2 furnished secondary alcohol **45** in 70 % yield. Finally reduction (Fe/HCl, H_2O and DMF) of nitro functionality to amine which displaces

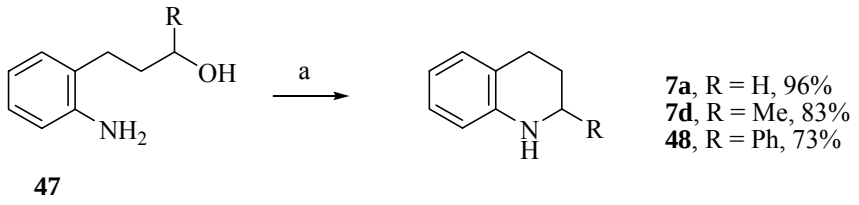
tosylate to afford 3-hydroxy tetrahydoquinoline followed by its protection as tosylamide gave **46** in 66% yield (**Scheme 11**).



Scheme 11: (a) DIBAL-H, toluene, 0 ºC, 75%; (b) $Ti(O^iPr)_4$ (10 mol%), (+)-diethyl tartrate (14 mol%), ^{t}BuOOH, 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)[22]

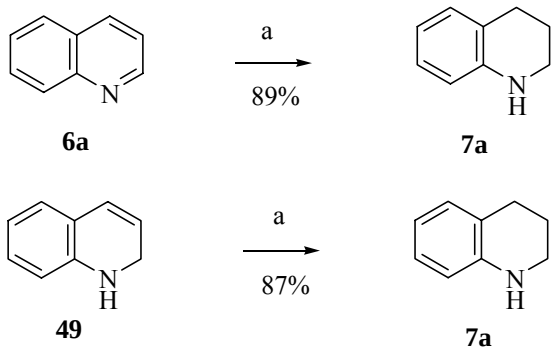
Fujita *et al.* had employed $[CpIrCl_2]_2/K_2CO_3$ catalyzed cyclization of 3-(2-aminophenyl)propanol (**47**) to give tetrahydroquinoline (**7a, 7d** and **48**) in high yields (**Scheme 12**).



Scheme 12: $[CpIrCl_2]_2$ (5.0 mol % Ir), K_2CO_3 (10 mol%), toluene, 111 °C, 20 h.

Fujita's approach (2004)[23]

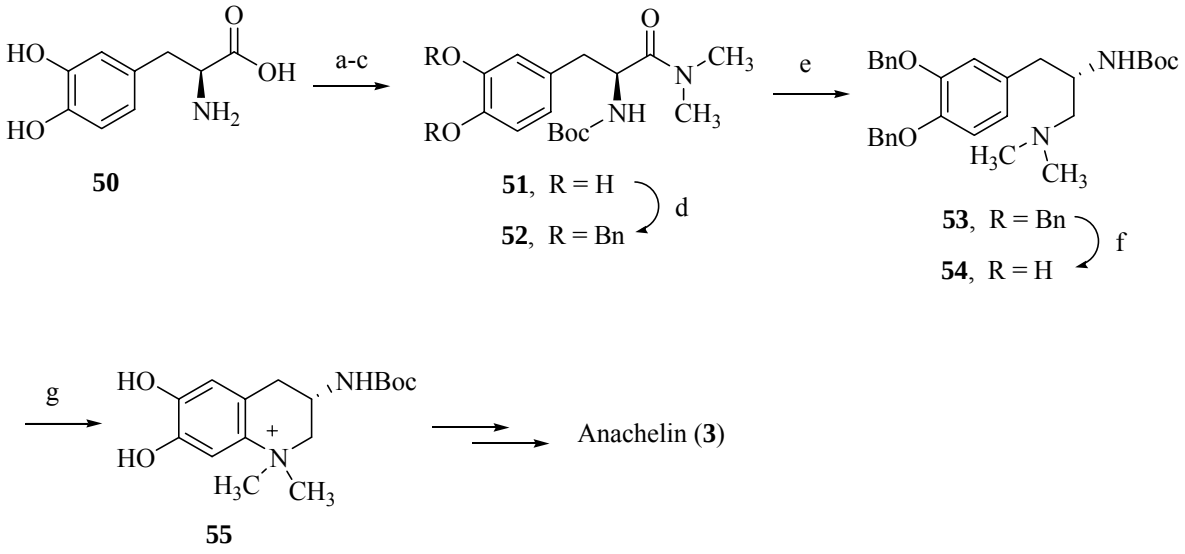
Fujita *et al.* have used Ir-catalyzed transfer hydrogenation of quinoline **6a** and dihydroquinoline **49** to provide tetrahydroquinoline **7a** in high yields. Addition of acid (CF_3CO_2H or $HClO_4$) considerably accelerates the rate of the reaction whereas addition of water minimizes the formation of byproducts (**Scheme 13**).



Scheme 13 : (a) $[CpIrCl_2]_2$ (1mol % Ir), aq.$HClO_4$ (0.20 mmol) 2-propanol (9.5 mL), H_2O (0.5 mL), reflux, 17 h.

Gademann's approach (2004)[24]

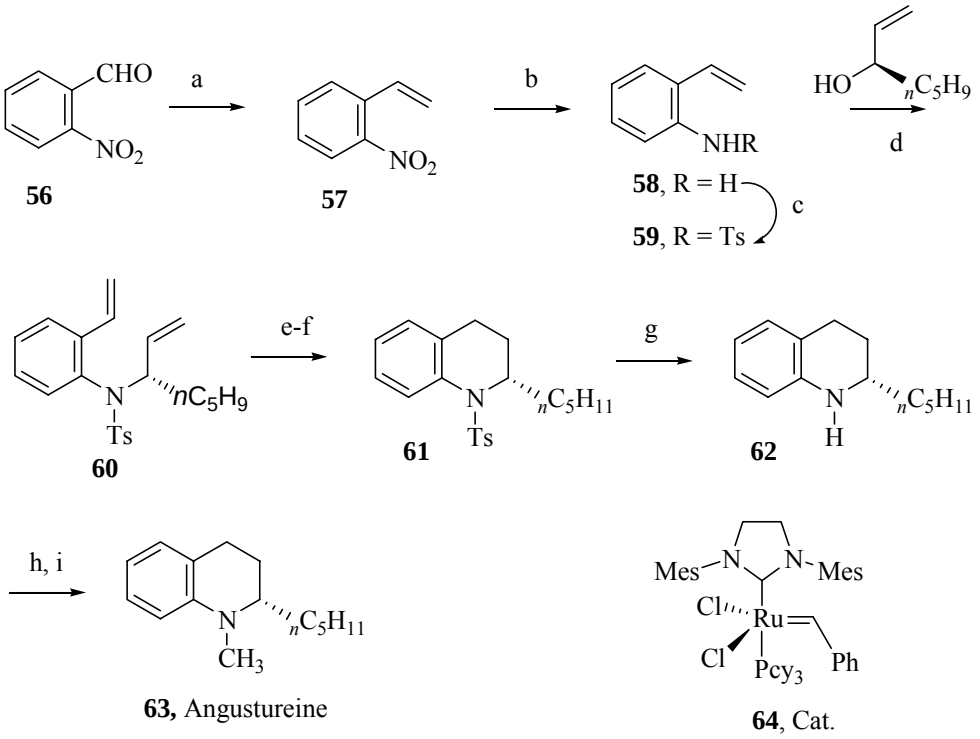
Gademann *et al.* have described oxidative aza-annulation of amine **54** using dianisyltellurium oxide. *N*-Boc-protection of amine and conversion of acid group in **50** to dimethyl amide gave **51** in 61% yields. Further protection of phenol as its benzyl ethers **52** and reduction (BH_3·THF) of amide in **52** gave amine **53.** Deprotection of benzyl ether underwent oxidative cyclization with dianisyltelluriumoxide provided key intermediate **55** for the synthesis of Anachelin (**3**) (**Scheme 14**).



Scheme 14: (a) Boc_2O, aq. NaOH, dioxane; (b) BuOCOCl, THF; (c) $HN(CH_3)_2$; (d) $CsCO_3$, BnBr, acetone, reflux; (e) BH_3·THF; (16% over three steps starting from **50**); (f) Pd/C (10%), H_2 (1 atm), MeOH, AcOH, 99%; (g) dianisyltelluriumoxide, CH_2Cl_2, 69%.

Nishida's approach (2005)[25]

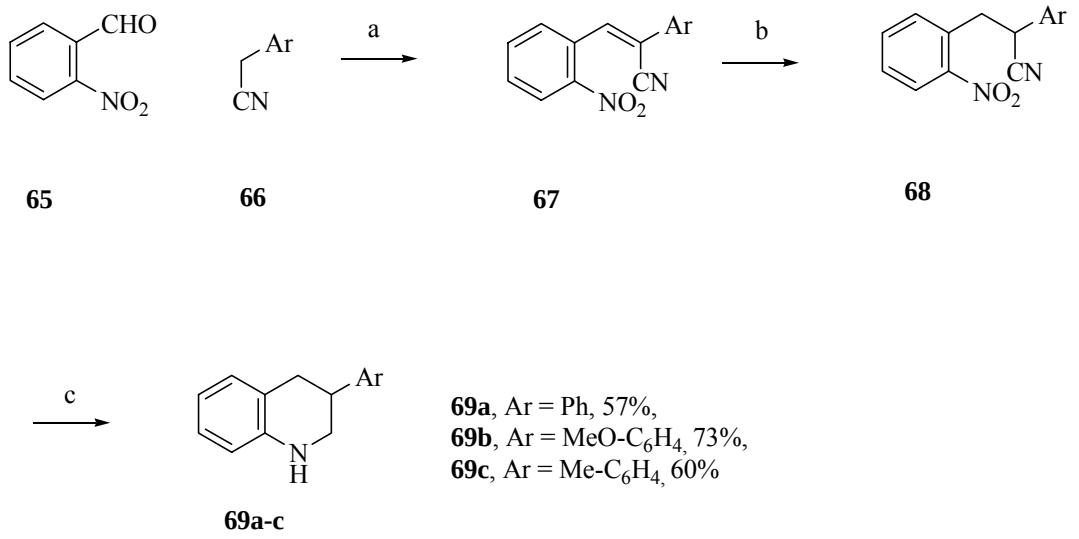
This approach utilized Ru-catalyzed ring closing metathesis (RCM) to construct dihydroquinoline core. Wittig olefination of *o*-Nitro benzaldehyde (**56**) gave nitrostyrene (**57**), which was subjected to reduction of nitro group (Zn/AcOH) to give the corresponding *o*-aminostyrene **58**. Protection of amine in **58** as tosymide **59** (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 α,ω-diene **60** in 78% yield. The diene was subjected to ring closing metathesis (RCM) with Grubbs' catalyst **64** gave the corresponding 1,2-dihydroquinoline in 92% yield which was subsequently hydrogenated over Adam's catalyst in MeOH to provide tetrahydroquinoline **61** in 94% yield and 99.7% ee. Finally detosylation of **61** to free amine **62** and subsequent methylation of the free nitrogen gave (+)-(*S*)-angustureine (**63**) in 80% yield (**Scheme 15**).



Scheme 15: (a) Ph_3PMeBr, $KN(TMS)_2$, THF, 25 ºC, 1 h, 90%; (b) Zn powder, AcOH, 25 ºC, overnight, 72%; (c) TsCl, pyridine, CH_2Cl_2, 25 ºC, 1 h, 86%; (d) DEAD, PPh_3, THF, 25 ºC, 2 h, 78%; (e) Ru catalyst **64**, CH_2Cl_2 (0.01 M), 50 ºC, 1 h, 92%; (f) PtO_2, H_2, MeOH, 25 ºC, 12 h, 94%; (g) anthracene sodium, DME, -65 ºC, 10 min, 99%; (h) MeI, K_2CO_3, THF, reflux, 10 h, 80%.

Yang's approach (2006)[26]

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 (**65**) with aryl propionitrile **66** and subsequent reduction of double bond with $NaBH_4$ provided **67,** which was subjected for reduction of nitro derivative with H_2 over 20% Pd/C and reductive cyclization with cyano group afforded 3-aryltetrahydroquinoline **69a-c** in 57-73% yields (**Scheme 16**).



65 **66** **67** **68**

69a-c

Scheme 16: (a) Na, C_2H_5OH, 5 h; (b) $NaBH_4$, THF, CH_3OH; (c) H_2, 30%Pd/C, THF, CH_3OH.

1.1.3 Present Work

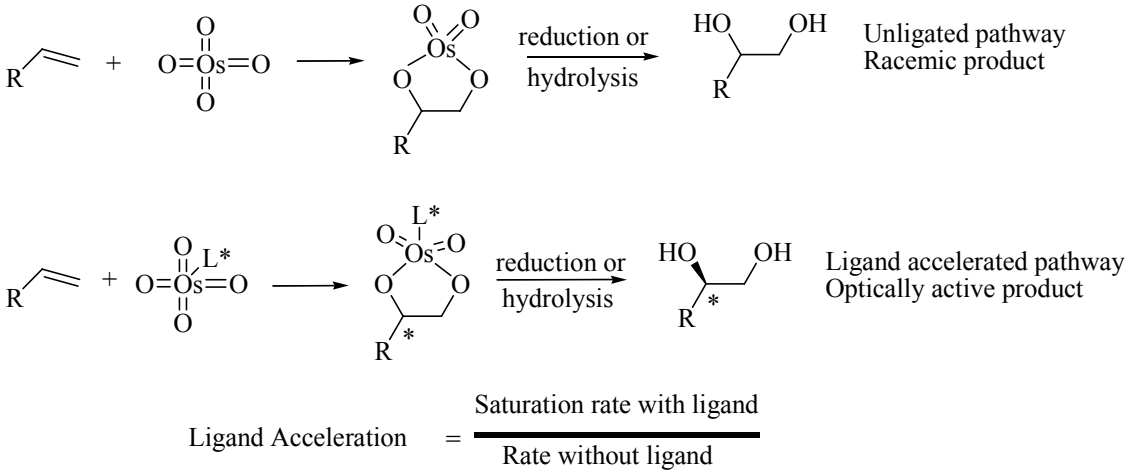
1.1.3.1 Objective

As can be seen, the reported methods for the literature for the synthesis of tetrahydroquinoline mainly deal with racemic synthesis. Other disadvantages include lengthy synthetic routes, need of protection and deprotection of functional groups, low overall yield and use of expensive reagents. In this context, a more practical and efficient synthesis of functionalized tetrahydroquinoline derivatives is highly desirable. In this section, we describe a novel method for efficient synthesis of tetrahydroquinoline which make use of cobalt catalyzed reduction of cyclic sulphites.

Since this chapter deals with two potentially important reactions [asymmetric dihydroxylation (AD) and $CoCl_2 \cdot 6H_2O$ catalyzed reduction with $NaBH_4$], a brief account of Sharpless Asymmetric dihydroxylation (AD) and $CoCl_2 \cdot 6H_2O$ catalyzed reduction with $NaBH_4$ is described as under.

Asymmetric Dihydroxylation (AD)

In recent years, much attention has been focused on the catalytic asymmetric synthesis. It often has significant economic advantages over stoichiometric asymmetric synthesis for industrial-scale production of enantiomerically pure compounds. All these asymmetric reactions crucially depend on ligand acceleration effect (LAE).[27] Among all these reactions, Sharpless catalytic Asymmetric Dihydroxylation (AD) is one of the most important practical and widely used reaction in organic synthesis. It has become the most general method for the preparation of optically active *vicinal-syn*-diols from activated as well as inactivated olefins.[28]



Scheme 17: Mechanism of OsO_4-catalyzed dihydroxylation of olefin

In 1936, Criegee *et al.*[29] have found that addition of pyridine or any other tertiary amine to osmylation of olefins, accelerates the rate of reaction considerably. A major breakthrough has occurred in the field of asymmetric oxidation when Sharpless *et al*.[28b] demonstrated that asymmetric induction could be achieved when chiral amines were added to OsO_4-mediated asymmetric oxidation of olefins. Among the various ligands screened best results were obtained with ligands which were representatives of the

cinchona alkaloid family, dihydroquinidine (DHQD) and dihydroquinine (DHQ) (**Scheme 1**).[30]

To improve the %ee of the chiral diol, the second catalytic cycle of AD should be avoided and this was achieved by employing the $K_3Fe(CN)_6$ as reoxidant and using biphasic conditions **(Fig. 2)**.

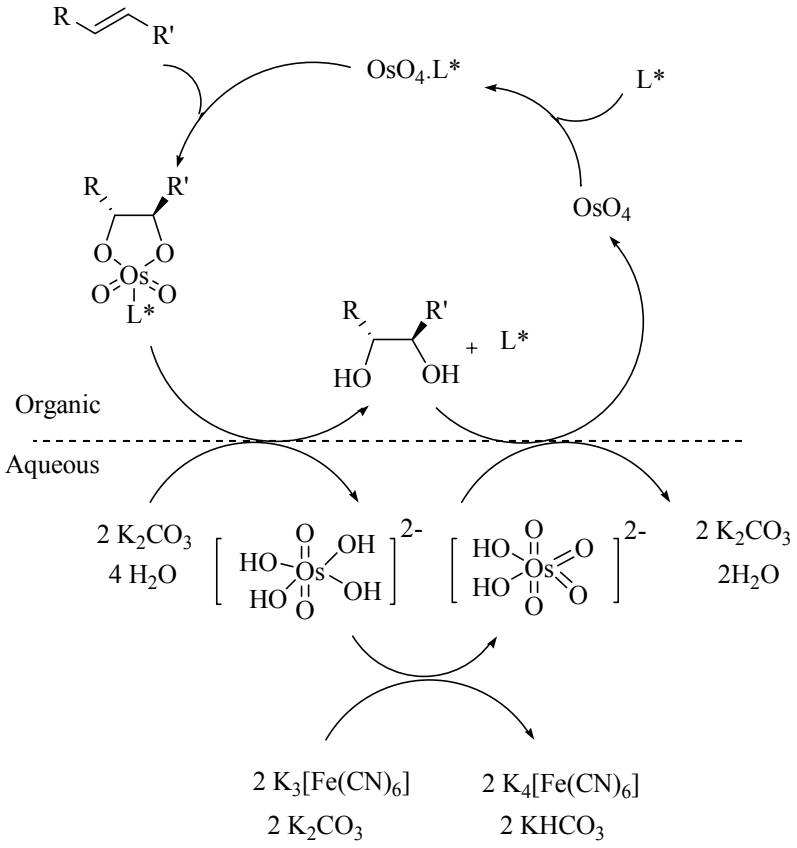
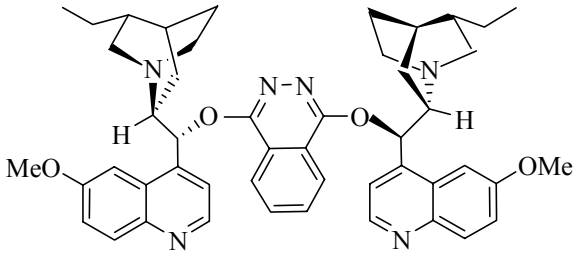


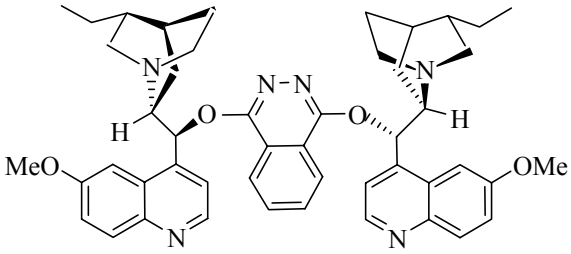
Fig. 2: Catalytic cycle for AD using $K_3Fe(CN)_6$ as co-oxidant

These conditions helped in protecting the organic osmate-(VI) monoglycolate ester (species **A**, **Fig. 2**) from inopportune oxidation prior to hydrolysis and thereby releasing the diol and ligand to the organic phase and osmium-(VI) to the aqueous phase. Subsequently, osmium-(VI) obtains reoxidized and recycled into the catalytic cycle. Further improvement in the AD was realized by the addition of methyl sulfonamide

($MeSO_2NH_2$) to the reaction mixture. It also helps to accelerate the hydrolysis of the species **A**, thus facilitating the dihydroxylation smoothly. Addition of methyl sulfonamide also allowed carrying out the reactions of 1,2-di- tri- and tetra- substituted olefins at 0 ºC, which improved the selectivity as well as enantiomeric excess. In order to develop the asymmetric version of the Os-catalyzed AD reaction, Sharpless and coworkers have screened various chiral ligands and found out that the derivatives of cinchona alkaloids gave excellent results. Among all the 250 derivatives of cinchona alkaloid ligands screened, the *bis*-DHQ **70** or DHQD **71** ethers of phthalazine-1, 4-diol have proven to be the best for obtaining high enantioselective diols[31] **(Fig. 3)**.



$(DHQ)_2$-PHAL (**70**)



$(DHQD)_2$-PHAL (**71**)

Fig. 3: Ligands for asymmetric dihydroxylation reaction

Studies have demonstrated the importance of enzyme-like binding pocket of the dimeric cinchona alkaloid for high enantioselectivity of the chiral diols.[32] Sharpless *et al*.[28] have shown that the facial selectivity for both ligands **70** and **71** is different, based on their ability to induce the ee into the diols. This observation has led to the development of mnemonic model **(Fig. 4)** in which olefin with the constraints will be attacked either from the top (i.e. β) face in the presence of dihydroquinidine (DHQD) derivatives or from the bottom (i.e. α) face in the presence of dihydroquinine (DHQ) derived ligand.

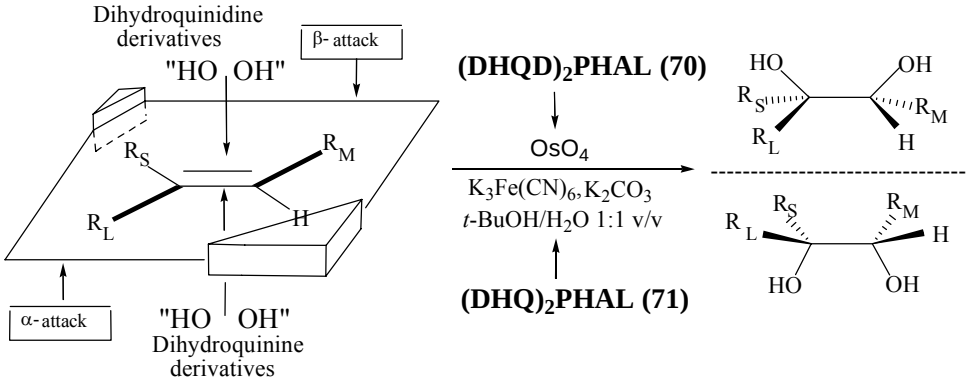


Fig. 4: Enantioselectivity mnemonic scheme

Transition metal boride catalyzed reduction

Since the pioneering discovery of nickel-catalyzed hydrogenation by Paul Sabatier, organic chemists have been fascinated with transition metals and their compounds as promoters for other synthetically important reductions. In the last 40 years, metal hydrides, particularly sodium borohydride and lithium aluminum hydride, have emerged as preeminent reducing agents in modern organic chemistry.[33] These are extraordinarily versatile reagents capable of reducing most functional groups. Moreover by attaching organic ligands at boron or aluminum or changing the metal counter ion, one can modulate the scope, regio and stereoselectivity of such reductions. Literally hundreds of substituted boron and aluminum hydrides have been described in the chemical literature and dozens are now commercially available.[34]

More recently, transition metal salts have been used as catalysts or additives in combination with $NaBH_4$ and $LiAlH_4$, to modify or enhance the properties of these reagents. Nearly every conceivable combination of salt and hydride has been investigated with the concomitant development of many useful new synthetic methods.[35] The resulting systems are complex, however, and in most cases virtually nothing is known about

mechanism or reactive intermediates. Boron and aluminum hydrides may combine with metal halides in several different ways: (1) simple metathesis (e.g., LiCl + $NaBH_4$, $LiBH_4$, + NaCl), (2) reduction of the metal halide to the metal, (3) conversion of metal halide to metal hydride: (4) some combination of (2) and (3), viz., $FeC1_3$, + $LiBH_4$ = $Fe(BH_4)_2$, or (5) formation of a boride or aluminide.[36] Furthermore, it is often unclear whether the metal salt serves a true catalytic function or whether some transient, metalloidal complex formed *in situ* is the actual reducing agent.

Historically, borides were first produced by the combination of boron with metallic or metalloidal elements less electronegative than itself. For the most part, borides are very hard, high-melting, refractory substances whose structures and stoichiometries do not conform to the ordinary concepts of valence. H. I. Schlessinger discovered a much simpler synthesis in his pioneering work on borohydrides. Combinations of cobalt or nickel (or other metal salts) with aqueous $NaBH_4$ deposit finely divided black precipitates of Co_2B and Ni_2B (eq 1).

$$4NaBH_4 + 2CoC1_2 + 9H_2O = Co_2B + 3H_3BO_3 + 4NaC1 + 12.5H_2 \quad (1)$$

Because they actively catalyzed the decomposition of borohydride, these borides have been commonly used as a practical, controlled source of hydrogen (eq 2).

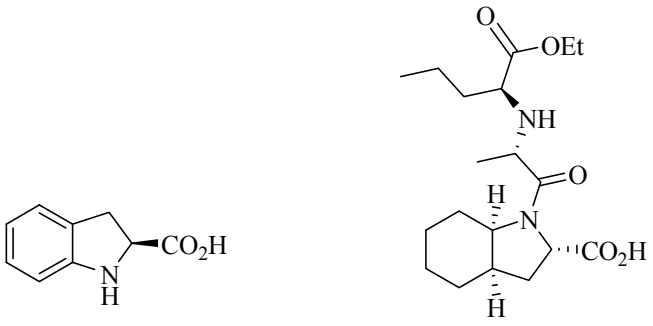
$$NaBH_4 + 2H_2O = NaBO_2 + 4H_2 \quad (2)$$

The actual composition of borides prepared from inorganic salts depends to a great extent on the specific mode of preparation. Maybury, Mitchell, and Hawthorne analyzed nickel and cobalt borides prepared in ethanol under N_2 using excess $NaBH_4$, and concluded that the stoichiometries Ni_2B and Co_2B inadequately represented their constitution.[37]

In dimethylformamide (DMF) reduction of $CoCl_2$ or $NiCl_2$ with $NaBH_4$, produced dark brown/black solutions[38] which comprised quite efficient systems for hydrogenation of alkenes, alkynes, azides, nitriles, alkyl halides, nitro compounds, amides, oximes, etc.[39] Simple reaction procedures and excellent yields of products coupled with high catalytic efficiency makes this method much more impressive and practical.

1.1.3.2 Results and Discussion

(*S*)-Indole-2-carboxylic acid (**72**) is a key intermediate in the synthesis of perindopril **73**, an orally active pharmaceutical used in the treatment of hypertension[40] (**Fig. 5**).

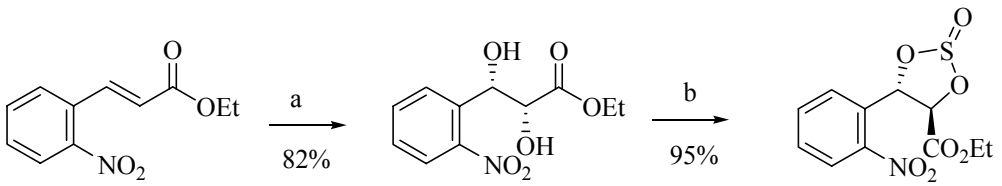


72 (*S*)-Indole-2-carboxylic acid

73 Perindopril

Fig. 5 : Structures of (*S*)-indole-2-carboxylic acid and perindopril

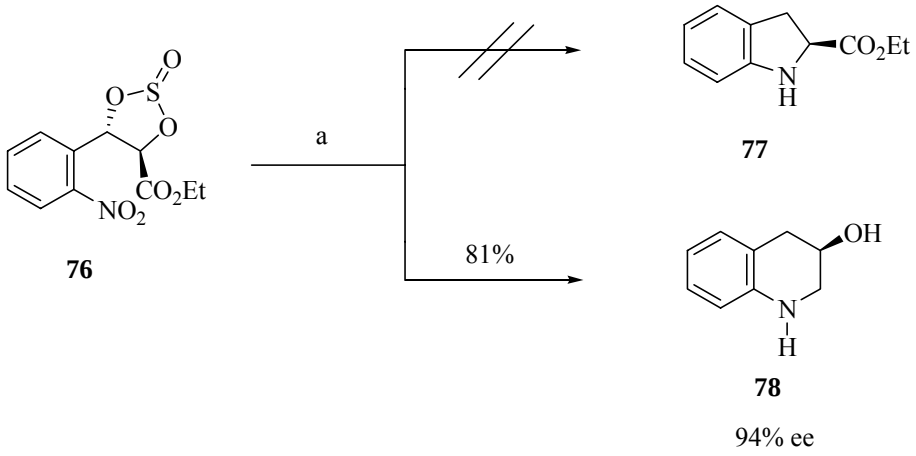
In order to synthesize (*S*)-indole-2-carboxylic acid (**72**), we visualized a strategy in which simultaneous reduction[41] of nitro cyclic suphite **76** could probably lead to the cyclized product **72**. Thus, *o*-nitrocinnamate **74**, prepared from Wittig-Horner olefination of *o*-nitrobenzaldehyde, was converted to the corresponding nitro diols **75** in 82% yield *via* Os-catalyzed asymmetric dihydroxylation (AD) using $(DHQ)_2$-PHAL as the chiral ligand. The nitro diol **75** was then readily transformed into the corresponding precursor nitro cyclic sulphite **76** ($SOCl_2$, Et_3N and CH_2Cl_2) in 95% yield (**Scheme 18**).



74 **75** **76**

Scheme 18: (a) K_2OsO_4 (0.2 mol%), $(DHQ)_2$-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%; (b) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 1 h, 95%.

In order to validate our hypothesis, nitro cyclic sulphite **76** was then subjected to reduction with 4 equivalents of $NaBH_4$ catalyzed by $CoCl_2 \cdot 6H_2O$. Surprisingly, the reaction took altogether a different course to give the cyclized 3-hydroxytetrahydroquinoline **78**, in a single step, as the only product in 81% yield, in stead of the expected cyclized ester **77**. Under the reaction conditions, it was observed that a simultaneous reduction of multifunctional groups took place, all occurring in a single step (**Scheme 19**).



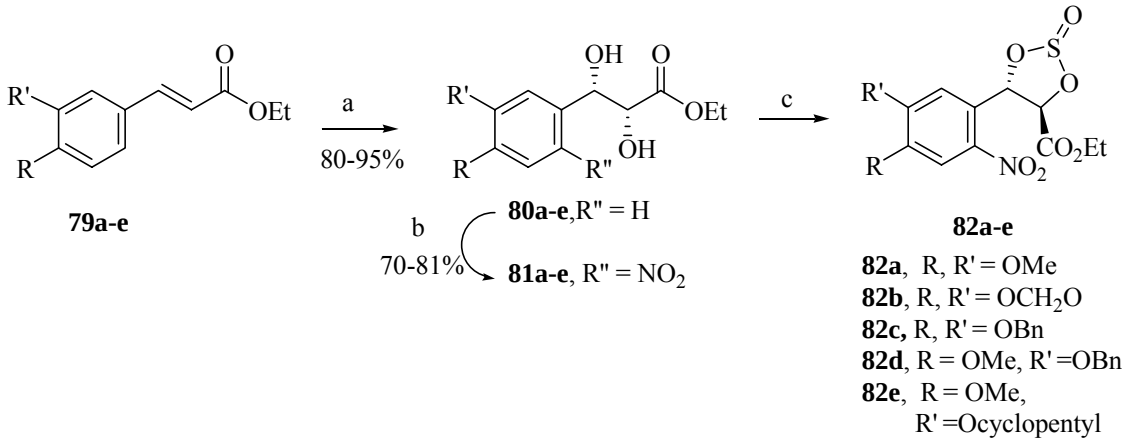
76 **77** **78**

94% ee

Scheme 19: (a) $CoCl_2 .6H_2O$ (1 mol%), $NaBH_4$ (4 equiv.), EtOH, 0-25 °C, 12 h.

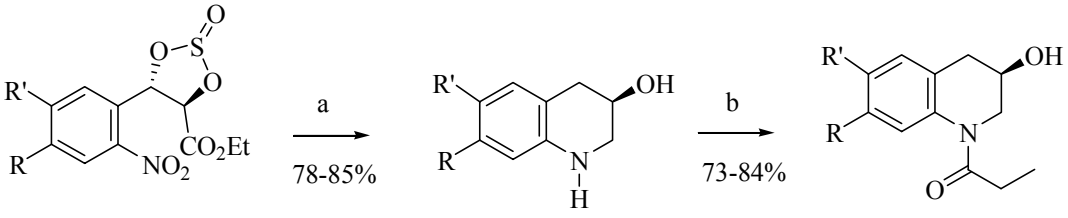
However, when nitro diol **75** was subjected to reduction under identical conditions, nitro group was unaffected. It was further observed that, nitro functionality was reduced when

nitro diol **75** was converted into its nitro cyclic sulphite **76**. Encouraged by the result, we became interested in carrying out the reduction of several nitro cyclic sulphites **82a-e**. To start with, the precursors (**82a-e**) were prepared in three steps starting from the corresponding *α,β*-unsaturated esters **79a-e.** Firstly, 3,4-disubstituted cinnamates **79a-e** were prepared in high yields by Wittig olefination of the corresponding benzaldehydes. The Os-catalyzed asymmetric dihydroxylation (AD) of the *α,β*-unsaturated esters **79a-e** using $(DHQ)_2$-PHAL as the chiral ligand gave the corresponding chiral diols, **80a-e** in 80-95% yields. Then, nitration of diol **80a-e** in acetic acid was carried out to afford nitrodiols **81a-e** in low yields, as considerable amount of byproducts were formed. However, when direct aromatic nitration of **80a-e** was carried out in biphasic medium (HNO_3, CH_2Cl_2), the corresponding nitro diols **81a-e** were formed in good yields with excellent regioselectivity. Nitro diols **81a-e** were then readily transformed to the corresponding nitro cyclic sulphites **82a-e** ($SOCl_2$, Et_3N and CH_2Cl_2) in quantitative yields (**Scheme 20**).



Scheme 20 : (a) K_2OsO_4 (0.1 mol%), $(DHQ)_2$-PHAL (0.5 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; (b) conc. HNO_3, CH_2Cl_2, 0-25 °C, 30 min.; (c) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 30 min.

When nitro cyclic sulphites **82a-e** were subjected to reduction with 4 equivalents of $NaBH_4$ using $CoCl_2 \cdot 6H_2O$ as the catalyst, conditions, we observed that all the nitro cyclic sulphites **82a-e** underwent complete reductions to give the corresponding cyclized tetrahydroquinol-3-ol derivatives **83a-e** in high yields with excellent enantioselectivity (**Scheme 21**).



82a-e **83a-e** **84a-e**

94-96% ee

Scheme 21: (a) $CoCl_2 .6H_2O$ (1 mol%), $NaBH_4$ (4 equiv.), EtOH, 0-25 °C, 12 h; (b) $(EtCO)_2O$, Et_3N, CH_2Cl_2, 0 °C, 6 h.

The results of reductions are presented in **Table 1.** As can be seen from **Table 1,** Co-catalyzed reduction of nitro cyclic sulphites **82a-e** clearly provides tetrahydroquinolin-3-ol **83a-e** in very high yields, which comprises several transformations taking place in a single step.

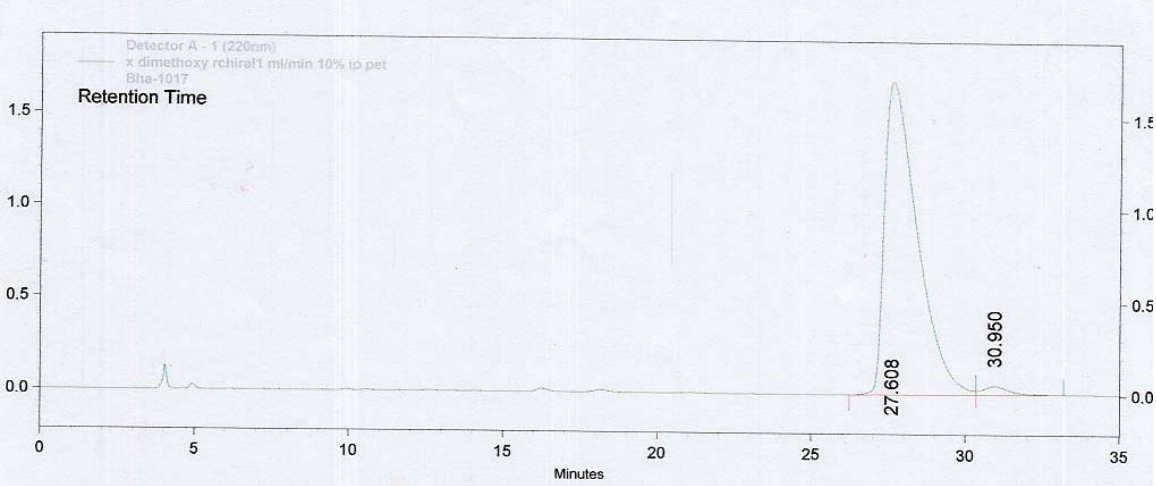
Table 1: Co-catalyzed synthesis of tetrahydroquinolin-3-ol **83**[a]

No	Nitro cyclic sulphites	Amino alcohol (**83**) Yield (%)[b]	Ee of **84** (%)[c]
1	R, R' = H (**76**)	(**78**) 82	95
2	R, R' = OMe (**82a)**	(**83a**) 78	96
3	R, R' = -OCH_2O-(**82b)**	(**83b**) 81	94
4	R, R' = OBn (**82c)**	(**83c**) 83	94
5	R = OMe, R' = OBn (**82d)**	(**83d**) 85	92
6	R = OMe, R' = Ocyclopentyl (**82e)**	(**83e**) 82	94

[a] reaction condition: nitro cyclic sulphites (2 mmol), $CoCl_2 \cdot 6H_2O$ (1 mol %), $NaBH_4$ (8 mmol), ethanol (10 mL), 0–25 ºC, 12 h.
[b] isolated yield after coloumn chromatograhphic purification.
[c] determined by chiral HPLC and Mosher's ester analysis.

Table 1 shows that synthesis of tetrahydroquinolin-3-ol **83a-e** can be achieved with a variety of substituted nitro cyclic sulphites **82a-e** using cheaply available reagents.

Since the optical purities of the tetrahydroquinol-3-ol derivatives **83a-e** could not be established by HPLC due to their difficulty in separation, the protection of amine function in **83a-e** as propyl amide (propionic anhydride, Et_3N and CH_2Cl_2) was carried out to give the respective amido alcohols **84a-e** in high yields, which facilitated their easy characterization by HPLC analysis. For example, chiral HPLC chromatogram of **84a** showed 95.5% ee (**Fig. 6**).



Detector A - 1 (220nm)

Pk #	Retention Time	Area	Area %
1	27.608	126448551	97.767
2	30.950	2887981	2.233
Totals		129336532	100.000

Fig. 6 : HPLC Chromatogram of 84a

Enantiomeric excess of **84a-e** was also determined by recording ^1H NMR of their Mosher's ester analysis. Thus, free hydroxyl moiety in amido alcohols **84a-e** was subjected to esterification (catalytic DMAP, DCC in CH_2Cl_2) with Mosher's acid [(*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid] and the resulting Mosher's esters

85a-e were analyzed by ^{1}H NMR to determine their %ee. For example, ^{1}H NMR spectrum of **84b** showed methyl proton signals at 3.48 (2.91H) for *R* isomer (*dr* 32:1, 94% ee) (**Fig. 7**).

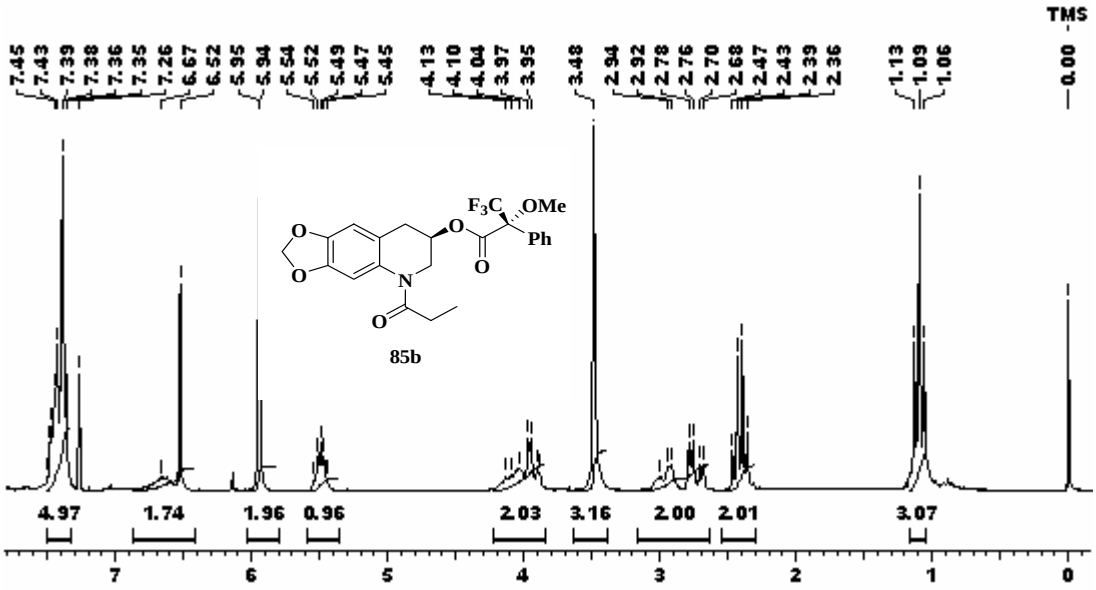


Fig. 7: ^{1}H NMR spectrum of Mosher's ester 85b

The formation of all the intermediates (**79a-e** to **82a-e**) as well as final products (**83a-e**) involved were confirmed unambiguously from their corresponding spectral analysis. For example, ^{1}H NMR of the nitro diol **81a** showed two typical signals at δ 4.51 (d) and 5.85 (d) due to methine protons (C**H**OH) and signals at δ 7.33 (s) and 7.65 (s) due to aromatic protons, thus confirming the formation of nitro diol **81a**. Its ^{13}C NMR spectrum showed four typical aromatic quaternary carbon signals at δ 132.3, 138.3, 146.6 and 152.1 (**Fig. 8**).

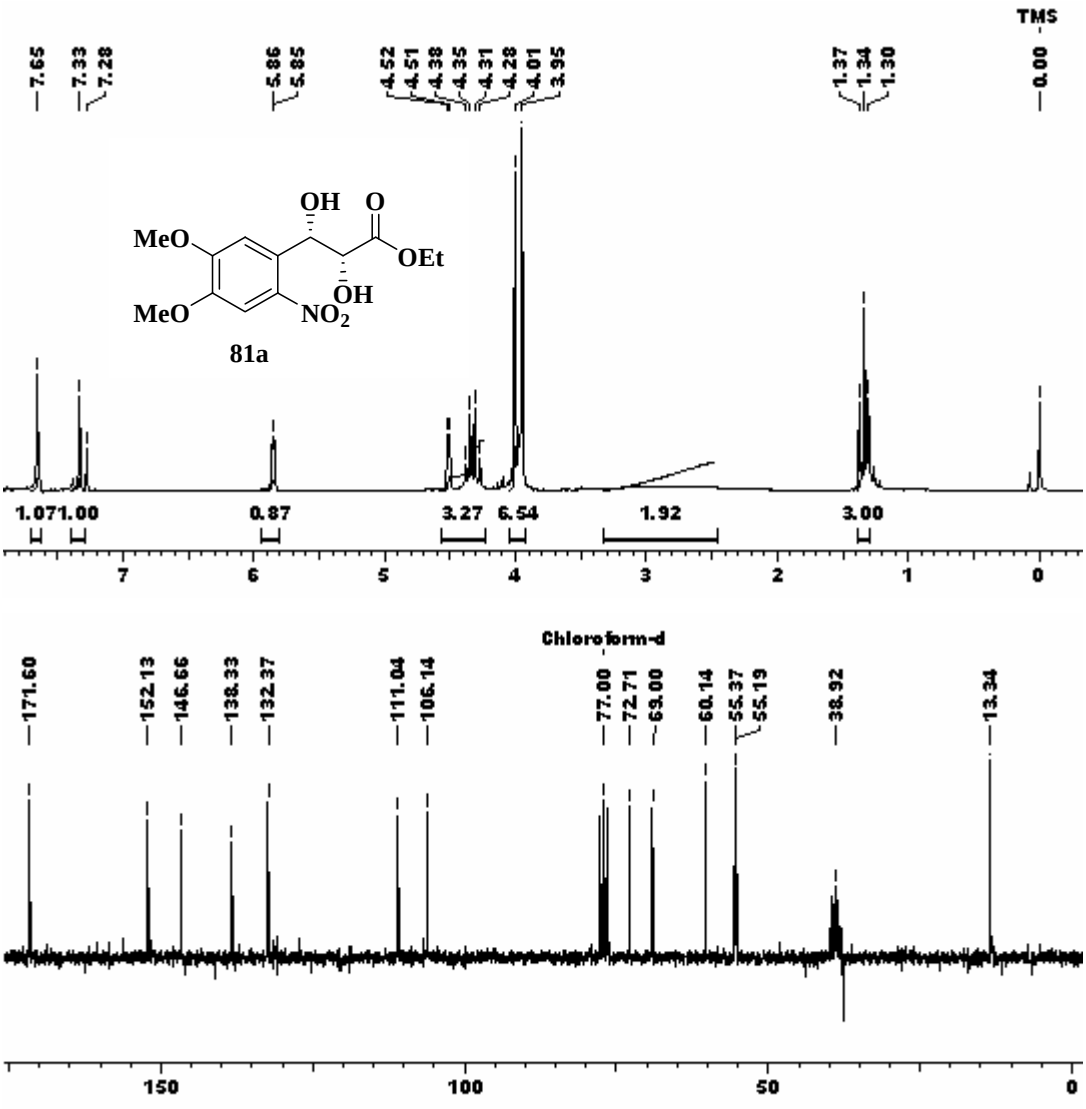


Fig. 8: ^{1}H and ^{13}C NMR spectra of nitrodiol 76a

Next, the formation of the tetrahydroquinolin-3-ol **83a** was confirmed by their ^{1}H NMR spectrum, which showed characteristic signals at δ 2.71-2.85 (dd), 2.92-3.02 (dd), 3.21 (m) corresponding to the benzylic methylene (C**H**$_2$) and methylene (C**H**$_2$N) protons respectively (**Fig. 8)**. Also signal at δ 4.19 (m) due to methine proton (C**H**OH) confirms the formation of 3-hydroxytetrahydroquinoline. Its ^{13}C NMR spectrum showed signals at δ 34.2 and 47.6 and 63.3 for two methylene carbons (Ar**C**H$_2$, N**C**H$_2$) and one methine

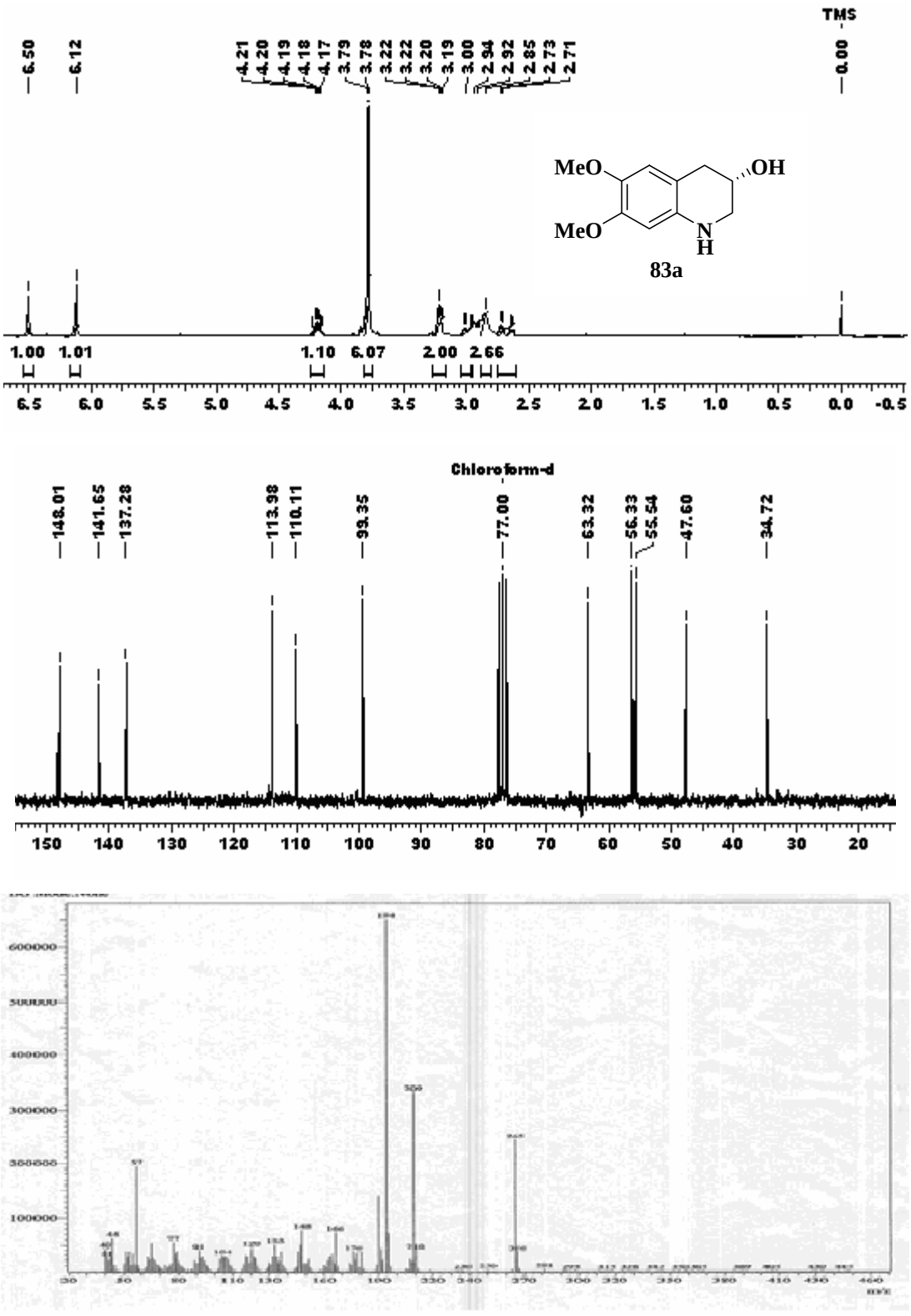
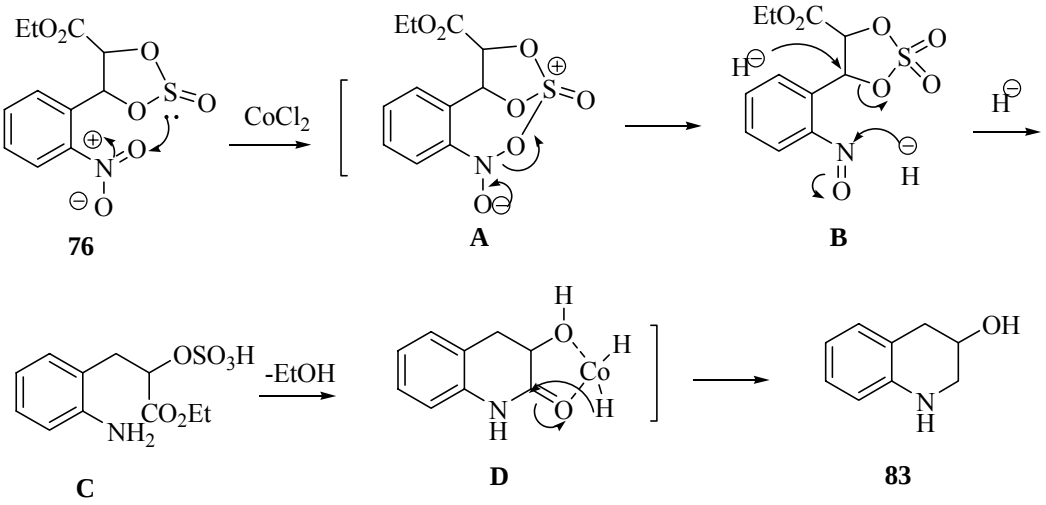


Fig. 9: ^{1}H, ^{13}C NMR and mass spectra of tetrahydroquinoline 83a

carbon (**C**HOH) respectively. Disappearance of carbonyl signal in IR and ^{13}C confirms the formation of 3-hydroxyquinoline **83a**.

We noticed that nitro functionality plays an important role in $CoCl_2$ catalyzed reductions of nitro cyclic sulphites. Controlled experiment showed that nitro group resist for reduction in the absence of cyclic sulphites and cyclic sulphites underwent hydrolysis in absence of nitro group. Co-catalyzed redox interaction took place between cyclic sulphite and nitro (species **A)** in **76** to give more reactive intermediate (species **B**). Reductive opening of cyclic sulphate and reduction of nitroso intermediate (species **C**) provides possibly α-hydroxy amide (species **D**) which was *in situ* reduced to the tetrahydroquinol-3-ol **83** by the way of coordination of cobalt hydride with hydroxyl moiety (**scheme 22**).



Scheme 22: Probable mechanistic pathway

1.1.4 Conclusion

In conclusion, we have developed a simple methodology involving a single step multifunctional reduction of cyclic sulphites **82a-e,** which gave the corresponding 3-hydroxy tetrahydroquinolines **83a-e** in high yields. Use of inexpensive, yet powerful

reducing agent $NaBH_4$ in combination with catalytic amount of $CoCl_2$ makes our synthesis more attractive. This method was found very effective in the asymmetric synthesis of bioactive compounds having tetrahydrquinoline core.

1.1.5 Experimental Section:

A typical experimental procedure for the preparation of (*E*)-ethyl 3-(2-nitrophenyl)acrylate (74):

To the stirred solution of 2-nitrobenzaldehyde (7.55 g, 50 mmol) in benzene (100 mL), $Ph_3P{=}CHCO_2Et$ (19.25 g, 55 mmol) was added. It was then refluxed for 4 h. under N_2 atmosphere. After the completion of reaction, benzene was distilled out gave crude product. Chromatographic purification of crude product [silica gel (230-400 mesh) and petrolium ether: Ethyl acetate (90:10) as eluent] afforded the nitro cinnamate **74** in 10.5 g yield.

Yield: 95%**,** gum, **IR** ($CHCl_3$): 756, 857, 974, 1037, 1095, 1184, 1202, 1216, 1251, 1275, 1291, 1319, 1347, 1368, 1393, 1444, 1477, 1573, 1607, 1640, 1716, 2984, 3023, 3415 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.36 (t, *J* = 7.3 Hz, 3H), 4.29 (q, *J* = 7.3 Hz, 2H), 6.35 (d, *J* = 16 Hz, 1H), 7.50 – 7.66 (m, 3H), 8.02 (d, *J* = 8 Hz, 1H), 8.10 (d, *J* = 16 Hz, 1H); **^{13}C NMR** ($CDCl_3$): δ 14.2, 60.7, 123.3, 124.8, 129.0, 130.1, 133.3, 139.7, 148.3, 165.4; **Analysis**: $C_{11}H_{11}NO_2$ requires C 59.63, H 5.01, N 6.33, found C 59.50, H 4.91, N 6.34%.

A typical experimental procedure for the preparation of (2*R*,3*S*)-ethyl 2,3-dihydroxy-3-(2-nitrophenyl)propanoate (75):

To the stirred solution of $K_3Fe(CN)_6$ (39.48 g, 120 mmol), K_2CO_3 (16.56 g, 120 mmol), and $MeSO_2NH_2$ (3.8 g, 40 mmol) in *tert*-BuOH (200 mL) and H_2O (200 mL), $(DHQ)_2$-PHAL (354 mg, 1 mol%) and K_2OsO_4 (19 mg, 0.2 mol%) were added and stirred for 30

min. Then, to the reaction mixture (*E*)-ethyl 3-(2-nitrophenyl)acrylate **(74)** (8.84g, 40 mmol) was added and allowed to stir for 24 h at 25 ºC. After completion of the reaction, sodium bisulphate (10 g) was added slowly at 0 ºC. The organic layer was separated and aqueous layer was extracted with ethyl acetate (3 x 300 ml), the combined organic layers were washed with brine (2 x 400 mL), dried over unhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product. Chromatographic purification using flash silica gel (230-400 mesh) and petroleum ether: ethyl acetate (60:40) as an eluent afforded 8.37g pure **75a**.

Yield: 82%; $[\alpha]^{D}_{25}$ +126.0 (*c* 1, $CHCl_3$); yellow solid, **mp**: 86 °C; **IR** ($CHCl_3$): 668, 757, 860, 1055, 1108, 1216, 1263, 1347, 1527, 1733, 3020, 3485 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.32 (t, *J* = 8.0 Hz, 3H), 3.22 (bs, 1H), 3.38 (bs, 1H), 4.30 (q, *J* = 8.0 Hz, 2H), 4.48 (d, *J* = 2.1 Hz, 1H), 5.67 (d, *J* = 2.1 Hz, 1H), 7.46 (t, *J* = 6 Hz, 1H,), 7.67 (t, *J* = 6 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.10, 62.32, 69.77, 73.43, 124.35, 128.44, 129.72, 133.21, 136.24, 147.62, 172.61; **Analysis** for $C_{11}H_{13}NO_6$ requires C 51.77, H 5.13, N 5.49; found C 51.65, H 5.33, N 5.54%.

A typical experimental procedure for the preparation of nitro cyclic sulphite (76a):

To the solution of diol **75a** (2.55g, 10 mmol) and triethylamine (4.2 ml, 30 mmol) in CH_2Cl_2 (50 mL) at 0 ºC, freshly distilled $SOCl_2$ (1.0 ml, 12 mmol) was added dropwise under nitrogen atmosphere. It was stirred at 0 ºC for 30 minutes (progress of reaction was monitored by TLC). The reaction mixture was quenched by the addition of cold water (20 mL) and a saturated solution of. $NaHCO_3$ (20 ml). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extract was

washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude product which decomposes on silica.

Yield: 95%; Gum; **IR** ($CHCl_3$): 667, 757, 962, 1045, 1217, 1350, 1531, 1610,1747, 2985, 3022, 3519 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.36 (t, *J* = 7.2 Hz, 3H), 4.36 (q, *J* = 7.2 Hz, 2H), 4.97 (d, *J* = 4.7 Hz, 1H), 6.93 (d, *J* = 4.7 Hz, 1H), 7.57-7.80 (m, 3H), 8.13-8.18 (dd, *J* = 1.2, 7.9 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.8, 62.7, 83.1, 83.2, 124.9, 129.9, 130.9, 131.1, 134.5, 147.6, 165.7.

A typical experimental procedure for the preparation (*R*)-1,2,3,4-tetrahydroquinolin-3-ol (78a):

To the stirred solution of nitro cyclic sulphite **76a** (10 mmol) and $CoCl_2 \cdot 6H_2O$ (23.8 mg, 1 mol %) in 95% ethanol (30 mL), $NaBH_4$ (24 mmol) was added at 0 ºC and reaction mixture was allowed to stir for 12 h at 25 ºC. After the completion of reaction, it was poured into ice cold water forms black precipitate. To the aqueous layer ethyl acetate (100 mL) was added and combined mixture was passed through celite. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine (2 x 50mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude product. Chromatographic purification of crude product using flash silica gel (230-400 mesh) and petroleum ether:ethyl acetate:Et_3N (60: 40:2) gave pure 1.22g of **78a**.

Yield: 1.222 g, 82%; gum, $[\alpha]^D_{25}$ +11.2 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$): 667, 756, 850, 1155, 1215, 1253, 1278, 1371, 1496, 1608, 1735, 2935, 2983, 3018, 3446 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.73-2.83 (dd, *J* = 3.5, 16.8 Hz, 1H), 2.99-3.09 (dd, *J* = 3.5, 16.8 Hz, 1H), 3.19-3.36 (m, 2H), 4.19-4.27 (m, 1H), 6.52 (d, *J* = 9.0 Hz, 1H), 6.67 (dt, *J* = 1.1, 7.5

Hz, 1H), 6.95-7.02 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 35.3, 47.6, 63.2, 114.1, 118.0, 118.6, 126.9, 130.4, 143.5; **Analysis** for $C_9H_{11}NO$ requires C, 72.46; H, 7.43; N, 9.39; found C, 72.22; H, 7.21; N, 9.49%.

A general experimental procedure for the preparation of (2*R*,3*S*)-ethyl 2,3-dihydroxy-3-(3,4-dialkyloxyphenyl)propanoate 80a-e:

To 500 mL RB flask was charged with $K_3Fe(CN)_6$ (45 mmol), K_2CO_3 (45 mmol), $MeSO_2NH_2$ (15 mmol), *tert*-BuOH (75 mL) and H_2O (75 mL). Reaction mixture was stirred for 10 min and $(DHQ)_2$-PHAL (1 mol%) and K_2OsO_4 (0.2 mol%) were added and stirred for additional 30 min. To the reaction mixture **79a** was added and allowed to stir for 24 h at 25 ºC. After completion of reaction, sodium bisulphate (5 g) was added slowly at 0 ºC. Organic layer was separated and aqueous layer was extracted with ethyl acetate (3 x 100 ml) combined organic layer was washed with brine (200 mL), dried over sodium sulphate and concentrated under reduced pressure to yield the crude products, Flash column chromatography purification [silica gel (230-400 mesh) and petroleum ether : EtOAc (60:40) as an eluent] afforded **80a-e** in pure form.

(2*R*,3*S*)-Ethyl 2,3-dihydroxy-3-(3,4-dimethoxyphenyl)propanoate (80a):

Yield: 95%; colorless solid; **mp:** 78 ºC; $[\alpha]^{D}_{25}$ +3.533 (*c* 1.5, $CHCl_3$); **IR** ($CHCl_3$): 848, 939, 1047, 1240, 1373, 1446, 1517, 1737, 2983, 3500 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.1 Hz, 3H), 3.88 (s, 3H), 3.90 (s, 3H), 4.27 (q, *J* = 7.1 Hz, 2H), 4.35 (d, *J* = 3.1 Hz, 1H), 4.95 (d, *J* = 3.1 Hz, 1H), 6.84-6.98 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.8, 55.6, 55.7, 61.7, 74.2, 74.8, 109.4, 110.6, 118.4, 132.4, 148.4, 148.6, 172.6; **Analysis** for $C_{13}H_{18}O_6$ requires C, 57.77; H, 6.71; found C, 57.47; H, 6.63%.

(2*R*,3*S*)-Ethyl 3-(benzo[*d*][1,3]dioxol-6-yl)-2,3-dihydroxypropanoate (80b):

Yield: 92%; colorless solid; **mp:** 62 ºC; $[\alpha]^{D}_{25}$ +1.5 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$): 846, 937, 1047, 1244, 1373, 1246, 1745, 2983, 3519 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.27 (t, *J* = 7.1 Hz, 3H), 2.91 (bs, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 4.27 (d, *J* = 3.1 Hz, 1H), 4.89 (d, *J* = 3.1 Hz, 1H), 5.94 (s, 2H), 6.77 (d, *J* = 8.0 Hz , 1H), 6.82-6.87 (dd, *J* =1.5, 8.0 Hz, 1H), 6.92 (d, *J* = 1.5 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.9, 61.8, 74.32, 74.9, 100.9, 106.9, 107.8, 119.6, 133.8, 147.1, 147.5, 172.5; **Analysis** for $C_{12}H_{14}O_6$ requires C, 56.69; H, 5.55; found C, 56.73; H, 5.53%.

(2*R*,3*S*)-Ethyl 3-(4-(benzyloxy)-3-methoxyphenyl)-2,3-dihydroxypropanoate (80c):

Yield: 80%; colorless solid; **mp:** 77 ºC; $[\alpha]^{D}_{25}$ + 1.2 (*c* 1, $CHCl_3$): **IR** ($CHCl_3$): 846, 837, 1049, 1244, 1361, 1479, 1751, 2985, 3519 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.19 (t, *J* = 7.2 Hz, 3H), 3.48 (bs, 2H), 3.84 (s, 3H), 4.16 (q, *J* = 7.2 Hz, 2H), 4.27 (d, *J* = 3.4 Hz, 1H), 4.87 (d, *J* = 3.4 Hz, 1H), 5.10 (s, 2H), 6.81 (m, 2H), 6.96 (d, *J* = 8.0 Hz, 1H), 7.26-7.43 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.8, 55.7, 61.7, 70.7, 74.7, 74.8, 110.0, 113.4, 118.4, 127.0, 127.6, 128.3, 132.9, 136.8, 147.5, 147.3, 172.5; **Analysis** for $C_{19}H_{22}O_6$ requires C, 65.88; H, 6.40; found , 65.84; H, 6.37%.

(2*R*,3*S*)-Ethyl 3-(3,4-bis(benzyloxy)phenyl)-2,3-dihydroxypropanoate (80d):

Yield: 85%; colorless solid; **mp:** 101 ºC; $[\alpha]^{D}_{25}$ +0.84 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$): 848, 1045, 1245, 1373, 1514, 1593, 1745, 2981, 3465 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.24 (t, *J* = 7.1 Hz, 3H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.25 (d, *J* = 2.9 Hz, 1H), 4.82 (d, *J* = 2.9 Hz, 1H), 5.14 (s, 2H), 5.15 (s, 2H), 6.89 (m, 2H), 7.04 (m, 1H), 7.28-7.48 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.9, 61.8, 71.1, 71.1, 74.2, 74.7, 113.3, 114.6, 119.3,

127.1, 127.3, 127.6, 127.6, 128.3, 133.2, 137.0, 137.1, 148.5, 148.7, 172.5; **Analysis** for $C_{25}H_{26}O_6$ requires C, 71.07; H, 6.20; found C, 71.01; H, 6.17%.

(2*R*,3*S*)-Ethyl 3-[4-(cyclopentyloxy)-3-methoxyphenyl]-2,3-dihydroxypropanoate (80e):

Yield: 81%; colorless solid; **mp:** 105 ºC; $[\alpha]^{D}_{25}$ +1.50 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$): 848, 1045, 1245, 1373, 1514, 1593, 1745, 2981, 3465 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.1 Hz, 3H), 1.57-1.94 (m, 8H), 2.62 (bs, 1H), 3.07 (bs, 1H), 3.83 (s, 3H), 4.25 (q, *J* = 7.1 Hz, 2H), 4.74-4.81(m, 1H), 4.88 (d, *J* = 2.9 Hz, 1H), 6.80-6.98 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.9, 23.9, 32.6, 55.8, 61.7, 74.3, 74.9, 80.1, 111.4, 113.2, 118.5, 132.3, 147.3, 149.59, 172.6; **Analysis** for $C_{17}H_{24}O_6$ requires C, 62.95; H, 7.46; found C, 62.90; H, 7.44%.

A general experimental procedure for the preparation of (2*R*,3*S*)-ethyl 2,3-dihydroxy-3-(4,5-dialkyloxy-2-nitrophenyl) propanoate (**81a-e**):

To the stirred solution of diol **80a-e** (10 mmol) in CH_2Cl_2 (40 mL), conc. HNO_3 (2 mL) was added dropwise at 0 °C. Reaction mixture was stirred for 30 min. and 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 unhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product which was purified by column chromatography [silica gel (230-400 mesh) and petroleum ether:EtOAc (60:40) as an eluent] gave pure **81a-e** in pure form.

(2*R*,3*S*)-Ethyl 2,3-dihydroxy-3-(4,5-dimethoxy-2-nitrophenyl)propanoate (81a):

Yield: 70%; yellow solid; **mp:** 131 ºC; $[\alpha]^{D}_{25}$ +105.23 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$): 787, 848, 937, 1049, 1240, 1371, 1747, 2985, 3460, 3640 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.34 (t, *J* = 7.1 Hz, 3H), 3.95 (s, 3H), 4.01 (s, 3H), 4.33 (q, *J* = 7.1 Hz, 2H), 4.51(d, *J* = 2.2 Hz, 1H), 5.85 (d, *J* = 2.2 Hz, 1H), 7.33 (s, 1H), 7.65 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.3, 55.1, 55.3, 60.1, 69.0, 72.7, 106.1, 111.0, 132.3, 138.3, 146.6, 152.1, 171.6; **Analysis** for $C_{13}H_{17}NO_8$ requires C, 49.52; H, 5.43; N, 4.44; found C, 49.65; H, 5.23; N, 4.55%.

(2*R*,3*S*)-Ethyl 2,3-dihydroxy-3-(5-nitrobenzo[*d*][1,3]dioxol-6-yl)propanoate (81b): **Yield**: 81%; yellow solid; **mp:** 138 ºC; $[\alpha]^{D}_{25}$ +138.5 (*c*1, $CHCl_3$); **IR** ($CHCl_3$): 786, 846, 937, 1049, 1240, 1373, 1747, 2985, 3463, 3643 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.33 (t, *J* = 7.1 Hz, 3H), 4.29 (q, *J* = 7.1 Hz, 2H), 4.46 (d, *J* = 2.3 Hz, 1H), 5.68 (d, *J* = 2.3 Hz, 1H), 6.11-6.14 (dd, *J* = 1.1, 4.4 Hz, 2H), 7.33 (s, 1H), 7.53 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.2, 60.0, 68.8, 72.7, 101.9, 103.3, 108.4, 134.8, 140.0, 145.9, 150.8, 171.3; **Analysis** for $C_{12}H_{13}NO_8$ requires C, 48.17; H, 4.38; N, 4.68; found C, 48.01; H, 4.23; N, 4.76%.

(2*R*,3*S*)-Ethyl 3-(4,5-bis(benzyloxy)-2-nitrophenyl)-2,3-dihydroxypropanoate (81c): **Yield:** 73%, yellow solid; **mp:** 141 ºC; $[\alpha]^{D}_{25}$ +105.34 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$): 763, 1132, 1215, 1683, 3388 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.30 (t, *J* = 7.1 Hz, 3H), 2.84 (bs, 1H), 3.19 (bs, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 4.45 (d, *J* = 1.5 Hz, 1H), 5.21 (s, 2H), 5.28 (s, 2H), 5.78 (d, *J* = 1.5 Hz, 1H), 7.30-7.47 (m, 11H), 7.72 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+ DMSO-d_6): δ 12.5, 58.9, 68.0, 68.9, 69.1, 71.9, 108.0, 112.7, 125.7, 126.0, 126.3, 126.4, 126.8, 131.9, 134.4, 134.6, 137.7, 145.1, 150.9, 170.6; **Analysis** for $C_{25}H_{25}NO_8$ requires C, 64.23; H, 5.39; N, 3.00; found C, 64.02; H, 5.49; N, 2.87%.

(2*R*,3*S*)-Ethyl 3-(4-(benzyloxy)-5-methoxy-2-nitrophenyl)-2,3-dihydroxypropanoate (81d):

Yield: 75%; yellow solid; **mp:** 138 ºC; $[\alpha]^{D}_{25}$ +102.25 (*c* 0.8, $CHCl_3$); **IR** ($CHCl_3$): 757, 1215, 1620, 2780, 3400 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.31 (t, *J* = 7.2 Hz, 3H), 1.65 (bs, 1H), 2.97 (bs, 1H), 4.00 (s, 3H), 4.31 (q, *J* = 7.2 Hz, 2H), 4.49 (d, *J* = 3.4 Hz, 1H), 5.20 (s, 2H), 5.83 (d, *J* = 3.4 Hz, 1H), 7.32 (s, 1H), 7.35-7.48 (m, 5H), 7.70 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.7, 55.9, 61.0, 69.5, 70.6, 73.2, 108.9, 111.4, 127.0, 127.7, 128.1, 132.8, 135.3, 138.7; **Analysis** for $C_{19}H_{21}NO_8$ requires C, 58.31; H, 5.41; N, 3.58; found C, 58.16; H, 5.28; N, 3.51%.

(2*R*,3*S*)-Ethyl 3-(4-(cyclopentyloxy)-5-methoxy-2-nitrophenyl)-2,3-dihydroxy-propanoate (81e) :

Yield: 81%; yellow solid; **mp:** 142 ºC; $[\alpha]^{D}_{25}$ +99.72 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$): 757, 1215, 1620, 3465 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.34 (t, *J* = 7.1 Hz, 3H), 1.58-2.08 (m, 10H), 3.91 (s, 3H), 4.33 (q, *J* = 7.1 Hz, 2H), 4.47 (d, *J* = 2.1 Hz, 1H), 4.87-4.99 (m, 1H), 5.81 (d, *J* = 2.1 Hz, 1H), 7.28 (s, 1H), 7.62 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+ DMSO-d_6): δ 13.3, 23.0, 31.6, 31.7, 55.1, 60.2, 69.0, 72.8, 79.7, 106.5, 113.1, 132.0, 137.8, 147.3, 151.1, 171.7; **Analysis** for $C_{17}H_{23}NO_8$ requires C, 55.28; H, 6.28; N, 3.79; found C, 55.12; H, 6.13; N, 3.83%.

A general experimental procedure for the preparation of (*R*)-1,2,3,4-tetrahydro-6,7-dialkyloxyquinolin-3-ol (83a-e)

To a stirred solution of nitro diol **81a-e** (6.0 mmol) and triethylamine (3.00 ml, 18 mmol) in CH_2Cl_2 (20 mL), was added freshly distilled thionyl chloride (0.5 ml, 7 mmol) drop-wise under nitrogen atmosphere at 0 ºC and allowed to stir at 0 ºC for 30-45 minutes

(monitored by TLC). The reaction mixture was quenched by the addition of cold water (20 mL) and a saturated solution of $NaHCO_3$ (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were washed with brine and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude products **82a-e,** which was then subjected for reduction without purification.

To the stirred solution of nitro cyclic sulphite **82a-e** (6 mmol) and $CoCl_2 \cdot 6H_2O$ (1 mol %) in 95% ethanol (30 mL), $NaBH_4$ (24 mmol) was added at 0 ºC and allowed to stir for 12 h at 25 ºC. After completion of reaction, it was poured into ice cold water to form black precipitate. To the aqueous layer, 100 mL of ethyl acetate was added and combined mixture was passed through celite. The organic layer was separated and aqueous layer was extracted with ethyl acetate (2 x 50 mL). Combined organic layers were washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the pure product. Chromatographic purification of the crude product [flash silica gel (230-400 mesh) and petroleum ether:ethyl acetate:Et_3N (60: 38:2)] gave pure tetrahydroquinolin-3-ol (**83a-e**) .

(*R*)-1,2,3,4-Tetrahydro-6,7-dimethoxyquinolin-3-ol (83a):

Yield: 78%; Gum; $[\alpha]^{D}_{25}$ +25.4 (*c* 1.26, $CHCl_3$); **IR** ($CHCl_3$): 769, 1215, 1423, 1647, 3456 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.63-2.73 (dd, *J* = 3.9, 16.5 Hz, 1H), 2.85 (bs, 2H), 2.92-3.02 (dd, *J* = 4.3, 16.5 Hz, 1H),3.19-3.29 (m, 2H), 3.78 (s, 3H), 3.79 (s, 3H), 4.15-4.23 (m, 1H), 6.12 (s, 1H), 6.50 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 34.2, 47.6, 55.5, 56.3, 63.3, 99.3, 110.1, 113.9, 137.2, 141.6, 148.0; **MS**: 209, 194, 176, 166, 148,

133, 120, 103, 91, 77, 65, 44; **Analysis** for $C_{11}H_{15}NO_3$ requires C, 63.14; H, 7.23; N, 6.69; found C, 63.09; H, 7.17; N, 6.61%.

(*R*)-5,6,7,8-Tetrahydro-[1,3]dioxolo[4,5-*g*]quinolin-7-ol (83b):

Yield: 81%; Gum, $[\alpha]^{D}_{25}$ +28.2 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$): 765, 1045, 1247, 1456, 2985, 3450 cm^{-1}; **^{1}H NMR (**200 MHz, $CDCl_3$): δ 2.18 (bs, 2H), 2.63-2.73 (dd, *J* = 3.5, 16.5 Hz, 1H), 2.92-3.03 (dd, *J* = 3.9, 16.5 Hz, 1H), 3.20-3.23 (dd, *J* = 1.4, 4.3 Hz, 2H), 4.17-4.25 (m, 1H), 5.82 (s, 2H), 6.15 (s, 1H), 6.48 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 35.1, 47.5, 63.1, 96.4, 100.1, 109.5, 110.1, 137.9, 139.9, 146.1; **Analysis** for $C_{10}H_{11}NO_3$ requires C, 62.17; H, 5.74; N, 7.25; found C, 62.11; H, 5.76; N, 7.21%.

(*R*)-6,7-Bis(benzyloxy)-1,2,3,4-tetrahydroquinolin-3-ol (83c)

Yield: 83%; Gum, $[\alpha]^{D}_{25}$ +30.5 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$): 767, 1217, 1504, 2927, 3016, 3402 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.74 (bs, 2H), 2.60-2.70 (dd, *J* = 3.4, 16.5 Hz, 1H), 2.89-2.99 (dd, *J* = 4.9, 16.5 Hz, 1H), 3.12-3.24 (m, 2H), 4.14-4.24 (m, 1H), 5.03 (s, 2H), 5.09 (s, 2H), 6.19 (s, 1H), 6.63 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 34.9, 47.5, 63.4, 71.2, 73.0, 102.2, 111.1, 119.3, 127.2, 127.5, 127.6, 127.6, 128.3, 128.4, 137.3, 138.4, 141.7, 148.7; **Analysis** for $C_{23}H_{23}NO_3$ requires C, 76.43; H, 6.41; N, 3.88; found C, 76.38; H, 6.37; N, 3.82%.

(*R*)-7-(Benzyloxy)-1,2,3,4-tetrahydro-6-methoxyquinolin-3-ol (83d)

Yield: 85%; Gum, $[\alpha]^{D}_{25}$ +25.2 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$): 765, 1217, 1404, 2927, 3405 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.64 (dd, *J* = 3.8, 16.5 Hz, 1H), 2.92-3.02 (dd, *J* = 4.2, 16.5 Hz, 1H), 3.17-3.18 (d, *J* = 3.0 Hz, 2H), 3.80 (s,3H), 4.16-4.24 (m, 1H), 5.07 (s, 2H), 6.13 (s, 1H), 6.56 (s, 1H), 7.30-7.44 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 34.7, 47.4, 56.7, 63.2, 70.2, 101.8, 110.8, 114.9, 126.9, 127.4, 128.2, 137.3, 142.3, 147.3;

Analysis for $C_{17}H_{19}NO_3$ requires C, 71.56; H, 6.71; N, 4.91; found C, 71.52; H, 6.75; N, 4.88%.

(*R*)-7-(Cyclopentyloxy)-1,2,3,4-tetrahydro-6-methoxyquinolin-3-ol (83e):

Yield: 82%; Gum; $[\alpha]^{D}_{25}$ +22.2 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$) 767, 1217, 1504, 2927, 3016, 3402 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.55-1.83 (m, 8H), 2.62-2.72 (dd, *J* = 4.1, 16.5 Hz, 1H), 2.91-3.01 (dd, *J* = 3.7, 16.5 Hz, 1H), 3.21-3.23 (d, *J* = 3.7 Hz, 2H), 3.76 (s, 3H), 4.16-4.23 (m, 1H), 4.54-4.65 (m, 1H), 6.11 (s, 1H), 6.52 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 23.5, 32.3, 34.6, 47.6, 55.5, 63.2, 81.4, 99.7, 110.3, 119.1, 137.7, 139.7, 149.5; **Analysis** for $C_{15}H_{21}NO_3$ requires C, 68.42; H, 8.04; N, 5.32; found C, 68.38; H, 8.01; N, 5.37%.

A general experimental procedure for the preparation of amido alcohol (84a-e)

To the stirred solution of tetrahydroquinolin-3-ol (**83a-e**) (4 mmol) and Et_3N (1.4 mL, 10 mmol) in 20 mL of CH_2Cl_2, propionic anhydride (6.5 mL, 5 mmol) was added at 25 ºC. Reaction mixture was stirred for 3 h. Progress of reaction was monitored by TLC and after completion of reaction, saturated $NaHCO_3$ (30 mL) was added. Organic layer was separated; aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). Combined organic layers were washed with brine (2 x 25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude products. Chromatographic purification [silica gel (230-400 mesh) and petroleum ether:ethyl acetate: (60: 40:)] gave amide **84a-e** in pure form.

1-[(*R*)-3,4-Dihydro-3-hydroxy-6,7-dimethoxyquinolin-1(2H)-yl]propan-1-one (84a)

Yield: 82%; Gum; $[\alpha]^{D}_{25}$ +8.69 (*c* 1.15, $CHCl_3$); **IR** ($CHCl_3$): 846, 937, 1240, 1388, 1514, 1660, 1751, 2983, 3529 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.18 (t, *J* = 7.3 Hz,

3H), 2.56 (q, *J* = 7.3 Hz, 2H), 2.67-2.78 (dd, *J* = 4.6, 16.5 Hz, 1H), 2.98-3.09 (dd, *J* = 5.4, 16.5 Hz, 1H), 3.86 (s, 6H), 3.74-3.95 (m, 2H), 4.32 (m, 1H), 6.63 (bs, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 8.6, 27.4, 35.0, 49.7, 55.6, 65.0, 108.0, 111.1, 122.4, 130.7, 146.3, 174.3; **MS:** 265, 209, 194, 176, 166, 148, 133, 120, 104, 91, 77, 57, 44; **Analysis** for $C_{14}H_{19}NO_4$ requires C, 63.38; H, 7.22; N, 5.28; found C, 63.43; H, 7.19; N, 5.22%.

1-[(*R*)-7,8-Dihydro-7-hydroxy-[1,3]dioxolo[4,5-g]quinolin-5(6H)-yl]propan-1-one (84b)

Yield: 85%; Gum; $[\alpha]^{D}_{25}$ +12.7 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$): 847, 1242, 1515, 1650, 1753, 2983, 3530 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.11 (t, *J* = 7.3 Hz, 3H), 2.30 (q, *J* = 7.3 Hz, 2H), 2.66-2.77 (dd, *J* = 4.6, 16.6 Hz, 1H), 2.92-3.02 (dd, *J* = 6.4, 15.6 Hz, 1H), 3.75-4.09 (m, 2H), 5.24 (m, 1H), 5.96 (s, 2H), 6.60 (s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 8.9, 27.3, 35.5, 49.1, 65.9, 98.0, 108.2, 111.5, 122.1, 131.7, 145.2, 174.1; **Analysis** $C_{13}H_{15}NO_4$ requires C, 62.64; H, 6.07; N, 5.62; found C, 62.61; H, 6.01; N, 5.55%.

1-[(*R*)-6,7-Bis(benzyloxy)-3,4-dihydro-3-hydroxyquinolin-1(2H)-yl]propan-1-one (84c)

Yield: 77%; Gum; $[\alpha]^{D}_{25}$ +15.1 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$): 847, 1242, 1515, 1650, 1753, 2983, 3530 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.00 (t, *J* = 7.3 Hz, 3H), 2,18 (bs, 1H), 2.46 (q, *J* = 7.3 Hz, 2H), 2.58-2.69 (dd, *J* = 4.9, 16.4Hz, 1H), 2.87-3.00 (dd, *J* = 5.6, 16.5 Hz, 1H), 3.69-3.88 (m, 2H), 4.23 (m, 1H), 5.12 (s, 2H), 5.15 (s, 2H), 6.68 (bs, 2H), 7.30-7.45 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 9.5, 27.1, 35.1, 49.2, 65.8, 71.2, 73.0, 102.2, 111.1, 119.3, 127.2, 127.5, 127.6, 127.6, 128.3, 128.4, 137.3, 138.4, 141.7, 148.7, 173.2; **Analysis** for $C_{26}H_{27}NO_4$ requires C, 74.80; H, 6.52; N, 3.35; found C, 74.82; H, 6.57; N, 3.31%.

1-[(*R*)-6-(Cyclopentyloxy)-3,4-dihydro-3-hydroxy-7-methoxyquinolin-1(2H)-yl]propan-1-one (84e)

Yield: 73%; Gum; $[\alpha]^{D}_{25}$ +15.1 (*c* 1, $CHCl_3$); IR ($CHCl_3$): 849, 1243, 1515, 1650, 1753, 2983, 3530 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.17 (t, *J* = 7.4 Hz, 3H), 1.17-1.88 (m, 8H), 2.54 (q, *J* = 7.4 Hz, 2H), 2.64-2.74 (dd, *J* = 5.0, 16.3 Hz, 1H), 2.95-3.06 (dd, *J* = 5.3, 16.6 Hz, 1H), 3.81 (s, 3H), 3.72-3.90 (m, 2H), 4.27 (m, 1H), 4.73 (m, 1H), 6.60 (bs, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 10.1, 23.5, 27.5, 32.1, 35.1, 47.1, 55.4, 63.1, 81.3, 99.8, 110.1, 119.5, 137.4, 139.2, 149.5; 172.9; **Analysis** for $C_{18}H_{25}NO_4$ requires C, 67.69; H, 7.89; N, 4.39; found C, 67.62; H, 7.82; N, 4.32%.

A general experimental procedure for the preparation of Mosher's ester (85b-e)

To the stirred solution of alcohol (0.1 mmol), DCC (41 mg, 0.2 mmol) in CH_2Cl_2 (3 mL) Mosher's acid (26 mg, 0.11 mmol) in CH_2Cl_2 (1 mL) was added at 0 ºC and allowed to stir for 12 h at 25 °C. After the completion of reaction (monitored by TLC), solvent was distilled under reduced pressure and crude product was purified by column chromatography to give pure **84b-e**.

(2*R*)-(*R*)-5,6,7,8-Tetrahydro-5-propionyl-[1,3]dioxolo[4,5-g]quinolin-7-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (85b)

Yield: 35 mg, 75%; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.09 (t, *J* = 7.3 Hz, 3H), 2.41 (q, *J* = 7.3 Hz, 2H), 2.68-2.70 (dd, *J* = 5.0, 16.3 Hz, 1H), 2.92-3.02 (dd, *J* = 5.3, 16.6 Hz, 1H), 3.48 (s, 3H), 3.88-4.10 (m, 2H), 5.49 (m, 1H), 5.94 (s, 2H), 6.52 (s, 1H), 6.60 (s, 1H), 7.35-7.46 (m, 5H).

(2*R*)-(*R*)-6,7-Bis(benzyloxy)-1,2,3,4-tetrahydro-1-propionylquinolin-3-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (85c)

Yield: 42 mg, 66%; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.00 (t, *J* = 7.3 Hz, 3H), 2.46 (q, *J* = 7.3 Hz, 2H), 2.58-2.69 (dd, *J* = 4.9, 16.4 Hz, 1H), 2.87-3.00 (dd, *J* = 5.6, 16.5 Hz, 1H), 3.47 (s, 2.90 H), 3.54 (s, 0.10H) 3.69-3.88 (m, 2H), 3.97 (m, 1H), 5.12 (s, 2H), 5.15 (s, 2H), 6.68 (bs, 2H), 7.30-7.45 (m, 10H).

(2*R*)-(*R)*-6-(Cyclopentyloxy)-1,2,3,4-tetrahydro-7-methoxy-1-propionylquinolin-3-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (85e)

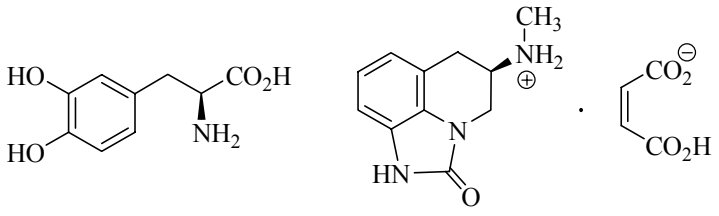
Yield: 39 mg, 73%; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.12 (t, *J* = 7.3 Hz, 3H), 1.60-1.94 (m, 8H), 2.42 (q, *J* = 7.3 Hz, 2H), 2.90-2.94 (dd, *J* = 3.9, 16.5 Hz, 1H), 3.07 (m, 1H), 3.43 (s, 2.91H), 3.47 (s, 0.09H), 3.81 (s, 3H), 4.11 (m, 1H), 4.70 (m, 1H), 5.46 (s, 1H), 6.66 (s, 1H), 7.34-7.46 (m, 5H).

Section 2:

Formal asymmetric synthesis of sumanirole maleate (PNU 95666-E)

1.2.1. Introduction:

Parkinson's disease, a neurodegenetive disease characterized by deteriorating motor function, is brought about by the loss of cells in the brain responsible for synthesizing the neurotransmitter dopamine. L-DOPA (**86**) is used for the treatment of Parkinson's disease. It may be noted that L-DOPA is converted to dopamine *in situ* by L-DOPA decarboxylase (**Fig. 10**).



86 L-DOPA

87 PNU 95666-E

Fig. 10: Structures of L-DOPA and PNU 95666-E

However, after a period of time, L-DOPA (**87**) loses its efficiency, requiring additional therapy with dopamine agonists to attempt to re-establish the necessary level of dopamine receptor activation; adverse side effects such as psychiatric disorders are also common with L-DOPA (**87**). Evidence suggests that it is the activation of D2 receptors in the striatum, an area of the brain associated with motor function that is responsible for drug efficacy. However, currently available dopamine agonist drugs are not selective and possess high affinity for other dopamine receptor subtypes.

Sumanirole maleate (PNU95666-E) (**87**) is a potent and highly selective agonist at the dopamine D2 receptor subtype and possesses potential as a treatment for Parkinson's disease with greatly diminished side-effect liability. PNU95666-E (**87**) also showed

better efficiency in treatment for Parkinson's disease in the early stages, possibly preventing the development of response fluctuations seen with long term L-DOPA therapy.[42]

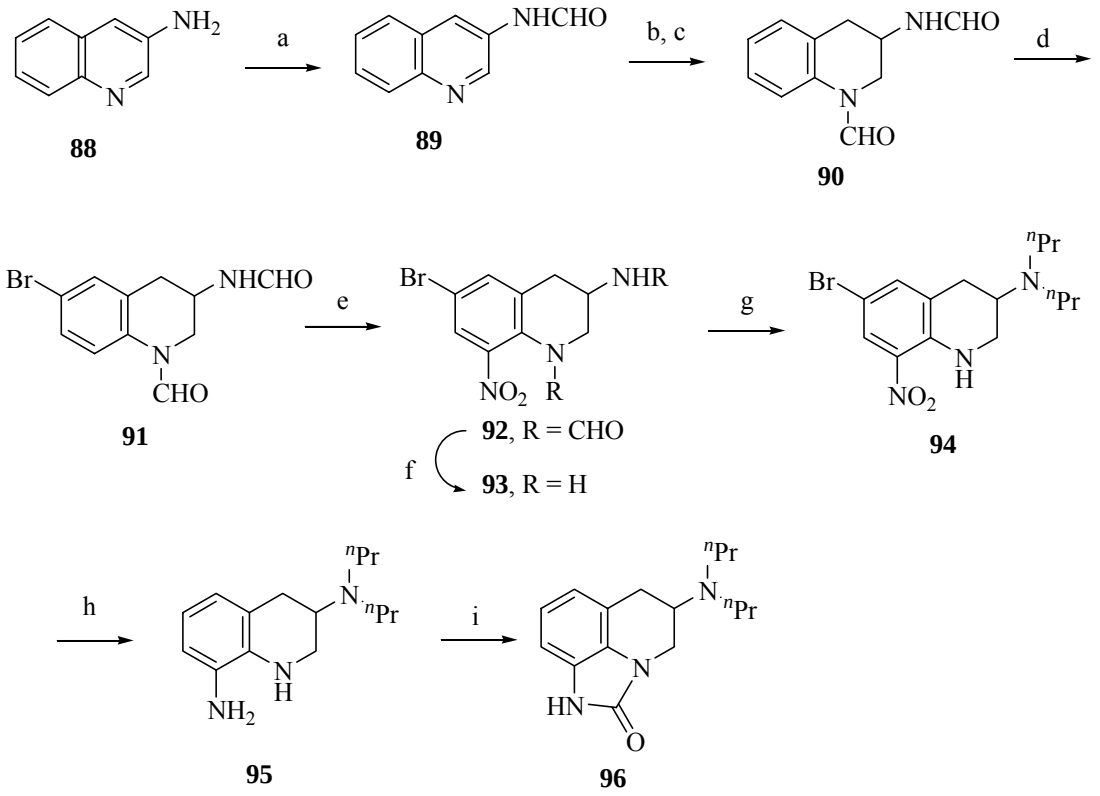
Sumanirole maleate (**87**) is a novel dopamine receptor agonist with high *in vitro* and *in vivo* selectivity for the D2 receptor subtype. It has greater than 200-fold selectivity for the D2 receptor subtype versus the other dopamine receptor subtypes in radioligand binding assays. In cell-based assays, PNU95666-E (**87**) is a fully efficient agonist, with EC_{50} values between 17 and 75 nM.

1.2.2 Review of literature

Literature search revealed that there are very few reports available for the synthesis of Sumanirole maleate (**87**) which are described below.[43-45]

Moon's Approach (1992)[43]

Moon *et al.* have reported catalytic hydrogenation (PtO_2) of 3-amidoquinoline **89** followed by amine protection provided diamidotetrahydroquinoline **90**. Aromatic nitration at *ortho* position was achieved in two steps; *para* bromination of amino tetrahydroquinoline **90** to give bromo tetrahydroquinoline **91** followed by *ortho* nitration gave nitro tetrahydroquinoline **92** in good yield. Acidic hydrolysis of amide **92** to diamine **93** followed by alkylation (^{n}PrI) of primary amine gave *N*,*N*-dipropylamino tetrahydroquinoline **94**. Reduction (10%Pd/C, H_2) of nitro group in **94** led to diamine **95** followed by reaction with 1,1'-carbonyldiimidazole provided racemic **96** in 83% yield (**Scheme 23**).

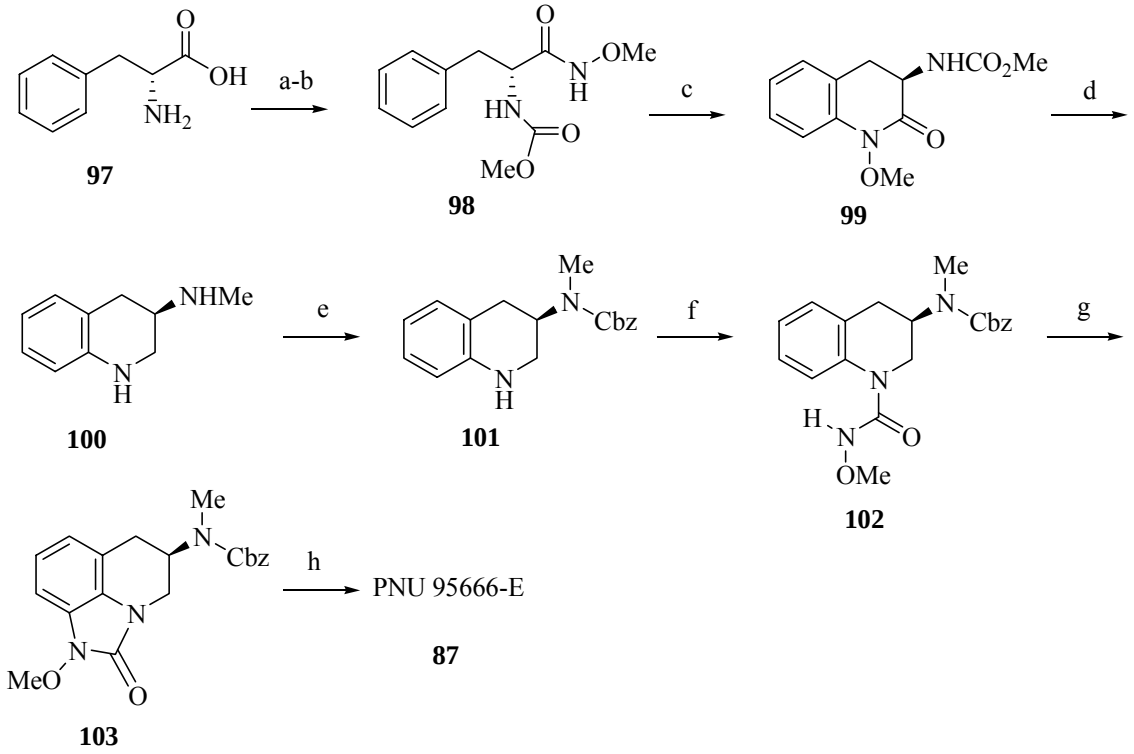


Scheme 23: (a) HCO_2H, Ac_2O, THF, 0 °C, 15 min, 84%; (b) PtO_2 (10 mol%), H_2 (50 lb), AcOH, 25 °C, 3 h, 69%; (c) HCO_2H, Ac_2O, THF, 0 °C, 15min, 84%; (d) Br_2, Na_2CO_3, AcOH, 25 °C, 30 min, 86%; (e) $NaNO_2$, TFA, 25 °C, 16 h, 74%; (f) EtOH, HCl, reflux, 1 h, 86%; (g) ^{n}PrI, Na_2CO_3, DMF, 100 °C, 5 h, 65%; (h) H_2, 10%Pd/C, EtOH, 18 h; (i) 1,1'-carbonyldiimidazole, DMF, 100 °C, 1 h, 83% for two steps.

Romero's approach (1997)[44]

Romero *et al.* have reported the synthesis of PNU 95666-E (**87**) by making use of D-phenylalanine (**97**) as chiral starting material. Protection of amine as its carbamate in **97** followed by amidation of acid moiety provided **98** in 61% yield. Bis(trifluoroacetoxy)iodobenzene/TFA mediated oxidative cyclization of **98** afforded lactum **99** in 85% yield. $BH_3{\cdot}SMe_2$ reduction of lactum **99** gave 3-methylamino-tetrahydriquinoline **100,** which was then subjected to selective protection of methyl amine to its benzyl carbamate **101** in 65% yield. Free amine group in **101** was converted to methoxyamine urea derivative **102** ($COCl_2$, Et_3N, $MeONH_2$ in THF) and subsequent

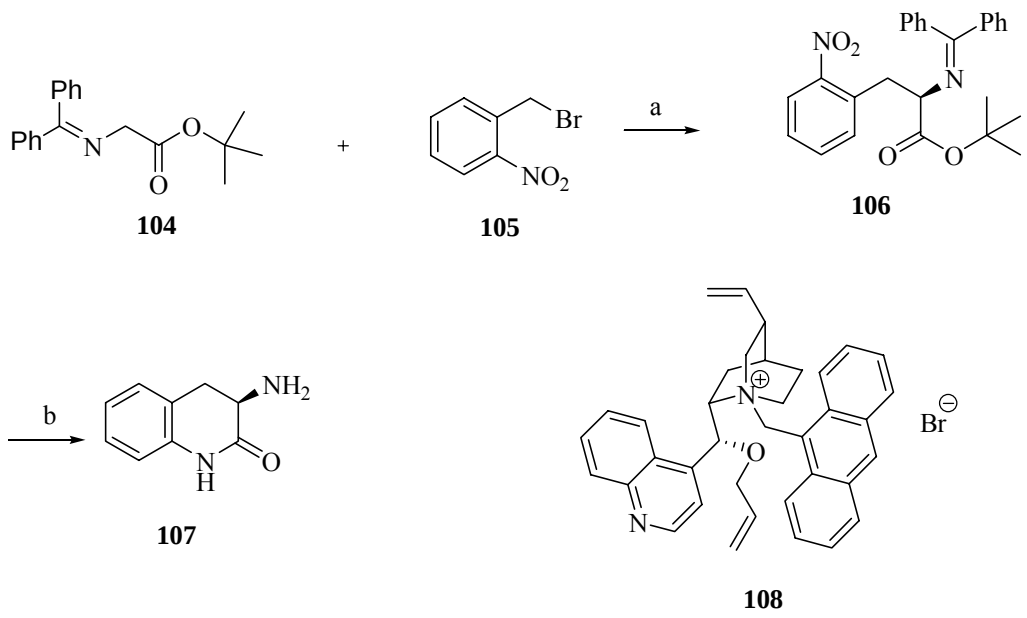
oxidative cyclization provided benzo-fused urea **103** in 78% yields. Finally, deprotection of benzyl carbamate and N-OMe in **103** [H_2 (50 psi), 20% $Pd(OH)_2$] was achieved to give PNU 95666E (**87**) in 84% (**Scheme 24**).



Scheme 24: (a) $ClCO_2OMe$, aq. NaOH, THF, -15-25 °C, 2 h; (b) NH_2OMe, EDC, 25 °C, 22 h, 61% over two steps; (c) $PhI(O_2CCF_3)_2$, CF_3CO_2H, CH_2Cl_2 , 0 °C, 1 h, 85%; (d) $BH_3{\cdot}SMe_2$, THF, 80 °C, 22 h; (e) *N*-(benzyloxycarbonyloxy)succinimide, Toluene, -40 °C, 30 min. 65% over two steps; (f) $COCl_2$, Et_3N, THF, 0 ºC, 1 h, then $MeONH_2$, Et_3N, 25 ºC, 48 h; (g) $PhI(O_2CCF_3)_2$, $CHCl_3$, 0-25 °C, 2 h, 78% over two steps; (h) H_2 (50 psi), 20% $Pd(OH)_2$, EtOH, 19 h, 84%.

Hulin's approach (2004)[45]

Hulin *et al.* have used chiral tetraalkylammonium salt **108** as chiral PTC catalyst for asymmetric alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester **104** with 2-nitrobenzyl bromide (**105**) to provide imine **106,** which on catalytic hydrogenation [10% Pd/C, H_2 (1 atm) and MeOH] provided (*R*)-3-amino-3,4-dihydroquinolin-2-one (**107**) in 65% yield (**Scheme 25**).



Scheme 25: (a) Chiral PTC **108** (7 mol%) $CsOH{\cdot}H_2O$, CH_2Cl_2, -30 °C,12 h, 92%; (b) 10% Pd/C, H_2 (1atm), MeOH, 2M HCl, 65%.

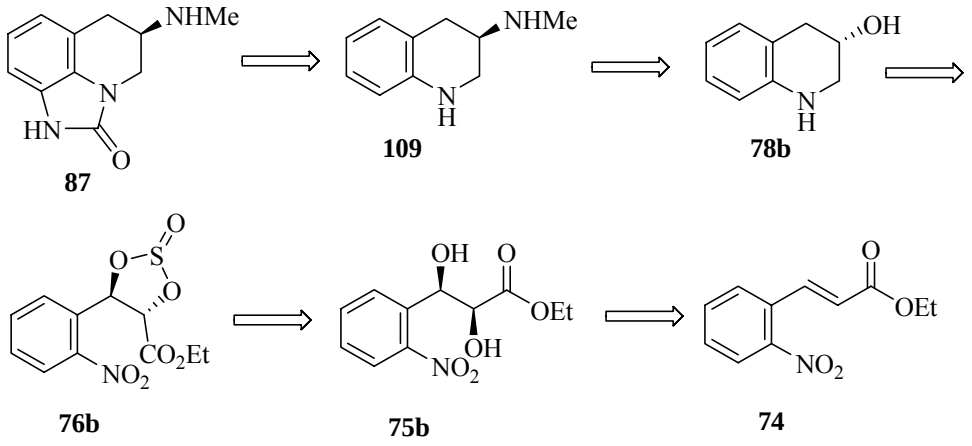
1.2.3 Present work

1.2.3.1 Objective

Literature search reveals that only three strategies namely chiral pool, asymmetric alkylation and resolution of racemates are available for the synthesis of sumanirole maleate, PNU95666-E (**87**). In section I of this Chapter, we have described a short and efficient synthesis of tetrahydroquinolin-3-ol (**78a**). In continuation of the work on Co-catalyzed reduction of nitro cyclic sulphite, a formal synthesis of sumanirole maleate, PNU95666-E (**87**) is described in this section.

Retrosynthetic analysis reveals that, for the synthesis of PNU95666-E (**87**), (*R*)-tetrahydro-*N*-methylquinolin-3-amine (**109**) turns out to be the key intermediate, which could be easily prepared from (*S*)- tetrahydroquinolin-3-ol (**78b**). We further visualized that amino alcohol **78b** could be prepared from Co-catalyzed reduction of nitro cyclic sulphite **76b**. The precursor nitro cyclic sulphite **76b** could be obtained from nitro diol

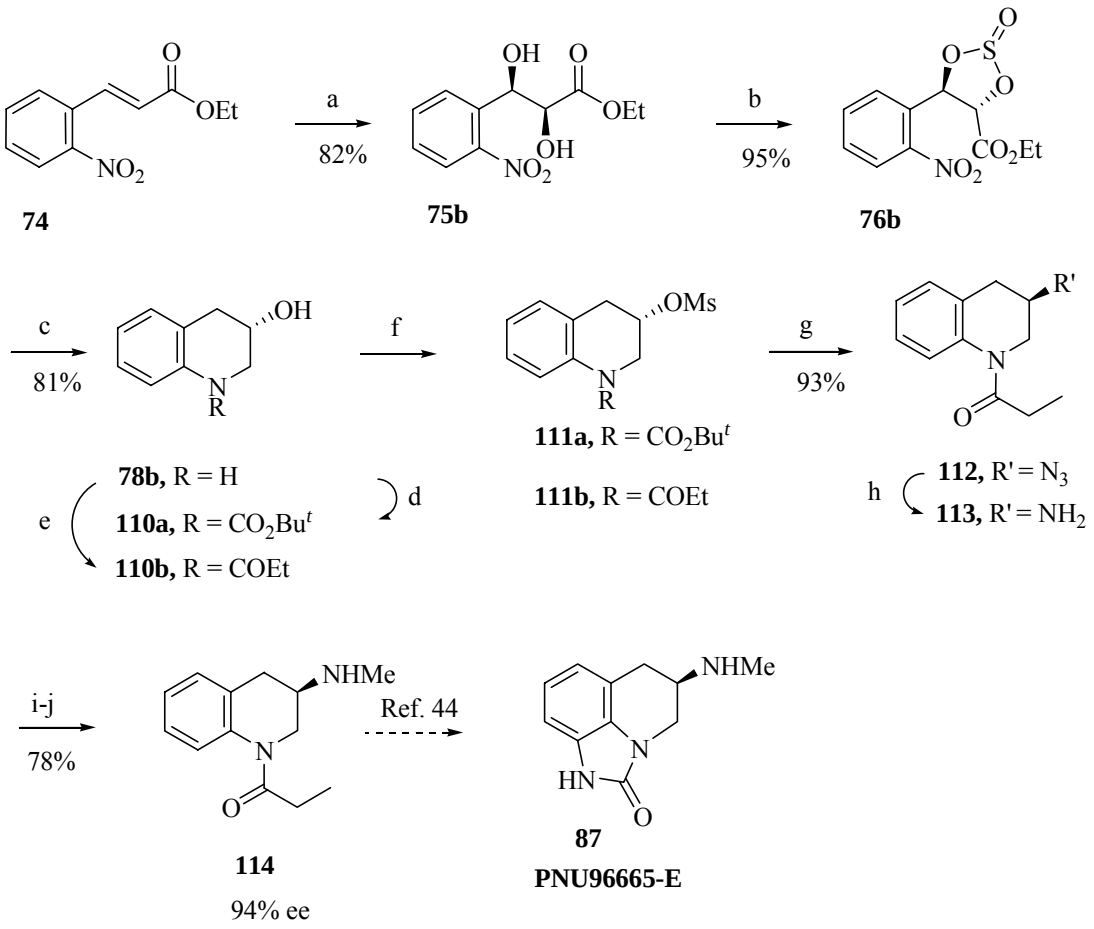
75b, which is realizable from asymmetric dihydroxylation (AD) of nitro cinnamate **74** (**Scheme 26**).



Scheme 26: Retrosynthetic analysis of PNU95666-E (**87**)

1.2.3.2 Results and Discussion:

The present synthetic route employed for the synthesis of PNU95666-E is shown in **Scheme 27**. Unsaturated nitro esters **74**, prepared from Wittig olefination of the corresponding nitrobenzaldehyde was converted to the corresponding diol **75b** in 82% yield *via* Os-catalyzed asymmetric dihydroxylation using $(DHQD)_2$-PHAL as the chiral ligand. The diol **75b** was readily transformed into the corresponding nitro cyclic sulphite **76b** ($SOCl_2$ and Et_3N in CH_2Cl_2) in 95% yield.



Scheme 27: (a) 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%; (b) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 1 h, 95%; (c) $CoCl_2 \cdot 6H_2O$ (1 mol%), $NaBH_4$, EtOH, 0-25 °C, 6 h, 81%; (d) $(C_2H_5CO)_2O$, Et_3N, CH_2Cl_2, 25 °C; (e) K_2CO_3, MeOH:H_2O, 25 °C, 92% over two steps; (f) MsCl, Et_3N, CH_2Cl_2, 0 °C, 10 min; (g) NaN_3, DMF, 80 °C, 16 h, 93% over two steps; (h) 10% Pd/C, H_2 (1atm), MeOH, 25 °C, 12 h; (i) HCHO, $MgSO_4$, CH_2Cl_2; (j) 10% Pd/C, H_2 (1atm), MeOH, 25 °C, 5 h, 78%.

Nitro cyclic sulphite **76b** was then subjected to one-pot reduction using $CoCl_2$ (1 mol%) and 4 equivalents of $NaBH_4$ to give tetrahydroquinolin-3-ol **78b,** in 81% yield. Formation of **78b** was confirmed by spectral data. For example, ^{1}H NMR spectrum of **78b** showed typical signals at δ 2.78 (dd) and 3.04 (dd) corresponding to benzylic methylene protons. Also signals at δ 3.21 (m) and 4.22 (m) correspond to methylene (*N*-C**H**$_2$) and methine

(C**H**OH) protons respectively. Its ^{13}C NMR showed two methylene and one methine (**C**HOH) carbon signals typically at δ 35.4, 47.6 and 63.3 respectively (**Fig. 11**).

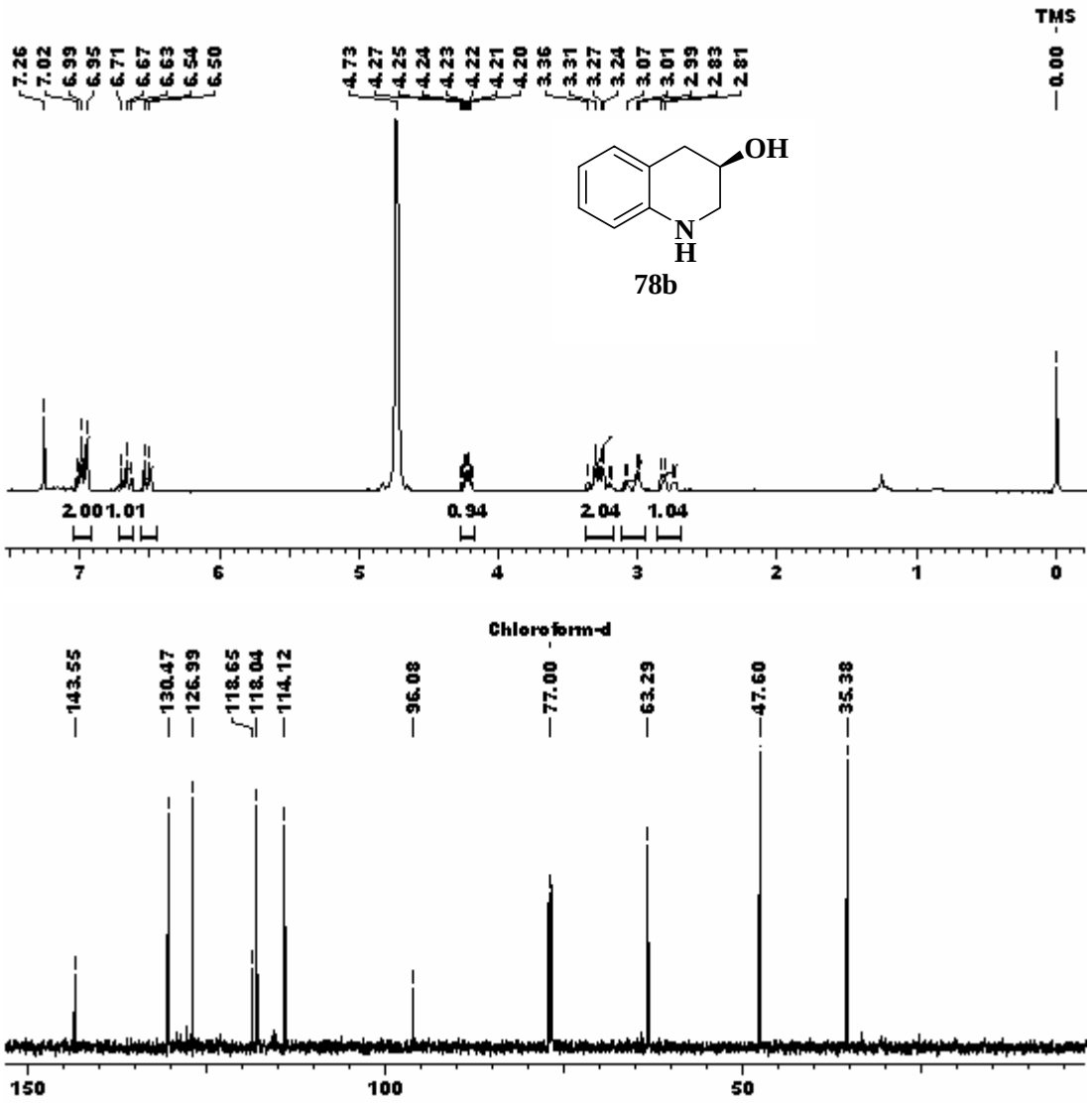


Fig. 11: ^{1}H and ^{13}C NMR spectra of amino alcohol 78b

Initially, amine function in **78b** was protected as *tert*-butyl carbamate **110a** [(*tert*-BuOCO)$_2$O, Et_3N and CH_2Cl_2], followed by protection of the free hydroxyl group as its mesylate **111a** (MsCl, Et_3N and CH_2Cl_2)**.** However, nucleophilic displacement of mesylate **111a** with azide anion under various conditions failed to give the required azido

product probably due to interference shown by the bulky nature of *tert*-butyl group. We observed that protection of amine **78b** as its amide **111b** [$(EtCO)_2O$, Et_3N and CH_2Cl_2] was found to be useful in subsequent steps, as described below. At this stage, enantiomeric excess of **110b** was determined by Mosher's ester analysis. Thus, free hydroxyl moiety in amido alcohol **110b** was subjected to esterification (catalytic DMAP, DCC in CH_2Cl_2) with Mosher's acid [(*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid] and the resulting Mosher's ester **115** was analyzed by ^{1}H NMR spectrum and enantiomeric excess was found to be 94 % (**Fig. 12**).

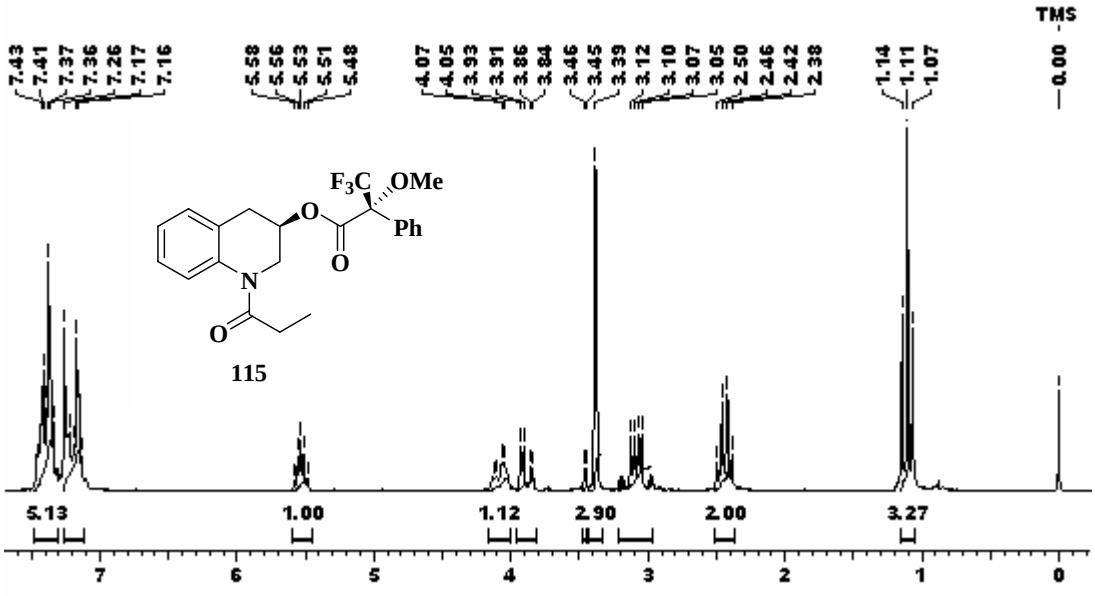


Fig. 12: ^{1}H NMR spectrum of Mosher's ester 115

Alcohol **110b** was then mesylated to give mesylate **111b** which was subjected to nucleophilic displacement with azide anion giving azide **112** in 93 % yield. Presence of azide functionality was confirmed from IR spectroscopy, which showed strong absorption band at 2106 cm^{-1}. Its ^{1}H NMR spectrum showed a typical signals at δ 3.77 (m) due to the methine proton (C**H**N_3) confirming the formation of azide **112**(**Fig. 13**).

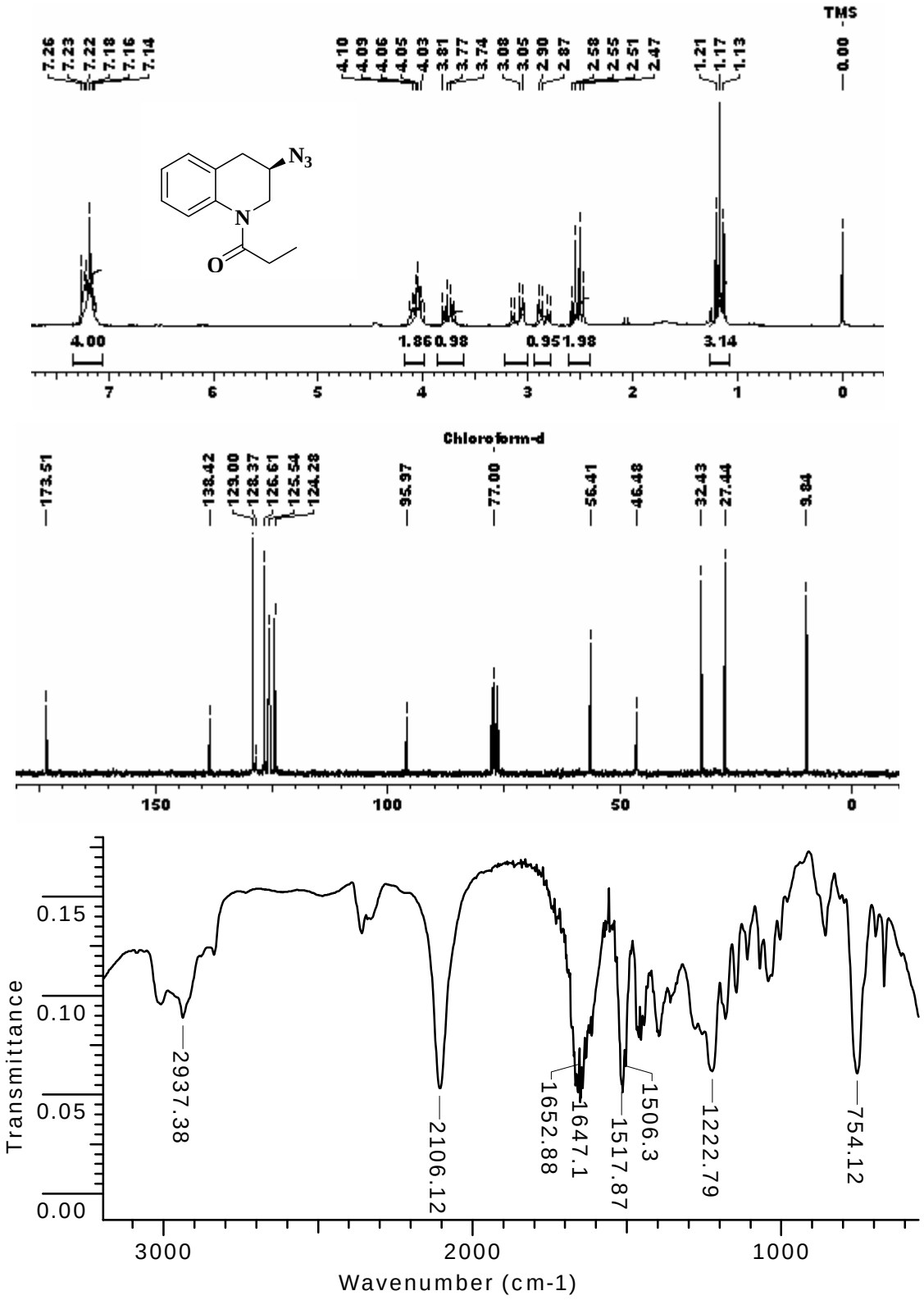


Fig. 13: ^{1}H, ^{13}C NMR and IR spectra of 3-azidotetrahydroquinoline 112

Its ^{13}C NMR spectrum showed methine (**C**HN_3) and carbonyl carbon signals at δ 46.4 and 173.5 respectively (**Fig. 13**). Reduction of azide moiety in **112** [10% Pd/C, H_2 (1 atm) in CH_3OH] gave 3-amino-tetrahydroquinoline **113,** which was transformed into the corresponding imine (40% HCHO, $MgSO_4$ and CH_2Cl_2) *in situ*, subsequent reduction of which [10% Pd/C, H_2 (1 atm)] provided *N*-methyl amine **114** in 78% yield. Its ^1H NMR spectrum showed a typical signal at δ 2.91 due to amino methyl proton (*N*-C**H**$_3$).

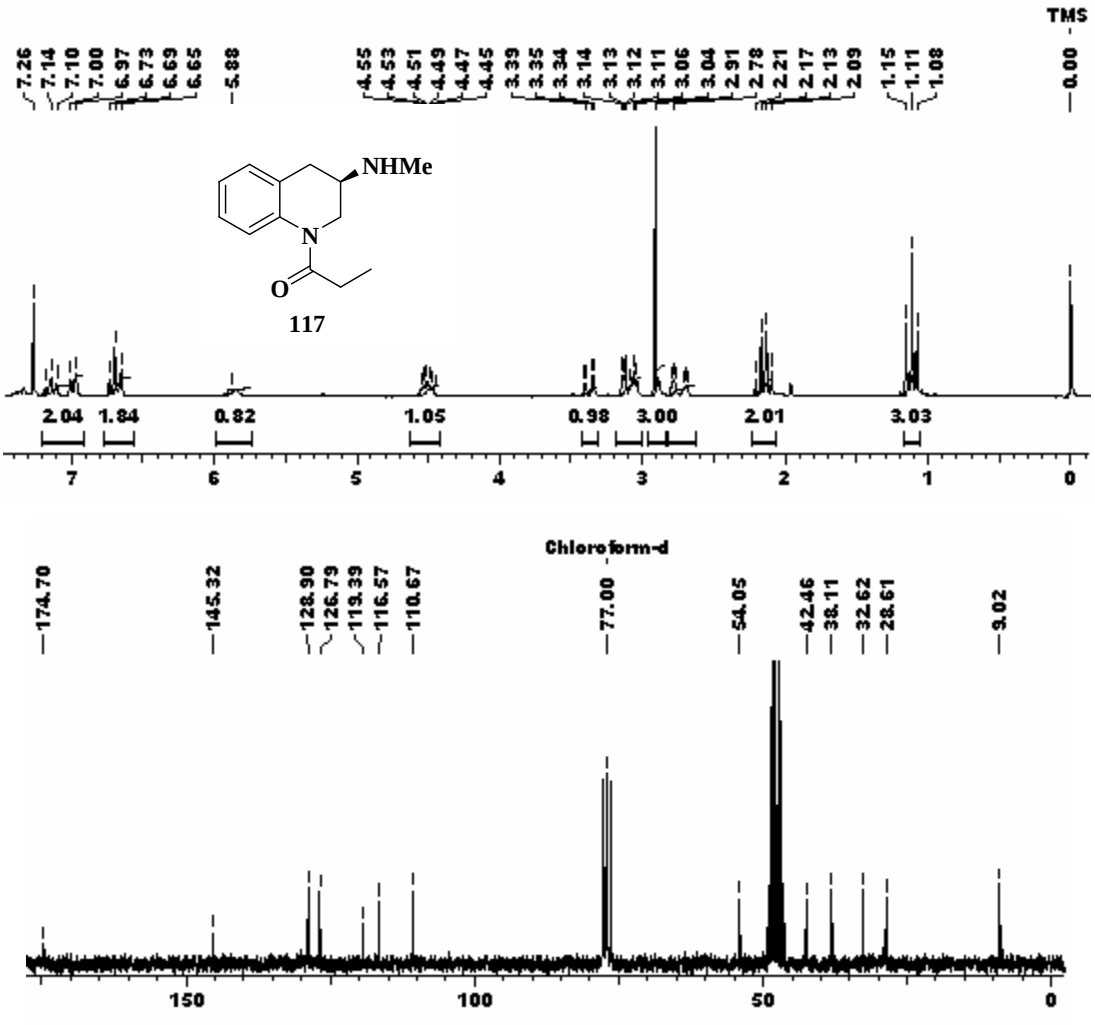


Fig. 12: ^1H and ^{13}CNMR spectra of tetrahydroquinoline methyl amine 114

Its ^{13}C NMR spectrum showed typical carbon signals at δ 38.1, 42.4 and 54.0 corresponding to the amino methyl (*N*-**C**H_3), methylene (*N*-**C**H_2) and methine (*N*-**C**H)

carbons respectively. Also signals for carbonyl carbon signal was observed at δ 174.7 (**Fig. 14**).

Further, synthesis of PNU95666-E (**87)** from **114** has been reported in the literature.[34]

1.2.4 Conclusion

In conclusion, we have achieved the formal synthesis of PNU 95666-E **(87**), which was obtained in 13% overall yield and 94% ee. We have successfully applied asymmetric dihydroxylation and Co-catalyzed multifunctional reduction as key steps for the synthesis of PNU 95666-E (**87).**

1.2.5 Experimental section

A typical experimental procedure for the preparation of (2*S*,3*R*)-ethyl 2,3-dihydroxy-3-(2-nitrophenyl)propanoate (75b):

To 500 mL RB flask were added, $K_3Fe(CN)_6$ (39.48 g, 120 mmol), K_2CO_3 (16.56 g, 120 mmol), $MeSO_2NH_2$ (3.8 g, 40 mmol), *tert*-BuOH (200 mL) and H_2O (200 mL). Reaction mixture was stirred for 10 min and $(DHQD)_2$-PHAL (1 mol%) and K_2OsO_4 (0.2 mol%) were added and stirred for additional 30 min. To the reaction mixture (*E*)-ethyl 3-(2-nitrophenyl)acrylate **(109)** (8.84g, 40 mmol) was added and allowed to stir for 24 h at 25 ºC. After completion of reaction, sodium bisulphate (10 g) was added slowly at 0 ºC. The organic layer was separated and aqueous layer was extracted with ethyl acetate (3 x 300 ml), combined organic layers were washed with brine (2 x 400 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product. Chromatographic purification of the crude product [flash silica gel (230-400 mesh) and petroleum ether: ethyl acetate (60:40) as an eluent] afforded 8.37g pure **75b**.

Yield: 82%; $[\alpha]^{D}_{25}$ −126.0 (*c* 1, $CHCl_3$); yellow solid, **mp**: 86 °C; %, **IR** ($CHCl_3$): 668, 757, 860, 1055, 1108, 1216, 1263, 1347, 1527, 1733, 3020, 3485 cm^{-1}; **^{1}H NMR** (200

MHz, $CDCl_3$): δ 1.32 (t, *J* = 8.0 Hz, 3H), 3.22 (bs, 1H), 3.38 (bs, 1H), 4.30 (q, *J* = 8.0 Hz, 2H), 4.48 (d, *J* = 2.1 Hz, 1H), 5.67 (d, *J* = 2.1 Hz, 1H), 7.46 (t, *J* = 6 Hz, 1H,), 7.67 (t, *J* = 6 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR** ($CDCl_3$): δ 14.1, 62.3, 69.7, 73.4, 124.3, 128.4, 129.7, 133.2, 136.2, 147.6, 172.6; **Analysis** for $C_{11}H_{13}NO_6$ requires C 51.77, H 5.13, N 5.49; found C 51.65, H 5.33, N 5.54%.

A typical experimental procedure for the preparation of nitro cyclic sulphite (76b):

To the stirred solution of nitro diol **75** (2.55g, 10 mmol) and triethylamine (4.2 ml, 30 mmol) in CH_2Cl_2 (50 mL) at 0 ºC, was added freshly distilled $SOCl_2$ (1.0 ml, 12 mmol) drop-wise under nitrogen atmosphere. The reaction mixture was stirred at 0 ºC for 30 minutes (progress of reaction was monitored by TLC). The reaction mixture was quenched by the addition of cold water (20 ml) and a saturated solution of $NaHCO_3$ (20 ml). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extract was washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure, crude cyclic sulphite **76b** which shows decomposition on silica. It was directly subjected for reduction.

Yield: 95%: Gum; **IR** ($CHCl_3$): 667, 757, 962, 1045, 1217, 1350, 1531, 1610,1747, 2985, 3022, 3519 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.36 (t, *J* = 7.2 Hz, 3H), 4.36 (q, *J* = 7.2 Hz, 2H), 4.97 (d, *J* = 4.7 Hz, 1H), 6.93 (d, *J* = 4.7 Hz, 1H), 7.57-7.80 (m, 3H), 8.13-8.18 (dd, *J* = 1.2, 7.9 Hz); **^{13}C NMR** (50MHz, $CDCl_3$): δ 13.8, 62.7, 83.1, 83.2, 124.9, 129.9, 130.9, 131.1, 134.5, 147.6, 165.7%.

A typical experimental procedure for the preparation (*S*)-1,2,3,4-tetrahydroquinolin-3-ol (78b):

To the stirred solution of nitro cyclic sulphite **76b** (10 mmol), $CoCl_2 \cdot 6H_2O$ (23.8 mg, 1 mol %) and 95 % ethanol (30 mL), $NaBH_4$ (24 mmol) was added at 0 ºC and allowed to stir for 12 h at 25 ºC. After completion of reaction, reaction mixture was poured into ice cold water forms black precipitate. To the aqueous layer 100 mL of ethyl acetate was added and combined mixture was passed through celite. The organic layer was separated and aqueous layer was extracted with ethyl acetate (2 x 50 mL). Combined organic layers were washed with brine (2 x 50 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product. Chromatographic purification of the crude product [silica gel (230-400 mesh) and petroleum ether: ethyl acetate: Et_3N (60: 40:2)] gave 1.22 g of **78b** in pure form**.**

Yield: 1.22 g, 82%; $[\alpha]^{D}_{25}$ –20.86 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$): 656, 1215, 1510, 1637, 3018, 3390 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.73-2.83 (dd, *J* = 3.5, 16.8 Hz, 1H), 2.99-3.09 (dd, *J* = 3.5, 16.8 Hz, 1H), 3.19-3.36 (m, 2H), 4.19-4.27 (m, 1H), 6.52 (d, *J* = 9.0 Hz, 1H), 6.67 (dt, J = 1.1, 7.5 Hz, 1H), 6.95-7.02 (m, 2H); **^{13}C NMR** ($CDCl_3$): δ 35.3, 47.6, 63.2, 114.1, 118.0, 118.6, 126.9, 130.4, 143.5; **Analysis** for $C_9H_{11}NO$ requires C, 72.46; H, 7.43; N, 9.39; found C, 72.42; H, 7.40; N, 9.44%.

A typical experimental procedure for the preparation of (S)-*tert*-butyl 3,4-dihydro-3-hydroxyquinoline-1(2H)-carboxylate(110a):

To the stirred solution of tetrahydroquinolin-3-ol (**112**) (745 mg, 5 mmol) and triethylamine (1.3 mL, 10 mmol) in CH_2Cl_2 (20 mL), was added $(Boc)_2O$ (1.530 g, 7 mmol) at 25 ºC and allowed to stir for 6 h. Progress of reaction was monitored by TLC and after completion of reaction, a saturated solution of NH_4Cl (20 mL) was added. The organic layer was separated; the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL).

Combined organic layers were washed with brine (2 x 25 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude products. Chromatographic purification of crude product [silica gel (230-400 mesh) and petroleum ether: ethyl acetate: (60: 40:) as eluent] gave 1.120 g of **110a** in pure form.

Yield 1.120 g, 90%; $[\alpha]^{D}_{25}$ –1.5 (*c* 1.4, $CHCl_3$); Gum**; IR** ($CHCl_3$): 761, 1051, 1245, 1755, 2358, 3463 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.48 (s, 9H), 2.85-2.96 (dd, *J* = 6.5, 16.1 Hz, 1H), 3.07-3.18 (dd, *J* = 5.4, 15.9 Hz, 1H), 3.29-3.52 (m, 2H), 4.98-5.04 (m, 1H), 6.50 (d, *J* = 7.6 Hz,1H), 6.63 (t, *J* = 7.6 Hz, 1H), 6.97 (t, *J* = 7.6 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 27.4, 31.9, 44.5, 68.8, 81.8, 113.9, 117.3, 126.8, 129.5, 143.2, 152.7; **Analysis** for $C_{14}H_{19}NO_3$ requires C, 67.45; H, 7.68; N, 5.62; found C, 67.32; H, 7.52; N, 5.56%.

A typical experimental procedure for the preparation of 1-[(*S*)-3,4-dihydro-3-hydroxyquinolin-1(2*H*)-yl]propan-1-one (110b):

To the stirred solution of tetrahydroquinolin-3-ol (**112**) (0.74 g, 5 mmol) and Et_3N (1.3 mL, 10 mmol) in 20 mL of CH_2Cl_2, propionic anhydride (7 mmol, 0.9 mL) was added at 25 ºC. Reaction mixture was stirred for 3 h. Progress of the reaction was monitored by TLC and after the completion of reaction, a saturated $NaHCO_3$ (30 mL) was added. The organic layer was separated; the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with brine (2 x 25 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product. Chromatographic purification of the crude product [silica gel (230-400 mesh) and petroleum ether:ethyl acetate: (60: 40:)] gave 944 mg of pure amide **110b**.

Yield: 944 mg, 92%; $[\alpha]^{D}_{25}$ –1.20 (*c* 1.4, $CHCl_3$); **IR** ($CHCl_3$): 761, 1051, 1245, 1755, 2358, 3463 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.16 (t, *J* = 7.4 Hz, 3H), 2.55 (q, *J* = 7.4 Hz, 2H), 2.74-2.85 (dd, *J* = 4.9, 16.5 Hz, 1H), 3.04-3.13 (dd, *J* = 5.7, 16.5 Hz, 1H), 3.76-3.85 (dd, *J* = 4.9, 13.3 Hz, 1H), 3.91-4.00 (dd, *J* = 4.9, 13.3 Hz, 1H), 4.28 (m, 1H), 7.10-7.23 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 9.9, 27.4, 35.7, 49.8, 65.7, 124.2, 125.4, 125.9, 129.3, 129.7, 138.5; **Analysis** for $C_{12}H_{15}NO_2$ requires C, 70.22; H, 7.37; N, 6.82; found C, 70.07; H, 7.24; N, 6.83%.

A typical experimental procedure for the preparation of (*S*)-1,2,3,4-tetrahydro-1-propionylquinolin-3-yl methanesulfonate (111a-b):

To the stirred solution of amide (0.82 g, 4 mmol) and triethylamine (1.3 mL, 10 mmol) in CH_2Cl_2 (20 mL), was added mesyl chloride (5 mmol, 0.4 mL) at 0 ºC. It was then stirred for 15 min. After completion of the reaction (monitored by TLC), a saturated solution of $NaHCO_3$ (30 mL) was added, the organic layer was separated and the aqueous layer was extracted with (2 x 50 mL CH_2Cl_2). The combined organic layers were washed with brine (2 x 25 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude product.

A typical experimental procedure for the preparation of 1-[(*R*)-3-azido-3,4-dihydroquinolin-1(2H)-yl]propan-1-one (112):

To the stirred solution of mesylate **111b** (4 mmol) in dry DMF (10 mL), NaN_3 (650 mg, 10 mmol) was added. Reaction mixture was stirred for 16 h at 80 ºC. After completion of reaction (monitored by TLC), it was poured into 50 mL of ice cold water and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (2 x 25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give

the crude product **112**. Chromatographic purification of crude product using flash silica gel (230-400 mesh) and petroleum ether: ethyl acetate: (70: 30:) gave pure 855 mg azide **112**.

Yield: 93%; gum, $[\alpha]^{D}_{25}$ –61.25 (*c* 1.1, $CHCl_3$); **IR** ($CHCl_3$): 752, 1222, 1517, 1652, 2106 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.17 (t, *J* = 7.4 Hz, 3H), 2.53 (q, *J* = 7.4 Hz, 2H), 2.79-2.90 (dd, *J* = 5.8, 16.4 Hz, 1H), 3.05-3.16 (dd, *J* = 6.6, 16.4 Hz, 1H), 3.71-3.81 (m, 2H), 4.00-4.13 (m, 1H), 7.10-7.26 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 9.4, 27.4, 32.4, 46.4, 56.4, 124.2, 125.5, 126.6, 128.3, 129.0, 138.4, 173.5; **Analysis** for $C_{12}H_{14}N_4O$ requires C, 62.59; H, 6.13; N, 24.33; found C, 62.51; H, 6.17; N, 24.28%.

A typical experimental procedure for the preparation of 1-[(*R*)-3-amino-3,4-dihydroquinolin-1(2*H*)-yl]propan-1-one (113):

To the solution of azide (460 mg, 2 mmol) in methanol (10 mL), 40 mg (10% Pd/C) was added. Resulting reaction mixture was stirred under H_2 (1 atm) for 12 h. After completion of reaction (monitored by TLC), it was filtered through celite and concentrated under reduced pressure to give the crude product. Chromatographic purification of the crude product using flash silica gel (230-400 mesh) and petroleum ether: ethyl acetate: Et_3N (50:45:5) gave pure amine **113**.

Yield: 95%; gum, $[\alpha]^{D}_{25}$ –13.33 (*c* 1.8, $CHCl_3$); **IR** ($CHCl_3$): 759, 1020, 1215, 1510, 1652, 1747, 3018, 3394 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.17 (t, *J* = 7.4 Hz, 3H), 2.54 (q, *J* = 7.4 Hz, 2H), 3.01-3.26 (m, 2H), 3.35-3.47 (m, 2H), 4.00-4.18 (m, 1H), 6.95-7.24 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 9.6, 29.5, 32.4, 41.68, 45.1, 114.1, 117.7, 118.2, 126.9, 130.2, 143.2, 173.4; **Analysis** for $C_{12}H_{16}N_2O$ requires C, 70.56; H, 7.90; N, 13.71; found C, 70.42; H, 7.99; N, 13.78%.

A typical experimental procedure for the preparation of 1-(3,4-dihydro-3-(methylamino)quinolin-1(2*H*)-yl)propan-1-one (114):

To the stirred solution of amine **113** and 40% HCHO (1 mL) in CH_2Cl_2 (10 mL), anhydrous $MgSO_4$ was added. Reaction mixture was stirred for 1 h at 25 °C and then $MgSO_4$ was filtered and washed with additional 25 mL of CH_2Cl_2, concentrated under reduced pressure gave crude imine. To the solution of crude imine in ethyl acetate (10 mL), 10% Pd/C (20 mg) was added. Resulting reaction mixture was stirred under H_2 (1 atm) for 5 h. After the completion of reaction (monitored by TLC), it was filtered through celite and concentrated under reduced pressure to give the crude product. Chromatographic purification of the crude product [silica gel (230-400 mesh) and petroleum ether: ethyl acetate: Et_3N (50:45:5)] gave pure methylamine **114**.

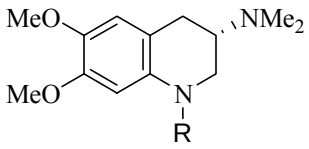
Yield: 78%; gum, $[\alpha]^{D}_{25}$ –57.9 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$): 761, 1025, 1210, 1510, 1652, 1752, 3029 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.15 (t, *J* = 7.4 Hz, 3H), 2.53 (q, *J* = 7.4 Hz, 2H), 3.03 (s, 3H), 3.10-3.27 (m, 2H), 3.87-3.96 (dd, *J* = 4.5, 13.9 Hz, 1H), 4.17-4.26 (dd, *J* = 4.5, 13.9 Hz, 1H), 5.19-4.29 (m, 1H), 7.15-7.24 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$+ DMSO-d_6): δ 10.9, 30.5, 34.5, 40.0, 44.4, 56.0, 112.6, 118.5, 121.3, 128.7, 130.8, 147.2,176.6; **Analysis** for $C_{13}H_{18}N_2O$ requires C, 71.53; H, 8.31; N, 12.83; found C, 71.51; H, 8.25; N, 12.77%.

Section III

Asymmetric synthesis of 1-[(*S*)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxy-quinolin-1(2*H*)-yl]alkanones

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)-6,7-dimethoxytetrahydroquinoline alkanones (**116-117)** have recently been identified as potentially interesting positive inotropic agents (**Fig 12**).[46]



116, R = COEt

117, R = COPr^{i}

Fig. 12: Structures of positive inotropic agents **116** and **117**

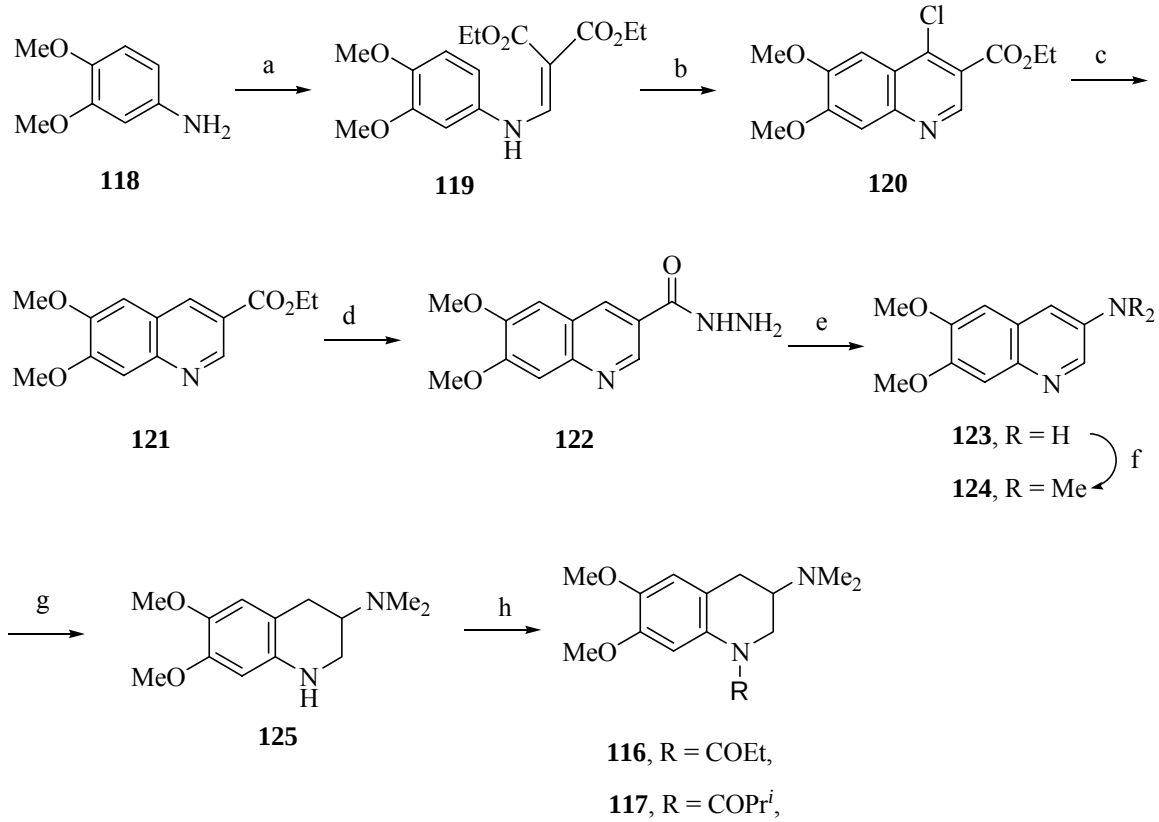
1.3.2 Review of literature

Literature search revealed that there is only one report available for the synthesis of 1-[(*S*)-3-(Dimethylamino)-6,7-dimethoxytetrahydroquinoline derivatives **(116-117**), which is described below.

Vecchietti's Approach (1994)[46]

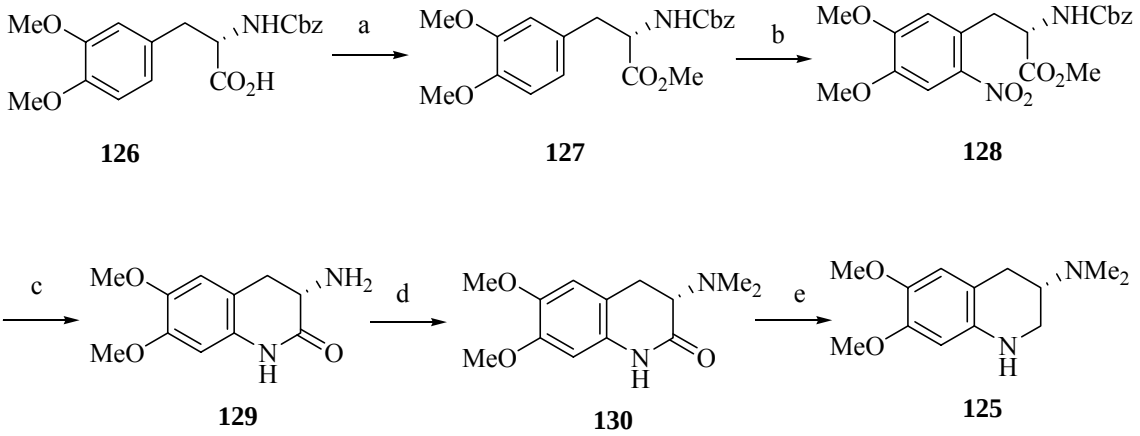
Vecchietti *et al.* have reported racemic synthesis of 1-[(*S*)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxy-quinolin-1(2*H*)-yl]alkanones (**116-117**). Diethyl 2-[(3,4-dimethoxyphenylamino)methylene]malonate **119,** obtained by the condensation of

ethoxymethylene malonate with 3,4-dimethoxyaniline (**118**), was cyclized ($POCl_3$ and DMF) to give chloro tetrahydroquinoline derivative **120**. Subsequent dechlorination (10% Pd/C, H_2 and AcOH) was achieved to give quinoline derivative **121.** This was subjected to Curtius rearrangement of **121** *via* hydrazine amide **122** to provide 3-aminoquionoline **123** in good yields. Subsequently, reductive amination of **123** (HCHO and HCOOH) gave **124,** which was subjected to ionic hydrogenation under high pressure (10%Pd/C, H_2 and AcOH) to give *N*,*N*-dimethyl amino tetrahydroquinoline **125.** Finally, acylation of amine in **126** (acyl chloride and CH_2Cl_2) furnished amides **116**-**117** in good yields (**Scheme 24**).



Scheme : 25 (a) $C_2H_5OCH{=}C(COOC_2H_5)_2$, heat,; (b) $POCl_3/PCl_5$; (c) H_2, 10% Pd/C, acetic acid; (d) $NH,NH_2{\cdot}H_2O$; (e) $NaNO_2$; (f) HCHO/HCOOH; (g) H_2, 10% Pd/C, acetic acid, 80%; (h) acyl chloride, CH_2Cl_2.

In another approach, the same authors have described the asymmetric synthesis of diamine intermediate **125** starting from chiral starting material. *N*-Cbz protected L–DOPA derivative **126** was esterified to give methyl ester **127,** which was regioselectively nitrated (conc. HNO_3 and AcOH) to give nitro derivative **128**. Nitro ester **128** 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 **129,** on reductive amination (10% Pd/C, HCHO and MeOH) gave *N, N*-dimethylamino quinolin-2-one **130.** Finally, $LiAlH_4$ reduction of **130** gave very low yield of 3-**(***N, N*-dimethylamino)quinoline **125** in 28% (**Scheme 26**).



Scheme : 26 (a) CH_3I, K_2CO_3, acetone, 60 °C, 6 h, 73%; (b) HNO_3, CH_3CO_2H, 15 °C, 3 h 76%; (c) 10% Pd/C, H_2 (4 atm), CH_3CO_2H, 91%; (d) 10% Pd/C, HCHO, 2N HCl, Et_2O, 40-50 °C, 90%; (e) $LiAlH_4$, DME, reflux, 24 h, 28%.

1.3.3 Present work

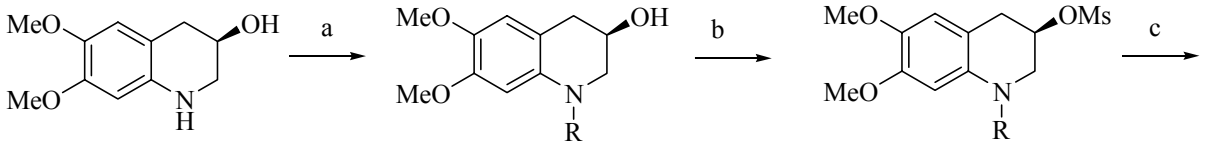
1.3.3.1 Objective

Review of literature reveals that only one report is available for the synthesis of 1-[(*S*)-3-(dimethylamino)3,4-dihydro-6,7-dimethoxy-quinolin-1(2*H*)-yl]alkanones (**116-117**). However, use of chiral starting material as well as the need to have several protecting groups in the synthesis make the existing method uneconomical. In section I of this Chapter, we have described an elegant method for the synthesis of 3-hydroxy tetrahydroquinoline derivatives **83a-e**. In continuation of the work on Co-catalyzed

reduction of nitro cyclic sulphites, we describe a short synthesis of 1-[(*S*)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxy-quinolin-1(2*H*)-yl]alkanones (**116-117**) in this section.

1.3.3.2 Results and Discussion

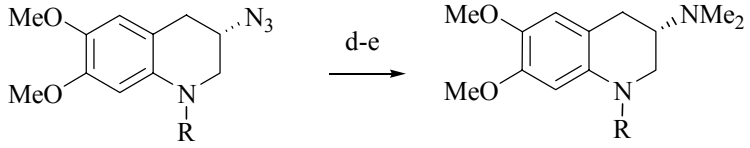
A general synthetic scheme for the synthesis of 1-[(*S*)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxy-quinolin-1(2*H*)-yl]alkanones (**116-117**) is shown in **Scheme 27**. The synthetic route for the tetrahydroquinolin-3-ol **83a** has been described in Section I. Amine function in **83a** was protected as its amides **131-132** [RCOCl or $(RCO)_2O$, Et_3N and CH_2Cl_2] in >90% yields.



83a

131, R = COEt, 95.5 % ee
132, R = $COPr^i$,

133, R = COEt,
134 R = $COPr^i$,



135, R = R = COEt
136, R = $COPr^i$

116, R = COEt
117, R = $COPr^i$

Scheme : 27 (a) $(RCO)_2O$, Et_3N, CH_2Cl_2, 0 °C, 91%; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 10 min; (c) NaN_3, DMF, 80 °C, 12 h, 91% over two steps; (d) H_2 (1atm) 10%Pd/C, MeOH, 25 °C, 12 h; (e) HCHO, HCO_2H, 80 °C, 3 h, 73% over two steps.

The ^{1}H NMR spectrum of **131** showed two typical proton signals at δ 1.18 and 2.56 corresponding to the methyl (C**H**$_3$) and methylene (C**H**$_2$) protons respectively. Also proton signals for benzylic methylene (ArC**H**$_2$), aminomethylene (*N*-C**H**$_2$) and methine

(C**H**OH) protons have appeared at δ 2.73 (dd), 3.03 (dd), 3.74-4.00 (m) and 4.32 (m) respectively. Its ^{13}C NMR spectrum showed characteristic carbon signals at δ 8.67 and 55.64 due to the methyl (CH_3) and methylene carbons (**C**H_2) of ethyl group. Also carbonyl signal at δ 174.3 confirms the formation of amide carbonyl group (**Fig. 13**).

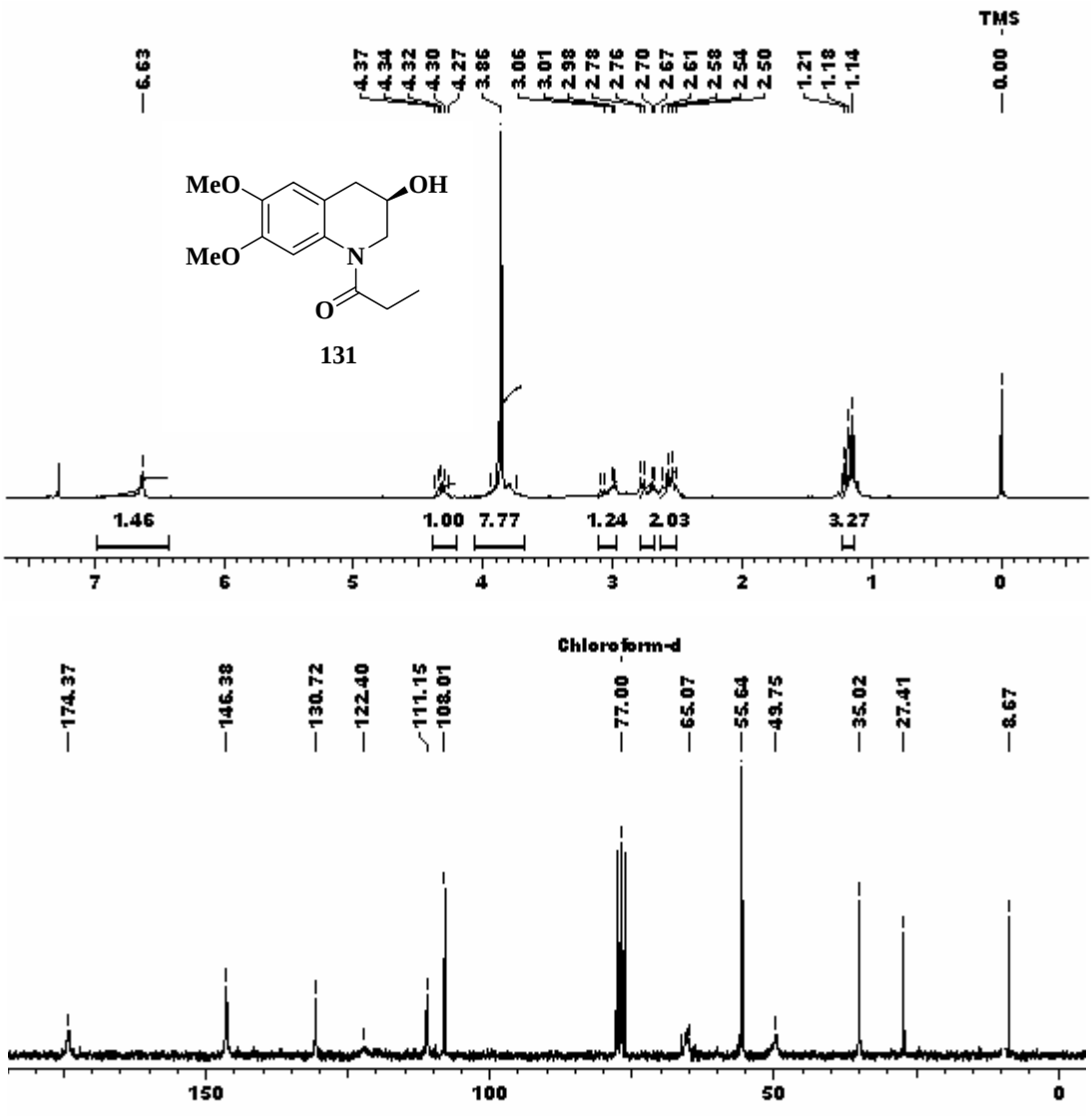


Fig. 13: ^{1}H and ^{13}C NMR spectra of alcohol 131

Enantiomeric excess of chiral alcohol **131** was determined by chiral HPLC and found to be 95.5%. Free hydroxyl moiety in **131-132** was then protected as its mesylate **133-134** (MsCl, Et_3N and CH_2Cl_2) followed by its displacement with azide anion (NaN_3, DMF) to

give azido quinolines **135-136** in 90-91% yields. The ^{1}H NMR spectrum of azide **135** showed a typical signal at δ 3.77 due to methine (C**H**N_3) proton. Its ^{13}C NMR spectrum also showed a downfield shift for methine (**C**HN_3) carbon signal at δ 56.18. Its IR spectrum showed a characteristic absorption band at 2110 cm^{-1} for azide group confirming the formation of azide product (**Fig. 14**).

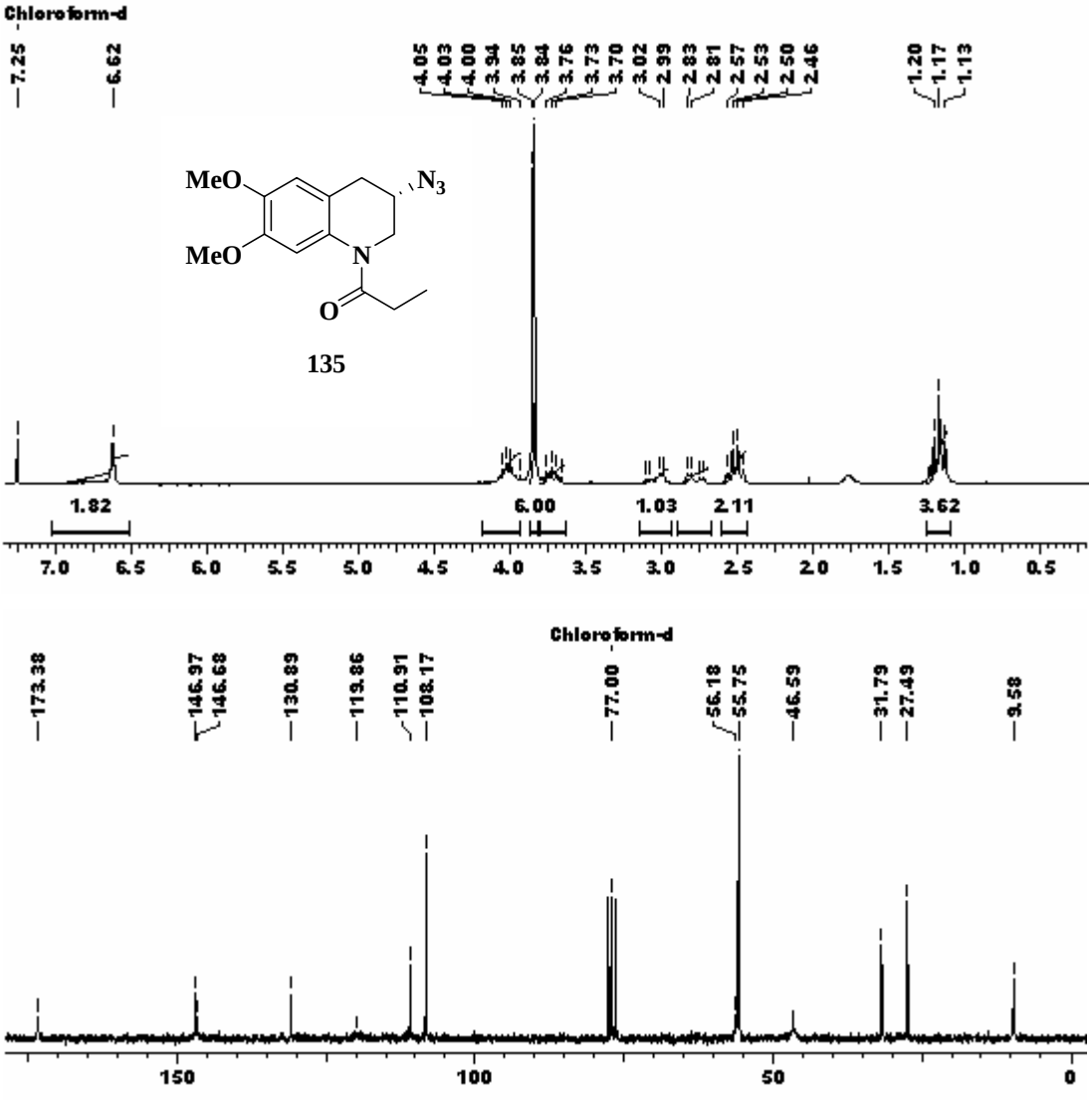


Fig. 14: ^{1}H and ^{13}C NMR spectra of azide 135

Catalytic hydrogenation of azide function in **135** and **136** was carried out to give the corresponding amines followed by its reductive amination (HCHO, HCO_2H) produced 1-[(*S*)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxy-quinolin-1(2*H*)-yl]alkanones (**116-117**). The ^{1}H NMR spectrum of **116** showed a typical singlet at δ 2.35 due to methyl amine protons [$N(CH_3)_2$]. Also signals at δ 41.33 and 41.46 in its ^{13}C NMR spectrum due to methyl amine carbons confirmed the formation of **116** (**Fig. 15**).

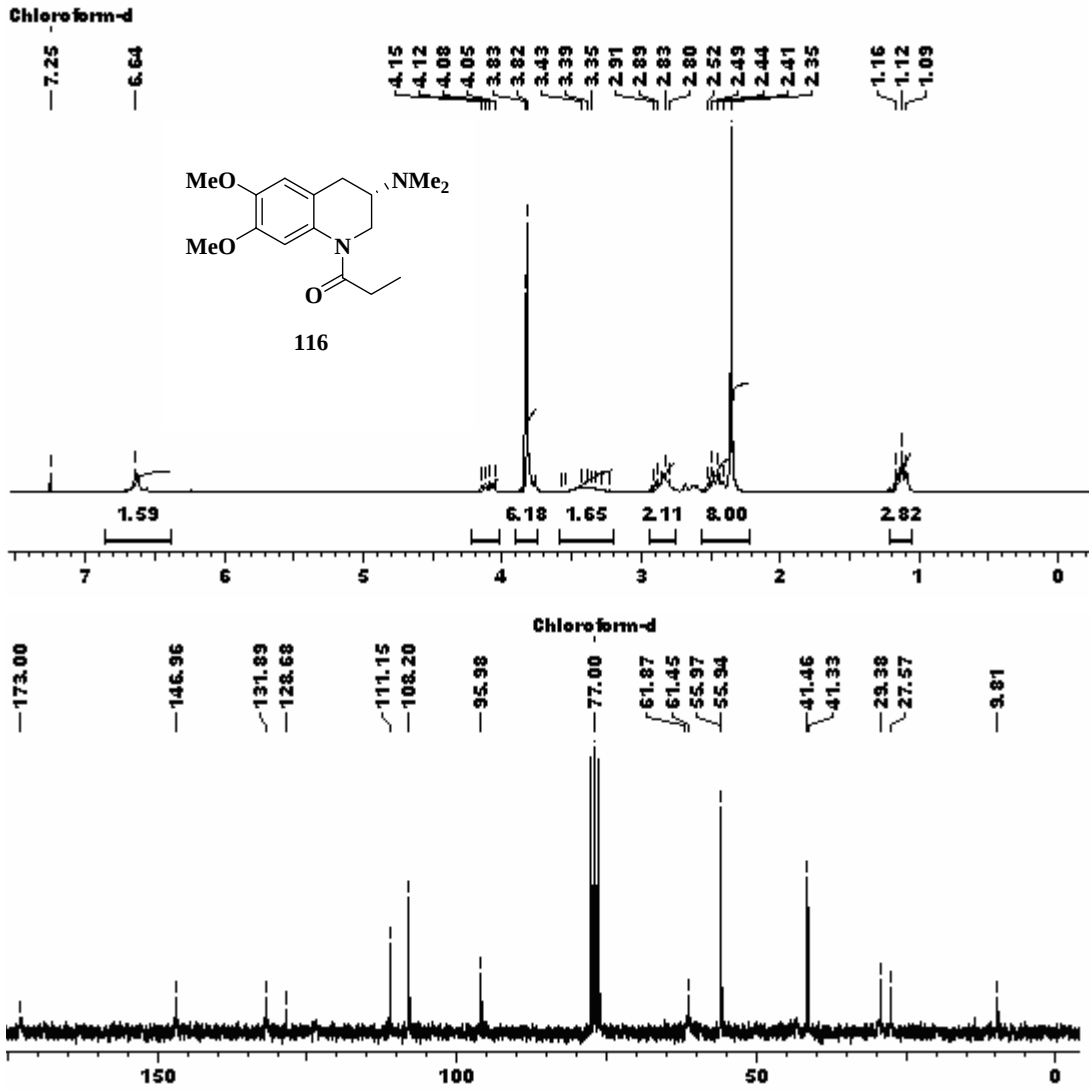


Fig. 15: ^{1}H and ^{13}C-NMR spectra of 116a

1.3.4 Conclusion

In conclusion, synthesis of 1-[(*S*)-3-(Dimethylamino)-6,7-dimethoxytetrahydroquinoline alkanones (**116-117)** have been achieved in 9 steps with 94% ee. We have utilized Asymmetric Dihydroxylation and Co-catalyzed multifunctional reduction as the key steps in the asymmetric synthesis of (*S*)-903.

1.3.5 Experimental Section

A general experimental procedure for the preparation of amide (131-132)

To the stirred solution of tetrahydroquinolin-3-ol **83a** (0.83 g, 4 mmol) and triethylamine (1.4 mL, 10 mmol) in of CH_2Cl_2 (20 mL), was added anhydride or acid chloride (5 mmol) at 25 ºC. Reaction mixture was stirred for 3 h. Progress of the reaction was monitored by TLC. After the reaction was complete, a saturated solution of $NaHCO_3$ (30 mL) was added. The organic layer was separated; the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with brine (2 x 25 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give a crude mass. Chromatographic purification of the crude product [silica gel (230-400 mesh) and petroleum ether: ethyl acetate: (60: 40) as eluent] gave amide **131-132** in pure form.

1-[(*S*)-3,4-Dihydro-3-hydroxy-6,7-dimethoxyquinolin-1(2H)-yl]propan-1-one (131):

Yield: 82%; Gum; $[\alpha]^{D}_{25}$ +8.69 (*c* 1.15, $CHCl_3$); **IR** ($CHCl_3$): 846, 1047, 1240, 1392, 1514, 1747, 2983, 3514 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.18 (t, *J* = 7.3 Hz, 3H), 2.56 (q, *J* = 7.3 Hz, 2H), 2.67-2.78 (dd, *J* = 4.6, 16.5 Hz, 1H), 2.98-3.09 (dd, *J* = 5.4, 16.5 Hz, 1H), 3.86 (s, 6H), 3.74-3.95 (m, 2H), 4.32 (m, 1H), 6.63 (bs, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 8.6, 27.4, 35.0, 49.7, 55.6, 65.0, 108.0, 111.1, 122.4, 130.7, 146.3, 174.3; **Analysis** for $C_{14}H_{19}NO_4$ requires C, 63.38; H, 7.22; N, 5.28; found C, 63.53; H, 7.19; N, 5.22%.

1-[(*S*)-3,4-Dihydro-3-hydroxy-6,7-dimethoxyquinolin-1(2H)-yl]-2-methylpropan-1-one (132):

Yield: 91%; Gum; $[\alpha]^{D}_{25}$ +9.5 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$): 846, 1049, 1238, 1514, 1660, 1737, 2979, 3463 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.10-1.15 (dd, *J* = 2.8, 7.1 Hz, 6H), 2.41-2.63 (m, *J* = 7.0 Hz, 1H), 2.71-2.82 (dd, *J* = 4.8, 16.5 Hz, 1H), 3.01-3.12 (dd, *J* = 5.3, 16.5 Hz, 1H), 3.12 (bs, 1H), 3.74-3.83 (dd, *J* = 5.0, 14.0 Hz, 1H), 3.96-4.12 (m, 1H), 3.87 (s, 6H), 5.22-5.32 (m, *J* = 5.4 Hz, 1H), 6.64 (bs, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 19.7, 19.9, 30.8, 35.3, 49.9, 55.9, 66.1, 108.0, 111.5, 131.2, 146.7, 146.9, 178.0; **Analysis** for $C_{15}H_{21}NO_4$ requires C, 64.50; H, 7.58; N, 5.01; found C, 64.37; H, 7.41; N, 5.08%**.**

A general procedure for the preparation of 1-[(*S*)-3-azido-3,4-dihydro-6,7-dimethoxyquinolin-1(2H)-yl]alkanone (133-134):

To the stirred solution of amide **133-134** (4 mmol) and triethyl amine (1.4 mL, 10 mmol) in 20 mL of CH_2Cl_2, mesyl chloride (5 mmol, 0.5 mL) was added at 0 ºC. It was then stirred for 15 min. After completion of the reaction (monitored by TLC), a saturated solution of $NaHCO_3$ (30 mL) was added, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with brine (2 x 25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude mesylate product. An attempt to purify mesylates was unsuccessful as they undergo elimination readily. Since the mesylates were difficult to purify, it was converted to the respective azides without purification. Formation of mesylate was confirmed by 1H NMR analysis of crude mesylate **133-134.**

(*R*)-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-propionylquinolin-3-yl methanesulfonate (133):

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.18 (t, *J* = 7.3 Hz, 3H), 2.52 (q, *J* = 7.3 Hz, 2H), 3.04 (s, 3H), 2.95-3.22 (m, 2H), 3.72-3.82 (m, 1H) 3.86 (s, 6H), 3.81-3.92 (m, 1H), 4.06-4.33 (m, 1H), 5.22 (m, 1H), 6.63 (bs, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 9.6, 27.4, 33.0, 38.3, 46.4, 55.8, 74.3, 108.2, 11.0, 128.5, 130.9, 147.1, 173.6.

(*R*)-1,2,3,4-Tetrahydro-1-(isobutyryl)-6,7-dimethoxyquinolin-3-yl methanesulfonate (134):

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.16 (d, *J* = 6.6 Hz, 3H), 2.97-3.23 (m, 3H), 3.06 (s, 3H), 3.72-3.82 (m, 1H) 3.87 (s, 6H), 4.07-4.31 (m, 2H), 5.25 (m, 1H), 6.67 (bs, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 19.5, 20.0, 30.8, 33.2, 38.5, 46.8, 75.9, 108.1, 11.3, 120.17, 131.3, 147.4, 177.5.

To the stirred solution of mesylate **133-134** in dry DMF (10 mL), was added NaN_3 (1.30 g, 20 mmol). It was then stirred for 16 h at 80 ºC. After completion of the reaction (monitored by TLC), it was poured into 50 mL of ice cold water and extracted with ethyl acetate (3 x 50mL). The combined organic layers were washed with brine (2 x 25 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude product. Chromatographic purification of crude product [silica gel (230-400 mesh) and petroleum ether: ethyl acetate: (70: 30:)] gave azide **135-136** in pure form.

1-[(*R*)-3-Azido-3,4-dihydro-6,7-dimethoxyquinolin-1(2*H*)-yl]propan-1-one (135):

Yield: 91%; Gum; $[\alpha]^{D}_{25}$ +38.2 (*c* 2, $CHCl_3$); **IR** ($CHCl_3$): 757, 1043, 1217, 1514, 1650, 1735, 2110, 3018 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.22 (t, *J* = 7.3 Hz, 3H), 2.57 (q, *J* = 7.3 Hz, 2H), 2.78-2.88 (dd, *J* = 5.5, 16.0 Hz, 1H), 3.04-3.15 (dd, *J* = 5.4, 16.6 Hz,

1H), 3.72-3.82 (m, 1H) 3.89 (s, 3H), 3.90 (s, 3H), 3.99-4.13 (m, 2H), 6.68 (bs, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 9.5, 27.4, 31.7, 46.5, 55.7, 55.7, 56.1, 108.1, 110.9, 119.8, 130.8, 146.8,146.9, 173.3; **Analysis** for $C_{14}H_{18}N_4O_3$ requires C, 57.92; H, 6.25; N, 19.30; found C, 57.88; H, 6.20; N, 19.33%.

1-[(*R*)-3-azido-3,4-dihydro-6,7-dimethoxyquinolin-1(2H)-yl]-2-methylpropan-1-one (136):

Yield: 91%; Gum; $[\alpha]^D_{25}$ +39.4 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$): 759, 1047, 1218, 1510, 1647, 1745, 2106, 3018 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.17 (t, *J* = 6.8 Hz, 6H), 2.73-2.84 (dd, *J* = 4.9, 15.7 Hz, 1H), 2.99-3.09 (dd, *J* = 4.9, 15.9Hz, 1H), 3.10-3.20 (q, *J* = 6.8 Hz, 1H), 3.69-3.80 (m, *J* = 7.2 Hz, 1H), 3.86 (s, 3H), 3.88 (s, 3H), 4.00-4.09 (m, 2H), 6.67 (bs, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 19.6, 19.8, 30.9, 32.0, 46.7, 55.9, 56.7, 108.1, 111.1, 131.2, 147.0, 147.3, 177.3; **Analysis** for $C_{15}H_{20}N_4O_3$ requires C, 59.20; H, 6.62; N, 18.41; found C, 59.14; H, 6.69; N, 18.44.

A general procedure for the synthesis of 1-[(*S*)-3-(Dimethylamino)-6,7-dimethoxytetrahydroquinoline alkanones (116-117):

To the solution of azide (2 mmol) in methanol (10 mL), was added 10% Pd/C (40 mg). It was stirred under H_2 atmosphere (balloon pressure) for 12 h. After the completion of reaction (monitored by TLC), it was passed through the celite and concentrated under reduced pressure afforded crude amine. To the crude amine 40% aq. solution HCHO (1 mL) and HCO_2H (2 mL) was added, resulting reaction mixture was refluxed for 3 h. After completion of reaction saturated $NaHCO_3$ solution (10 mL) was added and extracted with ethyl acetate (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 petroleum ether: ethyl acetate: triethyl amine (60:38:2) as eluent] gave pure **116** and **117**.

1-[(*R*)-3-(Dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1(2H)-yl]propan-1-one (116a):

Yield: 91%; **mp** 136 °C[lit.135-137 °C]; $[\alpha]^{D}_{25}$ –3.2 (*c* 1, EtOH) {lit. $[\alpha]^{D}_{25}$ –3.3 (*c* 1, EtOH)}[46]; **IR** ($CHCl_3$): 760, 1049, 1211, 1511, 1647, 1743, 3018, 3450 cm^{-1}; **^{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%.

1-[(*R*)-3-(Dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1(2H)-yl]-2-methylpropan-1-one (116b):

Yield: 91%; **mp** 119 °C [**lit.** 120-122 °C]; $[\alpha]^{D}_{25}$ –2.2 (*c* 1, EtOH); **IR** ($CHCl_3$): 759, 1047, 1215, 1510, 1640, 1747, 3010, 3459 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.12 (d, *J* = 6.7 Hz, 6H), 2.76 (s, 6H), 2.90-3.12 (m, *J* = 6.7 Hz, 1H) 3.10-3.18 (m, 2H), 3.38 (m, 1H), 3.75-3.83 (m, 2H), 3.75 (s, 3H), 3.78 (s, 3H), 3.75-3.83 (m, 2H), 6.90 (s,1H), 6.98 (s, lH); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 19.9, 26.5, 32.5, 41.9, 42.1, 56.1, 56.9, 61.1, 107.2, 111.1, 126.6, 131.4, 146.0, 175.1; **Analysis** for $C_{17}H_{26}N_2O_3$ requires C, 66.64; H, 8.55; N, 9.14; Found C, 66.61; H, 8.40; N, 9.02%.

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Chapter II

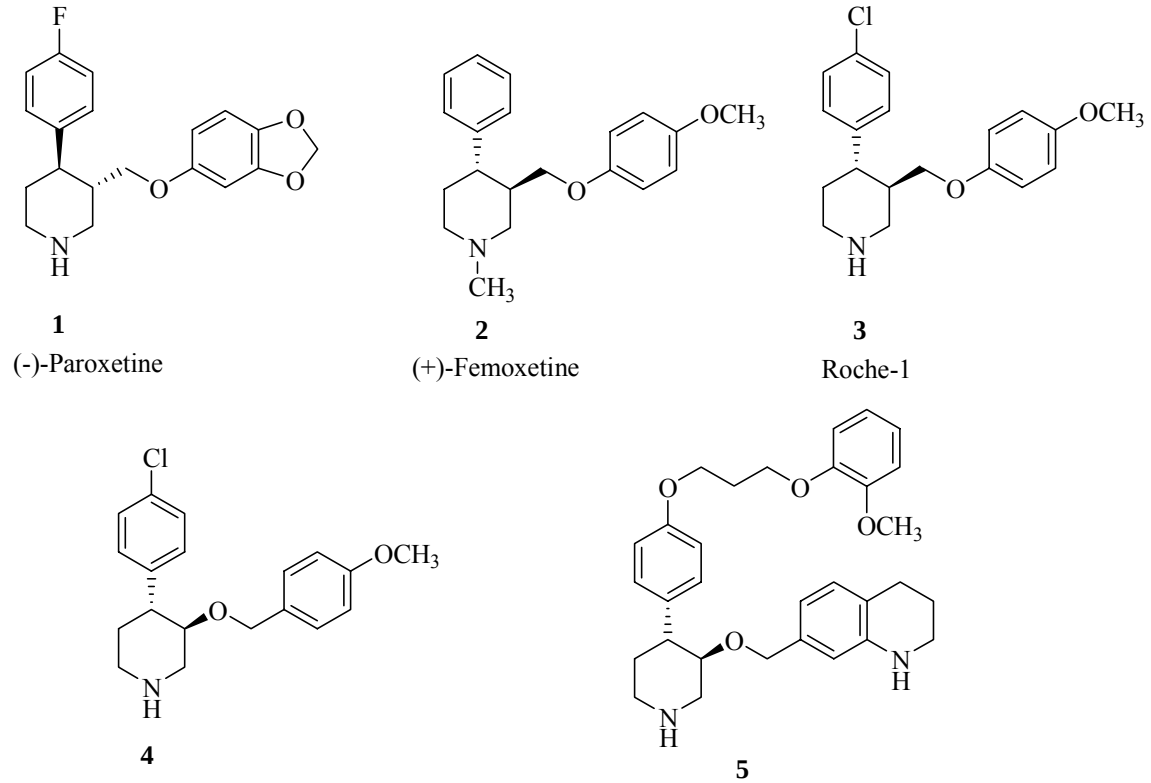
Pd-catalyzed Suzuki coupling of enol tosylate with boronic acids: A short synthesis of (±)-paroxetine and (±)-femoxetine, potent antidepressant drugs

Section I:

Pd-catalyzed Suzuki-Miyaura coupling of enol tosylate with boronic acids

2.1.1 Introduction:

Six-membered nitrogen containing heterocycles are abundant in nature and exhibit diverse and important biological properties.[1] Synthesis of piperidine ring-based alkaloids has been the subject of interest in recent years due to their biological activities.[2] Especially, substitutions at C-3 and C-4 positions in piperidine ring with an *anti* stereoselectivity is the most common and important feature of these compounds. The chiral piperidines e.g. (-)-paroxetine hydrochloride **1** and (+)-femoxetine **2** have emerged as the excellent selective serotonin reuptake inhibitors and are used in the treatment of depression and obsessive-compulsive disorders[2]



1 (-)-Paroxetine

2 (+)-Femoxetine

3 Roche-1

4

5

Fig 1: Structures of antidepressants drugs

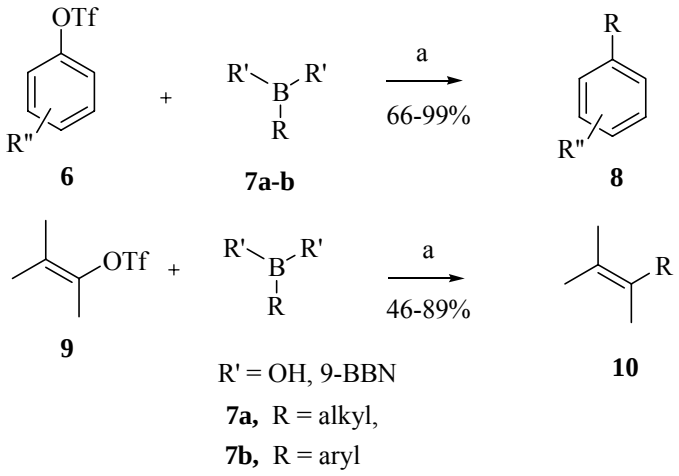
Other analogs such as roche-1 **3, 4** and **5** were also found to be non-peptide peptidomimetic type III inhibitors of rennin.[3] All these compounds consist of common piperidine ring at the center and aryl substitution at C-4 position, while C-3 position possesses hydroxylmethylene or methyleneoxy groups in an *anti* fashion (**Fig. 1**). Several attempts have been made in recent years for the synthesis of piperidine nucleus in view of their structural and biological importance.[4]

2.1.2 Review of literature

Several recent reviews are available in the literature for the Suzuki-type coupling reactions.[5] Some of the recently reported modifications of Suzuki-Miyaura coupling are listed below.

Suzuki's approach (1993)[6]

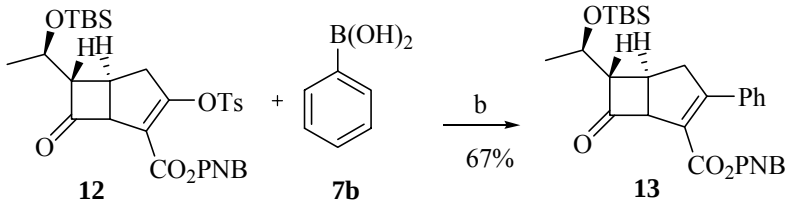
Suzuki *et al.* have reported $Pd(PPh_3)_4$-catalyzed reaction of enol triflates **6** and **9** with aryl and alkyl boronic acids **7a-b** to give the cross-coupled products **8** and **10** in high yields (**Scheme 1**).



Scheme 1: (a) $Pd(PPh_3)_4$ (2.5 mol%), aq. K_2CO_3, K_3PO_4 (1.5 equiv.), dioxane, 85 °C, 2 - 12 h.

Huffman's approach (1999) [7]

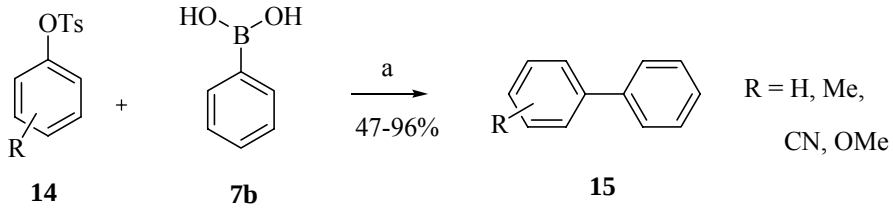
Huffman *et al.* have used $NiCl_2(dppf)_2$ or $PdCl_2(dppf)_2$ as catalysts for Suzuki-Miyaura cross-coupling of enol tosylate **12** with phenyl boronic acid **7b** to give the corresponding unsaturated ester **13** in 67% yield (**Scheme 2**).



Scheme 2: (a) $PhB(OH)_2$ (1.3 equiv.), $Pd(dppf)_2$ (10 mol %), aq. K_2CO_3, $Bu_4N^+Cl^-$, THF, 30 °C.

Monteiro's approach (2001) [8]

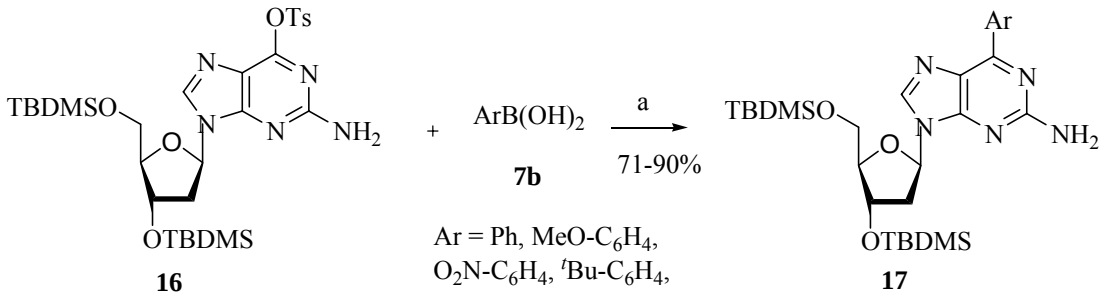
Monteiro *et al.* have reported $NiCl_2(PCy_3)_2$-catalyzed cross-coupling of aryltosylates **14** with arylboronic acids **7b** to give biphenyls **15**, promoted by large excess of PCy_3 as powerful ligand under milder reaction conditions (**Scheme 3**).



Scheme 3: (a) $NiCl_2(PCy_3)_2$ (1 - 5 mol %), K_3PO_4 (2 equiv.), dioxane, 130 °C, 14 - 60 h.

Lakshman's approach (2002) [9]

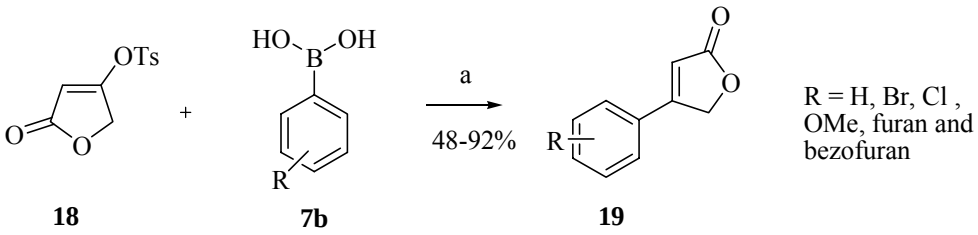
Lakshman *et al.* have used Suzuki-Miyaura coupling of *O*-arylsulfonate derivatives of 2'-deoxyguanosine **16** with aryl boronic acids **7b** to provide *O*-aryl derivatives of 2'-deoxyguanosine **17**. The Suzuki cross-coupling of tosylates were found to be faster as compared to the corresponding halides (**Scheme 4**).



Scheme 4: (a) $Pd(OAc)_2$ (7.1 µmmol), 2-(dicyclohexylphosphino)biphenyl (14.8 µmmol), K_3PO_4 (0.15 mmol), nucleoside sulfonate **16** (73.7 µmmol), boronic acid (1.5 molar equiv.), 1,4-dioxane (0.87 mL), 80 - 82 °C, 30 min, 71-90 %.

Wu's approach (2003) [10]

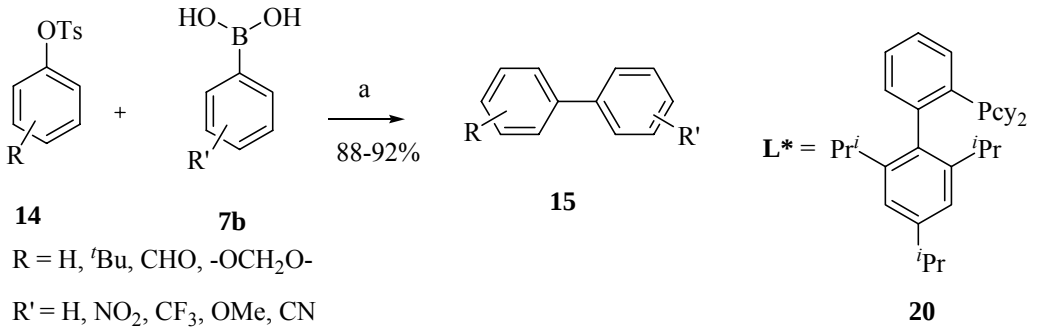
Wu *et al.* have described the synthesis of 4-substituted-2-(*5H*)-furanones (**19)** using palladium catalyzed cross-coupling of 4-tosyl-2(*5H*)-furanone **(18)** with boronic acids (**7b)** (**Scheme 5**)**.**



Scheme 5: (a) $PdCl_2(PPh_3)_2$ (5 mol %), aq. KF (2 M), THF, 60 °C, 2 -12 h.

Buchwald's approach (2003)[11]

Buchwald *et al.* have used $Pd(OAc)_2$ in catalytic amount in combination with a special type of phosphine ligand **20,** for Suzuki-Miyaura coupling of various enol tosylates **14** with aryl boronic acids **7b** to give the corresponding biphenyls **15** in good yields (**Scheme 6**)**.**



14 **7b** **15** **20**

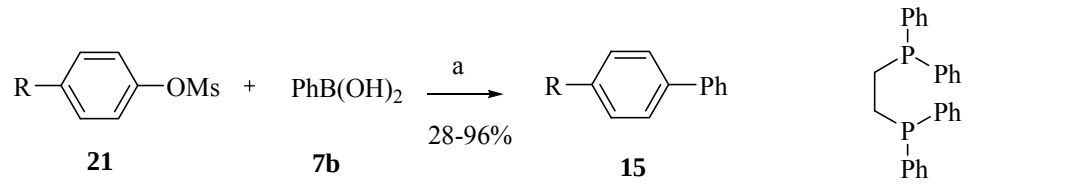
R = H, ^{t}Bu, CHO, -OCH_2O-

R' = H, NO_2, CF_3, OMe, CN

Scheme 6: ArOTs or vinylOTs (1 equiv), $ArB(OH)_2$ (2 equiv), $K_3PO_4 \cdot H_2O$ (3 equiv.), 2 mol % $Pd(OAc)_2$, 5 mol % L* **20**, THF, 80 °C.

Percec's approach (2004) [12]

Percec's *et al.* have used $NiCl_2$(dppe)-catalyzed cross-coupling of aryl mesylates **21**, arenesulfonates and aryl halides with arylboronic acids **7b**. $NiCl_2$(dppe) was found to be more efficient catalyst when excess of dppe **22** was used (**Scheme 7**)**.**



21 **7b** **15** **22**

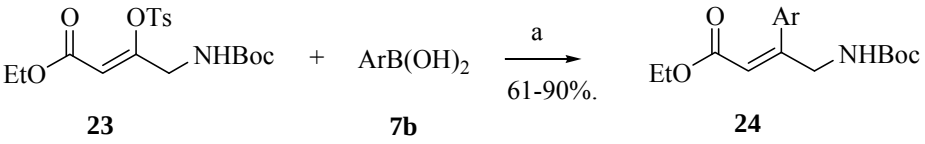
R = CH_3CO, CN, NHAc, OMe, OBn,

1,2–bis(diphenylphosphino) ethane (dppe)

Scheme 7: $NiCl_2(dppe)_2$ (5 mol %), K_3PO_4 (1.5 equiv.), toluene, 80 °C, 2 -12 h.

Baxter's approach (2005) [11]

Baxter's approach involves Suzuki-Miyaura coupling of enol tosylates **23** with aryl boronic acids **7b** to provide (*E*)-*γ*-amino-*α,β*-unsaturated esters **24** in high yields (**Scheme 8**)**.**



23 **7b** **24**

Scheme 8: (a) $PdCl_2(PPh_3)_2$ (5 mol%), enol tosylate (1.15 mmol), aryl boronic acid (1.73 mmol, 1.5 equiv.), THF (8 mL), 2 M Na_2CO_3 (3.68 mmol), 40 °C 12 h, 61-90%.

2.1.3 Present work

2.1.3.1 Objective

Review of literature reveals that several modifications in terms of catalysts, substrates and reaction conditions for Suzuki reactions have been reported. However, these metal-catalyzed coupling methods are mainly targeted for the preparation of simple biaryl compounds. Hence, better methods are needed for the synthesis of functionalized heterocyclic compounds, mainly dihydropyridines **29a-g,** which are potential intermediates for several drug molecules. Since this chapter deals with a key reaction namely Suzuki-Miyaura coupling of enol tosylates with aryl boronic acids, a brief account of Suzuki-Miyaura coupling is described as under.

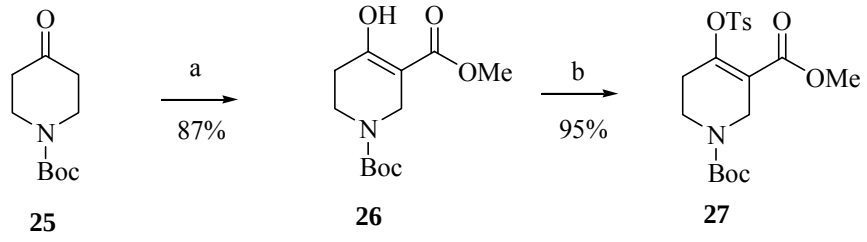
Suzuki-Miyaura coupling

Palladium-catalyzed cross-coupling between organoboronic acids and halides or triflates is typically known as Suzuki coupling reaction. Recent developments in catalysts have broadened the possible applications enormously, so that the scope of the reaction partners is not restricted to aryls, but includes alkyls, alkenyls and alkynyls. Potassium trifluoroborates and organoboranes or boronate esters are used in place of boronic acids. Some pseudohalides (e.g. triflates, tosylates) can also be used as coupling partners. Organoboron compounds are highly electrophilic, but the organic groups on boron are

weakly nucleophilic, thus limiting the use of organoboron reagents for the ionic reactions. The coordination of a negatively charged base to the boron atom has been recognized to be an efficient method of increasing its nucleophilicity to transfer the organic group on boron to the adjacent positive center (1,2-migration reaction). However, intermolecular transfer reaction such as the Grignard-like reaction is relatively rare. Fortunately, organoboron compounds, even organoboronic acids and esters, have sufficiently enough reactivity for the transmetalation to other metals. The palladium catalyzed cross-coupling reaction of organoboron compounds with organic halides, triflates and tosylates provides the broad scope in C-C bond formation reactions.

2.1.3.2 Results and Discussion

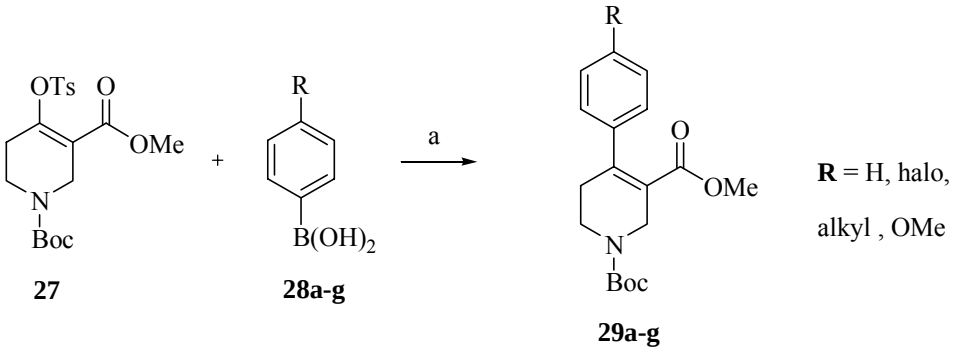
Synthetic route for the preparation of enol tosylates **27,** key coupling partners for the Suzuki-Miyaura coupling is shown in **Scheme 9**. The commercially available *N*-boc-4-piperidinone **25** was carbomethoxylated [$(MeO)_2CO$, NaH and DMF)] to give enol ester **26** in 87% yield. Enol ester **26** was then smoothly transformed into the corresponding precursor *viz* tosyl enol ester **27** (TsCl, Et_3N and CH_2Cl_2) in 95 % yield.



Scheme 9: (a) NaH, $(MeO)_2CO$, DMF, 25 °C, 12 h, 87 %; (b) TsCl, Et_3N, CH_2Cl_2, 25 °C, 12 h, 95% .

We, then, subjected enol tosylate **27** to Pd-catalyzed Suzuki-Miyaura coupling with 4-fluorophenylboronic acid. This Pd-catalyzed Suzuki-Miyaura cross-coupling proceeded smoothly to afford the corresponding conjugated ester **29a** in 78 % yield. We observed

that under the reaction conditions *N*-Boc functionality was unaffected, thus providing high yields of the protected coupled product **29a** only.



Scheme 10: (a) $PdCl_2(PPh_3)_2$ (5 mole %), $ArB(OH)_2$ (1.5 equiv.), aq. Na_2CO_3 (1.8 mL), THF (8 mL), 65 ^oC, 8 h, 77-89 %.

In order to generalize the scope of the reaction, we subjected various aryl boronic acids **28a-g** having Cl, F, CH_3, *tert*-butyl, OCH_3 groups as substituents in the aryl nucleus for coupling with enol tosylate **27** in the presence of Pd catalyst [catalyst $PdCl_2(PPh_3)_2$, aq. Na_2CO_3 (2 M), THF].

Table 1: Pd-catalyzed Suzuki-Miyaura coupling of aryl boronic acids **28a-g** with enol tosylate **27**: preparation of **29a-g** [a]

Entry	R **28a-g**	Yield of **29a-g** (%)[b]
a	4-F	78
b	H	87
c	4-Cl	82
d	2, 4-F	89
e	4-CH_3	83
f	4-MeO	85
g	4-*tert*-Butyl	77

[a]Reaction conditions**:** $PdCl_2(PPh_3)_2$ (5 mole %), $ArB(OH)_2$ (1.73 mmol), Enol tosylate (1.15 mmol), aq. 2 M Na_2CO_3 (1.8 mL), THF (8 mL), 50 ^oC, 8 h.
[b]isolated yield after column chromatographic purification.

The cross-coupling proceeded well to give the corresponding dihydropyridine derivatives **29a-g** in good yields. Results of the study are presented in **Table 1**.

We observed that various boronic acids **28a-g** underwent Suzuki-Miyaura coupling smoothly to give the coupled products in high yields (78-89%) under milder reaction conditions. Use of catalytic amount of $PdCl_2(PPh_3)_2$ and mild base (Na_2CO_3) were only required to obtain the coupled products. For example, haloaryl boronic acids with Cl, F substituents underwent cross-coupling to provide haloaryl piperidine derivatives in 82-89 yields, which were difficult to prepare by other conventional methods.

The formation of all the intermediates (**25** to **27**) as well as the final products (**29a-g**) were characterized unambiguously from their corresponding spectral analysis. For example, ^{1}H NMR of the enol tosylate **27** showed characteristic signals at δ 2.47, 7.37 and 7.84 corresponding to the benzylic methyl (ArC**H**$_3$) and aromatic protons (Ar**H**) of tosyl group respectively. Also three methylene proton signals were shown at δ 2.47 (m), 3.53 (t) and 4.17 (s) confirming the formation of enol tosylate **27**. Its ^{13}C NMR spectrum showed typical carbon signal at δ 21.5 corresponding to the benzylic methyl (Ar**C**H$_3$) crabon (**Fig. 3**).

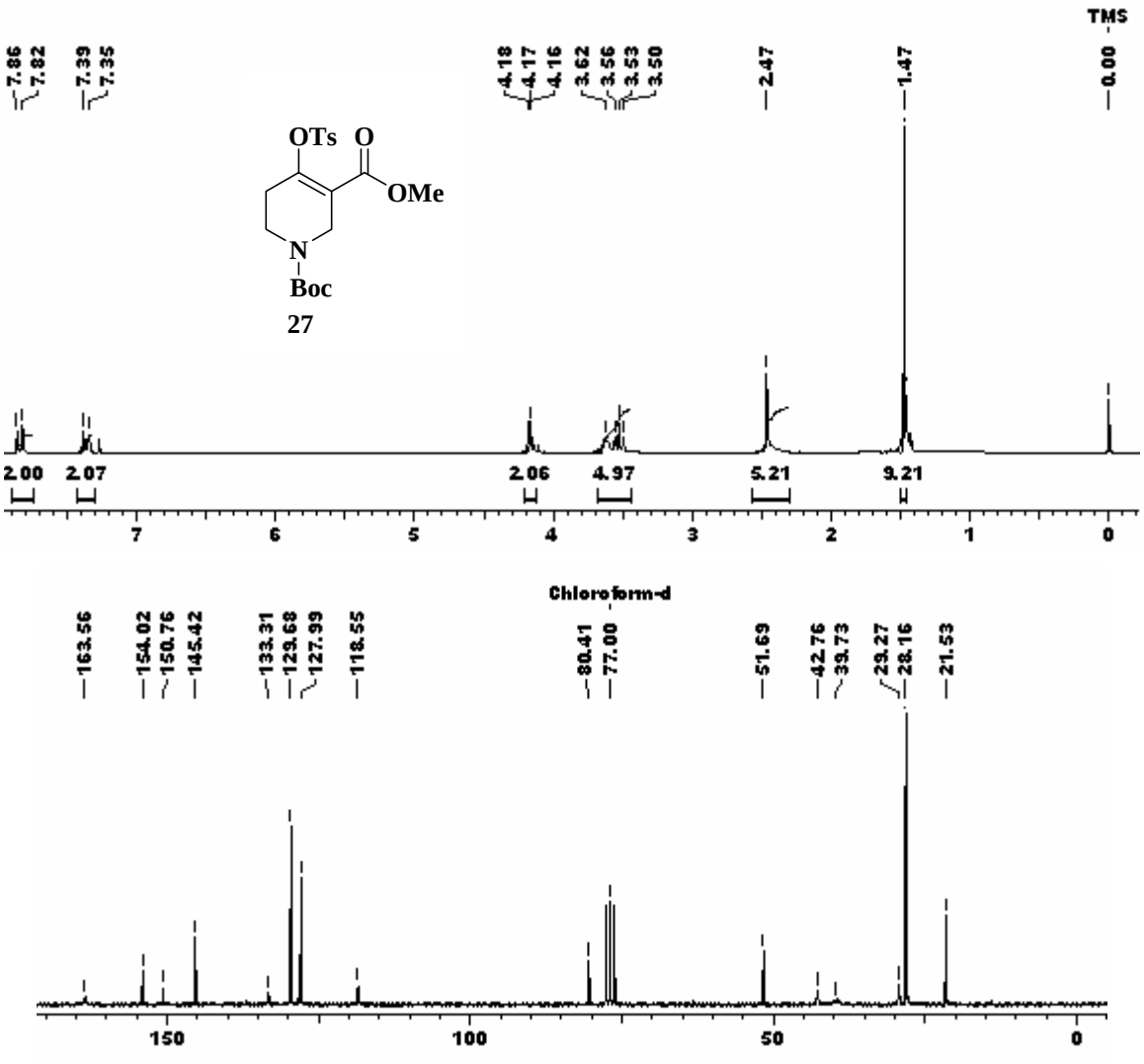


Fig. 3: ^{1}H and ^{13}C NMR spectra of enol tosylate 27

As another example, the ^{1}H NMR spectrum of **29a** showed typical signals at δ 2.47, 3.61 and 4.25 due to three methylene protons (C**H**$_2$) and signals at 6.98-7.12 (m) corresponding to the aromatic protons. Its ^{13}C NMR spectrum showed characteristic signals at δ 32.74, 39.20 and 43.63 due to methylene carbons (**C**H$_2$) and signals at 114.94 (d), 128.27 (d), 137.44 (d), 161.96 (d) for aromatic carbons respectively, thus confirming the formation of unsaturated ester **29a** (**Fig. 4**). Also, a characteristic absorption band in

its IR spectrum at 1695 cm^{-1} confirms the presence of conjugated ester carbonyl functionality.

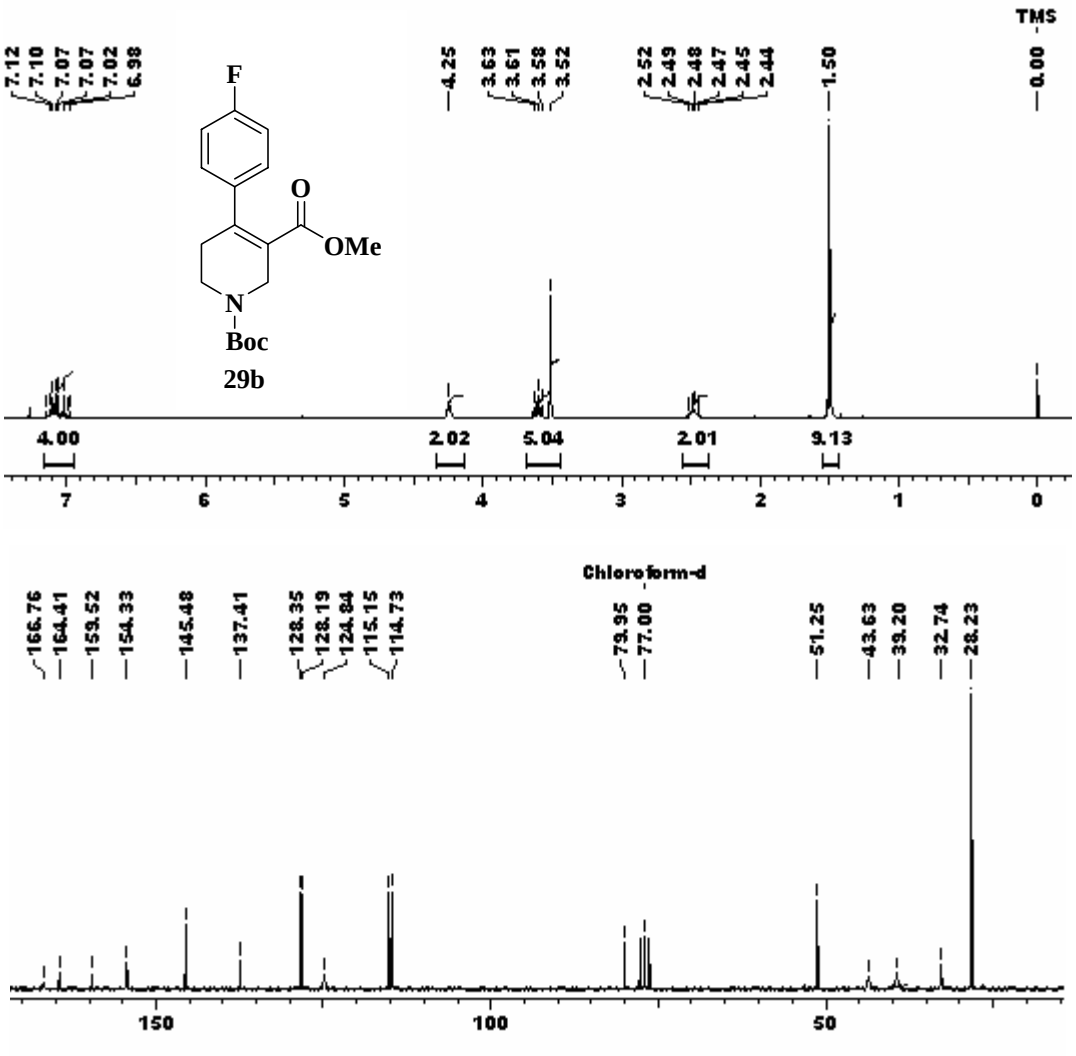


Fig. 4: ^{1}H and ^{13}C NMR spectra of piperdine derivative 29a

2.1.4Conclusion

In conclusion, we have developed a short and efficient catalytic method for the construction of tetrahydropyridine cores **29a-g** with substitutions at C-3 and C-4 position using Suzuki coupling of enol tosylate **27** with several aryl boronic acids **28a-g**. The products formed are valuable intermediates in the synthesis of various drugs such as

paroxetine **1**, femoxetine **2,** and Roche-1 **3**. The applications of this simple methodology are presented in the following section.

2.1.5 Experimental Section:

Preparation of *tert*-butyl 3-methyl 5,6-dihydro-4-hydroxypyridine-1,3(2*H*)-dicarboxylate (26):

To a stirred solution of NaH (2.0 g, 50 mmol) in dry DMF (20 mL), was added *tert*-butyl 4-oxopiperidine-1-carboxylate [3.98 g, 20 mmol in dry DMF (10 mL)] drop-wise under N_2 atmosphere at 0 °C. To the reaction mixture, dimethyl carbonate (4.5 g, 50 mmol) was added and allowed to stir for 12 h at 25 °C. After completion of reaction (monitored by TLC), a saturated solution of NH_4Cl (50 mL) and water (50 mL) was added. The aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined organic extract was washed with brine solution (2 x 50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product. Chromatographic purification of crude product [silica gel (230-400 mesh, petroleum ether: ethyl acetate (70:30) as eluent] afforded 4.53 g of enol ester **26** in pure form.

Yield: 89%; colourless liquid, **IR** ($CHCl_3$)**:** 759, 1168, 1249, 1669, 1751, 2979, 3346 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.48 (s, 9H), 2.37 (t, *J* = 6.0 Hz, 2H), 3.57 (t, *J* = 6.0 Hz, 2H), 3.78 (s, 3H), 4.06 (s, 2H), 11.98 (bs, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 28.15, 28.61, 40.04, 40.40, 51.32, 79.84, 95.28, 169.81, 170.79; **Analysis** for $C_{12}H_{19}NO_5$ requires C, 56.02; H, 7.44; N, 5.44; found 56.06; H, 7.41; N, 5.39;

Preparation of 1-(*tert*-butoxycarbonyl)-3-(methoxycarbonyl)-1,2,5,6-tetrahydropyridin-4-yl 4-methylbenzene sulfonate (27):

To a stirred mixture of enol ester **26** (3.855g, 15 mmol) and triethylamine (4.2 mL, 30 mmol) in dry dichloromethane (30 ml), was added tosyl chloride (3.03 g, 17 mmol) at 0 ºC. It was then allowed to stir for 12 h at 25 ºC. After completion of reaction mixture (monitored by TLC), water (50 mL) was added. The organic layer was separated and aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layer was washed with brine solution (2 x 50 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product. Chromatographic purification of the crude product [silica gel (230-400 mesh, petroleum ether: ethyl acetate (70:30) as eluent] afforded 5.67 g of enol tosylate **27** in pure form.

Yield: 93%; Gum, **IR** ($CHCl_3$): 756, 1053, 1166, 1242, 1423, 1703, 2979, 3016 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.47 (s, 9H), 2.47 (s, 3H), 2.24-2.58 (m, 2H), 3.53 (t, *J* = 5.8 Hz, 2H), 3.63 (s, 3H), 4.17 (t, *J* = 2.4 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.84 (d, *J* = 8.1 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 21.53, 28.16, 29.27, 39.57, 42.76, 51.69, 80.41, 118.55, 127.99, 129.68, 133.31, 145.42, 150.76, 154.02, 165.56. **Analysis** for $C_{19}H_{25}NO_7S$ requires C, 55.46; H, 6.12; N, 3.40; S, 7.79 found C, 55.32; H, 6.01; N, 3.22; S, 7.71%.

General procedure for Pd-catalyzed Suzuki coupling: preparation of 1-*tert*-butyl 3-methyl 4-(aryl)-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate (29a-f):

To a stirred solution of enol tosylate **27** (411mg, 1 mmol), $ArB(OH)_2$ **28** (1.7 mmol), $PdCl_2(PPh_3)_2$ (14 mg, 5 mol%) in THF (8 mL), was added 2 M Na_2CO_3 solution in demonized water (1.5 mL) under N_2 atmosphere. It was then refluxed for 8 h. After completion of the reaction (monitored by TLC), water (50 mL) was added. The aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic extract was

washed with brine solution (2 x 25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude products. Chromatographic purification of the crude products [silica gel (230-400 mesh, petroleum ether: ethyl acetate (70:30) as eluent] afforded **29a-e** in pure form.

1-*tert*-Butyl 3-methyl 4-(4-fluorophenyl)-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate (29a):

Yield: 260 mg, 78%; Gum, **IR** ($CHCl_3$): 763, 1159, 1238, 1417, 1510, 1693, 1783 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.50 (s, 9H), 2.48 (m, 2H), 3.52 (s, 3H), 3.61 (t, *J* = 5.7 Hz, 2H), 4.25 (t, *J* = 2.5 Hz, 2H), 6.98-7.15 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 28.23, 32.74, 39.46, 43.63, 51.25, 79.95, 114.73-115.15 (d), 124.84, 128.19-128.35 (d), 137.41-137.47 (d), 154.33, 159.52-164.41 (d), 167.32; **Analysis** for $C_{18}H_{22}FNO_4$ requires C, 64.46; H, 6.61; N, 4.18; found C, 64.48; H, 6.59; N, 4.21%.

1-*tert*-Butyl 3-methyl 5,6-dihydro-4-phenylpyridine-1,3(2*H*)-dicarboxylate (29b):

Yield: 276 mg, 87%; Gum, **IR** ($CHCl_3$): 756, 1053, 1166, 1242, 1423, 1703, 2973, 3010 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.51 (s, 9H), 2.48-2.55 (m, 2H), 3.49 (s, 3H), 3.61 (t, *J* = 5.8 Hz, 2H), 4.25 (t, *J* = 2.1 Hz, 2H), 7.11-7.15 (dd, *J* = 2.2, 7.8 Hz, 2H), 7.26-7.35(m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 27.92, 32.22, 39.15, 43.32, 50.77, 79.44, 124.13, 126.16, 127.00, 127.60, 141.24, 145.24, 153..94, 166.51; **Analysis** for $C_{18}H_{23}NO_4$ requires C, 68.12; H, 7.30; N, 4.41; found C, 68.10; H, 7.31; N, 4.43%.

1-*tert*-Butyl 3-methyl 4-(4-chlorophenyl)-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate (29c):

Yield: 291mg, 83%; Gum, **IR** ($CHCl_3$): 762, 1158, 1230, 1410, 1513, 1695, 1751 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.51 (s, 9H), 2.43-2.51 (m, 2H), 3.52 (s, 3H), 3.60 (t, *J* =

5.7, 2H), 4.24 (t, *J* = 2.6, 2H), 7.04 (d, *J* = 8.6 Hz, 2H), 7.30 (d, *J* = 8.6 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 28.38, 32.67, 39.48, 43.79, 51.55, 80.72, 124.50, 128.00, 128.35, 133.46, 139.83, 145.81, 155.12, 166.75; **Analysis** for $C_{18}H_{22}ClNO_4$ requires C, 61.45; H, 6.30; N, 3.98; found C, 61.48; H, 6.32; N, 3.94%.

1-*tert*-Butyl 3-methyl 4-(2,4-difluorophenyl)-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate (29d):

Yield: 315mg, 89%; Gum, **IR** ($CHCl_3$): 769, 1259, 1330, 1508, 1745, 2358, 3010 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.51 (s, 9H), 2.46 (m, 2H), 3.55 (s, 3H), 3.61 (t, *J* = 5.7 Hz, 2H), 4.28 (t, *J* = 2.5 Hz, 2H), 6.76-7.11 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 28.43, 32.54, 39.42, 43.65, 51.57, 80.26, 103.91 (t, *J* = 26.0 Hz), 111.15 (d, *J* = 25.9 Hz), 125.40 (dd, *J* = 4.0, 16.5 Hz),126.76, 129.40 (dd, *J* = 5.1, 9.5 Hz), 141.06, 154.06, 158.05 (dd, *J* = 11.7, 180.0 Hz), 162.98 (dd, *J* = 11.7, 180.0 Hz), 165.77; **Analysis** for $C_{18}H_{21}F_2NO4$ requires C, 61.18; H, 5.99; N, 3.96; found C, 61.13; H, 5.94; N, 3.96%.

1-*tert*-Butyl 3-methyl 5,6-dihydro-4-*p*-tolylpyridine-1,3(2*H*)-dicarboxylate (29e):

Yield: 275 mg, 83%; Gum, **IR** ($CHCl_3$): 769, 1163, 1217, 1681, 1731, 3020 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.50 (s, 9H), 2.35 (s, 3H), 2.45-2.54 (m, 2H), 3.51 (s, 3H), 3.59 (t, *J* = 5.7 Hz, 2H), 4.22 (t, *J* = 2.6 Hz, 2H), 7.02 (d, *J* = 8.1 Hz, 1H), 7.13 (d, *J* = 8.1 Hz, 1H) **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 20.77, 28.00, 32.23, 39.06, 43.44, 50.79, 79.39, 123.84, 126.20, 128.35, 136.61, 138.24, 145.73, 153.85, 166.65; **Analysis** for $C_{19}H_{25}NO_4$ requires C, 68.86; H, 7.60; N, 4.23; found C, 68.79; H, 7.62; N, 4.16%.

1-*tert*-Butyl 3-methyl 5,6-dihydro-4-(4-methoxyphenyl)pyridine-1,3(2*H*)-dicarboxylate (29f):

Yield: 295 mg, 85%; Gum, **IR** ($CHCl_3$): 767, 1037, 1176, 1242, 1514, 1681, 1731, 2931, 3018 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.50 (s, 9H), 2.49 (m, 2H), 3.52 (s, 3H), 3.59 (t, *J* = 5.7 Hz, 2H), 3.80 (s, 3H), 4.22 (t, *J* = 2.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 7.06 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 28.34, 32.48, 39.94, 43.94, 51.32, 54.89, 80.26, 114.51, 123.83, 127.92, 133.45, 145.88, 154.54, 159.00, 167.55; **Analysis** for $C_{19}H_{25}NO_5$ Requires C, 65.69; H, 7.25; N, 4.03; found C, 65.65; H, 7.21; N, 4.07%.

1-*tert*-Butyl 3-methyl 4-(4-*tert*-butylphenyl)-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate (29g)

Yield: 287mg, 77%; colorless solid; **mp:** 77-79 ºC (recrystallized in MeOH); **IR** ($CHCl_3$): 765, 1054, 1120, 1168, 1242, 1419, 1726, 2966 cm^{-1}; **^{1}H NMR** (200 MHz, CDCl3)**:** δ 1.32 (s, 9H), 1.50 (s, 9H), 2.50 (m, 2H), 3.49 (s, 3H), 3.60 (t, *J* = 5.7 Hz, 2H), 4.22 (t, *J* = 2.3 Hz, 2H), 7.04 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 28.42, 31.27, 32.57, 34.47, 39.47, 41.83, 51.20, 79.86, 124.25, 124.86, 126.37, 138.49, 146.02, 150.25, 154.32, 167.17; **Analysis** for $C_{22}H_{31}NO_4$ requires C, 70.75; H, 8.37; N, 3.75; found C, 70.71; H, 8.32; N, 3.72%.

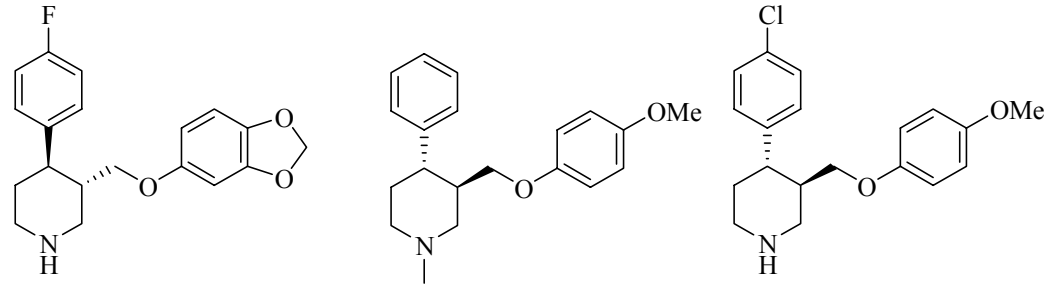
Section II

A short synthesis of (±)-paroxetine and (±)-femoxetine, anti-depressant drugs

2.2.1 Introduction:

The pharmacology of (±)-paroxetine:

(±)-Paroxetine (**1**) is a potent and selective inhibitor of the neuronal reuptake of serotonin (5-hydroxytryptamine; 5-HT), which was considered as an antidepressant drug in 1991.[2] It is also being studied in several other disorders with a presumed serotonergic component, primarily obsessive compulsive disorder (OCD) and panic disorder. In short term clinical trials in patients with depression, paroxetine produced clinical improvements that were significantly greater than those with placebo and similar to those achieved with other agents including tricyclic antidepressants (TCAs), maprotiline, nefazodone and the selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, fluvoxamine and sertraline.[14] Long term data suggest that paroxetine is effective in preventing relapse or recurrence of depression in patients treated for up to 1 year. In the elderly peoples, the overall efficacy of paroxetine was at least as good as that of comparator agents. Limited long term data show that paroxetine is effective in maintaining a therapeutic response over periods of 1 year (OCD) and up to 6 months (panic disorder). Preliminary data suggest that paroxetine has potential in the treatment of social phobia, premenstrual dysphoric disorder and chronic headache. Like the other SSRIs, paroxetine is better tolerated than the TCAs, causing few anti-cholinergic adverse effects. Serious adverse effects associated with paroxetine are very rare.



(-)-paroxetine **1** (+)-femoxetine **2** Roche-1 **3**

Fig : 6 Structures of anti-depressants drugs such as (-)-paroxetine **1**, (+)-femoxetine **2**, and peptidomimetic inhibitor Roche-1 **3**.

Social phobia, also known as social anxiety disorder, is a highly prevalent disorder with significant morbidity. Patients with social phobia frequently develop co-morbid psychiatric disorders such as depression and substance abuse, and the disorder impacts significantly on social and occupational functioning. It has been suggested that the selective serotonin reuptake inhibitors (SSRIs) are useful in the management of this disorder, but few controlled trials have been undertaken in this regard.

In conclusion, paroxetine is effective and well-tolerated drug candidate for the treatment of depression. It also appears to be a useful alternative to other available agents for the treatment of patients with OCD or panic disorder.

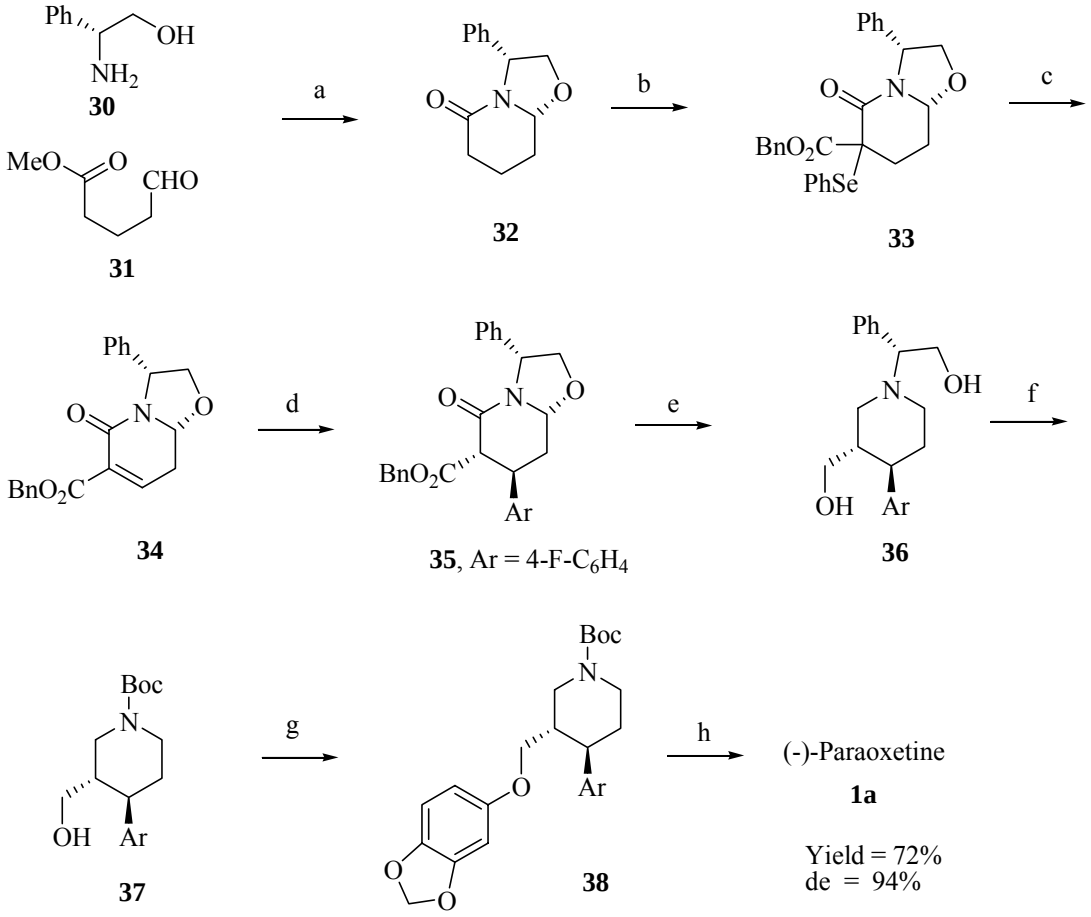
2.2.2 Review of Literature

Literature search revealed that in view of biological importance of (-)-paroxetine **132**, several synthetic approaches have been reported, [18] which are described below.

Amat's approach (2000)[19]

Amat *et al*. have reported the synthesis of (-)-paroxetine **1a** utilizing (*R*)-phenylglycinol **30** as a chiral starting material. Reaction of (*R*)-phenylglycinol **30** with methyl 5-oxopentanoate **31** gave bicyclic lactam *cis*-**32,** which was converted to **33** (LiHMDS, $ClCO_2Bn$, PhSeCl) followed by its oxidation with O_3 to provided unsaturated lactum **34**

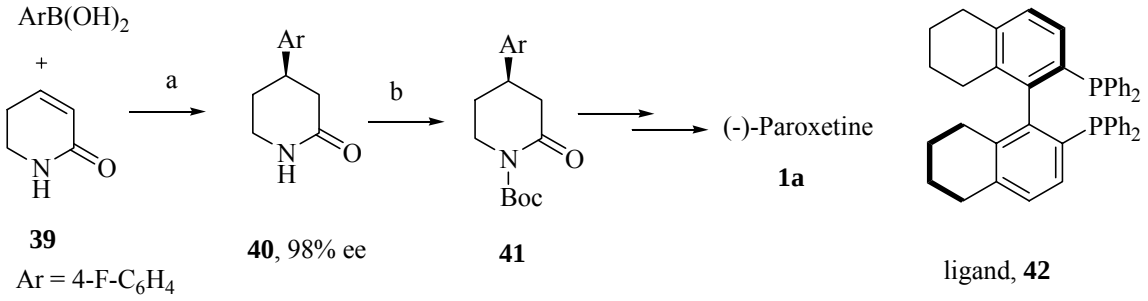
in two steps. Michael addition of lithium aryl cyanocuprate onto the unsaturated ester **34** gave enantiopure *trans*-3,4-substituted 2-piperidone derivative **35** in 64% yield. Reductive cleavage of arylated bicyclic lactam **35** produced diol **36** in 75% yield. Debenzylation of **36** [$Pd(OH)_2$] followed by protection by Boc gave **37** in 57% yield. The Boc protected piperidine **37** was mesylated and etherified with sesmol affording **38** in 66 % yield. Deprotection of *N*-Boc with TFA generated (-)-paroxetine **1a** in 72% yield (**Scheme 11**).



Scheme 11: (a) Toluene, 110 ºC, azeotropic water removal, 36 h, 86 %; (b) LiHMDS, $ClCO_2Bn$, PhSeBr, THF, -78 °C, 77%; (c) O_3, CH_2Cl_2, -78 °C; then O_2, 25 °C; (d) ArCu(CN)Li, THF, -78 °C, 64%; (e) (i) 10% Pd/C, HCO_2NH_4, MeOH, 25 °C, then toluene, reflux, 85%; (ii) $AlCl_3$, $LiAlH_4$, THF, -78 °C to 25 °C, 50%; (f) 20 % $Pd(OH)_2$/C, H_2, $(t\text{-BuOCO})_2O$, EtOAc, 25 °C, 57%; (g) MsCl, Py, 10 °C, then NaH, sesamol, THF, reflux, 66%; (h) TFA, CH_2Cl_2, 25 °C, 72%.

Hayashi's approach (2001)[20]

Hayashi *et al.* reported the formal synthesis of (-)-paroxetine **1a** *via* Rh-catalyzed Michael addition of aryl boronic acid to 5,6-dihydro-2(1*H*)-pyridinone **39** to give 4-aryl-2-piperidinone **40** using chiral bisphosphine ligand **42** in 70% yield and 98% ee. The amide moiety in 4-aryl-2-piperidinone **40** was protected to give **41,** the key intermediate for the synthesis of (-)-paroxetine **1a** (**Scheme 12**).

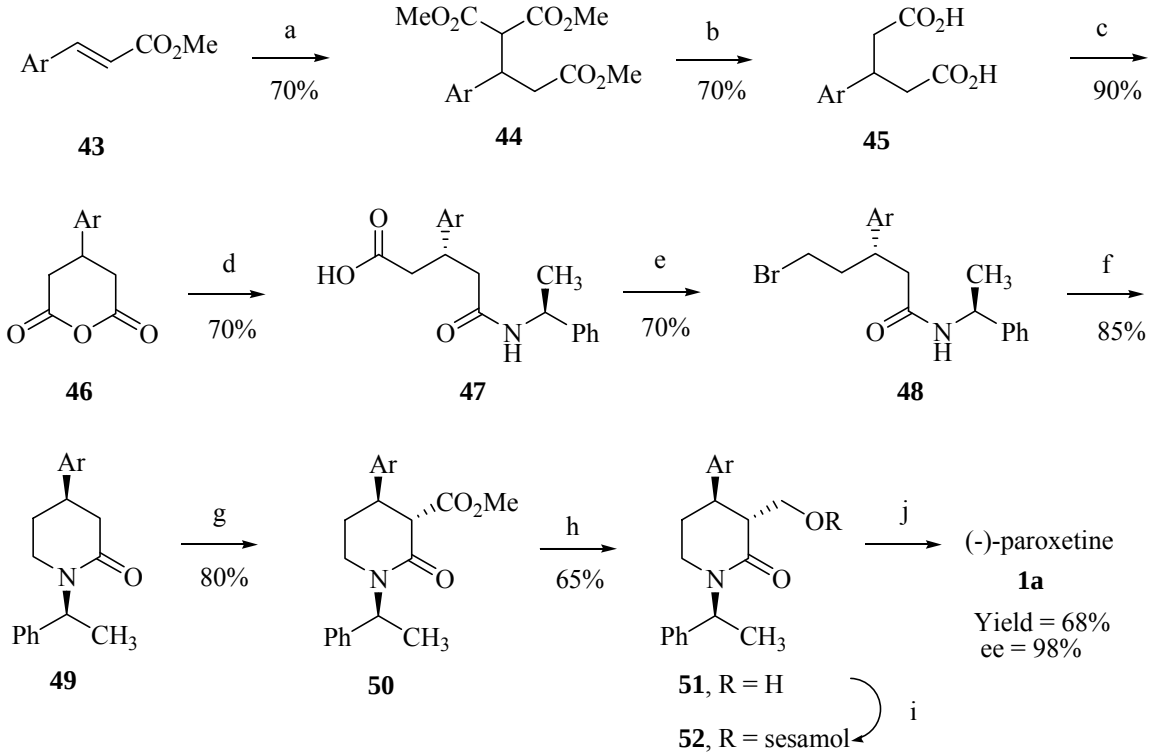


Scheme 12: (a) $Rh(acac)(C_2H_4)_2$ (3 mol %), ligand **42** (3.3 mol %), dioxane:H_2O (10:1), 40 °C, 3 h, 98 % ee, 70 %; (b) $(Boc)_2O$, DMAP, CH_3CN, reflux, 82 %.

Liu's approach (2001) [21]

Liu *et al.* have used (*S*)-methylbenzylamine for the desymmetrization of the prochiral 3-substituted glutaric anhydride **46.** Diacid **45** was prepared from 4-fluorocinnamic acid methyl ester **43** in three steps (Michael addition to ester **43**, hydrolysis of triester **44** followed by decarboxylation of acid). The prochiral 3-substituted glutaric anhydride **46** was then obtained by dehydration of **45** using acetyl chloride. Desymmetrization of *meso*-3-substituted glutaric anhydride **46** with (*S*)-methylbenzylamine was achieved in toluene at -78°C generating chiral acid **47** which was further reduced and brominated to bromo **48.** It was then cyclized (NaH in THF) leading to piperidin-2-one moiety **49**. Acylation of **49** followed by reduction of amide moiety in piperidin-2-one **50** with lithium aluminum hydride afforded 3-hydroxymethylpiperidine **51**. Finally, mesylation of

alcohol followed by its etherification with sesomol provided ether **52,** which was subjected to deprotection of benzyl amine gave (-)-paroxetine **1a (Scheme 13).**

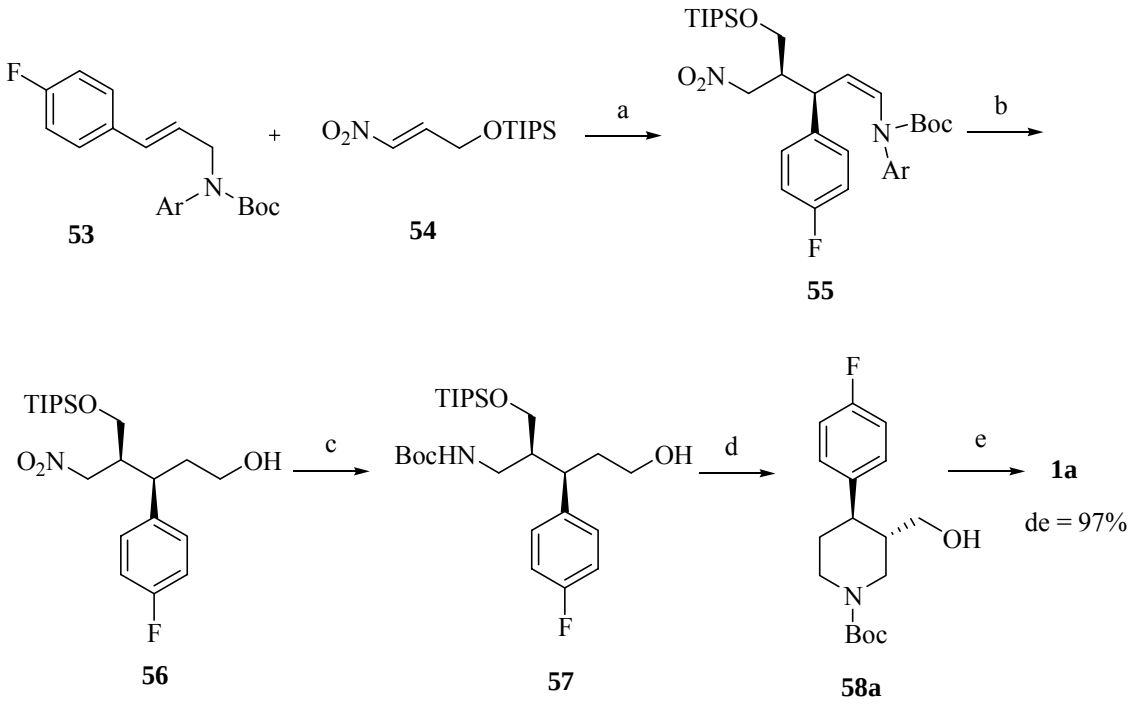


Scheme 13: (a) NaOMe, $CH_2(CO_2Me)_2$, MeOH, reflux, 20 h, 70%; (b)(i) 1N NaOH, reflux, 20 h; (ii) conc. HCl, reflux, 20 h, 70% (two steps); (c) AcCl, reflux, 20 h, 90%; (d) (*S*)-methylbenzylamine, Et_3N, toluene, -78°C, 10 h, 25 ºC, 10 h, 70%; (e) (i) Et_3N, isobutyl chloroformate, THF, -78 to 0 °C, 20 h; (ii) $NaBH_4$, H_2O, 0-25 °C, 20 h, 86%; (iii) PBr_3, conc. HBr, 0-25°C, 4 days, 70%; (f) NaH, THF, reflux, 20 h, 85%; (g) LDA, MeO_2CCN, THF, -78 ºC, 4 h, 80 %; (h) $LiAlH_4$, THF, reflux, 72 h, 65%; (i) (i) MsCl, CH_2Cl_2, 25°C, 20 h; (ii) sesamol, Na, *n*-PrOH, reflux, 36 h; (j) (i)HCl, 64%; (ii) 10% Pd/C, H_2 (1atm), MeOH, 68%.

Beak's approach (2001)[22]

Beak *et al.* have used sparteine-mediated asymmetric addition of allyl amine onto nitroalkene **54**. Conjugated addition of *N*-Boc protected allyl amine **53** [*n*-BuLi in the presence of (-)-sparteine under standard conditions] onto nitroalkene **54** provided the desired enecarbamate (*S*,*S*)-**55** in 83% yield as a single diastereomer. Hydrolysis of **55** followed by its reduction with $NaBH_4$ provided the nitro alcohol **56** in 88% yield.

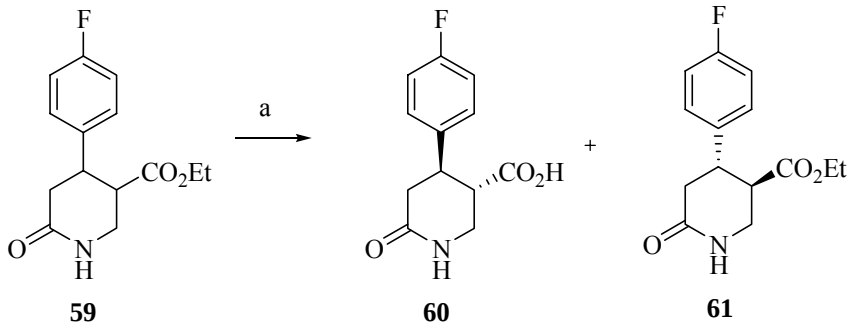
Reduction of the nitro functionality *via* transfer hydrogenation and subsequent Boc-protection afforded **57** in 95% yield. Cyclization and deprotection of **57** afforded **58a** in 83% yield. Mesylation of **58a** followed by displacement with sesamol and subsequent deprotection gave **1a** in 72% yield and 97 % de (11 steps, 41% from **53**) (**Scheme 14**).



Scheme 14: (a) *n*-BuLi (1 equiv.), (-)-sparteine (1.2 equiv.), toluene, -78 ºC, de 99 %, 83 %; (b) (i) HCl, $CHCl_3$, 25 ºC.; (ii) $NaBH_4$, MeOH, 25 ºC, 86 %; (c) (i) cat. Pd/C, HCO_2NH_4, MeOH, 25 ºC; (ii) $(Boc)_2O$, CH_2Cl_2, 25 ºC, 95 %; (d) (i) MsCl, Et_3N, CH_2Cl_2, 25 ºC; (ii) KO*t*-Bu, THF, reflux, 12 h.; (iii) TBAF, MeOH, 25 ºC, 83 %.; (e) (i) MsCl, Et_3N, CH_2Cl_2, 25 ºC; (ii) NaH, sesamol, DMF, 100 ºC, 6 h.; (iii) TFA, MeOH, 25 ºC, 3 h, 97 % de, 72 %.

Guisan's approach (2002)[23]

Guisan *et al.* have reported a formal synthesis of (-)-paroxetine *via* enantioselective hydrolysis of racemic piperidin-2-one ester **59** using a commercially available lipase from *C. antarctica A* (CAL-A) with a substrate concentration of 50 mM. The chiral acid **60** was separated from ester **61,** and could be transformed to (-)-paroxetine by known sequence of reactions (**Scheme 15**).

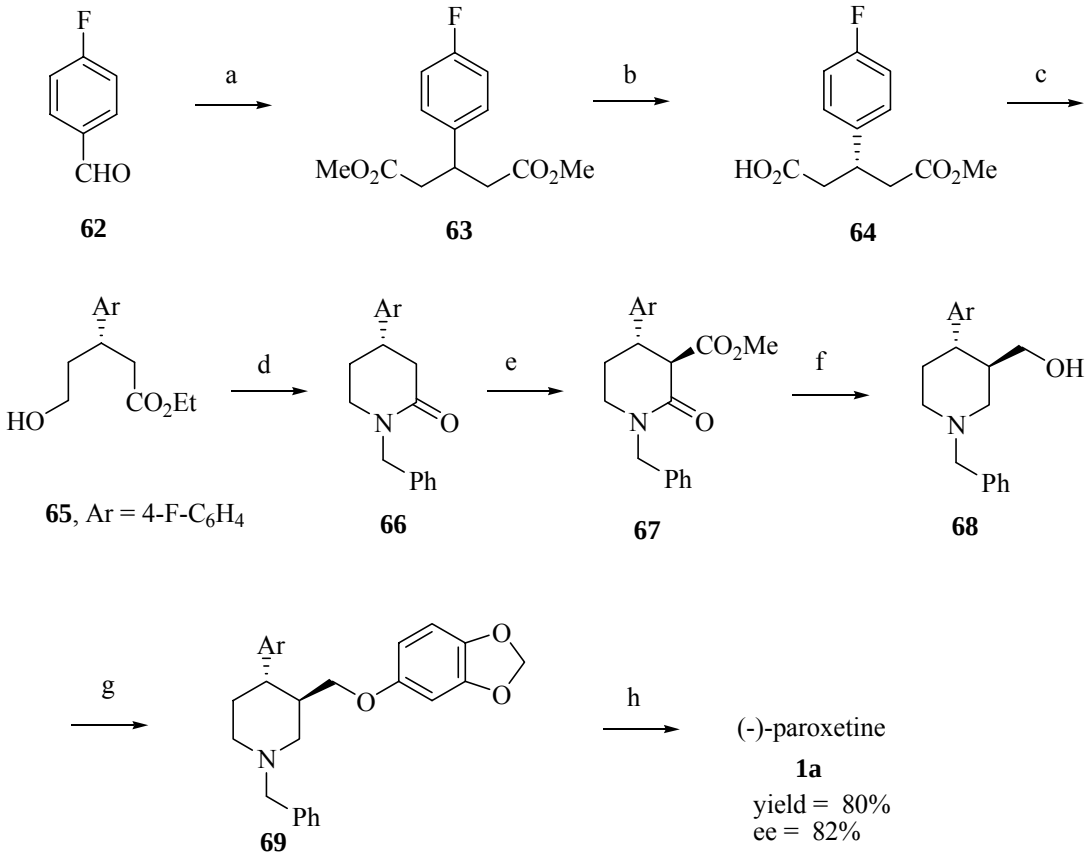


59 **60** **61**

Scheme 15: (a) CAL-A, Na_3PO_4 (5 ml, 10 mM, pH 7), 45 ºC, substrate concentration 2 mM, 50 h, 45 %.

Yu's approach (2003)[24]

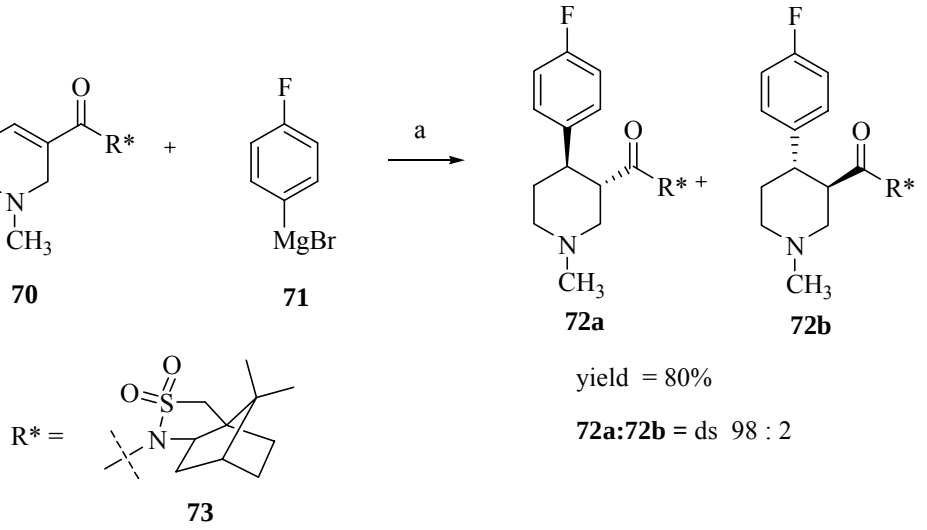
Yu *et al.* have reported the synthesis of (-)-paroxetine using dynamic kinetic resolution of prochiral diester **63**. Thus, 4-fluorobezaldehde was converted to bis-ester **63,** which was subjected to enzymatic hydrolysis with *pig liver esterase* to afford optically active acid ester **64** in 86% yield and 95% ee. Selective reduction of the acid functionality in **64** with $BH_3 \cdot SMe_2$ provided alcohol **65,** which was further mesylated and treated with benzylamine to provide the lactam **66** in 82% yield and 99% ee. Acylation of lactam **66** afforded **67** (88%). Reduction of **67** with either LAH (71%) or BH_3.THF in refluxing THF (92%) gave amino alcohol **68**. Etherification (80%) followed by hydrogenolysis of the benzyl group in **69** (93%) completed the synthesis of (-)-paroxetine **1a** (**Scheme 16**).



Scheme 16: (a) (i) diethyl malonate , NaOH, 150 ºC, 75 %; (ii) aq. 10 % HCl, MeOH, 60 ºC, 75 %; (b) PLE (*pig liver esterase*) (*p*H 7.0), 10 % aq. acetone, 95 % ee, 86 %; (c) $BH_3 \cdot SMe_2$, THF, 94 %; (d) (i) MsCl, Et_3N, toluene; (ii) $BnNH_2$, Et_3N, toluene, 99 % ee, 82 %; (e) NaH, NaOMe, $(MeO)_2CO$, toluene, 100 ºC, 88 %; (f) $BH_3 \cdot THF$, 93 %; (g) (i) MsCl, Et_3N, toluene; (ii) sesamol, NaH, DMF, 60 ºC, 80 %; (h) (i) cat. 5 % Pd/C, H_2 (70 psi), ^{i}PrOH, AcOH; (ii) HCl gas.

Murthy's approach (2003)[25]

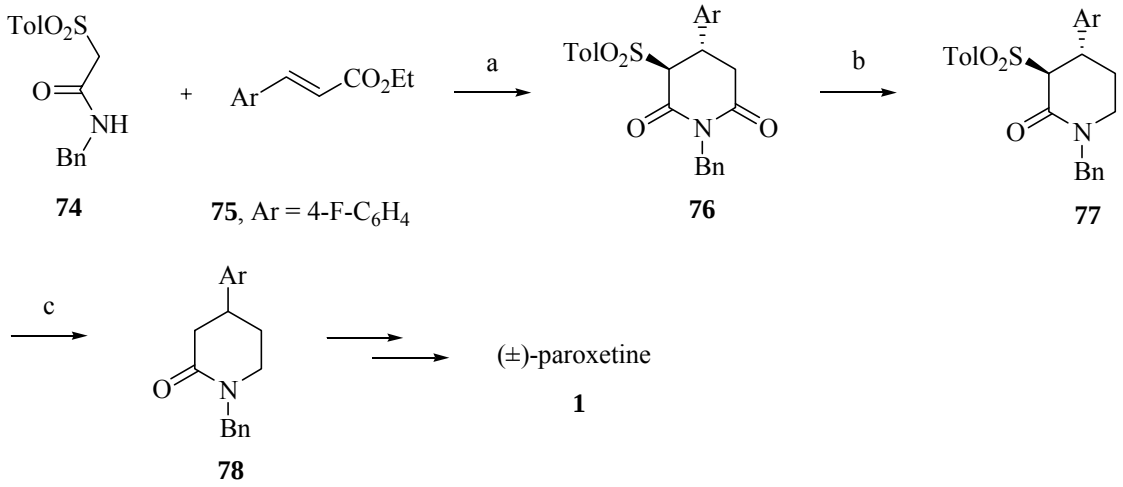
Murthy *et al.* have used the asymmetric conjugate addition of 4-fluorophenylmagnesium bromide **71** onto chiral α, β-unsaturated ester **70** to produce chiral adduct **72** in 80 % yield (98:2 de), for the formal synthesis of 3,4-disubstituted piperidine, a key intermediate in the synthesis of (-)-paroxetine (**1a**). The most selective auxiliary was found to be Oppolzer's (1*S*)-(-)-camphorsultam **73** (**Scheme 17**).



Scheme 17: (a) **70** (1 equiv.), **71** (1.3 equiv.), Et_2O:toluene (1:1), -10 ºC, 4 h, 80 %.

Chang's approach (2003)[26]

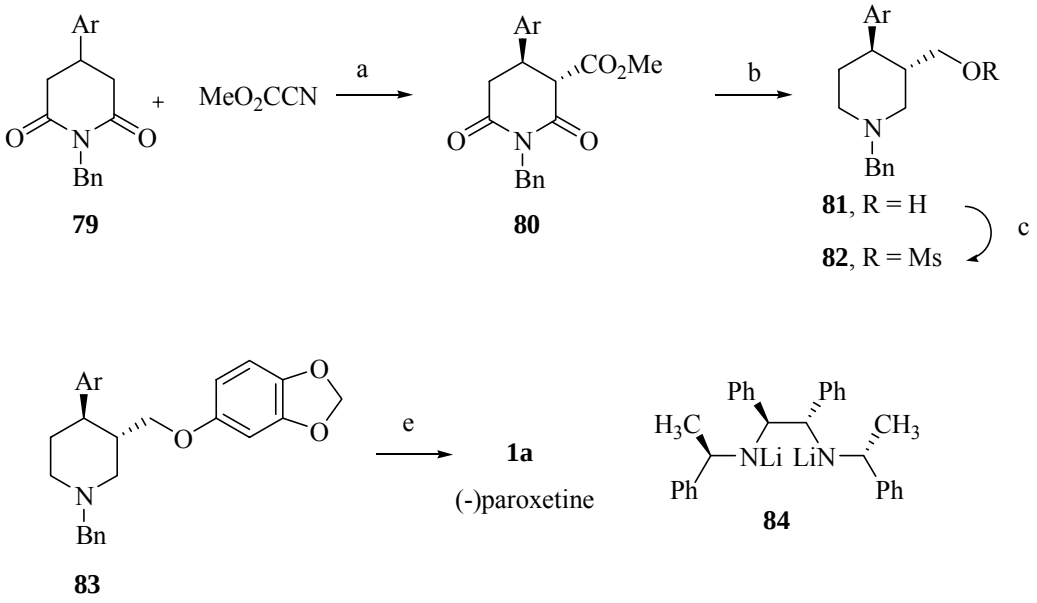
Chang *et al.* have used conjugated addition of **74** onto the unsaturated ester **75** to prepare *N*-alkyl-3-sulfonyl glutarimide **76.** This was then subjected for selective reduction of amide moiety in **76** gave 4-substituted 3-sulfonyl-δ-lactams **77.** Further, desulfurization with Na-Hg and Na_3PO_4 led to **78**, an important intermediate in the synthesis of (±)-paroxetine **1** (**Scheme 18**).



Scheme 18: (a) NaH, THF, 80 ºC, 1 h, 75 %; (b) Et_3N, $LiAlH_4$, THF, 80 ºC, 3 h, 76 %; (c) Na-Hg, Na_3PO_4, MeOH, 25 ºC, 2 h, 90 %.

Simpkins's approach (2003)[27]

Simpkins's approach involves asymmetric desymmetrisation of prochiral imide **79** using a chiral lithium amide base **84** in its bis-lithiated form, which produced the desired imide **80** in 71 % yield, with 97 % of ee as a single diastereoisomer. Reduction of imide **80** (97% ee) gave piperidine alcohol **81**, to which the appropriate sesamol side-chain was introduced by conventional means, *via* the intermediate mesylate **82**. Deprotection of the piperidine nitrogen then gave the desired drug substance **1a** as the free amine after base treatment in 54 % yield (**Scheme 19**).

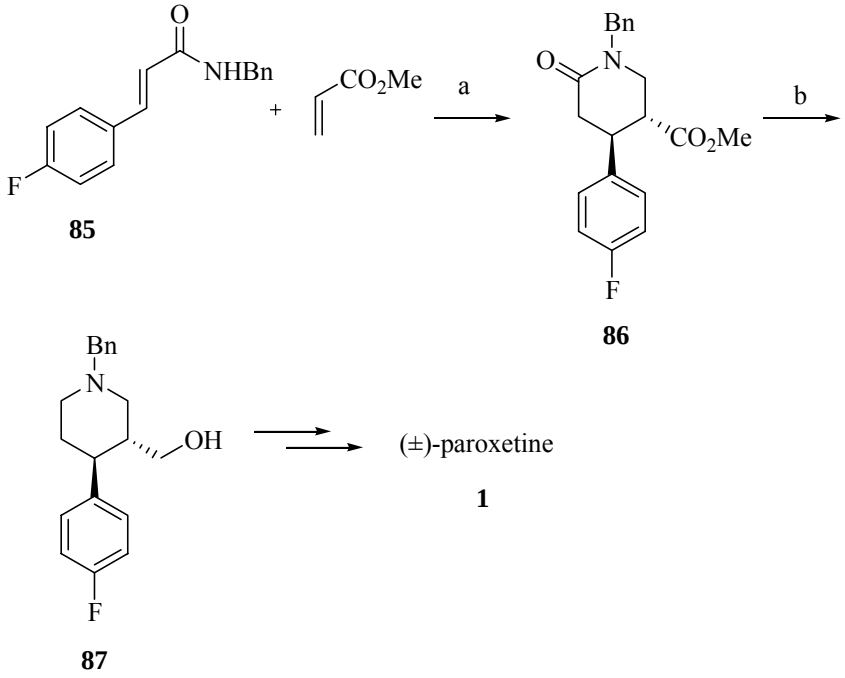


Scheme 19: (a) *n*-BuLi (1 equiv.), (-) sparteine (1.2 equiv.), toluene, -78 ºC, 97 % ee, 71 %; (b) $LiAlH_4$ (5 equiv.), THF, reflux, 12 h, 90 %; (c) MsCl, pyridine, CH_2Cl_2, 72 %; (d) sesamol (5 equiv.), NaOMe (5 equiv.), MeOH, 12 h, 55%; (e) (i) $CH_3CHClOCOCl$, 0 to 25 ºC and then reflux 3 h; (ii) MeOH, NaOH, reflux, 2 h, 54 %.

Takasu's approach (2003)[28]

Takasu *et al*. have reported recemic synthesis of paroxetine making use of intermolecular aza-double Michael addition of unsaturated amide **85** with methyl acrylate (TBSOTf, Et_3N in *tert*-BuOH:dichloroethane) leading to functionalized piperidin-2-one **86** as a

mixture of *anti* and *syn*. Without separation, epimerization of **86** (NaOMe) was achieved to give *trans*-**86** followed by its reduction with $LiAlH_4$ furnished the known piperidinol **87**, (**Scheme 20**).

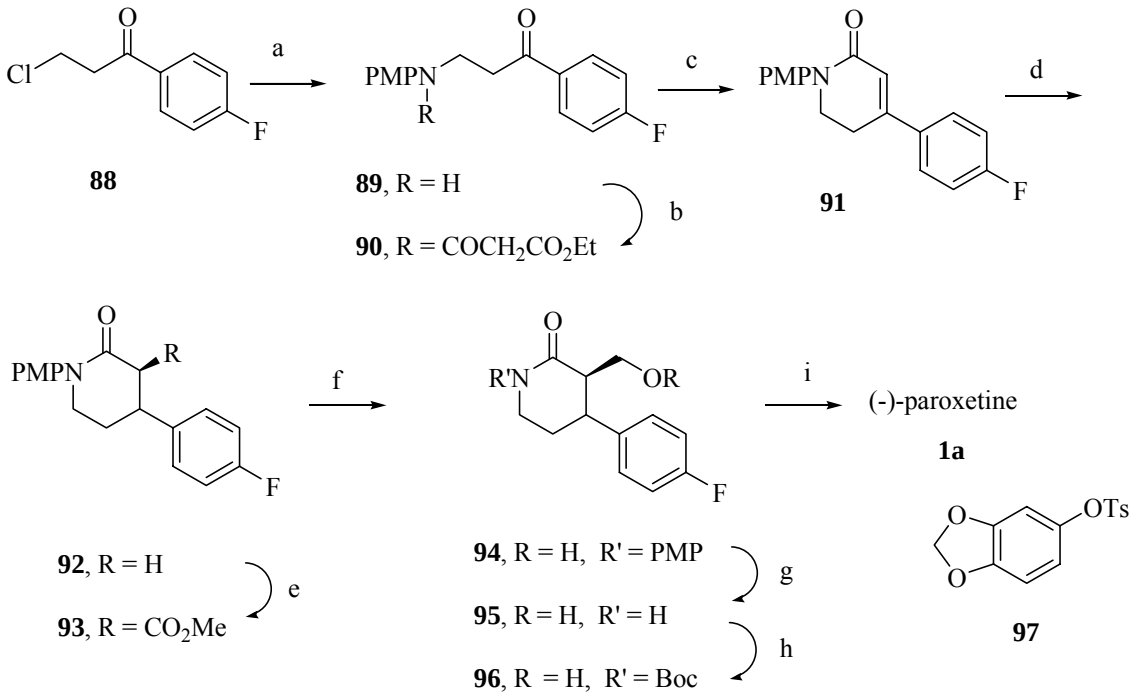


Scheme 20: (a) TBSOTf (1.2 equiv.), Et_3N (0.7 equiv.), *tert*-BuOH (0.25 equiv.), $ClCH_2CH_2Cl$, 25 °C; (ii) NaOMe, MeOH:toluene, reflux (58% for two steps); (b) $LiAlH_4$ (2 equiv.), THF, reflux, 56 %.

Buchwald's approach (2003)[29]

Buchwald *et al.* have employed Cu(I)/*p*-tolBINAP as catalyst for the enantioselective 1,4-reduction of lactams, as shown in **Scheme 21**. 4-Fluoro-3-chloropropiophenone (**88**) was converted to aminoketone **89** followed by amidation gave amide **90.** Subsequently, condensation followed by decarboxylation was achieved (NaOMe) to provide unsaturated lactam 91 **in** 76% yield. The lactam **91** was subjected to asymmetric reduction [catalyst Cu(I)/*p*-tolBINAP, PMHS in *tert*-AmOH} to give **92** in 90% yield and 90% ee. This intermediate **92** was converted to **94** in two steps (81% overall yield) using previously

reported conditions. The oxidative removal of the PMP functionality to give amine **95** which was protected as its carbamate with $(Boc)_2O$ affording **96** in 75% yield. Etherification with **97** followed by deprotection of *N*-Boc group in **96** gave **1a** in 52% (**Scheme 21**).

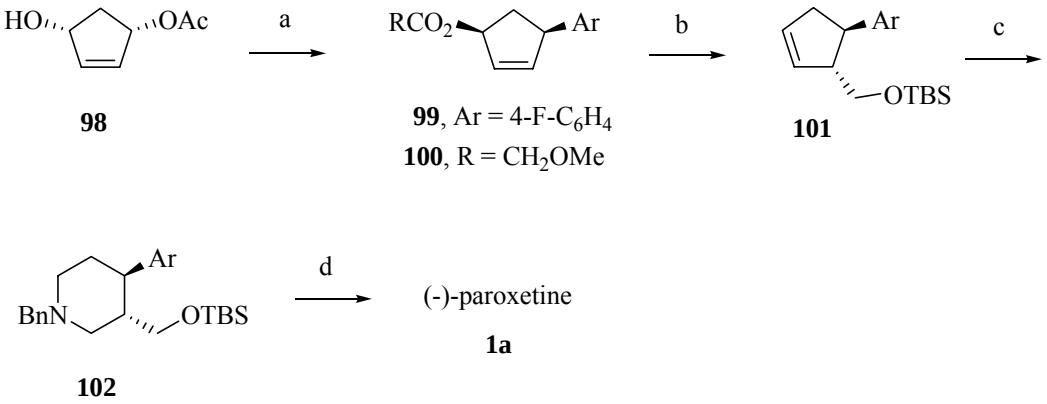


Scheme 21: (a) $PMPNH_2$ (1.1 equiv), Et_3N (1.2 equiv), THF, reflux, 75%; (b) $ClCOCH_2CO_2Et$ (1.1 equiv), Na_2CO_3 (sat), CH_2Cl_2. (c) NaOEt (4 equiv), EtOH, reflux, 74% (two steps). (d) PMHS (16 equiv), *t*-AmOH (16 equiv), (*S*)-*p*-tol-BINAP (0.5 mol %), $CuCl_2$ (2.5 mol %), *t*-BuONa (5 mol %), C_6H_5F, air, 23 ºC 90%, 90% ee. (e) NaH (6 equiv), MeOH (3 equiv), $(MeO)_2CO$ (3 equiv), toluene, reflux, 86%. (f) BH_3,THF, reflux, 97%. (g) CAN (4 equiv), CH_3CN:H_2O (3:1). (h) $(Boc)_2O$ (2.0 equiv), NaOH (1.5 equiv), toluene, H_2O, 75% (two steps). (i) **97** (1.3 equiv), Cs_2CO_3 (1.5 equiv), xylene, 130 ºC; (ii) TFA, CH_2Cl_2, 52% (two steps).

Kobayashi's approach (2004)[30]

In Kobayashi's approach, *trans*-cyclopentene derivative **101** was prepared from monoacetate **99** by a sequence of reactions: (i) 4-FC_6H_4MgCl/CuCN (cat.), 87%; (ii) AcOH, DIAD, PPh_3, 90%; (iii) (*i*-PrO)Me_2SiCH_2Cu·MgICl (3 equiv), THF, 2 h, 90 % to produce **101**. Ozonolysis of **101** proceeded well in *n*-PrOH to afford the diol in 85% yield

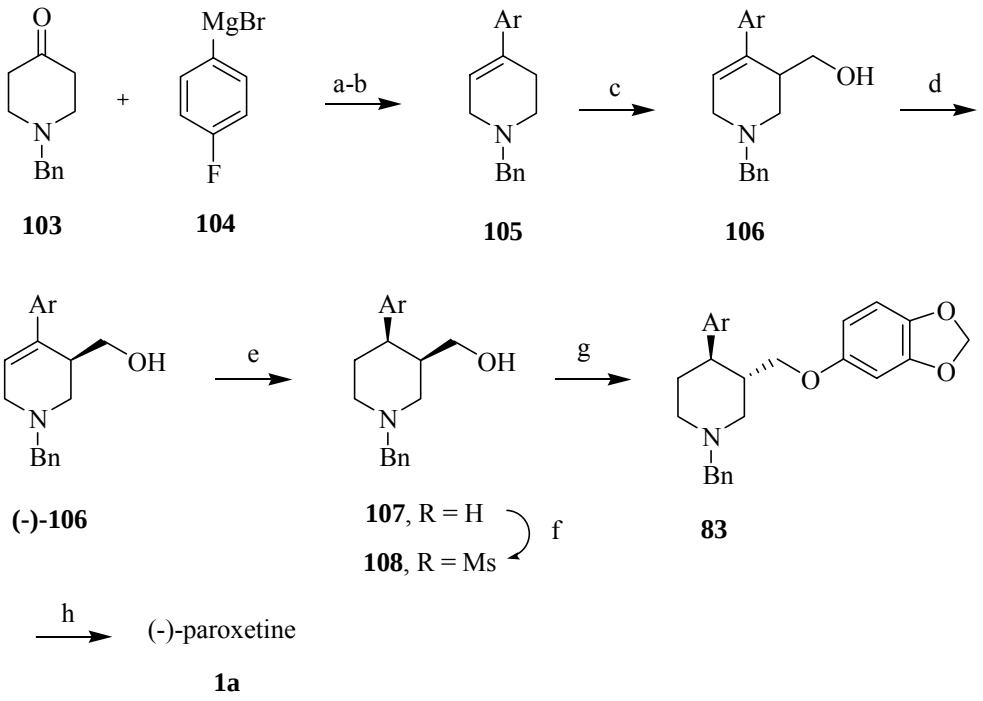
after reductive workup with $NaBH_4$. Subsequently, diol was converted into iodide and finally, on treatment with $BnNH_2$ at 115 ºC for 2 h in dioxane produced *trans* piperidine **102** in 54% overall yield. Deprotection of piperidine **102** followed by etherification produced (-)-paroxetine **1a** in 70 % yield and 80 % ee (**Scheme 22**).



Scheme 22: (a) (i) 4-F-C_6H_4MgCl (3 equiv), CuCN (0.3 equiv), THF, 25 °C, 87 %; (ii) $MeOCH_2CO_2H$, DIAD, PPh_3,-78 ºC, 90 %; (b) (i) (*i* PrO)$Me_2SiCH_2Cu{\cdot}MgICl$ (3 equiv), THF, 2 h, 90 %; (ii) H_2O_2, KF, $KHCO_3$, 60–65 ºC; (c) (i) O_3, -70 ºC then Me_2S; (ii) $NaBH_4$, 0 ºC; (iii) I_2, imidazole, PPh_3; (iv) $BnNH_2$, dioxane, 115 ºC, 60 %; (d) (i) TFA, CH_2Cl_2, 25 °C; (ii) H_2, (t-$BuOCO)_2O$, 20% $Pd(OH)_2$/C, EtOAc, 25 °C, 50%; (iii) MsCl, Py, 10 °C, then NaH, sesamol, THF, reflux, 70%; (iv) TFA, CH_2Cl_2, 25 °C, 70%.

Nemes's approach (2004)[31]

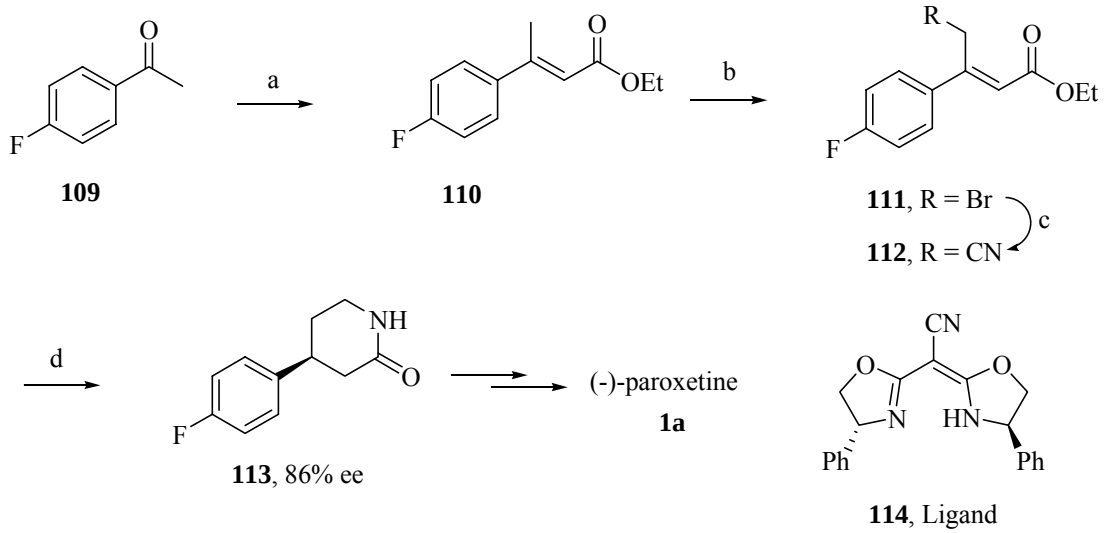
Nemes *et al.* have employed the resolution of alcohol strategy for the synthesis of (-)-paroxetine. Thus, Grignard reaction of *p*-fluorophenyl magnesium bromide **104** onto *N*-benzyl,4-piperidinone **103** followed by dehydration provided olefin **105** in 73 % yield. The Prins reaction of **105** afforded racemic tetrahydropyridine-3-methanol **106**, which was subjected to classical resolution (-)-dibenzyl tartarate providing (-)-**106** in 41% yield. The stereoselective reduction (H_2, Pd/C) led to *cis*-piperidine-3-methanol (3*R*,4*R*)-**107.** Further, it was converted to (-)-paroxetine **1a** with known sequence of reactions (**Scheme 23**).



Scheme :23 (a) THF, toluene; (b) *p*-TsOH, ClC_6H_5, reflux, 3 h,73%; (c) $(CH_2O)_n$, HCl, H_2SO_4, H_2O, 80 °C, 1 h, 60%,; (d) (-)-dibenzoyltartaric acid, acetone; (e) (i) 10% Pd/C, H_2, AcOH, HCl, H_2O, 40 °C, 78%; (ii) NaOH, H_2O, (iii) (-)-dibenzoyltartaric acid, acetone; (f) $MeSO_2Cl$, Et_3N, CH_2Cl_2; (g) NaOH, H_2O, xylene, ^{s}BuOH,140 °C; (h) 10% Pd/C, H_2 (5 atm), *i*PrOH, 40 °C.

Sudalai's approach (2005)[32]

In our previous approach, we described $CoCl_2$ catalyzed asymmetric reduction of *γ*-cyano-*α*,*β*-unsaturated ester **112** to afford key lactam **113** for the formal syntheis of (-)-paroxetine. The unsaturated ester **110,** prepared from 4-fluoro acetophenone (**109**), was subjected to allylic bromination (catalytic AIBN, NBS) to give **111**. Displacement of the bromide group in **111** with cyanide (NaCN in DMF) gave nitrile **112**. Asymmetric reduction of **112** with catalytic amount of $CoCl_2$ usinng chiral ligand **114** provided **113** in 99% yield and 86% ee (**Scheme 24**).

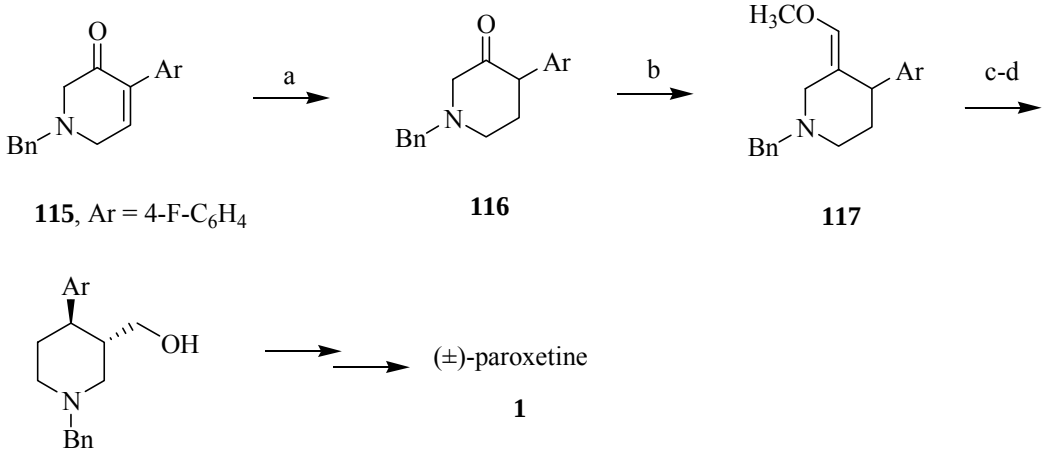


109 **110** **111**, R = Br **112**, R = CN **113**, 86% ee **1a** **114**, Ligand

Scheme 24: (a) (i) Ethyl bromo acetate (12 mmol.), $ArCOCH_3$ (10 mmol), Zn dust (12 mmol), dry benzene, 80 ºC, 6 h; (ii) *p*-TSA (10 mol %), benzene, Dean-Stark, 80 ºC, 12 h, 80 %; (b) AIBN (10 mol %), NBS, CCl_4, reflux, 12 h, 84 %; (c) NaCN, dry DMF, 25 ºC, 81%; (d) cyano ester (1 mmol), $CoCl_2$ (1 mol %), Ligand **114** (1.1 mol %), $NaBH_4$ (4 mmol), DMF: EtOH (1:1), 25 ºC, 24 h, 99 %, 86 % ee.

Krische's approach (2006)[33]

Krische *et al.* have reported the racemic synthesis of paroxetine **1.** Reduction of conjugated double bond in *α*-aryl tetrahydropyridine **115** produced saturated ketone **116**



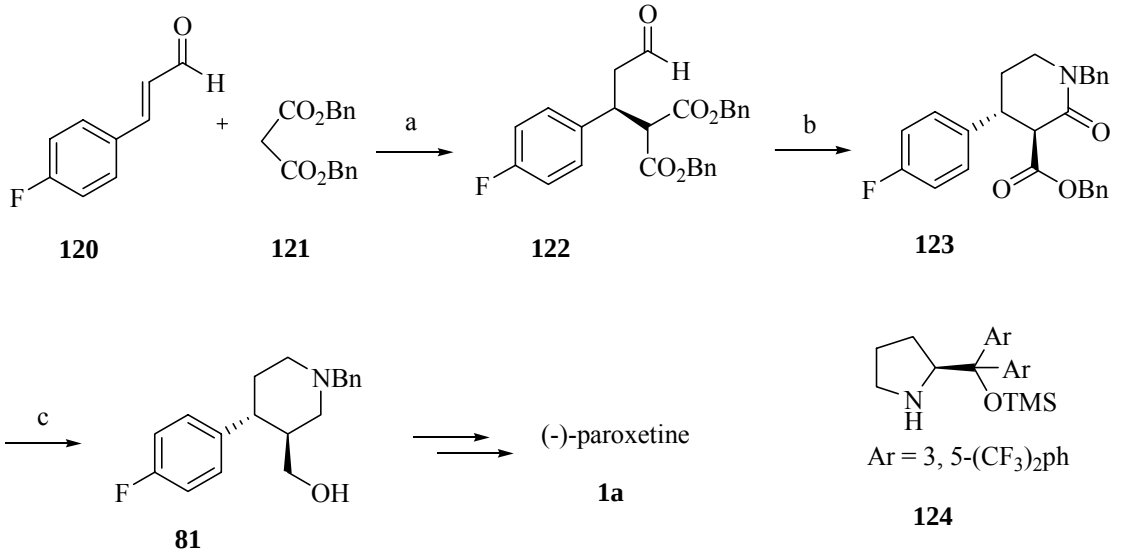
115, Ar = 4-F-C_6H_4 **116** **117** **81** **1**

Scheme :25 (a) L-Selectride, THF, –78 °C, 87%; (b) Ph_3PCH_2OMeCl, NaHMDS, THF, 0 °C, 65%; (c) 0.1 M H_2SO_4, THF, 50 °C; (d) $NaBH_4$, EtOH, 25 °C, 63% over two steps.

followed by Wittig reaction gave vinyl ether **117** in good yields. Finally, hydrolysis of vinyl ether to aldehyde its subsequent reduction gave the known alcohol **81** (**Scheme 25**).

Jørgensen's Approach (2006)[34]

Jørgensen *et al.* have used organocatalytic route for the synthesis of paroxetine which involving Michael addition of dibenzyl malonate **121** onto (*E*)-3-(4-fluorophenyl) acrylaldehyde (**120**) to giving dibenzyl 2-[(*S*)-1-(4-fluorophenyl)-2-formylethyl]malonate (**122**). Reductive amination of aldehyde **122** with benzyl amine followed by intramolecular cyclization gave lactum **123**. Further, reduction of ester and amide groups in **123** was achieved with $LiAlH_4$ to produce the known intermediate **81** (**Scheme 26**).

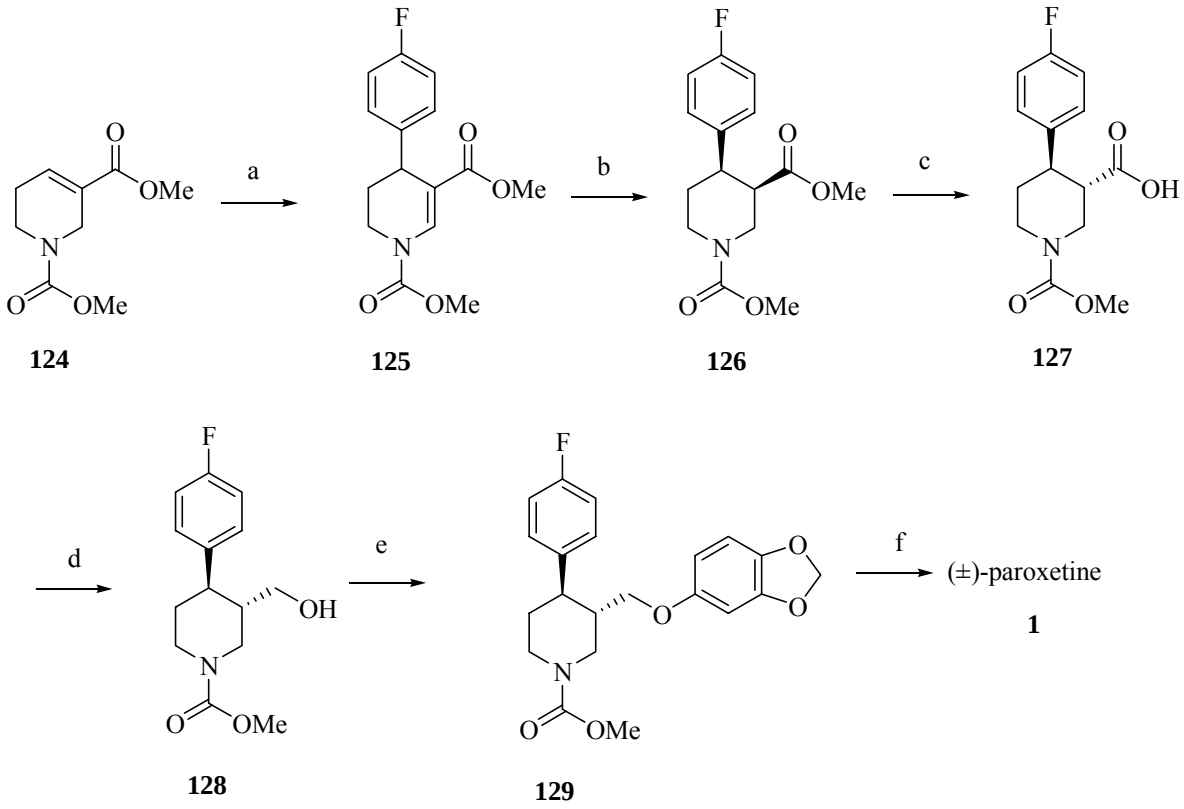


Scheme 26: (a) 10% catalyst EtOH, 0 ºC (b) $PhCH_2NH_2$, $NaBH(OAc)_3$, dioxane, 70%; (c) $LiAlH_4$, THF, 85%.

Correia's approach (2006)[35]

Correia *et al.* have reported racemic synthesis of paroxetine utilizing Heck arylation of *α,β*-unsaturated ester **124** to afford tetrahydopyridine **125**. Reduction of double bond to give *syn*-piperidine **126** followed by epimerization and hydrolysis gave acid **127**. Chemoselective reduction of acid **127** was achieved to provide alcohol **128** which was

transformed to ether **129.** Finally deprotection of methyl carbamate gave paroxetine **1** (**Scheme 27**).

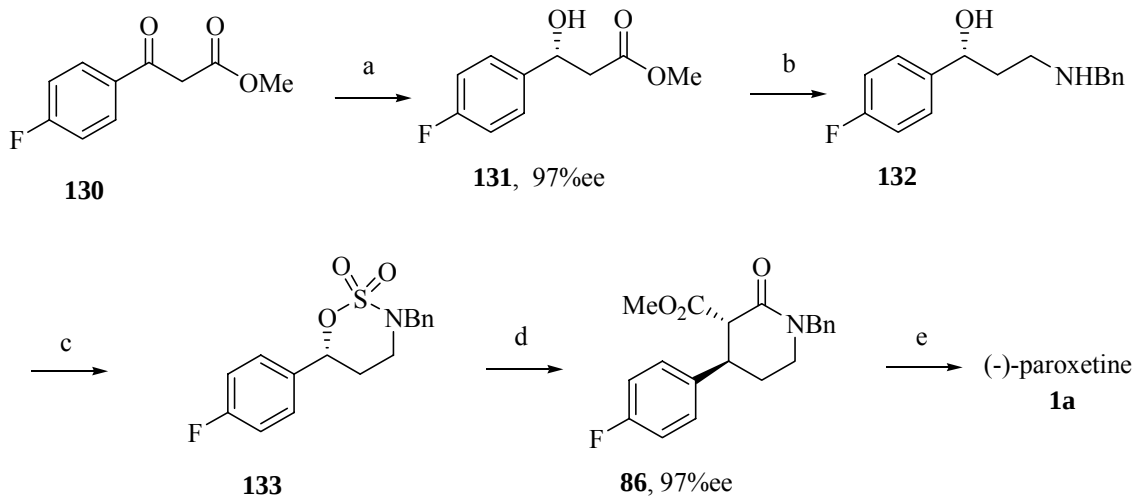


Scheme :27 (a) $Pd(OAc)_2$ (10 mol%), 4-$FC_6H_4N_2BF_4$, CH_3CN:H_2O (1:1), 60 ºC, 4 h, 74%; (b) Mg, MeOH, ultrasound, 24 h, 100 %; (c) CH_3ONa, MeOH, 65 °C, 12 h, 64%; (d) BH_3·SMe_2, THF, 25 °C, 84%; (e)(i) $MeSO_2Cl$, Et_3N, CH_2Cl_2;(b) NaH, sesamol, DMF, reflux, 3 h, 56%.

Gallagher's approach (2007)[36]

Gallagher *et al.* have used [(*S*)-Cl-MeO-BIPHEP]Ru-(cymene)Cl as catalyst in the asymmetric reduction of β-keto ester **130** to form the corresponding β-hydroxy ester **131** in 97% ee. Amidation of ester in **131** was carried out by treating benzyl amine with **131** in presence of Et_3Al followed by its reduction with $LiAlH_4$ afforded amino alcohol **132**. Treatment of amino alcohol **132** with $SOCl_2$ gave sulfonamide **133,** which on

nucleophilic substitution with dibenzyl malonate gave the known lactam **86** with 97% ee (**Scheme 28**).



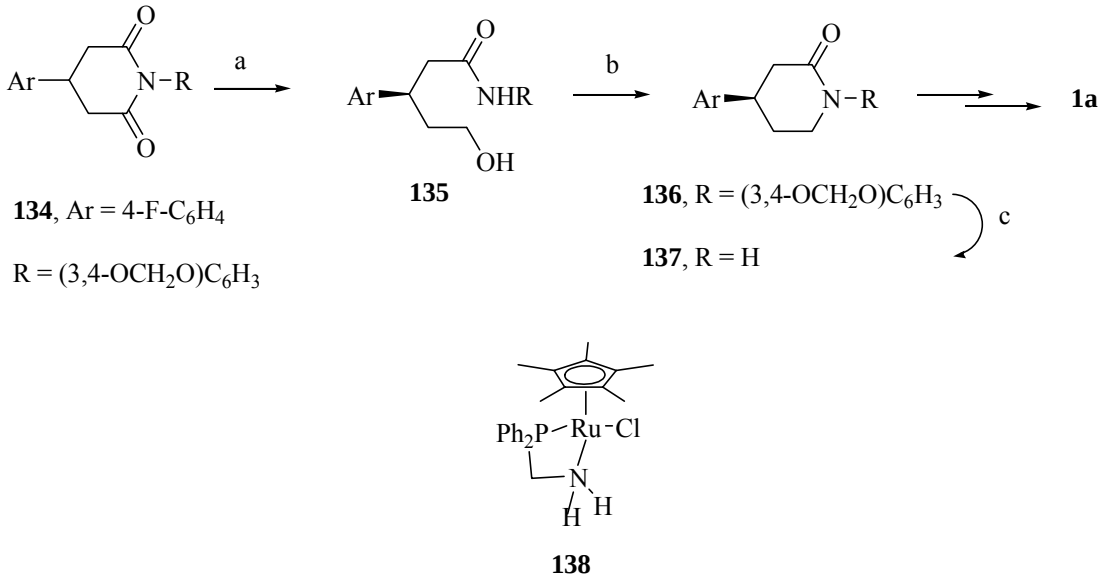
130 **131**, 97%ee **132**

133 **86**, 97%ee

Scheme 28: (a) [((*S*)-Cl-MeO-BIPHEP)Ru-(cymene)Cl]Cl-CH_2Cl_2 (0.5 mol%), H_2 (8 bar), MeOH, 60 ºC, 95%; (b) (i) $AlMe_3$, $BnNH_2$, PhMe, 0 ºC to 25 °C, 100%; (ii) $LiAlH_4$, THF, reflux, 98%; (c) (i) $SOCl_2$, Et_3N, imidazole, CH_2Cl_2, -20 ºC to 0 ºC, 95%; (ii) $RuCl_3$ (0.25 mol%), $NaIO_4$, MeCN:H_2O, 0 ºC, 87%; (d) dimethyl malonate, NaH, DMF, 60 ºC; then 5 M HCl; then PhMe, 110 °C, 70%; (e) (i) $LiAlH_4$, THF, reflux; (ii) MsCl, Et_3N, CH_2Cl_2; (iii) sesamol, NaH, DMF, 90 ºC, 52% over 3 steps; (iv) 10% Pd/C (35%), H_2 (6 bar), ^{i}PrOH, AcOH, 50 ºC, then aq. HCl, ^{i}PrOH (82%).

Ikariya's approach (2007)[37]

Ikariya's approach describes asymmetric hydrogenation of prochiral glutarimides **134** with a chiral Ru-catalyst **138** catalyst to give chiral amido alcohol **135**. Subsequently alcohol **135** was transformed to the corresponding bromide and its intramolecular cyclization using NaH to obtain chiral amide **136**. Deprotection of *N*-aryl amine in **136** was achieved using CAN to afford the known amide **137**.



134, Ar = 4-F-C_6H_4

R = (3,4-OCH_2O)C_6H_3

135

136, R = (3,4-OCH_2O)C_6H_3

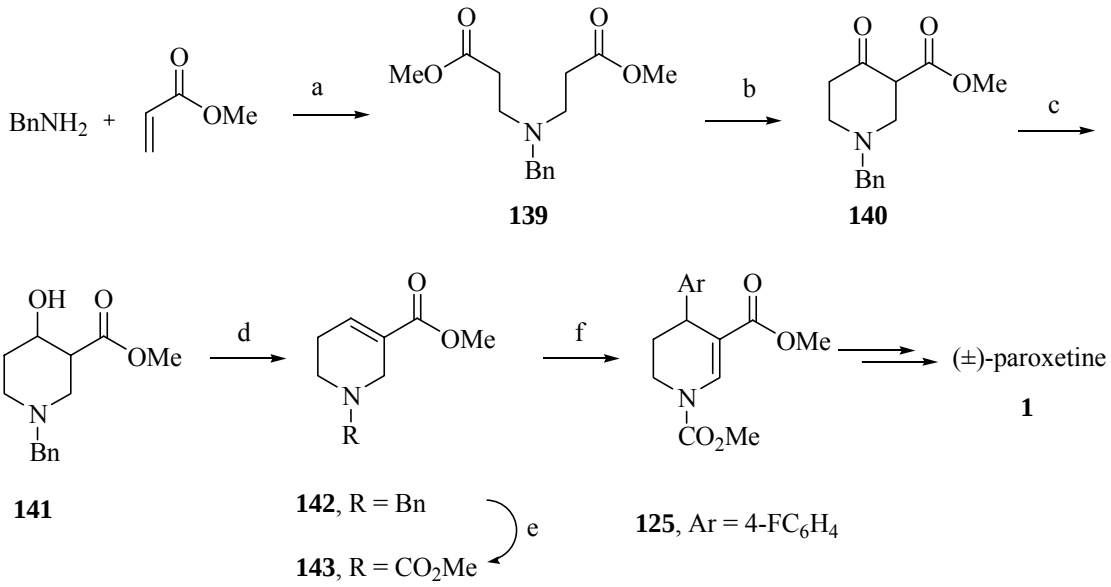
137, R = H

138

Scheme 29: (a) Catalyst. **138** (10 mol%), H_2 (3 Mpa), KO*t*-Bu, ^{i}PrOH, 80 ºC, (b)(i) CBr_4, PPh_3, CH_2Cl_2, 14 h, 65%; (ii) NaH, THF, 85 °C, 24 h, 54% ; (c) CAN, H_2O, 25 °C, 35%.

Chavan's approach (2007)[38]

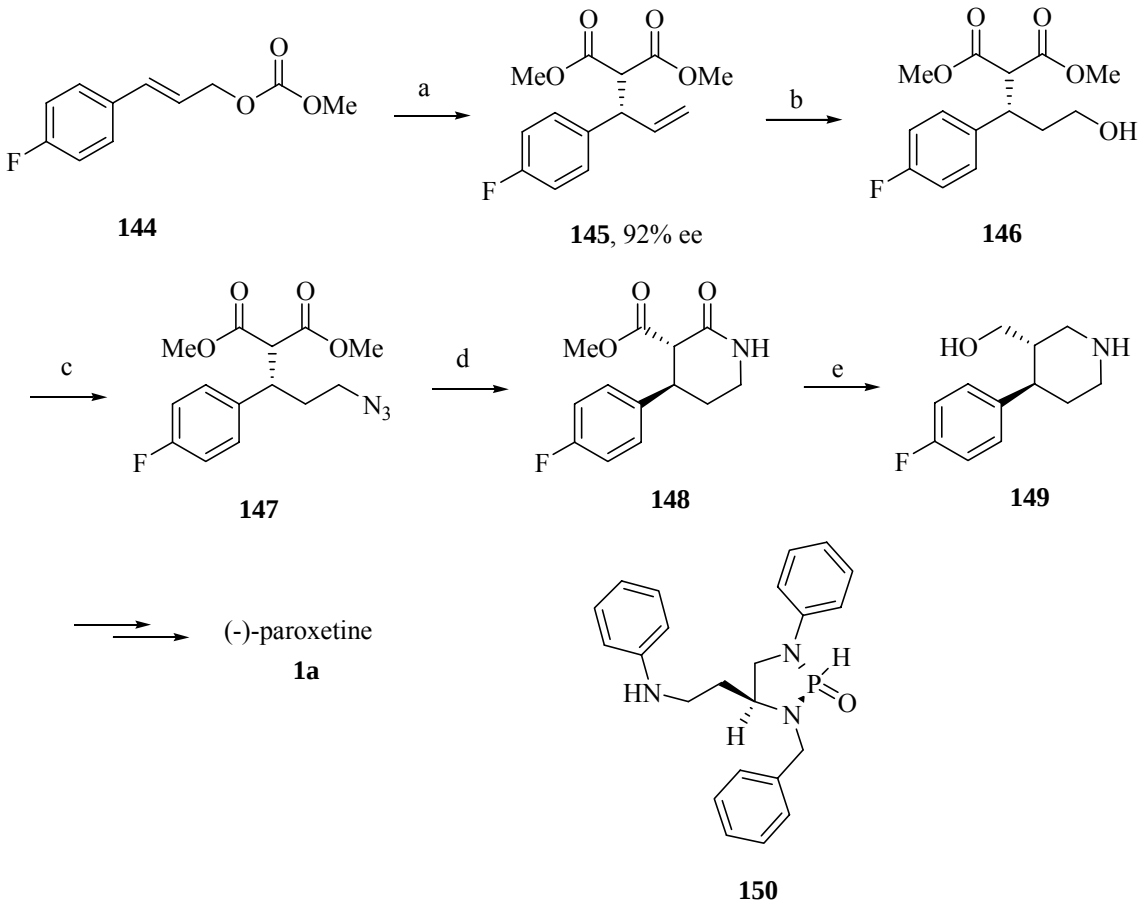
Chavan *et al.* have reported racemic formal synthesis of paroxetine **1**. Amino diester **139,** prepared by double Michael addition of benzyl amine onto methyl acrylate. It was then subjected to Dieckmann condensation to give ketoester **140**, which was reduced and *β*-hydroxy ester **141.** This hydroxyester underwent simultaneous elimination after mesylation to afford the olefin **142**. Benzyl group in **142** was then exchanged with methyl carbamate **143**, followed by Heck arylation of **143** furnished the known intermediate **125** in moderate yields (**Scheme 29**).



Scheme 30: (a) Et_3N, reflux (neat), overnight, 90%; (b) NaH, PhH, reflux, 3 h, 82%; (c) $NaBH_4$, MeOH, 0-25 °C, 2 h; (d) MsCl, Et_3N, CH_2Cl_2, 0-25 °C, overnight, 75% (for two steps); (e) $ClCO_2Me$, $NaHCO_3$, CH_2Cl_2, 25 °C, 24 h, 80%; (f) $Pd(PPh_3)_4$, K_2CO_3, Bu_4NBr, 120 °C, 2 d;

Hamada's approach (2007)[39]

Hamada's approach describes the use of Ir-catalyzed asymmetric malonate addition onto allylic carbonate **144** with chiral diaminophosphine oxide **150** as a ligand affording **145** in 92%. Hydroboration of olefin **145** gave alcohol **146** followed by its conversion to an azide **147** *via* mesylate (90% yield). Azide **147** was then treated with Lindlar's catalyst in toluene/MeOH (5/1) under hydrogen atmosphere to provide lactam **148** in 93% yield as a single diastereomer (*anti*/*syn* = >99/1). Subsequent reduction of **148** with BH_3·THF complex gave (-)-**149** in 99%yield (**Scheme 30**).



144 **145**, 92% ee **146**

147 **148** **149**

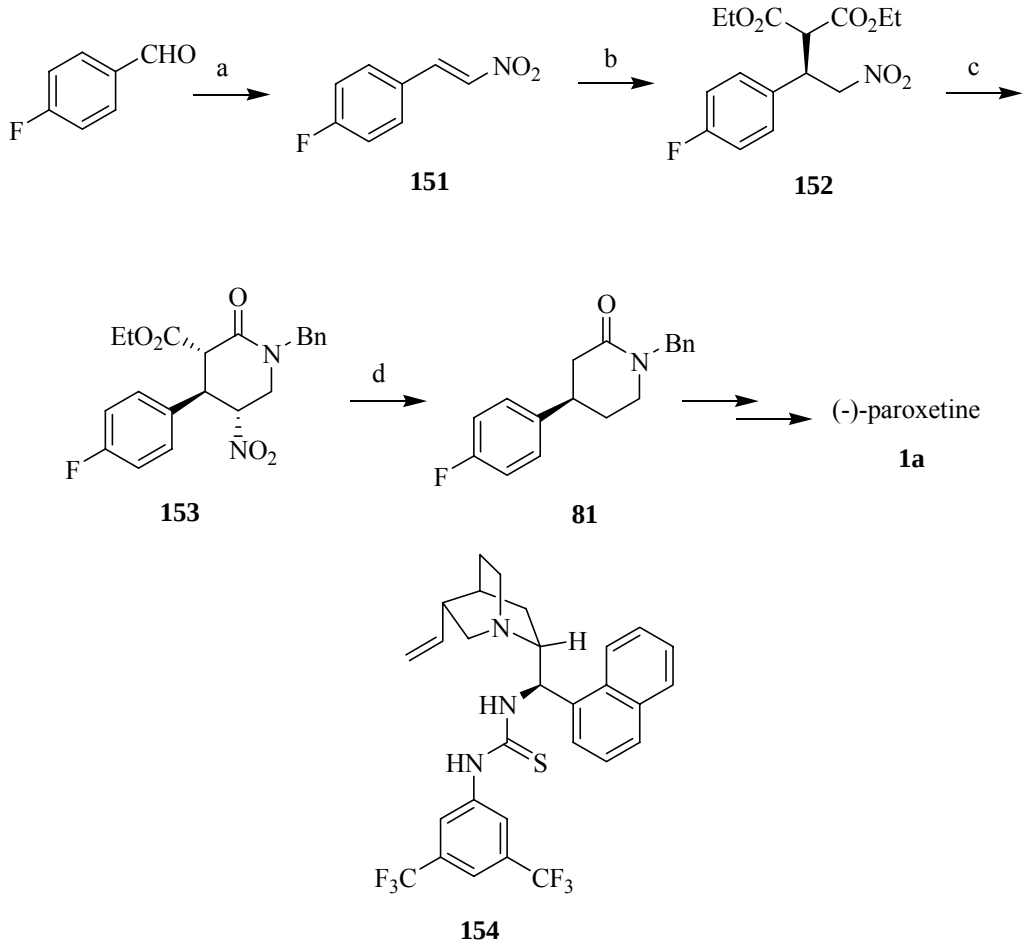
1a

150

Scheme :30 (a) Ir cat. (5 mol %), ligand **150** (5 mol %), $NaPF_6$ (10 mol %), LiOAc (10 mol %), dimethyl malonate (3 eq), BSA (3 eq), CH_2Cl_2, 25 °C; (b) $RhCl(PPh_3)_3$ (2 mol %), 9-BBN, THF, rt then 30% H_2O_2, pH 7 buffer, 85%; (c) (i) MsCl, NEt_3, CH_2Cl_2, -30 °C; (ii) NaN_3, DMF, 50 °C, 90% (2 steps); (d) Lindlar's cat. H_2, toluene:MeOH (5:1), 25°C, 93% (dr = >99:1); (e) BH_3·THF, THF, reflux , 99%.

Dixon's approach (2008)[40]

Dixon *et al.* have used Michael addition of malonate nucleophile onto nitro olefin **151** catalyzed by a bifunctional organo-catalyst **154** for obtaining nitro diester **152** in 92 % yield and 99% ee. Nitro derivative **152** was then subjected to nitro-Mannich lactamization (HCHO, $BnNH_2$ in MeOH) to give lactum **153.** Further decarboxylation and reductive removal of nitro group was achieved with tributyltin hydride and AIBN to afford the known lactum **81** (**Scheme 31**).



Scheme: 31 (a) CH_3NO_2, NH_4OAc, reflux, 24 h, 92%; (b) catalyst **154**, dimethyl malonate, CH_2Cl_2, –20 °C, 72 h, 92%, 99% ee.(c) HCHO (37% solution in water), benzylamine, MeOH , reflux, 16 h, 68%; (d) Bu_3SnH, AIBN, toluene, 110 °C, 78%.

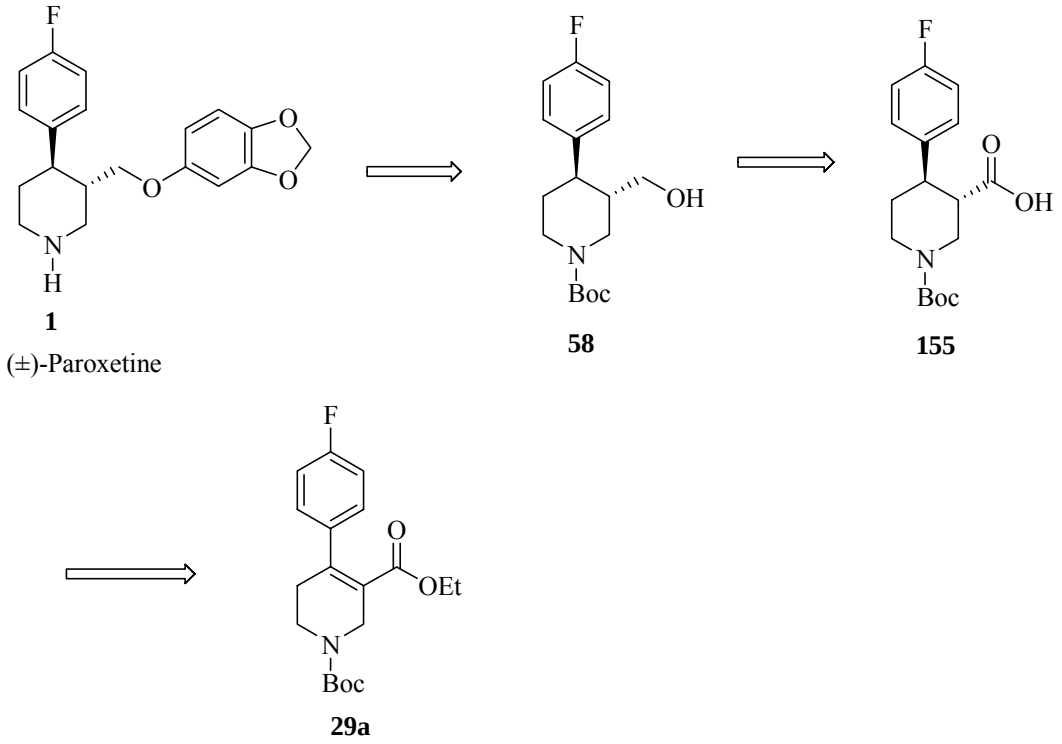
2.2.3 Present Work

2.2.3.1 Objective

Literature search revealed that several strategies such as classical resolution, chemo-enzymatic and enantioselective synthesis have been reported for the synthesis of (±)-paroxetine (**1**) (*vide supra*). However, these methods suffer broadly from disadvantages such as low overall yields, the need for separation of diastereoisomers and the use of expensive reagents. In this context, a more practical approach for the synthesis of (±)-paroxetine (**1**) is highly desirable.

2.2.3.2 Results and Discussion

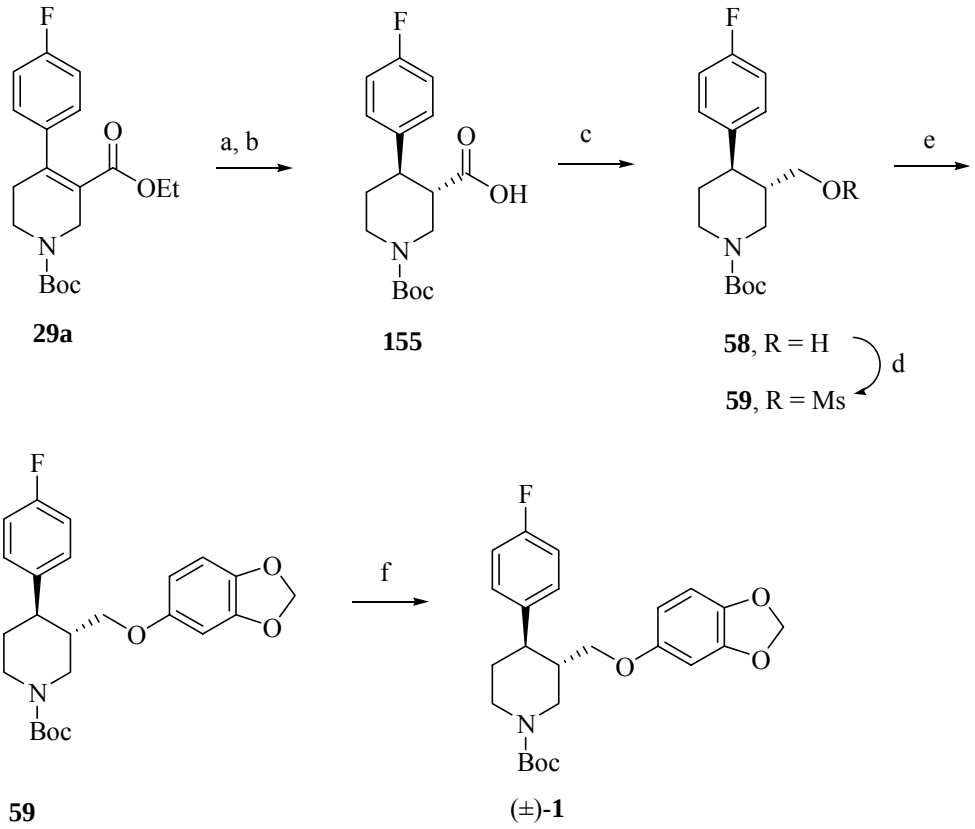
Retrosynthetic analysis reveals that, for the synthesis of (±)-paroxetine **1**, alcohol **58** could be taken as the key intermediate, which may be readily prepared from the corresponding acid **155**. We further visualized that acid **155** could be prepared by the reduction followed by base catalyzed epimerization of unsaturated ester **29a**. The preparation of **29a** *via* Pd-catalyzed Suzuki-Miyaura coupling of enol tosylate **27** with boronic acid **28a,** has already been described in **Section 1** of this chapter.



Scheme 32: Retrosynthetic analysis of (±)-paroxetine **1**

The synthetic route for the synthesis of (±)-paroxetine is depicted in **Scheme 33**. Initially, we were interested in the asymmetric reduction of C=C bond in tetrahydropyridine derivative **29a.** For such reductions, we employed several catalytic conditions [catalyst $CoCl_2$, semicorrin ligand in combination with $NaBH_4$ and $RuCl_2$·BINAP and H_2 (700

psig)]. However, unsaturated ester **29a** failed to undergo reduction. This is probably due to the presence of have tetrasubstituted C=C, conjugation of C=C bond with ester carbonyl and *N*-Boc moieties that resist chiral reduction. However, simple, non-chiral hydrogenation of **29a** [10% Pd/C, H_2 (1atm) in MeOH] was achieved to give saturated ester, which was subjected to basic hydrolysis without purification (*tert*-BuOK in refluxing MeOH:H_2O) to produce *anti* acid **155** in 93% yield.



29a **155** **59**

Scheme 33: (a) H_2 (1 atm), 10% Pd/C (10 wt %), MeOH, RT, 24 h. 99%; (b) ^{t}BuOK, MeOH, 65 °C, 12 h. 93% ; (c) $BH_3 \cdot SMe_2$, THF, 0 °C, 12 h. 91% ; (d) MsCl, Et_3N, DCM, RT, 3 h ; (e) sesamol **11**, NaH, DMF, 110 °C, 2 h then 16 h, 25 °C, 91%; (f) TFA, CH_2Cl_2 0-25 °C, 6 h, 82 %.

The ^{1}H NMR spectrum of acid **155** showed typical signals at δ 1.54-1.75 (m, 2H), 2.63 2.95 (m, 4H) and 4.19-4.43 (dd, 2H) corresponding to three methylene (C**H**$_2$) and a pair of methine (CH) protons of piperdine ring. Its ^{13}C NMR showed characteristic signals at

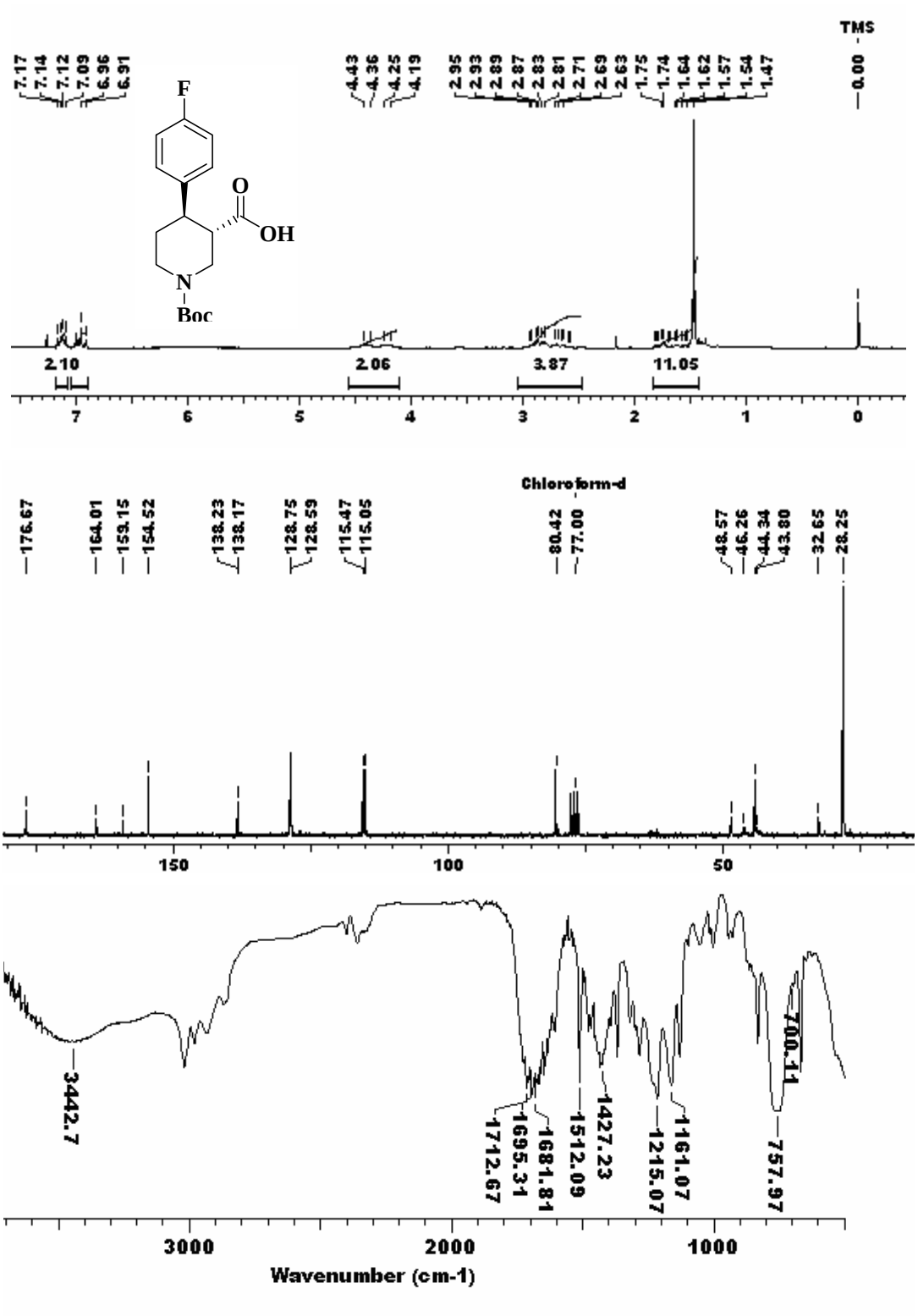


Fig. 7: ^{1}H and ^{13}C NMR and IR spectra of acid 155

δ 32.65, 43.88 and 46.15 due to three methylene (**C**H_2) carbons and signals at δ 44.34 and 48.57 due to two methine (**C**H) carbons respectively. Also a typical carbonyl signal at δ 176.6 in its ^{13}C NMR and a strong absorption band at 1712 cm^{-1} in its IR specrum confirmed the presence of carboxylic acid functionality in **155 (Fig. 7)**.

Chemoselective reduction of carboxylic acid function in **155** with $BH_3 \cdot SMe_2$ in dry THF gave the key alcohol **58** in 91% yield. Free alcohol moiety in **58** was protected as its mesylate followed by its displacement with sesamol gave the Boc-protected (±)-paroxetine **59**. Finally, deprotection of *N*-Boc group in **59** was achieved to obtain (±)-paroxetine **1** in 87% yield. Its ^{1}H NMR spectrum showed characteristic signals at δ 5.87 for methylene protons (-OC**H**$_2$O-) and disappearance of signals for *tert*-butyl group confirms the formation of (±)-paroxetine **1** (**Fig. 8**). The spectral values of (±)-paroxetine **1** are in complete agreement with the reported values.[19]

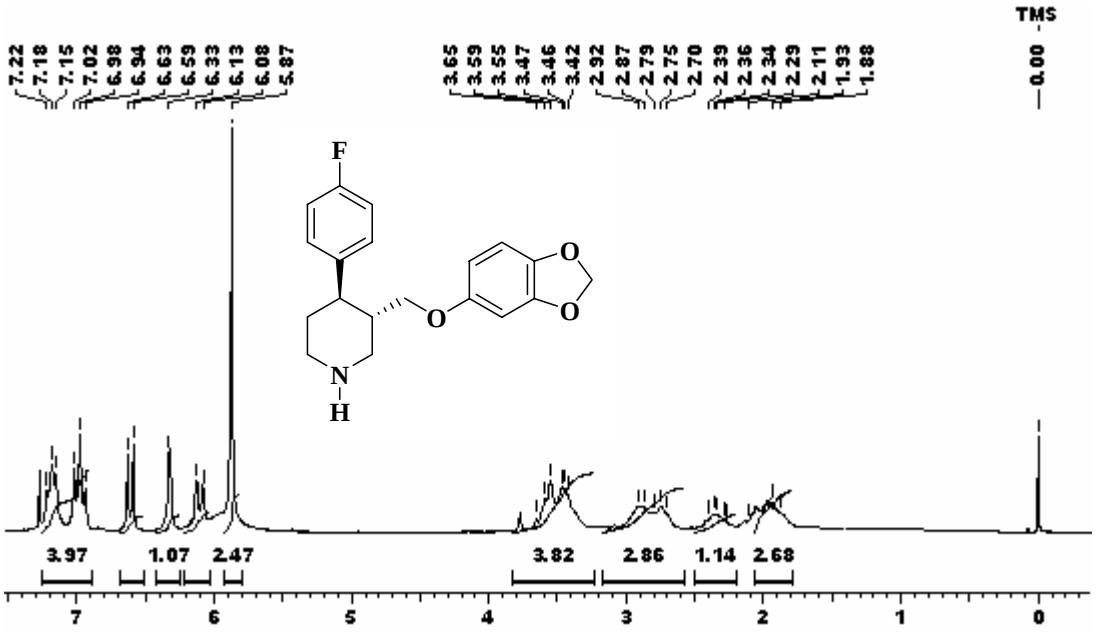
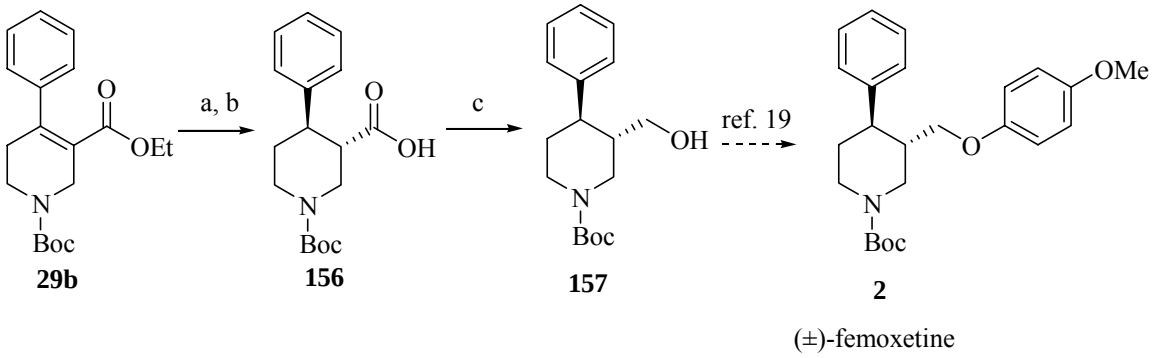


Fig. 8: ^{1}H NMR spectrum of (±)-paroxetine (1)

The synthetic route for the formal synthesis of (±)-femoxetine **2** is presented in **Scheme 34**. Reduction of C=C bond in **29b** (10% Pd/C, H_2 (1 atm) in MeOH) was achieved to give the saturated ester, which was subjected to *in situ* hydrolysis (*tert*-BuOK in MeOH: H_2O) to give the *anti* acid **156** in 93% yield. Chemoselective reduction of acid **156** with $BH_3 \cdot SMe_2$ in dry THF gave the known alcohol **157** in 91% yield. The further transformation of **157** into (±)-femoxetine **2** has been reported in the literature[19] (**Scheme 34**).



Scheme 34: (a) 10% Pd/C (10 wt %), H_2 (1 atm), MeOH, RT, 24 h. 99%; (b) ^{t}BuOK, MeOH, 65 °C, 12 h. 93% ; (c) $BH_3 \cdot SMe_2$, THF, 0 °C, 12 h. 91% .

2.2.4 Conclusion

In conclusion, we have successfully developed a simple and practical method for the synthesis of (±)-paroxetine (**1**) and a formal synthesis of (±)-femoxetine (**2**), which are important anti-depressant drugs presently sold in the market. The method described, here in is an elegant one with a high overall yield, employing Suzuki reaction of enol tosylate **27** with the corresponding boronic acid **28** as the key steps.

2.2.5 Experimental section

General procedure for the preparation of (±)-1-(*tert*-butoxycarbonyl)-4-aryl-piperidine-3-carboxylic acid (155-156):

To a solution of **29a** or **29b** (3 mmol) in 10 mL of methanol, 10% Pd/C (100 mg) was added. It was then stirred under H_2 (1 atm) for 12 h. After completion of the reaction (monitored by TLC), reaction mixture was then passed through celite and concentrated under reduced pressure. To this reduced product methanol (10 mL) and *tert*-BuOK (1 g) were added. The reaction mixture was then refluxed for 12 h. After completion of the reaction (monitored by TLC), methanol was distilled off under reduced pressure and a saturated solution of NH_4Cl (20 mL) was added. The aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine solution (2 x 20 mL), dried over unhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude acid product. Chromatographic purification [silica gel (230-400 mesh) petroleum ether: ethyl acetate (70:30) as eluent] of crude product gave acid **155** and **156** in pure form.

1-(*tert*-Butoxycarbonyl)-4-(4-fluorophenyl)piperidine-3-carboxylic acid (155):

Yield: 93%; Gum, **IR** ($CHCl_3$): 757, 1161, 1215, 1427, 1512, 1712, 3442 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.47 (s, 9H), 1.37-1.83 (m, 2H), 2.58-2.95 (m, 4H), 4.19-4.50 (dd, *J* = 12.1, 12.8 Hz, 2H), 6.91-7.00 (t, *J* = 8.7 Hz, 2H), 7.09 (dd, *J* = 5.4, 8.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.2, 32.6, 44.3, 46.1, 48.5, 80.4, 115.05-115.47 (d, *J* = 21.2 Hz), 128.59-128.75 (d, *J* = 7.7 Hz), 138.17-138.23 (d, *J* = 3.29 Hz), 154.52, 159.15-184.01 (d, *J* = 244.0 Hz), 176.6; **Analysis** for $C_{17}H_{22}FNO_4$ requires C, 63.14; H, 6.86; N, 4.33; found C, 63.11; H, 6.82; N, 4.35%.

1-(*tert*-Butoxycarbonyl)-4-phenylpiperidine-3-carboxylic acid (156):

Yield:93%; Gum, IR ($CHCl_3$): 763, 1224, 1280, 1446, 1714, 1714, 3411 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ1.48 (s, 9H), 1.45-1.90 (m, 2H), 2.44-2.90 (m, 4H), 4.25-4.57 (dd, *J* = 12.4, 12.9 Hz, 2H), 7.10-7.27 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 25.4, 28.2, 43.1, 45.3, 46.5, 51.0, 79.4, 126.5, 127.3, 128.1, 142.3, 154.3, 171.9; **Analysis** for $C_{17}H_{23}NO_4$ C, 66.86; H, 7.59; N, 4.59; found C, 66.62; H, 7.33; N, 4.41%.

A general procedure for preparation of (±)-*tert*-butyl 4-aryl-3-(hydroxymethyl)piperidine-1-carboxylate:

To the stirred solution of acids **155** or **156** (2 mmol) in dry THF (10 mL), was added $BH_3{\cdot}SMe_2$ (3 mmol) dropwise with syringe at 0 ºC under N_2 atomosphere and allowed for stir for 12 h at 25 ºC. After completion of reaction (monitored by TLC), methanol (5 mL) was added and allowed to stir for 30 min at 25 ºC. To the reaction mixture, water (50 mL) and ethyl acetate (50 mL) were added. The organic layer was separated and aqueous layer was extracted with ethyl acetate (2 x 25 mL). The combined organic layer was washed with brine solution (2 x 25 mL), dried over unhyd. Na_2SO_4, concentrated under reduced pressure to give the crude alcohols. Chromatographic purification [silica gel (230-400 mesh) petroleum ether: ethyl acetate (70:30) as eluent] of the crude products gave alcohols **58** and **157** in pure form.

***tert*-Butyl 4-(4-fluorophenyl)-3-(hydroxymethyl)piperidine-1-carboxylate (58):**

Yield: 91%; colorless solid; **mp**: 145–147 ºC; **IR** (KBr): 754, 835, 1028, 1668, 1601, 1345, 1263, 1229, 1257, 1114, 3032, 3448 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.47 (s, 9H), 1.54-1.75 (m, 2H), 2.63-2.95 (m, 4H), 3.30-3.50 (m, 2H), 6.91-7.00 (t, *J* = 8.7 Hz, 2H), 7.09 (t, *J* = 8.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.25, 32.65, 43.88, 44.34, 46.15, 48.57, 80.42, 115.05-115.47 (d, *J* = 21.2 Hz), 128.59-128.75 (d, *J* = 7.7 Hz),

138.17-138.23 (d, *J* = 3.3 Hz), 154.52, 159.15-164.01 (d, *J* = 244.0 Hz), 176.67; **Analysis** for $C_{17}H_{24}FNO_3$ requires C, 66.00; H, 7.82; N, 4.53; found C, 66.23; H, 7.71; N, 4.59%.

***tert*-Butyl 3-(hydroxymethyl)-4-phenylpiperidine-1-carboxylate (157):**

Yield: 91%; colorless solid; **mp:** 132-133 °C; **IR** ($CHCl_3$): 658, 1152, 1670, 1692, 3400 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.48 (s, 9H), 1.60-1.74 (m, 3 H), 2.51 (td, *J* = 11.3, 4.1 Hz, 1H), 2.69 (dd, *J* = 13.2, 11.5 Hz, 1H), 2.78 (m, 1 H), 3.25 (dd, *J* =11.0, 6.5 Hz, 1H), 3.42 (dd, *J* = 11.0, 3.3 Hz, 1H), 4.20 (m 1 H), 4.36 (m, 1H), 7.15-7.35 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 25.0, 28.4, 29.7, 42.4, 43.4, 45.2, 57.6, 80.0, 126.9, 128.4, 142.5, 155.7; **Analysis** for $C_{17}H_{25}NO_3$ requires C, 70.07; H, 8.65; N, 4.81; found 70.14; H, 8.45; N, 4.71%.

Preparation of (±)-*tert*-butyl 3-{(benzo[*d*][1,3]dioxol-6-yloxy)methyl}-4-(4-fluorophenyl)piperidine-1-carboxylate (59):

To a 25 mL two neck RB flask, charged with alcohol **58** (1 mmol), Et_3N (0.2 mL, 2 mmol) and CH_2Cl_2 (10 ml), was added MsCl (1.5 mmol) at 0 ºC. Reaction mixture was stirred for 30 min. After completion of reaction (monitored by TLC), a saturated solution of $NaHCO_3$ (20 mL) was added. The organic layer was separated and aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were washed with brine solution (25 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure and dried under reduced pressure to give crude mesylate, which was subjected for etherification without purification.

^{1}H NMR (200 MHz, $CDCl_3$**)** δ 1.48 (s, 9H), 1.60-2.05 (m, 3H), 2.58-2.78 (m, 3H), 2.89 (s, 3H), 3.77-4.01 (m, 2H), 4.12-4.42 (m, 2H), 6.98 -7.19 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 28.1, 31.3, 36.7, 40.8, 43.5, 46.1, 69.3, 79.6, 115.4, 128.5, 139.7, 154.3, 161.5.

To the oven dried two necked RB flask equipped with reflux condenser was charged with NaH (1.5 mmol), sesamol (1 mmol) and DMF (5 mL). The reaction mixture was heated for 100 ºC for 30 min. It was then cooled to 25 C and then crude mesylate (1 mmol in 2 mL DMF) was added. Reaction mixture was stirred for 12 h at 25 ºC. After completion of reaction (monitored by TLC), water (30 mL) and ethyl acetate (30 mL) were added. The organic layer was separated and aqueous layer was extracted with ethyl acetate (2 x 25 mL). Combined organic layers were washed with brine solution (25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product. Chromatographic purification of crude product [silica gel (230-400 mesh) petroleum ether: ethyl acetate (60:40) as eluent] gave *N*-Boc paroxetine **59** in pure form.

Yield: 91%; gum**, IR** ($CHCl_3$): 879, 1247, 1600, 1690, 2880 cm $^{-1}$; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.50 (s, 9H), 1.60-2.05 (m, 4H), 2.60-2.87 (m, 2H), 3.39-3.62 (m, 2H), 4.20-4.46 (m, 2H), 5.89 (s, 2H), 6.13 (dd, *J* = 2.5, 8.4 Hz, 1H), 6.44 (d, *J* = 2.5 Hz, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 6.98 (t, *J* = 8.7 Hz, 2H), 7.18 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.2, 33.8, 36.8, 40.8, 43.6, 43.9, 46.1, 68.3, 79.6, 115.4, 128.4, 137.9, 157.0, 163.1, 161.6; **Analysis** for $C_{24}H_{28}FNO_5$ requires C, 67.12; H, 6.57; N, 3.26; found C, 67.02; H, 6.41; N, 3.21%.

Preparation of (±)-paroxetine (1)

To the stirred solution of *tert*-butyl carbamate of paroxetine **59** in CH_2Cl_2 (2 mL), TFA (2 mL) was added at 0 ºC. Reaction mixture was then allowed to stirr at 25 ºC for 6 h. After completion of the reaction, solvent was distilled out under reduced pressure and then a saturated NH_4Cl (10 mL) and ethyl acetate (20 mL) was added. The organic layer was

separated and the aqueous layer was extracted with ethyl acetate (2 x 20 mL). The combined organic layer was washed with brine solution (25 mL), dried over anhyd. Na_2SO_4 concentrated under reduced pressure to give the crude product. Chromatographic purification of the crude product [silica gel (230-400 mesh) petroleum ether: ethyl acetate (50:50) as eluent] gave (±)-paroxetine **1** in pure form.

Yield: 82%; **gum, IR** ($CHCl_3$): 814, 1037, 1129, 1184, 1224, 1260, 1431,1465, 1508, 1602, 1701, 2877, 2962, 3033 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.88-2.11 (m, 2H), 2.29-2.39 (m, 1H), 2.70-2.92 (m, 3H), 3.42-3.65 (m, 4H), 5.87 (s, 2H), 6.11 (dd, *J* = 1.7, 8.4 Hz, 1H), 6.33 (d, *J* = 1.7 Hz, 1H), 6.61 (d, *J* = 8.4 Hz, 1H), 6.98 (t, *J* = 8.7 Hz, 2H), 7.18 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 29.7, 40.0, 42.3, 44.7, 47.3, 68.0, 97.8, 101.0, 105.4, 107.7, 115.5, 128.9, 138.0, 141.8, 153.8, 161.6; **Analysis** for $C_{19}H_{20}FNO_3$ requires C, 69.29; H, 6.12; N, 4.25; found C, 69.11; H, 6.26; N, 4.19%.

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Chapter III

$CoCl_2$-catalyzed chemoselective reduction of carboxylic esters with $NaBH_4$: asymmetric synthesis of (R)-tolterodine

Section I

$CoCl_2$-Catalyzed chemoselective reduction of esters with $NaBH_4$

3.1.1 Introduction

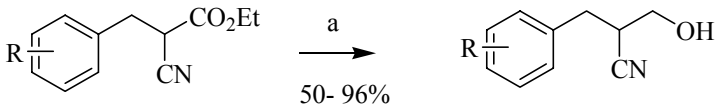
Reduction of carboxylic acids and esters is one of the most important reactions in organic chemistry.[1] Sodium borohydride ($NaBH_4$), lithium aluminum hydride (LAH), borane (BH_3), diisobutyl aluminum hydride (DIBAL-H) are some of common reducing agents known. Inspite of high reactivity of LAH, it was associated with drawbacks such as tedious workup procedure and poor chemoselectivity. Although DIBAL-H, an expensive reagent, is effective for the reduction of carboxylic esters with good chemoselectivity, it becomes unfavorable on large scale preparations. $BH_3 \cdot SMe_2$, another important reducing agent capable of reducing carboxylic acids yet fails to reduce carboxylic ester moiety. $NaBH_4$ is a mild, inexpensive yet powerful reducing agent capable of reducing wide range of functional groups such as aldehydes, ketones and imines.[2] Despite its low reactivity towards carboxylic acids and esters, recent studies indicate that the reactivity of $NaBH_4$ towards carboxylic acids and esters can indeed be enhanced by the addition of certain additives.

3.1.2 Review of literature

Several recent reviews are available in the literature for the reduction of carboxylic acids and esters with borohydrides.[3] Some of the recently reported modifications to enhance the reactivity of $NaBH_4$ for reduction of C=C bonds, carboxylic acids and esters by the addition of certain additives or by changing the structure of ester moiety which are presented below.

Bonds approach (1963)[4]

Bond *et al.* have reported the selective reduction of carboxylic ester in cyanoesters **1** to give cyanoalcohols **2** using $NaBH_4$ in diglyme in 50-95% yields (**Scheme 1**).



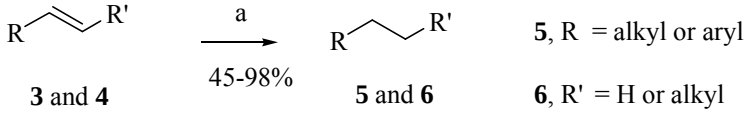
1 **2**

R = H, alkyl, OMe,

Scheme 1: (a) $NaBH_4$ (3 equiv.), diglyme, 25 °C, 3 h.

Chung's approach (1979)[5]

Chung *et al.* have reported the use of $CoCl_2 \cdot 6H_2O$ in combination with $NaBH_4$ for the reduction of C=C bond in styrenes **3** and aliphatic alkenes **4** to give the corresponding saturated alkanes **5-6** in 45-98% yields (**Scheme 2**).



3 and **4** **5** and **6**

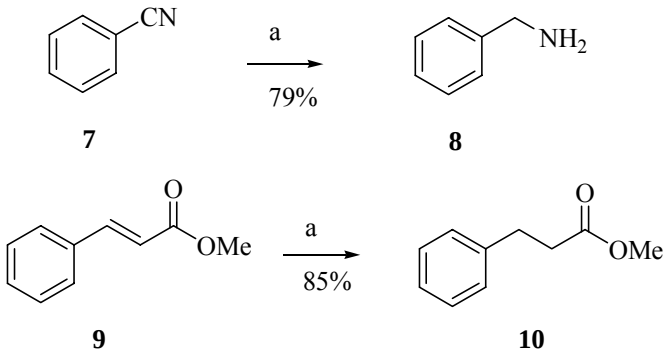
5, R = alkyl or aryl

6, R' = H or alkyl

Scheme 2: (a) $CoCl_2 \cdot 6H_2O$ (1 equiv.), $NaBH_4$ (2 equiv.) EtOH, 25 °C, 10 min-6 h.

Ganem's approach (1982)[6]

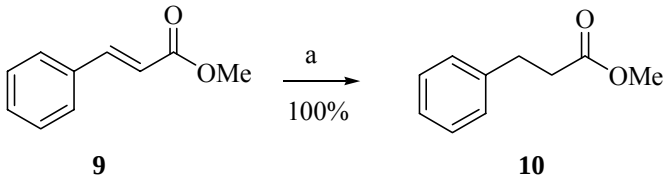
Ganem *et al.* have described the use of $CoCl_2$ in combination with $NaBH_4$ to reduce the benzonitrile (**7**) to give the corresponding benzylamine (**8**) in 79% yield. Also $CoCl_2/NaBH_4$ was found to be effective for reductions of C=C bond in conjugated esters **9** to give the saturated esters **10** in good yields (**Scheme 3**).



Scheme 3: (a) $CoCl_2 \cdot 6H_2O$ (1 equiv.), $NaBH_4$ (5 equiv.) MeOH:H_2O (5:2), 25 °C, 2-5 h.

Narisada's approach (1989)[7]

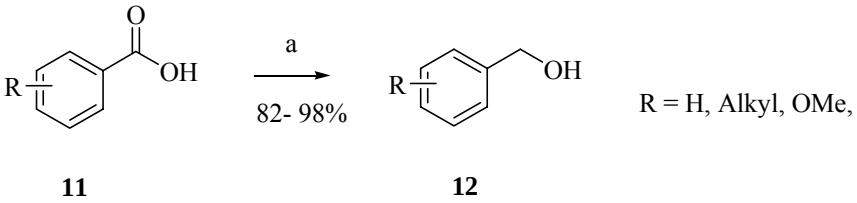
Narisada *et al.* have used Cu_2Cl_2 in combination with $NaBH_4$ for the reduction of C=C bond in α,β-unsaturated esters **9** to obtain the saturated esters **10** in high yields (**Scheme 4**).



Scheme 4: (a) Cu_2Cl_2 (0.75 equiv.), $NaBH_4$ (10 equiv.) MeOH: THF (7:3), 25 ºC, 2 h.

Periasamy's approach (1991)[8]

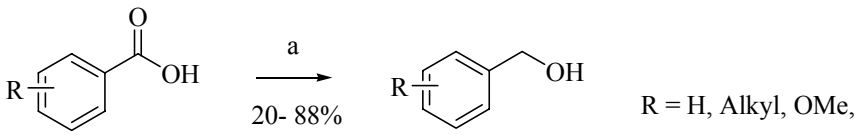
Periasamy *et al.* have reported I_2-promoted reduction of the carboxylic acids **11** with $NaBH_4$ to give the corresponding alcohols **12** in 82-98% yields (**Scheme 5**).



Scheme 5: (a) $NaBH_4$ (1.2 equiv.), I_2 (0.5 equiv.), THF, 25 ºC 1 h.

Periasamy's approach (1992)[9]

In another report, Periasamy *et al.* have used catechol in combination with TFA to promote the reduction of carboxylic acids **11** with $NaBH_4$ to afford alcohols **12** in 20-88% yields (**Scheme 6**).

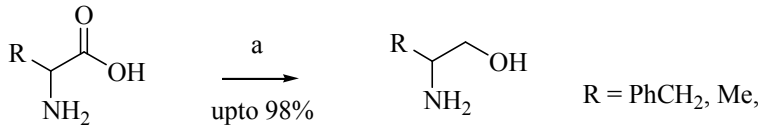


11 **12**

Scheme 6: (a) $NaBH_4$ (1 equiv.), catechol (2 equiv.), TFA (1 equiv.), THF, 4-12 h**.**

Abiko's approach (1992)[10]

Abiko *et al.* have used conc. H_2SO_4 in combination with $NaBH_4$ to promote reduction of amino acids **13** to give the corresponding amino alcohols **14** in high yields (**Scheme 7**).

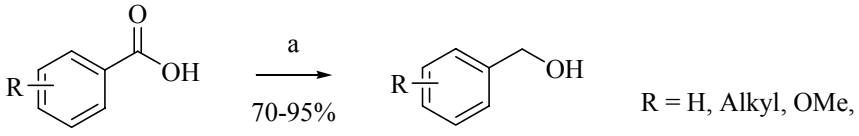


13 **14**

Scheme 7: (a) $NaBH_4$ (2.5 equiv.), H_2SO_4 (0.5 equiv.), THF, 4 h**.**

Narasimhan's approach (1995)[11]

Narasimhan *et al.* have used $Zn(BH_4)_2$ for the reduction of aryl carboxylic acids **11** to the corresponding benzyl alcohols **12** in 70-95% yields (**Scheme 8**).

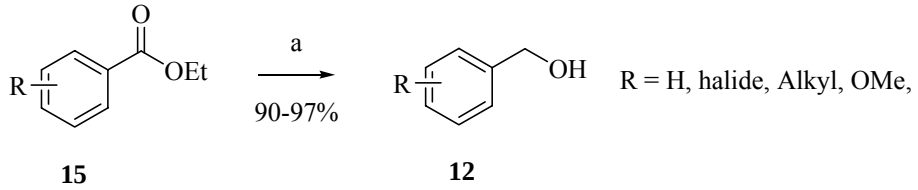


11 **12**

Scheme 8: (a) $Zn(BH_4)_2$ (0.5 equiv.), THF, 67 °C, 1-6 h**.**

Pittman's approach (2003)[12]

Pittman *et al.* have used LiCl in combination with $NaBH_4$ for the reduction of carboxylic esters **15** to give the respective alcohols **12** in 90-97% yields (**Scheme 9**).

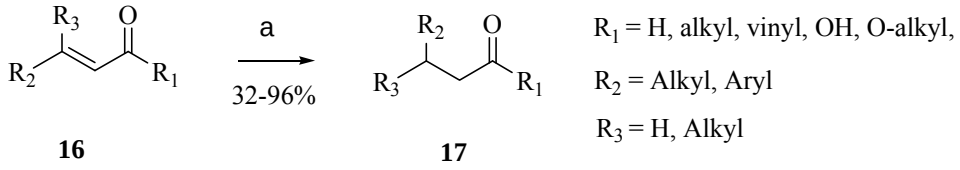


15 **12**

Scheme 9: (a) LiCl (1equiv.), $NaBH_4$ (1equiv.), diglyme , 162 ºC, 1 h

Khurana's Appraoach (2004)[13]

Khurana *et al.* have used nickel boride prepared *in situ* from $NiCl_2{\cdot}6H_2O$ and $NaBH_4$, in methanol–water at ambient temperature for the chemoselective reduction of C=C bond in *α,β*-unsaturated aldehydes, ketones, carboxylic acids, and esters **16** to give the corresponding saturated carbonyl compounds **17** (**Scheme 10**).

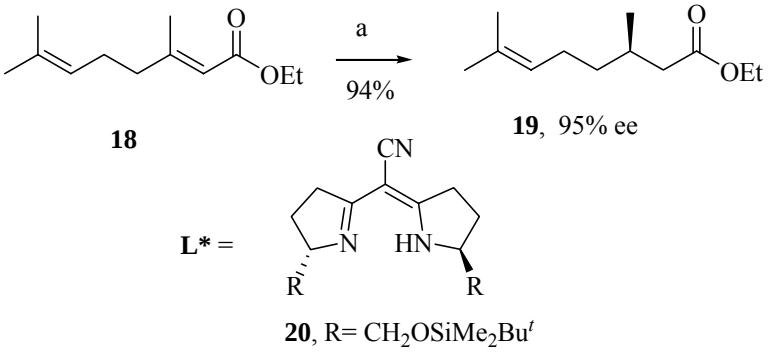


16 **17**

Scheme 10: (a) $NiCl_2{\cdot}6H_2O$ (5 equiv.), $NaBH_4$ (5 equiv.) MeOH:H_2O, 25 ºC, 0.25-10 h.

Reiser's approach (2005)[14]

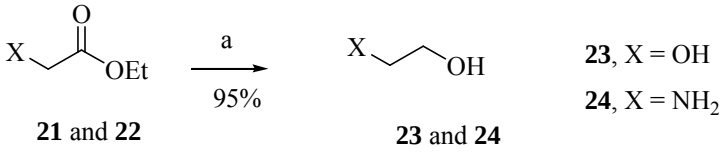
Reiser *et al.* have used $CoCl_2$ in combination with ligand **20** for the enantioselective reduction of C=C bond in *α,β*-unsaturated carbonyl compounds with sodium borohydride. *β*-Trisubstituted *α,β*-unsaturated esters **18** and amides were readily converted to their corresponding saturated counterparts **19** with enantioselectivities up to 97% ee (**Scheme 11**).



Scheme 11: $CoCl_2 \cdot 6H_2O$ (1 mol%), L* **20** (1.1 mol%), $NaBH_4$ (2 equiv.) EtOH;DMF (1:1), 25 °C, 24 h.

Zhu's approach (2006)[15]

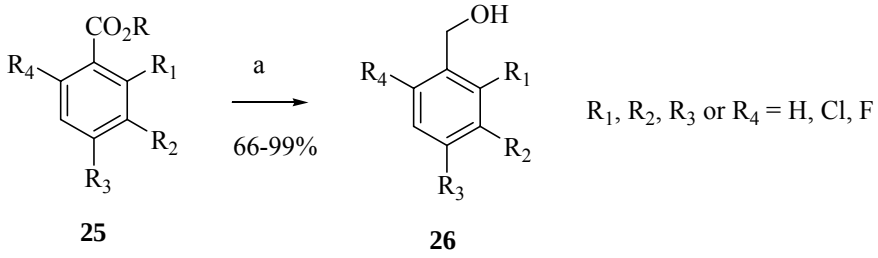
Zhu *et al.* have reported the reduction of *α*-hydroxy and *α*-amino esters **21** and **22** with $NaBH_4$ to give the corresponding diols **23** and amino alcohols **24** in high yields (**Scheme 12**).



Scheme 12: (a) $NaBH_4$ (1 equiv.), diglyme, 30 °C, 3 h.

De Souza's Approach (2006)[16]

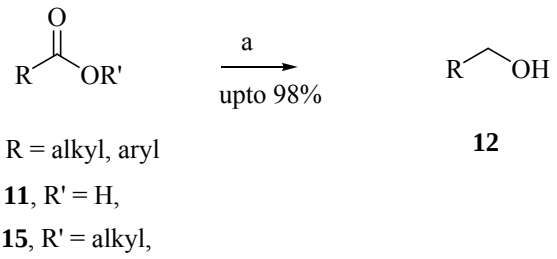
De Souza *et al.* have described reduction of several aromatic ethyl isopropyl and benzyl esters **25** with $NaBH_4$: MeOH system in refluxing THF to their corresponding alcohols **26** in 66-99% yield (**Scheme 13**).



Scheme 13: (a) $NaBH_4$ (6.0 equiv.), MeOH (8 mL), THF, 70 ºC.

Zhang's approach (2007)[17]

Zhang *et al.* have used KBH_4 in combination with $MgCl_2$ to reduce acids **11** and esters **15** to the respective alcohols **12** in high yields (**Scheme 14**).



Scheme 14 : $KBH_4 \cdot MgCl_2$ (1.2 equiv.), THF, 66 °C, 2 h.

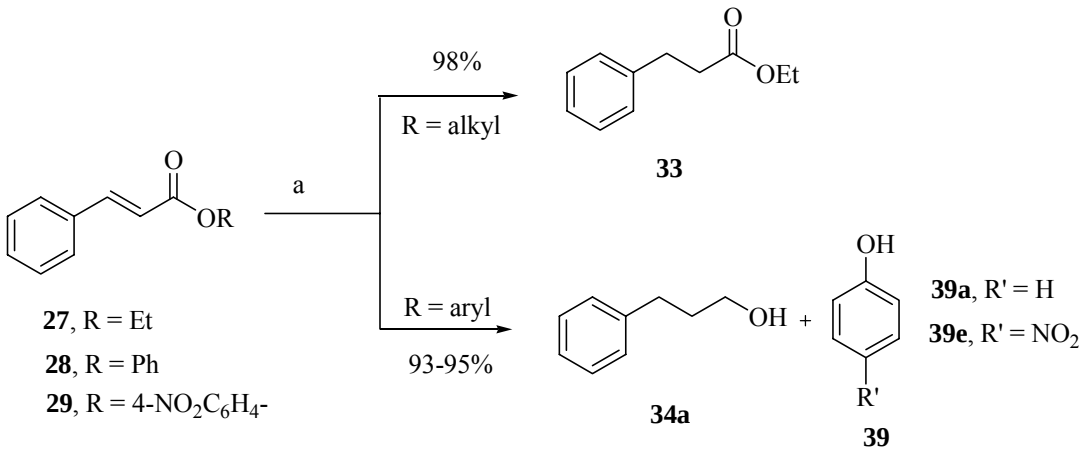
3.1.3 Present work

3.1.3.1 Objective

Review of literature reveals that several modifications in terms of additives, reaction conditions, etc have been reported for the reduction of carboxylic acids and esters with $NaBH_4$. The modifications also include substitutions at α-position by groups such as OH, NH_2 and CN. Although several reducing reagents are known to reduce carboxylic ester moiety to the corresponding alcohols, these are costly, difficult to handle and often requires harsh conditions. In recent years, reactivity of $NaBH_4$ has been increased by the addition of metal salts like $CoCl_2$, $MgCl_2$, $CaCl_2$, LiCl and $ZnCl_2$. A combination of catalytic $CoCl_2$ with $NaBH_4$ has been extensively used for the reduction of C=C in α,β-unsaturated esters, but it fails to reduce ester functionality under the reaction conditions. In this section, we describe the use of $CoCl_2$ as catalyst in the reduction of carboxylic esters with $NaBH_4$ to the corresponding saturated alcohols under ambient reaction conditions.

3.1.3.2 Results and Discussion

In our study, for the preparation of phenyl-3-phenylpropanoate, we visualized Co-catalyzed reduction of C=C bond in *phenyl* cinnamate (**28**) with $NaBH_4$. Accordingly, we subjected *phenyl* cinnamate (**28**) for the reduction of C=C bond with $CoCl_2 \cdot 6H_2O$ (1 mol %) and of $NaBH_4$ (2 equiv.) in ethanol. Unexpectedly, we found that, under the reaction conditions, ester moiety was also reduced simultaneously to give the corresponding 3-phenylpropanol (**34a**) in 95 % yield. However, carboxylic ester moiety in *ethyl* cinnamate (**27**) was found to be unaffected under the same reduction conditions giving ethyl 3-phenylpropanoate (**33**) in 98 % yield (**Scheme 15**).

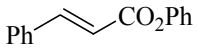
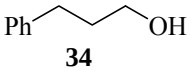
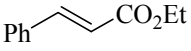
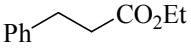
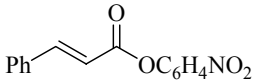
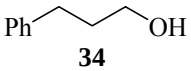
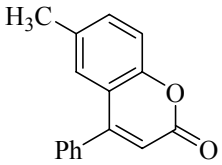
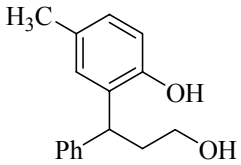
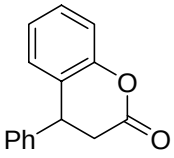
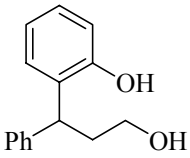
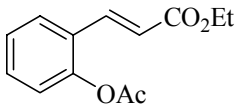
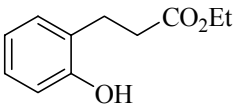


Scheme 15: (a) Unsaturated ster (2 mmol), $NaBH_4$ (4 mmol), $CoCl_2.6H_2O$ (1 mol%), EtOH (10 mL), 0-25 ˚C, 10 h.

In order to generalize the scope of the reaction, we subjected coumarin (**30**) and dihydrocoumarin (**31**) to $CoCl_2$-catalyzed reduction with $NaBH_4$. We found that both C=C bond and carboxylic ester group underwent reductions simultaneously to give the corresponding saturated alcohols **35** and **36** respectively in 89-93 % yields. Interestingly, (*E*)-ethyl 3-(2-acetoxyphenyl)acrylate (**32**) under the reaction conditions underwent selective reduction of C=C only along with deacylation of acetate moiety, thus the ethyl

ester moiety was unaffected giving saturated ester **37** in 95 % yield. Results of the study are presented in **Table 1**, which showed that phenyl esters can be easily reduced to the corresponding phenols in high yields.

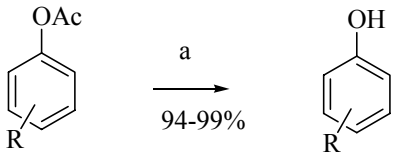
Table 1: $CoCl_2 \cdot 6H_2O$-catalyzed chemoselective reduction of phenyl esters with $NaBH_4$[a]

No	Ester	Product	Yield (%)[b]
a	 **28**	 **34**	95[c]
b	 **27**	 **33**	98
c	 **29**	 **34**	93[d]
d	 **30**	 **35**	89
e	 **31**	 **36**	93
f	 **32**	 **37**	95

[a] Reaction condition : Ester (2 mmol), $NaBH_4$ (4 mmol), $CoCl_2.6H_2O$ (1 mol%), EtOH (10 mL), 0-25 ˚C, 10 h.
[b] isolated yields after chromatographic purification.
[c] phenol was isolated in quantitative yield.
[d] 4-$NO_2C_6H_4OH$ was isolated in quantitative yield.

Moreover, phenols can be protected as phenyl acetates and deprotected under strong basic as well as acidic conditions. We found that our reagent was quite effective in reductively deprotecting acetyl groups. Thus, we subjected various phenyl acetates for

reductions with $CoCl_2 \cdot 6H_2O$ (1 mol%) and $NaBH_4$ (2 equiv.), which afforded the corresponding phenols in excellent yields (**Scheme 16**).



38a-h **39a-h**

Scheme 16: (a) ArOAc (2 mmol), $NaBH_4$ (4 mmol), $CoCl_2.6H_2O$ (1 mol%), EtOH (10 mL), 0-25 ˚C, 10 h.

Several phenolic acetates **38a-h** underwent reduction to give free phenols **39a-h** in excellent yields (**Table 2**). Notably, under the reaction conditions reducible functional groups such as halide, NO_2, and CN were found to be unaffected.

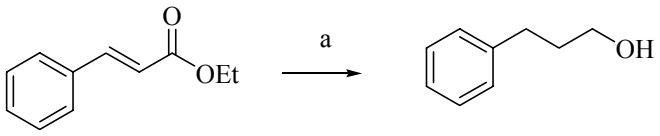
Table 2: $CoCl_2 \cdot 6H_2O$-catalyzed chemoselective reduction of phenyl esters with $NaBH_4$[a]

No	Phenyl acetates (**38a-h**)	Products (**39a-h**)	Yield (%)[b]
a	C_6H_5OAc	C_6H_5OH	99
b	2-$H_3CC_6H_4OAc$	2-$H_3CC_6H_4OH$	98
c	2-$H_3COC_6H_4OAc$	2-$H_3COC_6H_4OH$	97
d	4-BrC_6H_4OAc	4-BrC_6H_4OH	97
e	4-$O_2NC_6H_4OAc$	4-$O_2NC_6H_4OH$	95
f	4-$EtO_2CC_6H_4OAc$	4-$EtO_2CC_6H_4OH$	94
g	1-Naphthyl-OAc	1-Naphthol	98
h	3-AcO-pyridine	3-Hydroxypyridine	97

[a] Reaction condition : Ester (2 mmol), $NaBH_4$ (4 mmol), $CoCl_2.6H_2O$ (1 mol%), EtOH (10 mL), 0-25 ˚C, 10 h.
[b] isolated yields after chromatographic purification.

We thus observed that $CoCl_2$ effectively catalyzes the reduction of phenyl esters to give the corresponding saturated alcohols in high yields. However, such modification of ester moiety with aryl substitution limits the scope of the reaction as alkyl ester reduction was found to be more atom economical. To increase the reactivity of $NaBH_4$, additives such

as transition metal salts have been extensively studied in recent years. We have reasoned that an elegant combination, comprising catalytic amount of $CoCl_2 \cdot 6H_2O$ in combination with several amines may be effective for the reduction of carboxylic esters with $NaBH_4$. Thus, we subjected reduction of *ethyl* cinnamate to reduction with catalytic amount of $CoCl_2$ in combination with $NaBH_4$, in the presence of various amines. Systematic study on effect of addition of various amines like $PhNH_2$, Et_3N, DMAP and diisopropyl amine in the Co-catalyzed reductions was also carried out. We then found that diisopropyl amine was an effective additive for the Co-catalyzed reduction of simple carboxylic esters (**Scheme 17**).

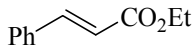
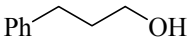
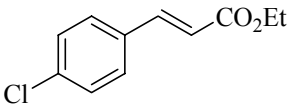
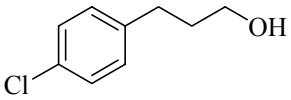
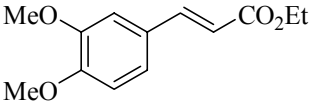
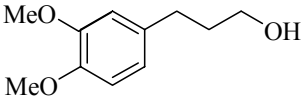
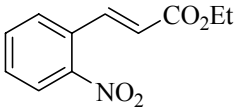
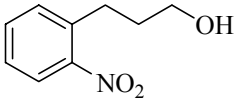
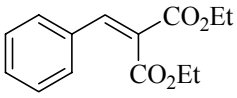
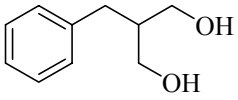
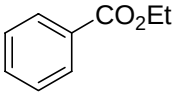
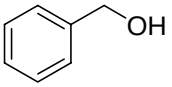
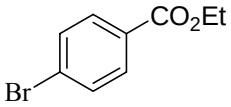
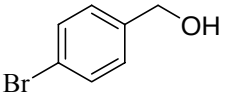
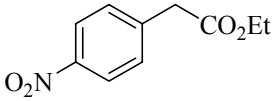
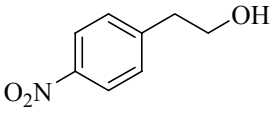
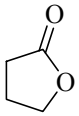
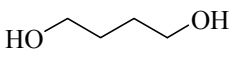


27 **34**

Scheme 17: (a) Ester (2 mmol), $NaBH_4$ (4 mmol), $CoCl_2 \cdot 6H_2O$ (5 mol%), $^{i}Pr_2NH$ (10 mol%), EtOH (10 mL), 50-60 ˚C, 24 h.

Systematic study was further carried out on different esters; the results of which are presented in **Table 3**. Various carboxylic esters underwent reductions to give the corresponding alcohols in good yields. Reducible functional groups such as NO_2, CN and halides again were found to be unaffected. In these cases reductions underwent slowly requiring 12-24 hours and 5-10% catalyst as compared to phenyl esters.

Table 3: $CoCl_2 \cdot 6H_2O$-$^iPr_2NH$-catalyzed chemoselective reductions of esters with $NaBH_4$[a]: Role of diisopropyl amine[a]

No	Ester (**27a-i**)	Additive (10 mol %)	Product (**34a-i**)	Yield (%)[b]
a		$^iPr_2NH$		95
		DMAP		12
		Et_3N		30
b		$^iPr_2NH$		87
c		$^iPr_2NH$		82
d		$^iPr_2NH$		87
e		$^iPr_2NH$		94
f		$^iPr_2NH$		87
g		$^iPr_2NH$		82
h		$^iPr_2NH$		79
i		$^iPr_2NH$		81

[a]Reaction condition : Ester (2 mmol), $NaBH_4$ (4 mmol), $CoCl_2 \cdot 6H_2O$ (5 mol%), $^iPr_2NH$ (10 mol%), EtOH (10 mL), 0-25 ˚C, 24 h.
[b]isolated yields after chromatographic purification.

Mechanism:

Mechanistically, it may be reasoned that participation of the oxygen lone pair in resonance with aromatic rings results in a higher carbonyl bond order in phenyl esters than in the corresponding ethyl esters so that the addition of 'hydride' from the reagent is faster to the more reactive phenyl esters, which is rate determining; thus probably accounting for higher selectivity (**Fig. 1**).

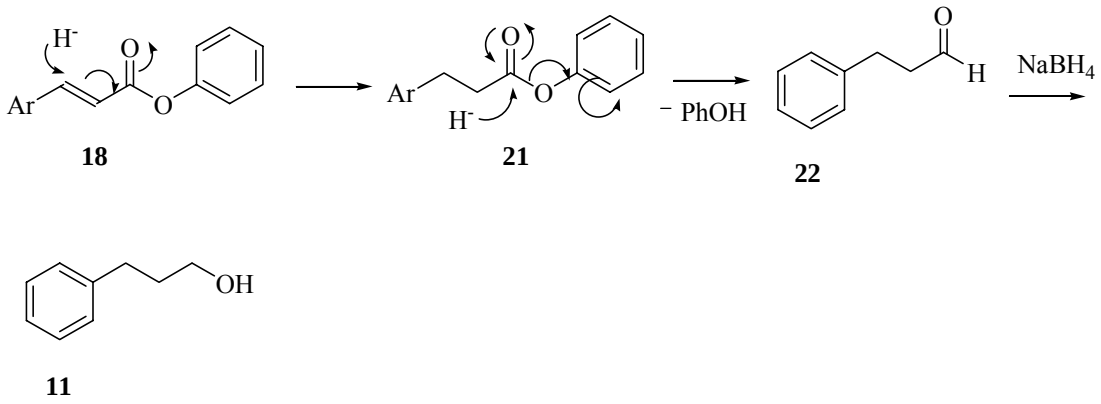


Fig. 1: Mechanism of *phenyl* ester reductions with $NaBH_4$

Generally, $CoCl_2$ reacts with $NaBH_4$ to give the reactive intermediate $Co(BH_4)_2$.[5, 6] Probably, diisopropyl amine makes a complex with $Co(BH_4)_2$, which enhances the reactivity of hydride towards the simple esters to give the corresponding alcohols (**Fig. 2**).

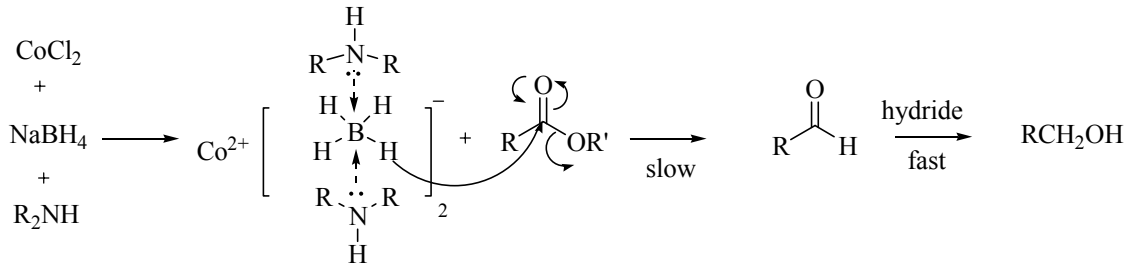


Fig. 2: Mechanism of *carboxylic* ester reduction with catalytic $CoCl_2$: R_2NH /$NaBH_4$

The formation of all products was confirmed unambiguously from their corresponding spectral analysis. For example, ^{1}H NMR of the **36** showed characteristic signals at δ 2.15-2.40 (m), 3.53-3.78 (m) and 4.60 (dd) due to methylene (C**H**$_2$) and methine (C**H**) protons respectively. Its ^{13}C NMR showed signals at δ 37.0, 38.5 and 60.5 due to the methine (**C**H) and two methylene (**C**H$_2$) carbons respectively (**Fig. 3**).

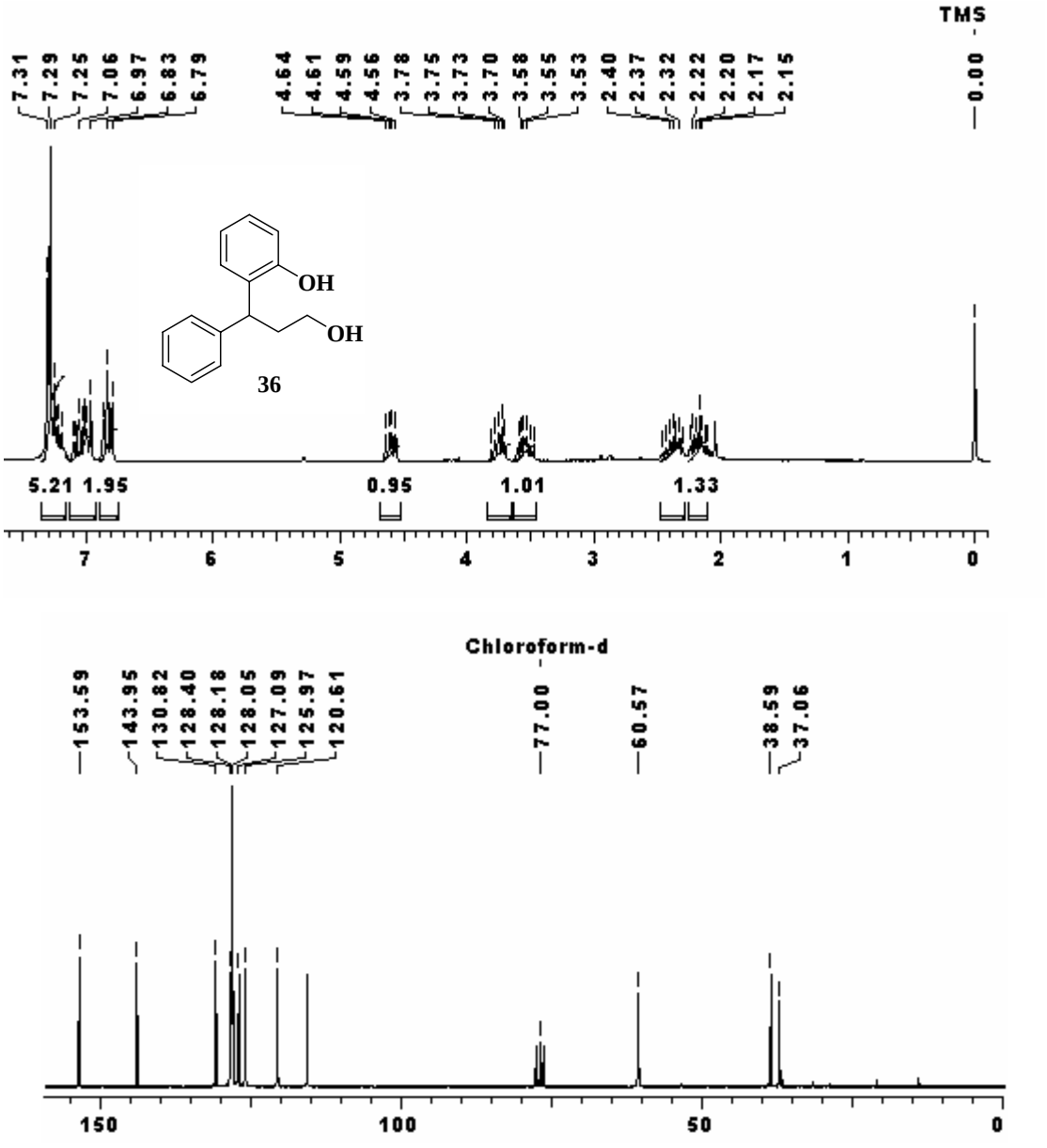


Fig. 3: ^{1}H and ^{13}C NMR spectra of alcohol 36

As a second example, the ^{1}H NMR of nitro alcohol **34d** showed characteristic signals at δ 1.94 (m), 2.99 (t), 3.72 (t) due to methylene (C**H**$_2$) protons and typical aromatic signals 7.35-7.53 (m) 7.90 (dd) due to aromatic protons. Its ^{13}C NMR showed a characteristic signal at δ 61.6 due to methylene (**C**H$_2$OH) confirming formation of alcohol **34d (Fig. 4)**.

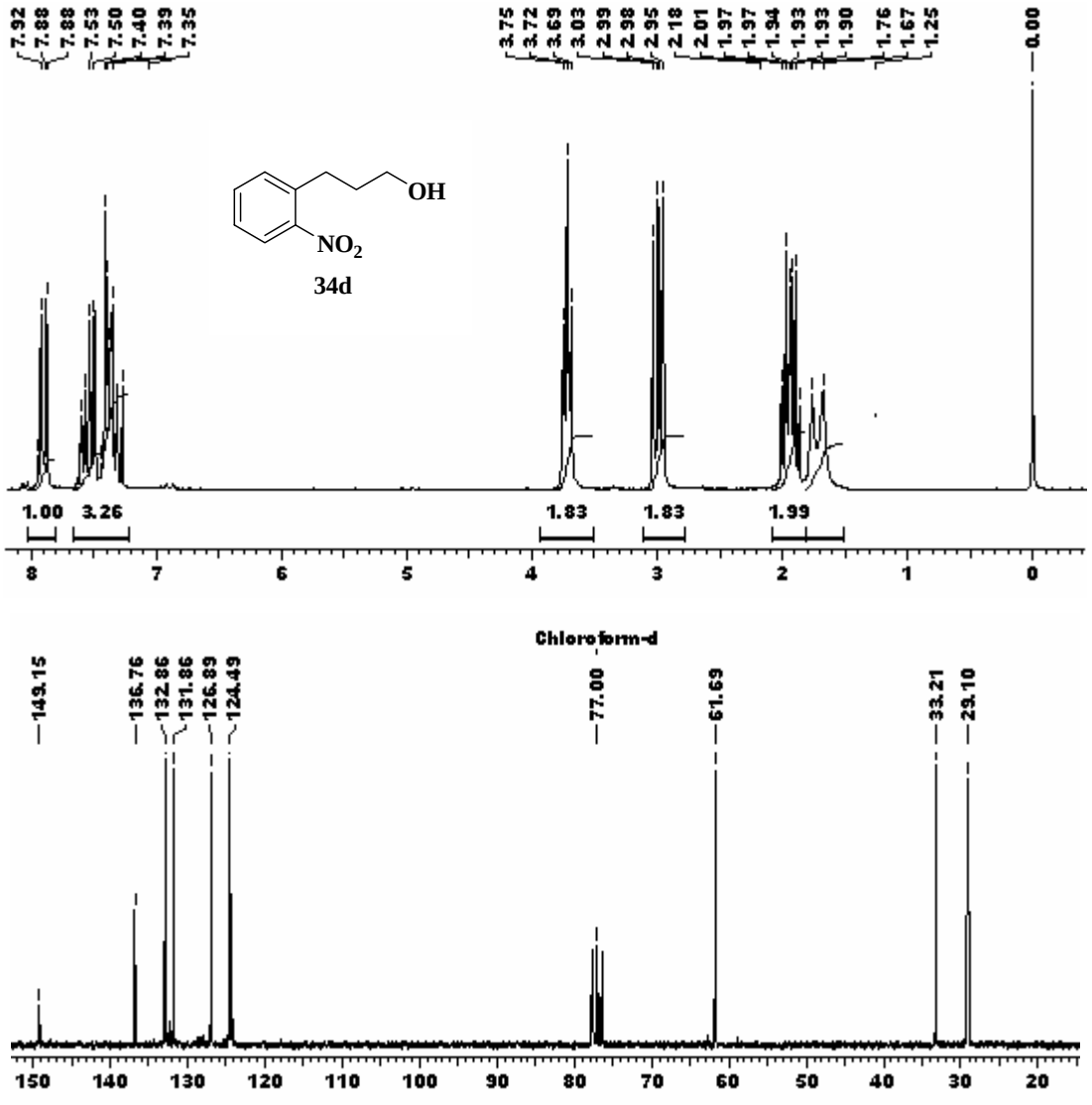


Fig. 4: ^{1}H and ^{13}C NMR spectra of nitro alcohol 34d

3.1.4 Conclusion

In conclusion we have described use of $NaBH_4$ in combination with catalytic amount of $CoCl_2$ to reduce the phenyl esters in high yields and chemoselectivity. We have described the use of a new elegant catalytic combination comprising $CoCl_2$ and diisopropyl amine for the reduction of alkyl carboxylic esters to give saturated alcohols in high yields. This reduction procedure was found to be a good alternative for the use of strong reducing agents like LAH and DIBAL-H which are costly and difficult to handle.

3.1.5 Experimental section

General experimental procedure for the reduction of esters (**28-32**):

To a stirred solution of esters **28-32** (2 mmol) and $CoCl_2 \cdot 6H_2O$ (4.7 mg, 1mol %) in 95% ethanol (10 mL), $NaBH_4$ (152 mg, 4 mmol) was added slowly at 0 °C. It was then allowed to stir for 10 h at 25 °C. After completion of the reaction (monitored by TLC), it was quenched with addition of water (20 mL) and ethyl acetate (20 mL) forming dark black solution, which was passed through celite. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product. Chromatographic purification of crude product [silica gel (230-400 mesh, petroleum ether: ethyl acetate (70:30) as eluent] afforded alcohols **33-37** in pure form.

Ethyl 3-phenylpropanoate (33):

Yield: 98%; colorless liquid; **IR** ($CHCl_3$): 698, 744, 968, 1029, 1060, 1454, 1495, 1747 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.25 (t, *J* = 7.3 Hz, 3H), 2.65-2.72 (m, 2H), 2.81-2.91 (m, 1H), 4.15 (q, *J* = 7.3 Hz, 2H), 7.15-7.33 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$):

δ 13.9, 30.6, 35.3, 59.8, 125.9, 127.9, 128.1, 140.3, 172.6; **Analysis** for $C_{11}H_{14}O_2$ requires C, 74.13; H, 7.92; found C, 74.11; H, 7.95%.

3-(Phenyl)propan-1-ol (34a):

Yield: 95%; colorless liquid; **IR** ($CHCl_3$): 698, 744, 968, 1029, 1060, 1454, 1495, 3325 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.44 (bs, 1H), 1.84-1.95 (m, 2H), 2.70 (t, *J* = 8.0 Hz, 2H), 3.65 (t, *J* = 6.3 Hz, 2H), 7.13-7.31 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 31.11, 33.73, 63.39, 126.73, 127.14, 128.15, 140.43; **Analysis** for $C_9H_{12}O$ requires C, 79.37; H, 8.88; found C, 79.32; H, 8.82%.

2-(3-Hydroxy-1-phenylpropyl)-4-methylphenol (35):

Yield: 93%; colorless solid, **mp:** 77 ºC; **IR** ($CHCl_3$)**:** 702, 818, 1037 1255, 1446, 1504, 1610, 3170, 3419 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.05-2.45 (m, 2H), 2.17 (s, 3H), 3.46-3.59 (m, 1H) 3.70-3.80 (m, 1H), 4.56 (dd, *J* = 5.9, 9.9 Hz, 1H) 6.69-6.88 (m, 3H), 7.17-7.31 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.1, 36.9, 38.3, 59.7, 114.9, 125.1, 126.5, 127.6, 127.9, 128.0, 130.2, 144.4, 151.6; **Analysis** for $C_{16}H_{18}O_2$ requires C, 79.31; H, 7.49; found C, 79.27; H, 7.47%.

2-(3-Hydroxy-1-phenylpropyl)phenol (36):

Yield: 93%; Gum; **IR** ($CHCl_3$): 700, 746, 808, 1020, 1238, 1367, 1454, 1595, 1610, 2923, 3211, 3413 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.10-2.44 (bs, 1H and m, 2H), 3.50-3.78 (m, 2H), 4.56-4.64 (dd, *J* = 6.0, 9.9 Hz, 1H), 6.83 (t, *J* = 8.0 Hz, 1H), 6.97-7.10 (m, 2H), 7.19-7.31 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 37.0, 38.5, 60.5, 115.7, 120.6, 125.9, 127.0, 128.0, 128.1, 128.4, 130.8, 143.9, 153.5; **Analysis** for $C_{15}H_{16}O_2$ requires C, 78.92; H, 7.06; found C, 78.90; H, 7.03%.

Ethyl 3-(2-hydroxyphenyl)propanoate (37):

Yield: 95%; gum ; **IR** ($CHCl_3$): 698, 746, 965, 1029, 1060, 1454, 1479, 1745, 3170, 3420 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.23 (t, *J* = 7.2 Hz, 3H), 1.68 (bs, 1H), 2.67-2.75 (m, 2H), 2.86-2.94 (m, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 6.86-6.94 (m, 2H), 7.07-7.16 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.9, 24.9, 34.8, 61.0, 116.5, 127.7, 130.3, 154.2, 175.2; **Analysis** for $C_{11}H_{14}O_3$ requires C, 68.02; H, 7.27; found C, 68.12; H, 7.11%.

A general experimental procedure for the reduction of phenol acetates (38a-h):

To a stirred solution of phenol acetates **38a-h** (2 mmol) and $CoCl_2 \cdot 6H_2O$ (4.7 mg, 1 mol %) in 95% ethanol (10 mL), was added $NaBH_4$ (76 mg, 2 mmol) slowly at 0 °C. It was then stirred for 1-2 h at 25 °C. After completion of the reaction (monitored by TLC), it was quenched with the addition of water (20 mL) and ethyl acetate (20 mL) forming dark black solution, which was passed through celite. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 20mL). The combined organic layer was washed with brine (2 x 20 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product. Chromatographic purification of crude product [silica gel (230-400 mesh, petroleum ether: ethyl acetate (70:30) as eluent] afforded phenols **39a-h** in pure form.

Phenol (39a):

Yield: 99%; colorless solid, **mp:** 42 ºC; **IR** ($CHCl_3$): 752, 810, 887, 1218, 1365, 1498, 1595, 3342 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.00 (bs, 1H), 6.85-6.95 (m, 2H), 6.94-7.01 (m, 1H), 7.25-7.33 (m, 2H); **^{13}CNMR** (50 MHz, $CDCl_3$): δ 115.4, 120.9, 129.6, 154.9; **Analysis** for C_6H_6O requires C, 76.57; H, 6.43; found C, 76.53; H, 6.47%.

2-Methylphenol (39b):

Yield: 98%; Gum; **IR** ($CHCl_3$): 752, 842, 1043, 1108, 1242, 1463, 1504, 1593, 3386 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.25 (s, 3H), 6.75-6.87 (m, 2H), 7.04-7.14 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 15.6, 114.9, 120.5, 124.1, 126.8, 130.9, 153.5; **Analysis** for C_7H_8O requires C, 77.75; H, 7.46; found C, 77.71; H, 7.44%.

2-Methoxyphenol (39c):

Yield: 97%; Gum; **IR** ($CHCl_3$): 746, 833, 916, 1024, 1108, 1224, 1259, 1502, 1595, 3427, 3527 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.89 (s, 3H), 5.58 (bs, 1H), 6.83-6.93 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.6, 110.7, 114.5, 119.9, 121.3, 145.6, 146.5; **Analysis** for $C_7H_8O_2$ requires C, 67.73; H, 6.50; found C, 67.71; H, 6.52%.

4-Bromophenol (39d)

Yield: 97%; white solid, **mp**: 62 ºC; **IR** ($CHCl_3$): 821, 1072, 1242, 1436, 1488, 1587, 3271 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.95 (bs,1H), 6.72 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 8.8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 113.0, 117.1, 132.4, 154.2; **Analysis** for C_6H_5BrO requires C, 41.65; H, 2.91; found C, 41.60; H, 2.89%.

4-Nitrophenol (39e):

Yield: 95%; yellow solid, **mp**: 119 ºC; **IR** ($CHCl_3$): 756, 810, 1112, 1215, 1286, 1489, 1612 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 6.28 (s, 1H), 6.92 (d, J = 9.2 Hz, 2H), 8.18 (d, J = 9.2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 115.0, 125.2, 139.4, 163.2; **Analysis** for $C_6H_5NO_3$ requires C, 51.80; H, 3.62; N, 10.07; found C, 51.82; H, 3.59; N, 10.02%.

Ethyl 4-hydroxybenzoate (39f):

Yield: 94%; colorless solid, **mp**: 115 ºC; **IR** ($CHCl_3$): 771, 850, 1016, 1168, 1454, 1591, 1612, 3213 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.38 (t, J = 7.1 Hz, 3H), 4.36 (q, J = 7.1 Hz, 2H), 6.89 (d, J = 8.9 Hz, 2H), 7.96 (d, J = 8.9 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$):

δ 13.6, 59.7, 114.6, 120.6, 130.9, 161.1, 165.8; **Analysis** for $C_9H_{10}O_3$ requires C, 65.05; H, 6.07; found C, 65.02; H, 6.06%.

1-Naphthol (39g):

Yield: 98%; colorless solid, **mp:** 95 °C; **IR** ($CHCl_3$) 765, 788, 1043, 1083,1271, 1369, 1458, 1579, 1598, 2929, 3255 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.40 (bs, 1H), 6.77 (dd, 1.1, 7.3 Hz, 1H), 7.27 (dt, 1.1, 7.3 Hz, 1H), 7.39-7.51 (m, 3H), 7.76-7.83 (m, 1H), 8.11-8.18 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 110.1, 120.2, 121.3,125,2, 125.9, 126.2, 126.9,130.9, 156.9; **Analysis** for $C_{10}H_8O$ requires C, 83.31; H, 5.59; found C, 83.12; H, 5.32%.

Pyridin-3-ol (39h):

Yield: 98%; colorless solid, **mp:** 125 °C; **IR** ($CHCl_3$): 798, 1280, 1375, 1458, 2854, 2923, 2956 cm^{-1}; **H NMR** (200 MHz, $CDCl_3$): δ 7.26-7.35 (m, 2H), 8.08-8.11 (dd, J = 1.9, 4.3 Hz, 1H), 8.28-8.30 (dd, J = 0.9, 2.5 Hz, 1H), **^{13}C NMR** (50 MHz, $CDCl_3$): δ 121.0, 122.6, 136.4, 138.4, 152.6; **Analysis** for C_5H_5NO requires C, 63.15; H, 5.30; N, 14.73; found C, 63.11; H, 5.33; N, 14.71%.

A general experimental procedure for the reduction of esters: addition of diisopropyl amine:

To a stirred solution of esters **27a-i** (2 mmol), $CoCl_2{\cdot}6H_2O$ (24 mg, 5 mol %) and diisopropyl amine (0.02 mL, 10 mol %) in 95% ethanol (10 mL), $NaBH_4$ (152 mg, 4 mmol) was added slowly at 25 °C. It was then stirred for 24 h at 50-60 °C. After completion of the reaction (monitored by TLC), it was quenched with addition of water (20 mL) and ethyl acetate (20 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 20 mL). The combined organic layers were

washed with brine (2 x 20 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude products. Chromatographic purification of crude product [silica gel (230-400 mesh, petroleum ether: ethyl acetate (70:30) as eluent] afforded alcohols **34a-i** in pure form.

3-(4-Chlorophenyl)propan-1-ol (34b):

Yield: 87%; gum, **IR** ($CHCl_3$): 754, 968, 1029, 1060, 1454, 1495, 3325 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.76 (bs, 1H), 1.78-1.92 (m, 2H), 2.67 (t, *J* = 7.3 Hz, 2H), 3.61 (t, *J* = 7.3 Hz, 2H), 7.12 (d, *J* = 8.5, 2H), 7.24 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 31.1, 33.7, 61.3, 128.1, 129.5, 131.2, 140.0; **Analysis** for $C_9H_{11}ClO$ requires C, 63.35; H, 6.50; Found C, 63.32; H, 6.52%.

3-(3,4-Dimethoxyphenyl)propan-1-ol (34c):

Yield: 82%; gum, **IR** ($CHCl_3$): 745, 857, 968, 1029, 1060, 1460, 1495, 3498 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.64 (bs, 1H), 1.61-1.95 (m, 2H), 2.67 (t, *J* = 8.1 Hz, 2H), 3.68 (t, *J* = 8.1 Hz, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 6.72-6.86 (m, 3H); **^{13}C NMR** (50 MHz $CDCl_3$): δ 31.5, 34.2, 55.7, 55.8, 62.1, 111.2, 111.6, 120.10 134.3, 147.0, 147.7; **Analysis** for $C_{11}H_{16}O_3$ requires C, 67.32; H, 8.22; found C, 67.28; H, 8.21%.

3-(2-Nitrophenyl)propan-1-ol (34d):

Yield: 87%; gum, **IR** ($CHCl_3$): 857, 968, 1029, 1060, 1245, 1440, 1507, 3430 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.67 (bs, 1H), 1.87-2.01 (m, 2H), 1.99 (t, *J* = 7.6 Hz, 2H), 3.72 (t, *J* = 6.2 Hz, 2H), 7.31-7.60 (m, 3H), 7.88-7.95 (dd, *J* = 1.2, 8.1 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 29.1, 33.2, 61.6, 124.4, 126.8, 131.8, 132.8, 136.7, 149.1; **Analysis** for $C_9H_{11}NO_3$ requires C, 59.66; H, 6.12; N, 7.73; found C, 59.63; H, 6.10; N, 7.75%.

2-Benzylpropane-1,3-diol (34e):

Yield: 94%; gum, **IR** ($CHCl_3$): 745, 857, 968, 1029, 1060, 1454, 1498, 3400 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.99-2.27 (m, 1H, and bs, 2H), 2.62 (d, *J* = 7.6 Hz, 2H), 3.63-3.85 (m, 4H), 7.17-7.36 (m, 5H); **^{13}C NMR** (50 MHz $CDCl_3$): δ 34.1, 43.7, 64.9, 126.0, 128.9, 139.8; **Analysis** for $C_{10}H_{14}O_2$ requires for C, 72.26; H, 8.49; found C, 72.23; H, 8.44;

Phenylmethanol (34f):

Yield: 94%; gum, **IR** ($CHCl_3$): 857, 968, 1495, 3498 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.99 (bs, 1H), 4.66 (s, 2H), 7.25-7.37 (m, 5H); **^{13}C NMR** (50 MHz $CDCl_3$): δ 64.3, 126.7, 127.1, 128.1, 140.6; **Analysis** for C_7H_8O requires C, 77.75; H, 7.46; found 77.72; H, 7.45%.

(4-Bromophenyl)methanol (34g):

Yield: 94%; gum, **IR** ($CHCl_3$): 968, 1029, 1060, 1501, 3390 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ1.88 (bs, 1H), 4.64 (s, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (50 MHz $CDCl_3$): δ 63.9, 121.1, 128.4, 131.3, 139.5; **Analysis** for C_7H_7BrO requires C, 44.95; H, 3.77; found C, 44.92; H, 3.73%.

2-(4-Nitrophenyl)ethanol (34i):

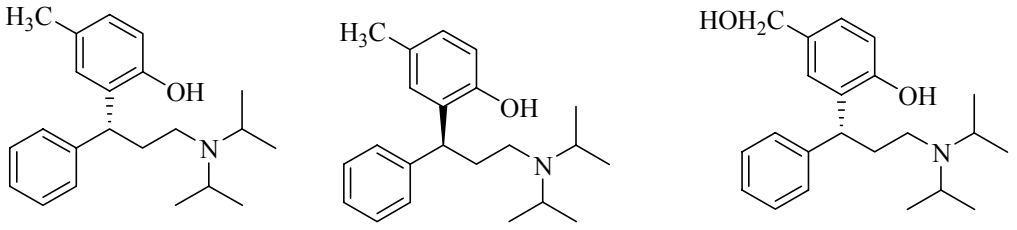
Yield: 94%; gum, **IR** ($CHCl_3$): 857, 1063, 1245, 1498, 3450; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.70 (bs, 1H), 2.96 (t, *J* = 6.3 Hz, 2H), 3.91 (m, 2H), 7.40 (d, *J* = 8.7 Hz, 2H), 8.15 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR** (50 MHz $CDCl_3$): δ 67.2, 121.2, 128.6, 146.1, 147.1;**Analysis** for $C_8H_9NO_3$ requires C, 57.48; H, 5.43; N, 8.38; found C, 57.44; H, 5.40; N, 8.35%.

Section II: Asymmetric Synthesis of (*R*)-tolterodine

3.2.1 Introduction

3.2.1.1 Pharmacology and use:

(*R*)-Tolterodine (**40a**) is a competitive muscarinic receptor antagonist.[18] Both urinary bladder contraction and salivation are mediated *via* cholinergic muscarinic receptors. (*S*)-tolterodine (**40b**) has shown a non-cholinergic spasmolytic activity and a weak sedative effect. After oral administration, tolterodine is metabolized in the liver, resulting in the formation of the 5-hydroxymethyl derivative (**40c**), a major pharmacologically active metabolite. The 5-hydroxymethyl metabolite, which exhibits an antimuscarinic activity similar to that of tolterodine, contributes significantly to the therapeutic effect. Both tolterodine and the 5-hydroxymethyl metabolite exhibit a high specificity for muscarinic receptors, since both show negligible activity and affinity for other neurotransmitter receptors and other potential cellular targets, such as calcium channels. Tolterodine (**40a**) has a pronounced effect on bladder function. The main effects of tolterodine are an increase in residual urine, reflecting an incomplete emptying of the bladder, and a decrease in detrusor pressure, consistent with an antimuscarinic action on the lower urinary tract. For the treatment of overactive bladder (with symptoms of urinary frequency, urgency, or urge incontinence)



40a (*R*)-Tolterodine

40b (*S*)-Tolterodine

40c 5-hydroxymethyltolterodine

Fig. 5: Structures of tolterodines and metabolite

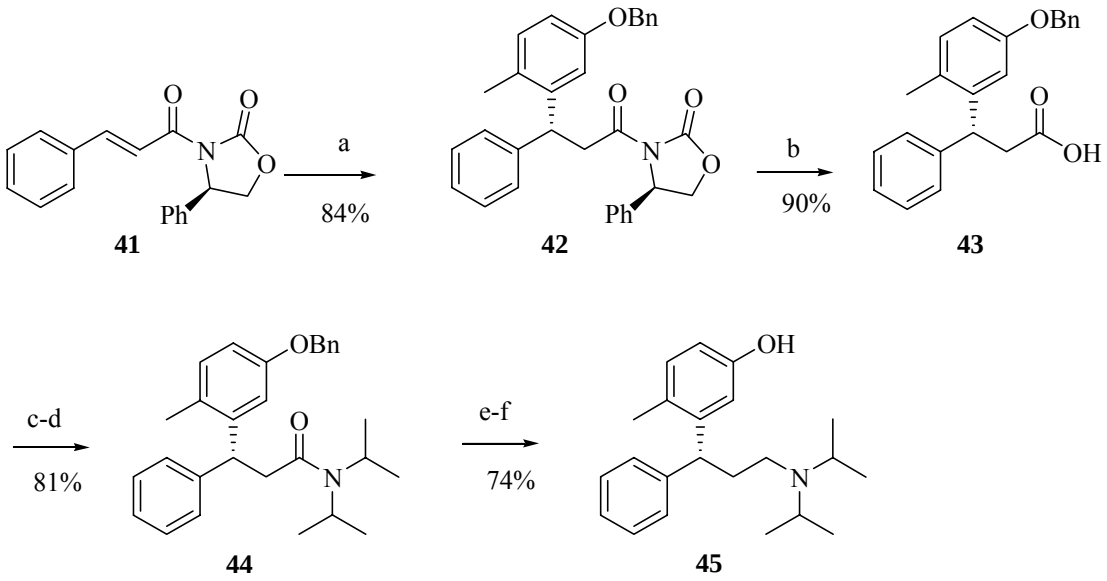
Tolterodine (**40a**) and its active metabolite, 5-hydroxymethyltolterodine, act as competitive antagonists at muscarinic receptors. This results in inhibition of bladder contraction, decrease in detrusor pressure and an incomplete emptying of the bladder.

3.2.2. Review of literature

Literature search reveals that very few reports are avalaible for the synthesis of (*R*)-tolterodine (**40a**), which are listed below.

Österlund's approach (1998)[19]

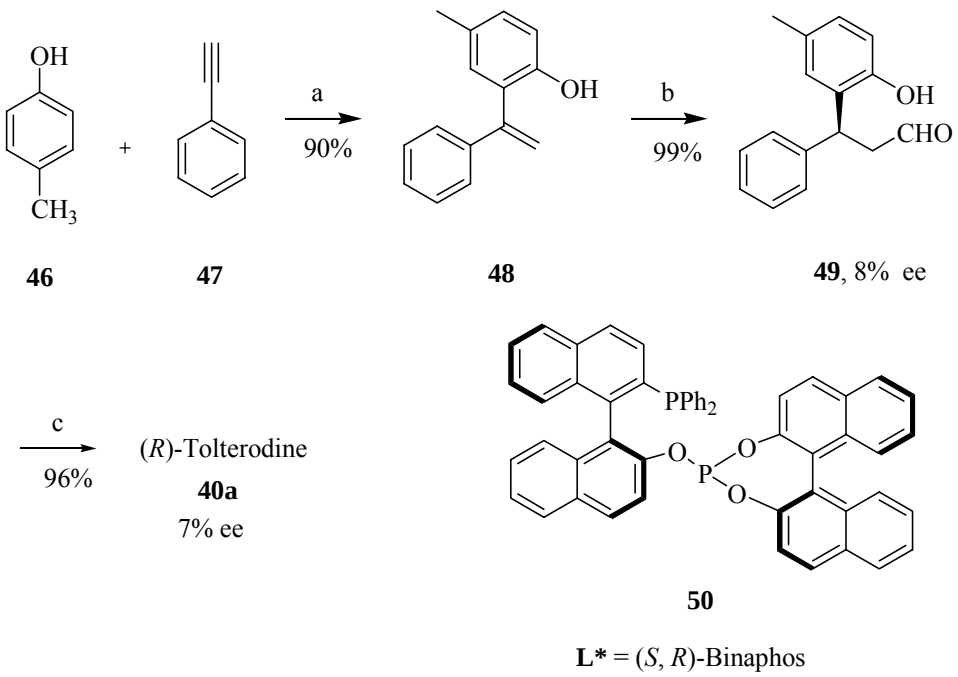
Österlund *et al.* have used chiral axazolidonone **41** for the asymmetric synthesis of (*R*)-tolterodine **40a**. Asymmtric Grignard addition of 2-benzyloxy-5-methylphenyl-magnesuim bromide onto chiral axazolidonone **41** gave Micheal adduct **42** in 84% yield, which on hydrolysis gave chiral acid **43** in 98% ee. The acid **43** was then converted to the corresponding amide **44** in 81%. Finally, reduction of amide **44** with $LiAlH_4$ followed by deprotection of benzyl ether [(Pd/C (10%), H_2 (1 atm)] gave (*R*)-tolterodine in 74% yield and 98% ee (**Scheme 18**).



Scheme 18: (a) 2-benzyloxy-5-methylphenyl bromide, Mg, THF, 65 ºC, 5 min, $CuBr_2 \cdot SMe_2$, THF, −50 ºC, then added **41**, −25 to−20 ºC, 2 h, 84 %; (b) LiOH, H_2O_2, THF:H_2O; (c) $SOCl_2$, py, C_6H_6, 50 ºC, 1 h; (d) $^{i}Pr_2NH$, Et_2O, 45 ºC, 1.5 h, 90 %; (e) $LiAlH_4$, Et_2O, 45 ºC, 12 h; (f) Pd/C (10%), H_2 (1 atm), MeOH, 25 ºC, 12 h, 74%.

Piccolo's approach (2002)[20]

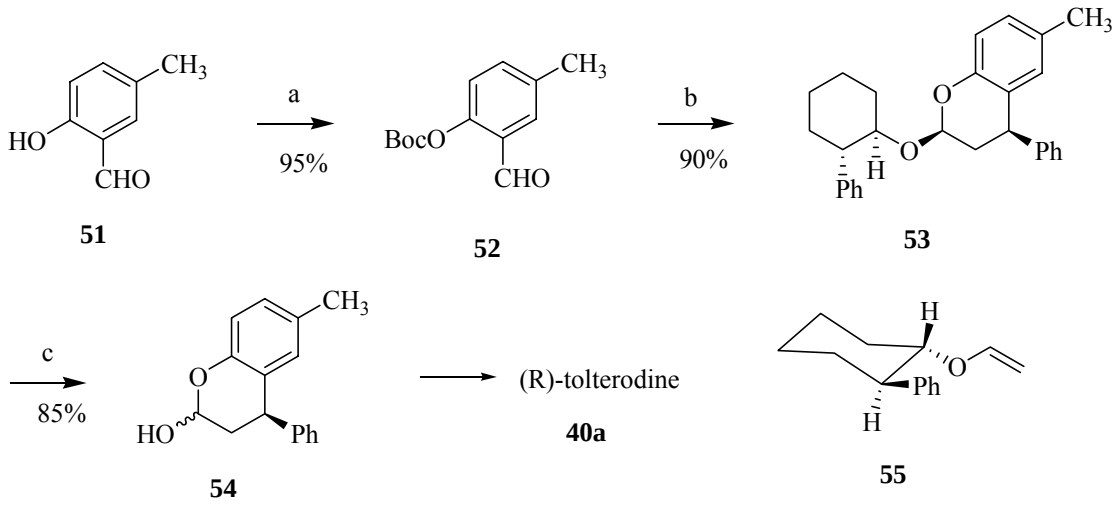
Piccolo *et al.* have reported a short synthesis of (*R*)-tolterodine utilizing Rh-catalyzed hydroformylation reaction of styrene. Hydroarylation of *p*-cresol (**46**) with phenylacetylene (**47**) gave the corresponding olefin **48,** which was subjected to Rh-catalyzed hydroformylation [CO/H_2 (100 atm)] using chiral phosphine **50** as ligand to give aldehyde **49** (7 %ee). Finally, reductive amination of aldehydes **49** [5% Pd/C, H_2 (3 atm), $^{i}Pr_2NH$ in MeOH] gave (*R*)-tolterodine **40a** in 7% ee (**Scheme 19**).



Scheme 19: (a) acidic Al_2O_3, 1,2 -dichlorobenzene, reflux, 72 h, 90%; (b) $Rh(CO)_2acac$(0.4 mol%); ligand **50** (1.6 mol%), CO/H_2 (100 atm), toluene, 100 ºC, 24 h, 99%; (c) Pd/C (5%), H_2 (3 atm), $^{i}Pr_2NH$, MeOH, 50 °C, 16 h, 96%.

Pettus's approach (2004)[21]

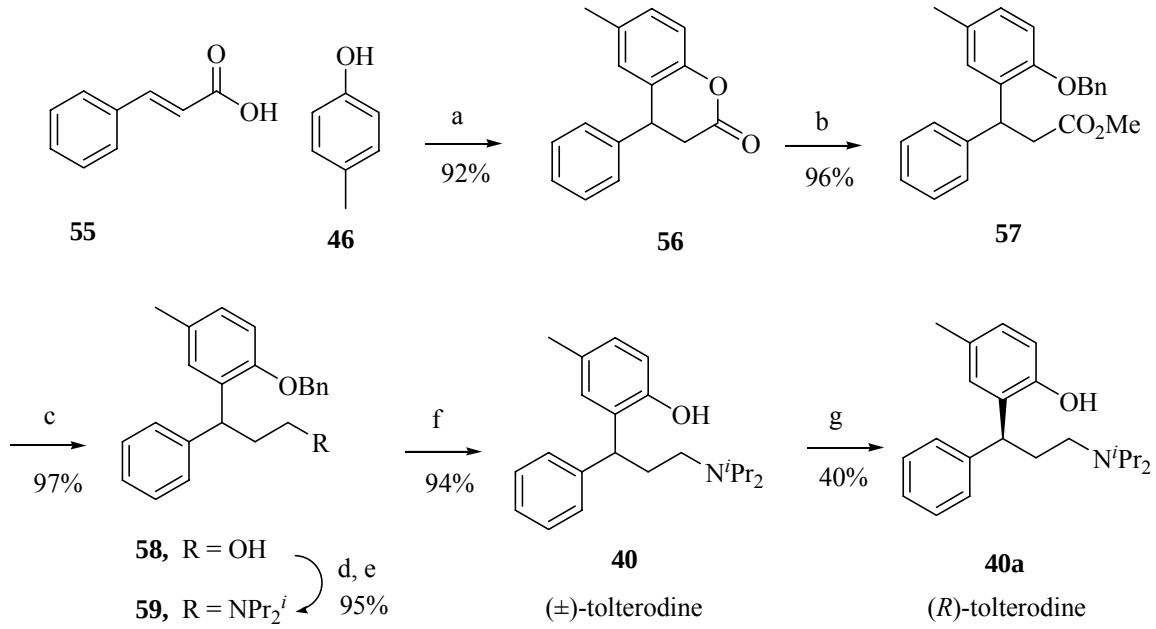
Pettus *et al.* have used *endo* selective [4 + 2] cycloaddition of *o*-quinone methides with chiral enol ether **55**. The aldehyde **52** prepared from *O*-Boc protection of phenol **51**, was subjected to [4 + 2] cycloaddition with chiral enol ether **37** in the presence of PhMgBr to give benzopyran **53** as single diasteriomer in 90% yield. Acid hydrolysis (CSA) of 53 gave lactol **54** in 85% yield. Further synthesis of (*R*)-tolterodine is known in literature (**Scheme 20**).



Scheme 20: (a) Boc_2O (1.1 equiv), Hunig's base (0.5 equiv), DMAP (cat.), 0.1M CH_2Cl_2; (b) PhMgBr (1.05 equiv), (-)-**55** (2 equiv), 0.1MEt_2O, -78 °C to rt, 3 h; (c) CSA (0.6 equiv), 0.1 M 1:1 H_2O/CH_3CN, 70 °C, 5 h.

Mathad's approach (2005)[22]

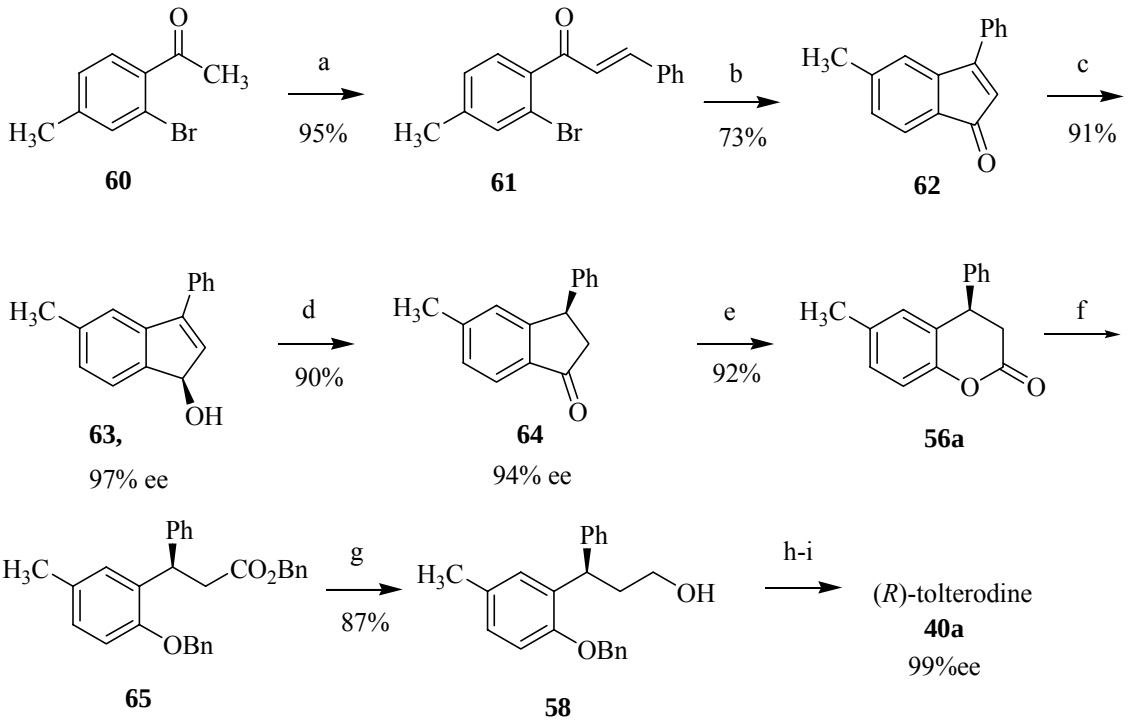
Mathad *et al.* have reported racemic synthesis of (±)-tolterodine **40**. Conc. H_2SO_4 mediated hydroarylation reaction of cinnamic acid with *p*-cresol gave dihydrocoumarin **56** which underwent trans-esterification with BnBr, K_2CO_3 in acetone:methanol mixture to give the corresponding methyl ester **57**. Reduction of methyl ester **57** to the alcohol **58** was achieved with Vitride in THF. Further alcohol **58** was transformed to its tosylate and its displacement with diisopropyl amine was achieved to give benzyl ether protected tolterodine **59**. Finally deprotection of benzyl ether was carried out with Raney Nickel to give racemic tolterodine **40**, which was subjected to resolution with L-(+)-tartaric acid gave (*R*)- tolterodine **40a** (**Scheme 21**).



Scheme 21: (a) H_2SO_4, 120-125 °C, 92%; (b) BnBr, K_2CO_3, acetone, CH_3OH, reflux, 96%; (c) Vitride, THF, 25-35 °C, 97%; (d) *p*-Toluene sufonyl chloride, EtN^iPr_2, CH_2Cl_2 25-35 °C, 99%; (e) $^iPr_2NH$, CH_3CN, 110-115 °C, 12-14 h, 95%; (f) H_2, Raney Ni, CH_3OH, 25-35 °C, 94%; (g) L-(+)-tartaric acid, CH_3CN, CH_3OH, 40%.

Andersson's approach (2005)[23]

Andersson *et al.* have used CBS reduction of chalcone **62** (prepared form substituted acetophenone **60** followed by Heck arylation of **61**) to the corresponding chiral allyl alcohol **63** in 97% ee. Allyl alcohol **63** was transformed to chiral indanone **64** (Et_3N, DABCO) which on Bayer-Villager oxidation (*m*-CPBA, TsOH) gave dihydrochromen-2-one **56a** in 92% yield and 94% ee. Hydrolysis of **56a** followed by dibenzylation (BnBr, K_2CO_3 in methanol) gave the benzyl protected ester **65** which was reduced ($LiAlH_4$) to the alcohol **58** (94% ee). Free alcohol in **58** was transformed to the amine by sequential reactions reported in literature (**Scheme 22**).

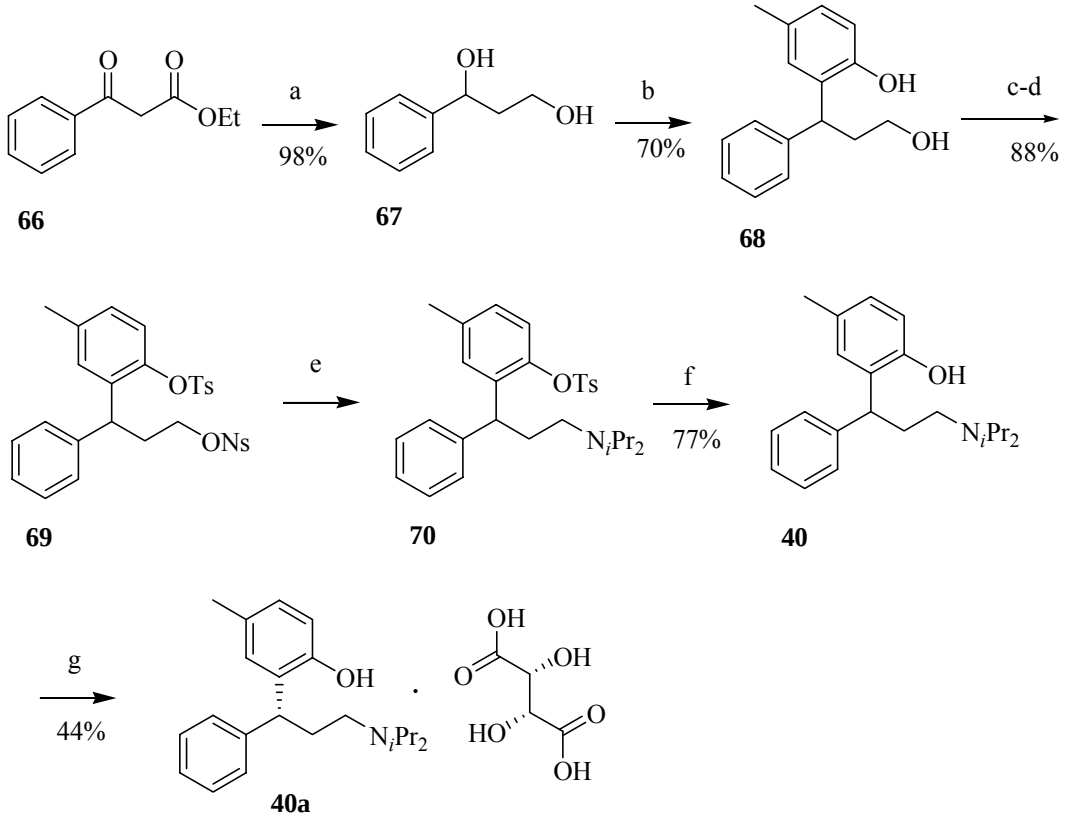


Scheme 22: (a) PhCHO, MeOH, MeONa, 0-25 °C, 16 h, 95%: (b) $PdCl_2$ (5mol%), PPh_3 (15 mol%), K_2CO_3 (2.2 equiv.), DMF, 130 °C, 1 h, 73%; (c) (*S*)-Me-CBS (5 mol%), BH_3·THF, THF, -20 °C, 2 h, 91%, 97%ee; (d) Et_3N, DABCO (20 mol%), THF, 60 °C, 4 h, 90%, 94%ee; (e) *m*-CPBA, TSOH·H_2O, MS 4 Aº, CH_2Cl_2, 4 °C, 92%, 94%ee; (f)(i) K_2CO_3, MeOH, reflux, 1 h; (ii) BnBr, NaI, Me_2CO, reflux; (g) $LiAlH_4$, THF, 25 °C, (87% over two steps); (h) 4-nitrophenylsulfonyl chloride, Et_3N, DMAP, 0 °C, 83%; (h) $^{i}Pr_2NH$, K_2CO_3, MeCN, reflux, 48 h, 81%; (i) Pd/C (10%), MeOH, H_2 (1 atm), 25 °C, 12 h, 97%, 99% ee.

Rhee's Approach (2007)[24]

Rhee *et al.* have used L-tartaric acid for the resolution of racemic tolterodine. Reduction ($NaBH_4$) of *β*-keto ester **66** to the corresponding diol **67** (98%) followed by $FeCl_3$-catalyzed Friedel-Craft alkylation with *p*-cresol afforded **68** in 70% yields. Further, phenol in **133** was protected as its tosylate (TsCl, aq. NaOH) and alcohol (NsCl, Et_3N) as its nosylate to give corresponding sulphonates **69** in 88% yield. Nucleophilic displacement of nosylate with diisopropylamine to give protected tolterodine **70,** which was after deprotection (aq. NaOH) gave (±)-tolterodine **40**. Subsequent resolution of

racemate with L-tartaric acid provided (*R*)-tolterodine tartarate **40a** in 44% yields (**Scheme 23**).



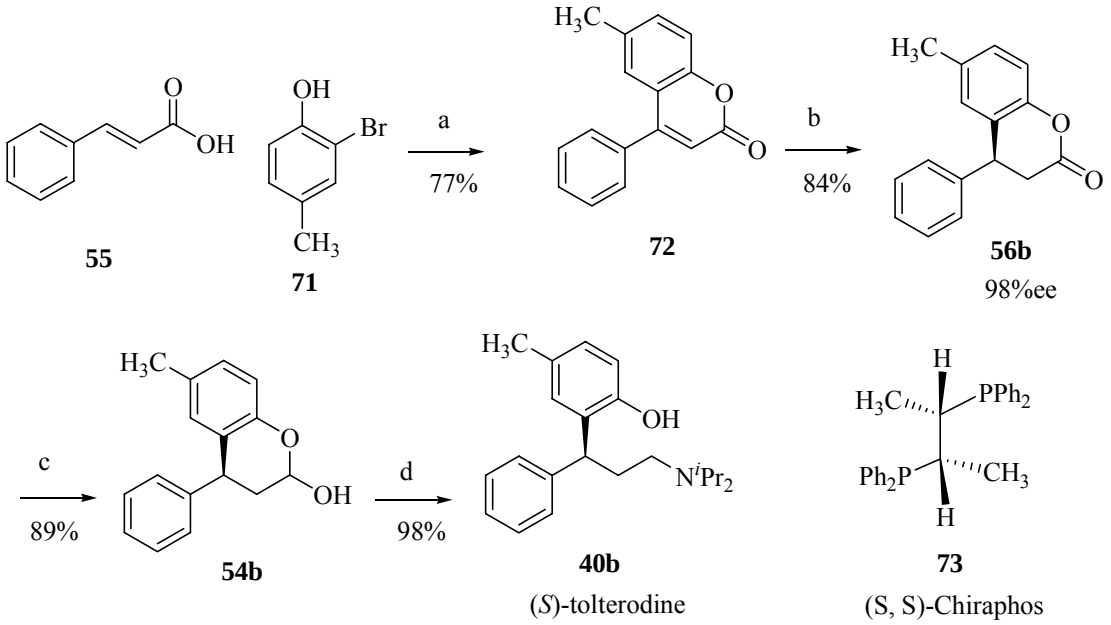
(*R*)-tolterodine tartarate,

Scheme 23: (a) $NaBH_4$, MeOH, rt, 30 min, 98%; (b) *p*-cresol, $FeCl_3 \cdot 6H_2O$, CH_2Cl_2, reflux, 1 d, 70%; (c) TsCl, NaOH, H_2O, CH_2Cl_2, 40 °C, 1 h; (d) NsCl, Et_3N, 0 °C, 2 h, 88%; (e) *i*-Pr_2NH, CH_3CN, reflux, 12 h; (f) (i)NaOH, MeOH, reflux, 4 h; (ii) HCl, CH_2Cl_2, rt, 1 h, 77%; (g) (i) NaOH, Na_2CO_3, CH_2Cl_2, rt, 1 h; (ii) L-tartaric acid, MeOH, acetone, reflux, 1 h, 44%.

Piccolo's Approach (2007)[25]

Piccolo *et al.* have reported enantioselective synthesis of (S)-tolterodine **40b** utilizing Rh-catalyzed asymmetric reduction of coumarin. Heck arylation of 2-bromo-4-cresol **71** with cinnamic acid (**55**) gave the coumarin derivative **72** which was subjected to Rh-catalyzed asymmetric reduction with phosphine ligand **73** to give the (*S*)-dihydrocoumarin. Subsequently, reduction of dihydrocoumarin **56b** with DIBAL-H gave hemiacetal **54b**

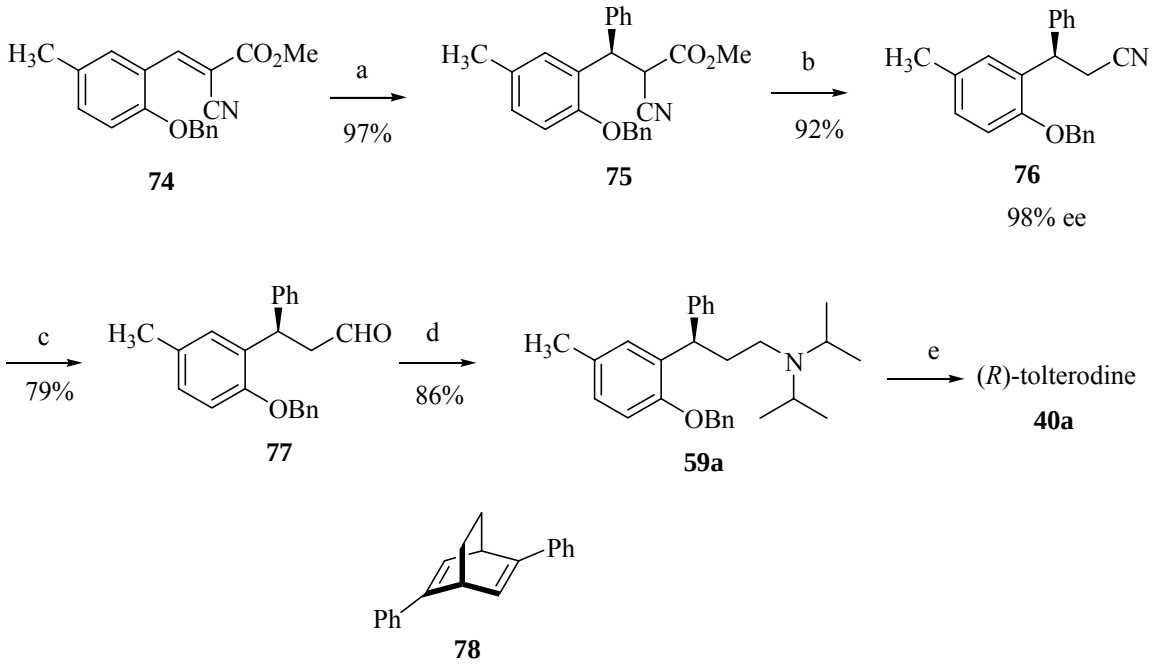
which upon reductive amination with diisopropyl amine gave the (*S*)-tolterodine **40b** in 98% ee (**Scheme 24**).



Scheme 24: (a) $Pd(OAc)_2$ (5mol%) Et_4NCl, $(Cy)_2MeN$, DMA , 95 °C, 48 h, 77%; (b) $[Rh(COD)Cl]_2$ (5 mol%), *S*,*S*-Chiraphos (10 mol%), H_2 (12 bar), MeOH, aq. 4 N NaOH, 50 °C, 24 h, 84%; (c) DIBAL-H, toluene , −25 ºC, 5 h, 89%; (d) Pd/C (10%), MeOH, H_2 (1atm), 25 °C, 12 h, 98%.

Hayashi's approach (2008)[26]

Hayashi *et al*. have used Rh-catalyzed asymmetric Michel addition of phenyl boronic acid to the arylmethylene cyanoacetates **74** with (*R*,*R*)-Ph-bod **78** as a chiral ligand to afford 3,3-diaryl-2-cyanopropanoates **75** in 97 % yield. Decarbomethoxylation of 75 (NaCN and LiI in DMF) gave nitrile **76** in 92% yield and 98 % ee, which was subjected to reduction (DIBAL-H) to provide aldehyde **77** in 79 % yield. Subsequently, reductive amination with diisopropyl amine gave **59a** which was converted to (*R*)-tolterodine **40a** (**Scheme 25**).



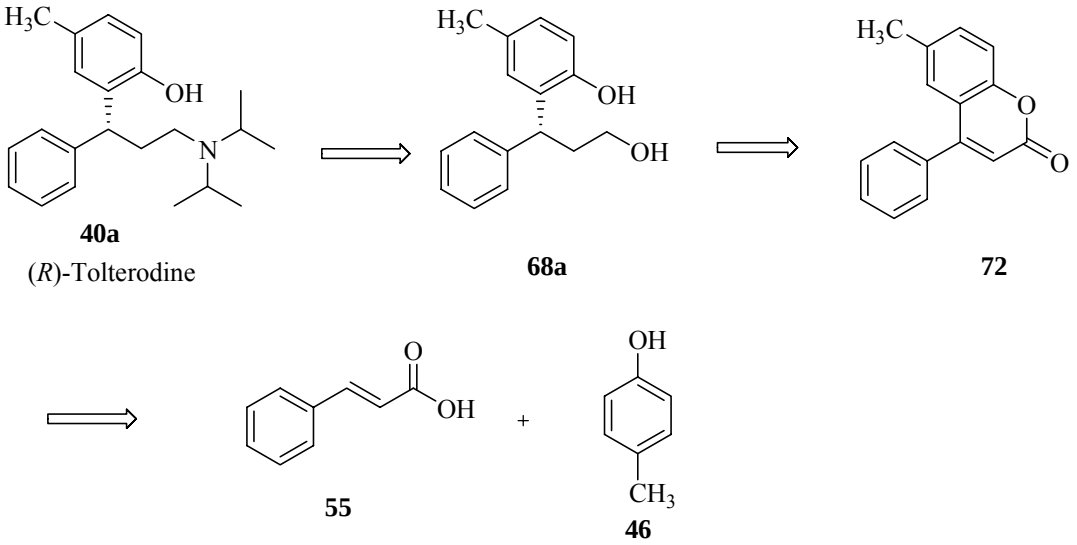
Scheme 25: (a) $PhB(OH)_2$ (1.5 equiv.), $RhCl(C_2H_4)_2$ (3 mol%), **78** (3.3 mol%), KOH (20 mol%), H_2O (1equiv.), dioxane, 30 °C, 2 h, 97%; (b) NaCN, LiI, DMF, 120 °C, 15 h, 92%, 98% ee; (c) (i) DIBAL, −40 °C, 6 h; (ii) MeOH, −40-0 °C, 1 h; (iii) NH_4Cl, rt, 30 min. 79%; (d) $NaBH(OAc)_3$, $^iPr_2NH$, $ClCH_2CH_2Cl$, 25 ºC, 15 min. 86%; (e) Pd/C (10%), MeOH, H_2 (1 atm), 25 °C, 12 h.

3.2.3 Present work

3.2.3.1 Objective

As can be seen from above descriptions, the literature methods for the synthesis of (*R*)-tolterodine employ either resolution of racemic tolterodine, use of high pressure reduction of coumarin derivative or employment of chiral auxiliary to prepare (*R*)-tolterodine. We became interested in the synthesis of pharmacologically important drug namely (*R*)-tolterodine *via* $CoCl_2$-catalyzed asymmetric reduction of coumarin derivative. The retrosynthetic analysis of (*R*)-tolterodine is shown in **Scheme 26.** We visualized that alcohol **68a** could be a key intermediate, which could in turn be obtained from asymmetric reduction of coumarin derivative**72**.

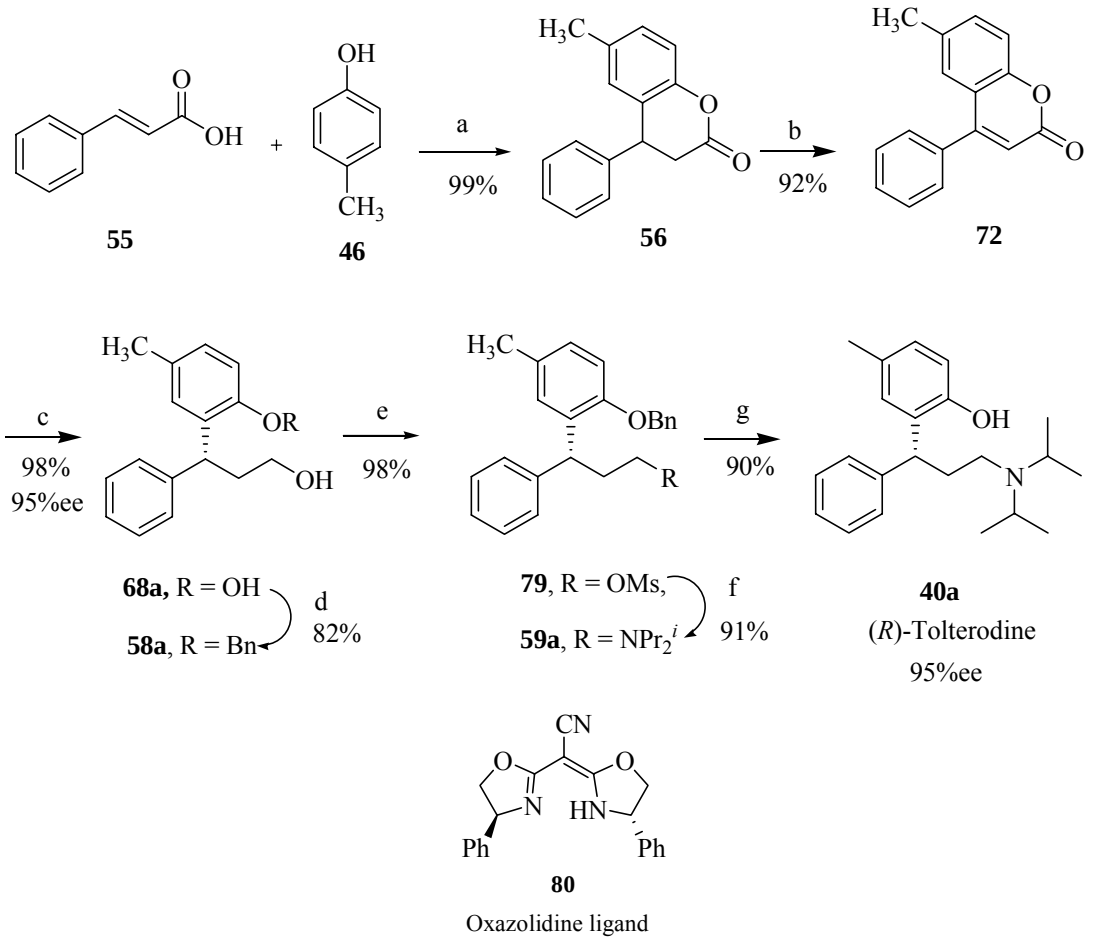
Compound **72** could be easily prepared *via* hydroarylation of cinnamic acid **55** with *p*-cresol **46** followed by aromatization with DDQ.



Scheme 26: Retrosynthetic analysis of (*R*)-tolterodine **40a**

3.2.3.2 Results and Discussion

Present synthetic scheme for the synthesis of (*R*)-tolterodine **40a** is shown in **Scheme 27**. In section I of Chapter IV, we have described a one-step, simple and efficient method for the synthesis of dihydrocoumarins.[27] By following our synthetic procedure, *p*-toluenesulphonic acid-mediated hydroarylation of cinnamic acid (**55**) with *p*-cresol (**46**) at 130 °C under solvent-free condition was carried out to give dihydrocoumarin derivative **56** in 99% yield, which on oxidative aromatization produced coumarin derivative **72** (DDQ in dioxane, reflux)[28] in 92 % yield. Its ^{1}H NMR spectrum showed characteristic signal at δ 6.35 (s) due to olefinic proton. Also, its IR spectrum showed a characteristic strong absorption band at 1735 cm^{-1} due to carboxylic ester carbonyl confirming the formation of coumarin derivative**72**.



Scheme 27: (a) *p*-TSA, 130 °C, 3 h, 99%; (b) DDQ, dioxane, 110 °C, 12 h, 92%; (c) $CoCl_2$: ligand **80**, $NaBH_4$, EtOH, DMF, 0 °C, 36 h, 98%; (d) BnBr, K_2CO_3, acetone, 60 °C, 12 h, 82%; (e) MsCl, Et_3N, CH_2Cl_2, RT, 30 min; (f) $^{i}Pr_2NH$, NaI, Na_2CO_3, DMF, 80 ºC, 6 h; (g) Pd/C (10 %), H_2 (1atm), MeOH, 12 h, 90%;

The $CoCl_2 \cdot 6H_2O$-catalyzed asymmetric reduction[29] of coumarin **72** with 4 molar equivalents of $NaBH_4$ using (4*S*)-(+)-phenyl-α-[(4*S*)-phenyloxazolidin-2-ylidine]-2-oxazoline-2-acetonitrile (**80**) as chiral ligand [ethanol/DMF 5:2] gave the saturated alcohol **68a** in 98% yield and 95% ee. Its ^{1}H NMR showed characteristic signals at δ 2.25 (m), 3.63 (m) and 4.56 (dd) due to two methylene (C**H**$_2$) and methine (C**H**) protons respectively. Its ^{13}C NMR showed characteristic signals at δ 36.9, 38.3 and 59.7

corresponding to the methine (**C**H) and two methylene (**C**H_2) carbons respectively confirming the formation of the saturated alcohol **68a** (**Fig. 6**).

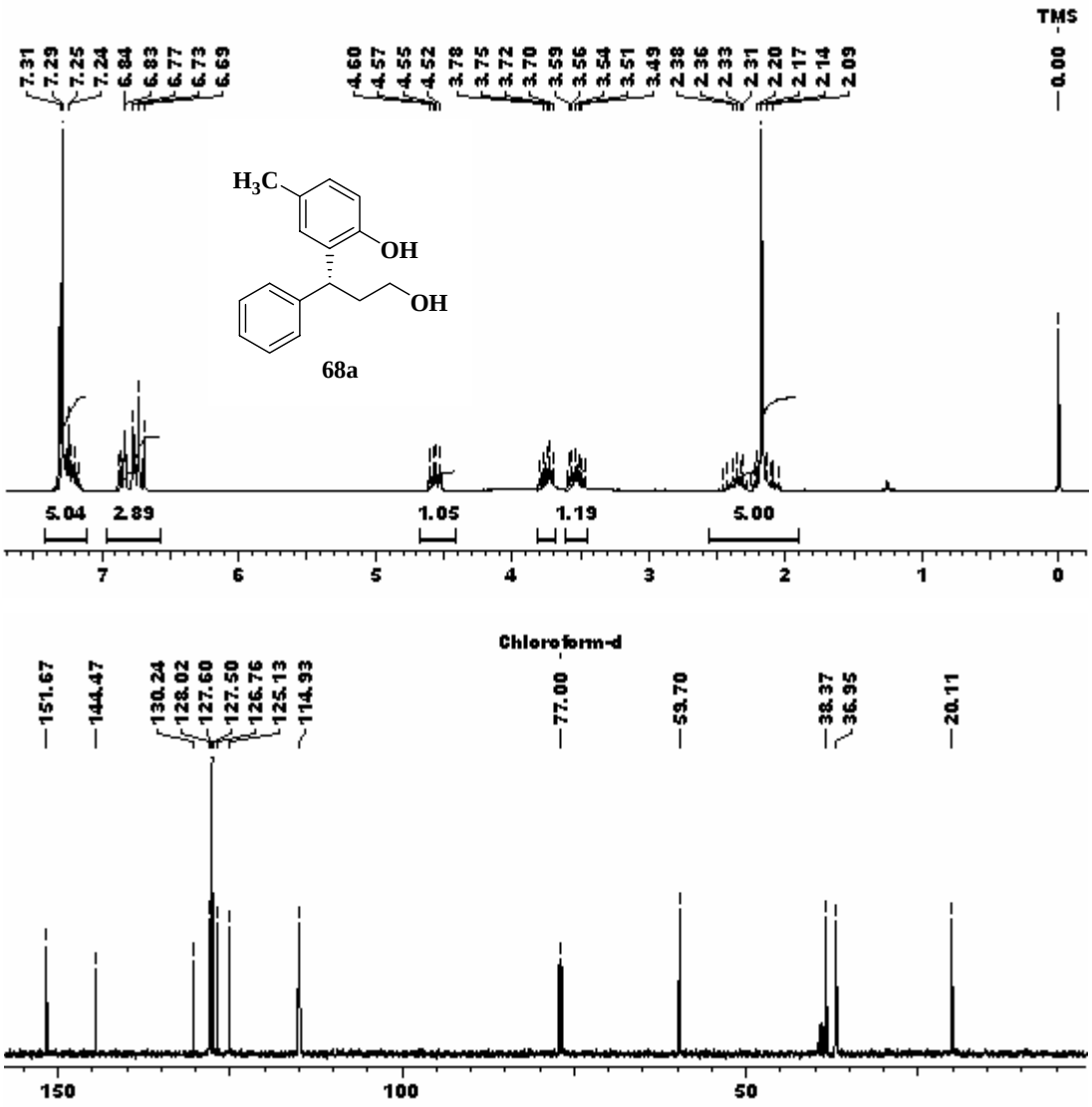


Fig. 6: ^{1}H and ^{13}C NMR spectra of 68a

The phenolic function in **68a** was readily protected as its benzyl ether **58a** (BnBr, K_2CO_3 in acetone, 82% yield). Its ^{1}H NMR spectrum showed characteristic signal at δ 5.00 (s) due to benzylic methylene (PhC**H**$_2$O) protons. Also a typical signal at δ 70.4 due to benzylic methylene (Ph**C**H_2O) carbon confirming the formation of benzyl ether **58a.** Free alcohol group was then protected as its mesylate **79** followed by its displacement with

diisopropylamine (catalytic NaI, Na_2CO_3, $^{i}Pr_2NH$, DMF)[30] gave benzyl protected (*R*)-tolterodine **59a** in 91% yield and 95% ee. Its ^{1}H NMR showed characteristic signals at δ 0.90 (d) due to four methyl (4 x C**H**$_3$) protons. Finally, reductive removal of benzyl ether was achieved to give (*R*)-tolterodine **40a** in 90% yield. Its ^{1}H NMR showed characteristic signals at δ 1.07 (d) and 1.13 (d) due to four methyl (4 x C**H**$_3$) protons. Also, a typical signal at δ 3.23 (m) is due to aminomethylene (C**H**$_2$N) protons**.**

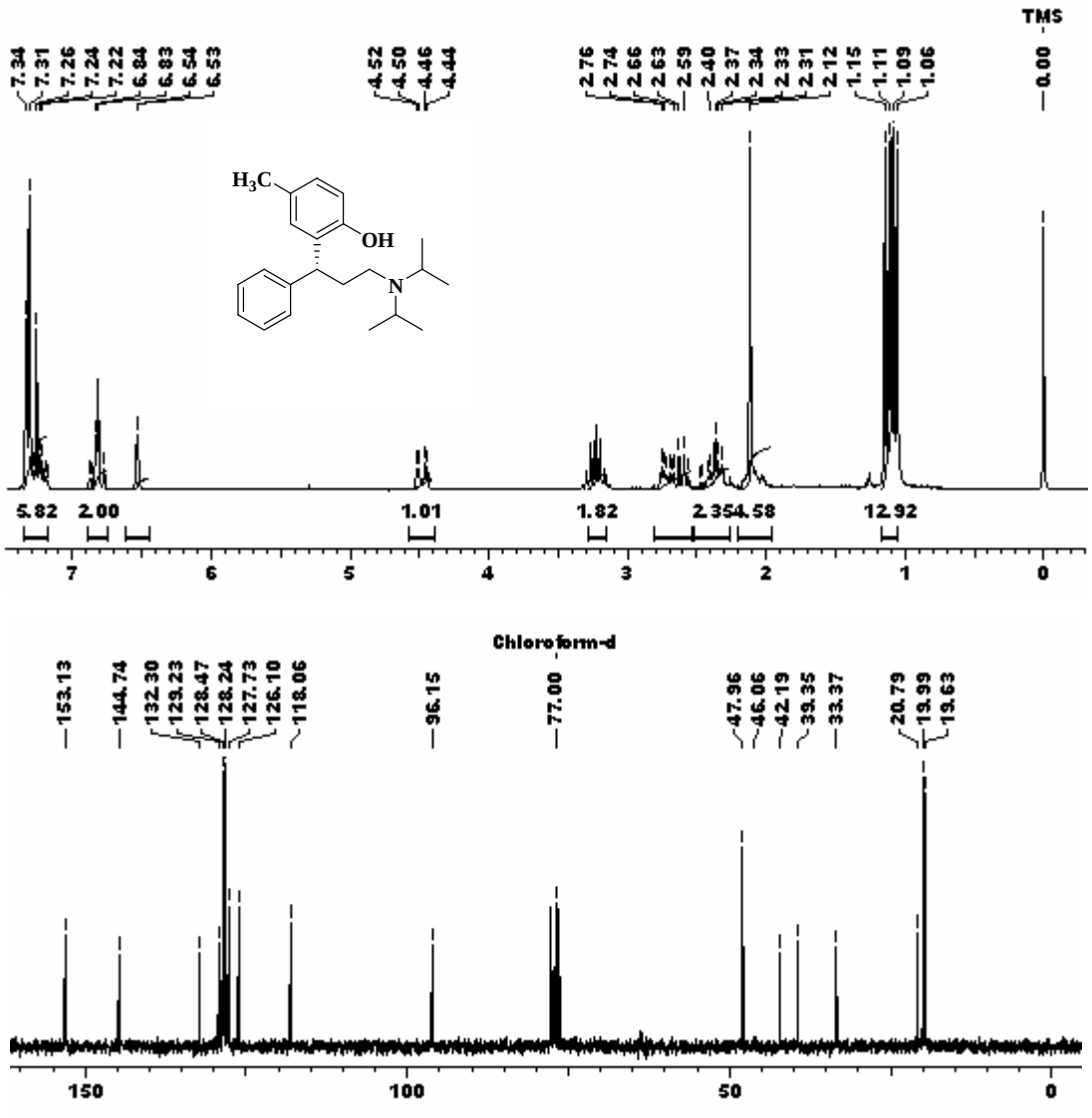
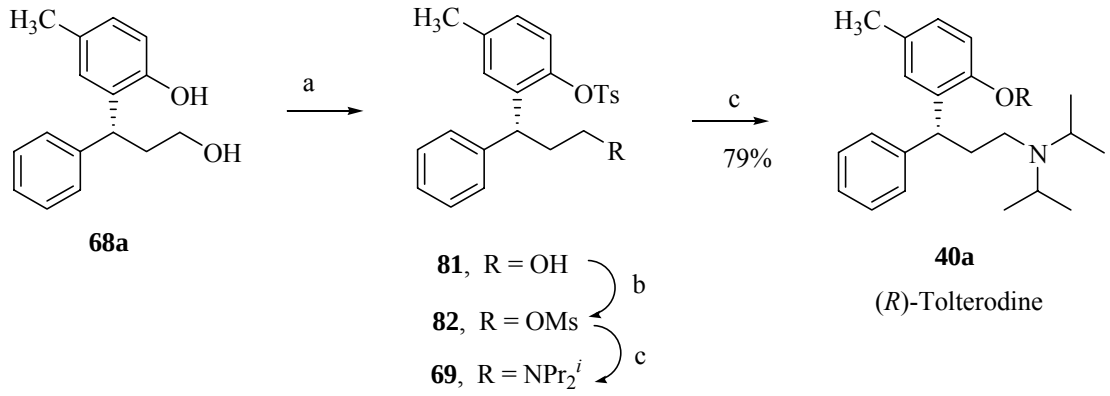


Fig. 7: ^{1}H and ^{13}C NMR spectra of (*R*)-tolterdione 40a

Its ^{13}C NMR showed characteristic signals at δ 19.6, 19.9 due to methyl (4 x **C**H_3) confirming the formation of tolterodine **40a (Fig. 7).**

It should be noted that when the phenolic function was protected as its benzyl ether **58a**, (*R*)-tolterodine **40a** was obtained in a lower yield due to the formation of mixtures of benzyl ethers arising out of protection of both the OH. However, chemoselective protection of the phenolic OH group in **68a** as its tosylate **81** (*p*-toluenesulfonyl chloride in CH_2Cl_2 and aq NaOH, 98% yield) was achieved to give a tosylate. Its ^1H NMR showed characteristic signals at δ 2.42(s), 7.31 (d) and 7.79 (d) corresponding to the methyl and aromatic protons of tosyl group (**Scheme 28**).



Scheme 28: (a) TsCl in CH_2Cl_2 then aq NaOH, 45 ºC, 3 h, 98%; (b) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C, 30 min; (ii) $^iPr_2NH$, NaI, Na_2CO_3, DMF, 80 ºC, 6 h, 92%; (c) aq.NaOH, MeOH reflux, 4 h, 79%.

Free alcohol group in **81a** was then protected as its mesylate **82**, followed by displacement of mesylate **82** with diisopropylamine (Na_2CO_3, NaI, in DMF) gave tosyl protected (*R*)-tolterodine **69.** Its ^1H NMR showed characteristic signals at δ 0.91 (d), 2.26 (s) and 2.45 (s) due methyl protons [(4 x C**H**$_3$) and a pair of ArC**H**$_3$ protons] respectively. Its ^{13}C NMR showed characteristic signals at δ 20.3, 20.6, 21.0 and 21.58 corresponding to methyl carbons (4 x **C**H_3) and a pair of Ar**C**H_3 carbons (**Fig. 8**).

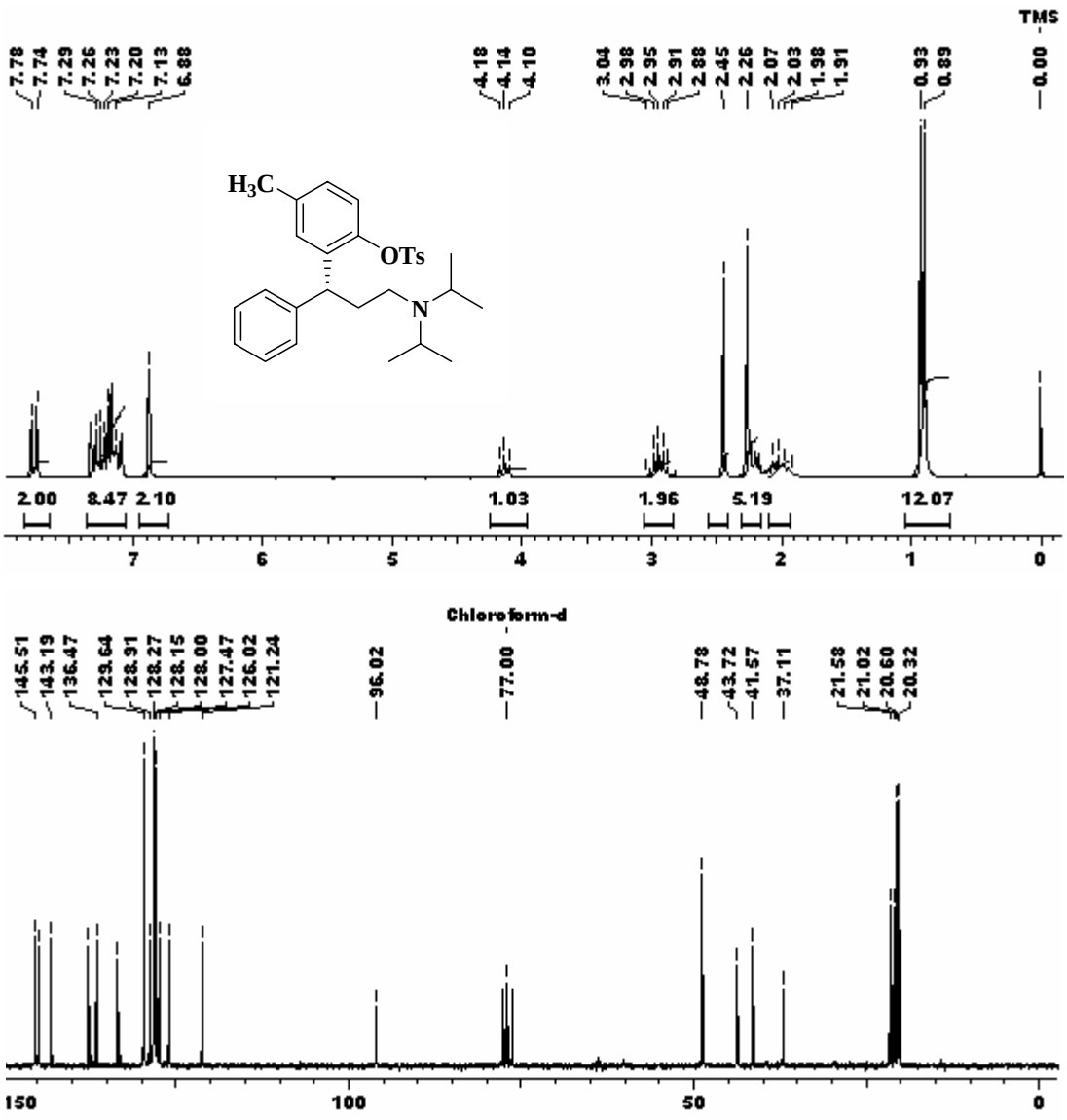


Fig. 8: ^{1}H and ^{13}C NMR spectra of tosyl protected tolterodine 69

Finally, tosyl group in **69** was hydrolyzed using basic conditions (aq. KOH) to afford (*R*)-tolterodine **40a** with an increased yield of 82%; $\{[\alpha]_{25}^{D}$ +21.8 (*c* 1.5, $CH_3OH)\}$.

3.2.4 Conclusion

In conclusion we have described a simple and practical synthesis of (*R*)-tolterodine *via* $CoCl_2$-oxazolidine ligand **80** catalyzed asymmetric reduction of coumarin derivatives **72** with $NaBH_4$ in 61% overall yield and 95% ee. Easy handling, milder reaction condition and high ee are some of the distinct features, which make this synthesis more practical and efficient.

3.2.5 Experimental section

Preparation of 6-methyl-4-phenylchroman-2-one (56):

A 25 mL round bottom flask equipped with a reflux condenser, was charged *p*-cresol (0.540 g, 5 mmol), cinnamic acid (0.740 g, 5 mmol) and *p*-toluenesulfonic acid (5 mmol). The reaction mixture was heated at 130 °C for 3 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled, quenched with addition of water (50 mL) and extracted with ethyl acetate (2 x 50 mL). The organic layers were washed brine (2 x 50 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to afford the crude product. Chromatographic purification of the crude product [silica gel (230-400 mesh) and petroleum ether: ethyl acetate (80:20)] gave 1.178 g of **56** in pure form.

Yield : 99%, 1.178 g, colorless solid, **mp** 84 °C; **IR** ($CHCl_3$):1045, 1209, 1499, 1769, 2561, 2900 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.26 (s, 3H), 3.01 (dd, *J* = 2.7, 6.9 Hz, 2H), 4.28 (t, *J* = 6.6Hz, 1H), 6.75 (bs, 1H), 6.98-7.16 (m, 4H), 7.27-7.31 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.7, 114.9, 116.8, 118.4, 126.5, 128.2, 128.7, 129.4, 132.7, 133.7, 135.1, 152.1, 153.4, 160.7; **Analysis** for $C_{16}H_{14}O_2$ required C, 80.65; H, 5.92; found C, 80.45; H, 5.72%.

Preparation of 6-methyl-4-phenyl-2*H*-chromen-2-one (72):

To a stirred solution of 6-methyl-4-phenylchroman-2-one (1.07 g, 4.5 mmol) in dry dioxane (25 mL), was added DDQ (1.59 g, 7 mmol) under N_2 atmosphere. It was then refluxed for 5 h. After completion of the reaction mixture, it was filtered through neutral alumina and concentrated under reduced pressure to give crude product. Chromatographic purification of crude product [silica gel (230-400 mesh) and petroleum ether: ethyl acetate (70:30)] gave 0.97 g of **72** in pure form.

Yield: 92%, 0.97 g, colorless solid, **mp:** 132-134 °C, **IR** ($CHCl_3$): 763, 1217, 1566, 1737, 3020 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.34 (s, 3H), 6.35 (s, 1H), 7.25-7.39 (m, 3H), 7.42- 7.49 (m, 2H), 7.51-7.56 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): 20.7, 114.9, 116.8, 126.5, 128.7, 129.4, 132.7, 133,7, 135,1, 152.1, 152.1, 155.4, 160.7 ; **Analysis** for $C_{16}H_{12}O_2$ requires C, 81.34; H, 5.12; Found: C, 81.33; H, 5.14%.

Preparation of 2-(3-hydroxy-1-phenylpropyl)-4-methylphenol (68a):

To a stirred solution of coumarin **72** (0.94 g, 4 mmol), $CoCl_2 \cdot 6H_2O$ (9.4 mg, 1 mol %) and ligand **80** (15.9 mg, 1.2 mol %) in 95% ethanol (8 mL) and dry DMF (2 mL), was added $NaBH_4$ (0.62 g, 16 mmol) slowly at –10 ºC. It was stirred at 0 ºC for 36 h. After the completion of the reaction (monitored by TLC), it was diluted with 50 mL of water and 50 mL of ethyl acetate. The organic layer was separated, washed with brine solution (2 x 20 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude product. Flash column chromatographic purification using silica gel (230–400 mesh) and petroleum ether/ethyl acetate (70:30) as eluent afforded 948 mg of the saturated alcohol **68a** in pure form.

Yield: 98%, Gum, $[\alpha]^{25}_D$ +71.8 (*c* 1.0, CH_3OH); **IR** ($CHCl_3$): 702, 818, 1037 1255, 1446, 1504, 1610, 3170, 3419 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.05-2.45 (m, 2H),

2.17 (s, 3H), 3.46-3.59 (m, 1H) 3.70-3.80 (m, 1H), 4.56 (dd, *J* = 5.9, 9.9 Hz, 1H) 6.69-6.88 (m, 3H), 7.17-7.31 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.1, 36.9, 38.3, 59.7, 114.9, 125.1, 126.5, 127.6, 127.9, 128.0, 130.2, 144.4, 151.6; Analysis: $C_{16}H_{18}O_2$ requires C, 79.31; H, 7.49; found C, 79.27; H, 7.47%.

3-[2-(Benzyloxy)-5-methylphenyl]-3-phenylpropan-1-ol (58a):

To a stirred solution of phenol **68a** (0.92 g, 3.8 mmol) and BnBr (0.6 mL, 4.8 mmol) in acetone (20 mL), was added dry K_2CO_3 (5.52 g, 40 mmol) at 25 °C. It was then refluxed under N_2 atmosphere for 12 h. After completion of reaction (monitored by TLC), it was filtered and concentrated under reduced pressure to give crude product. Chromatographic purification of crude product [silica gel (230-400 mesh) and petroleum ether: ethyl acetate (60:40)] gave 1.03 g of benzyl ether **58a** in pure form.

Yield: 82%; white solid, **mp**: 65 ºC; $[\alpha]^{D}_{25}$ +4.55 (*c* 1, $CHCl_3$) **IR** ($CHCl_3$): 759, 1026, 1217, 1496, 1602, 34444 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.24 (s, 3H), 2.12-2.38 (m, 2H), 3.54 (m, 2H), 4.60 (t, *J* = 7.6 Hz, 1H), 5.00 (d, *J* = 1.6 Hz, 2H), 6.76-6.95 (m, 3H), 7.16- 7.26 (m, 5H), 7.31-7.38 (m, 5H), **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.6, 37.5, 39.1, 60.9, 70.4, 112.0, 125.8, 127.40, 127.47, 127.7, 128.10, 128.13, 128.4, 128.7, 130.1, 132.8, 136.9, 144.4, 153.8; **Analysis** for $C_{23}H_{24}O_2$ requires C, 83.10; H, 7.28; found C, 83.08; H, 7.29%.

2-(3-Hydroxy-1-phenylpropyl)-4-methylphenyl 4-methylbenzenesulfonate (81):

To a stirred solution of phenol **68a** (0.48 g, 2 mmol) and tosyl chloride (0.42 g, 2.2 mmol) in dichloromethane (10 mL), was added aq. NaOH (3 mL, 1M) at 25 ºC. It was then refluxed for 3 h. After completion of the reaction (monitored by TLC), it was diluted with water (20 mL) and dichloromethane (20 mL). The organic layer was separated and

the aqueous layer was extracted with dichloromethane (20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude tosylate product. The crude product was purified by column chromatography using flash silica gel (230-400 mesh) and petroleum ether: ethyl acetate (8:2) as eluent afforded 0.77 g of tosylate **81** in pure form.

Yield 91%, Gum, $[\alpha]^{D}_{25}$ +11.2 (*c* 1, CH_2Cl_2); **IR** ($CHCl_3$):765, 1172, 1359, 1492, 1598, 3394 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.04-2.31 (m, 2H), 2.25 (s, 3H), 2.42 (s, 3H), 3.54 (t, *J* = 6.2 Hz, 2H), 4.46 (t, *J* = 7.7 Hz, 1H), 6.79-6.91 (m, 3H), 7.07-7.20 (m, 5H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.79 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): *δ* 20.1, 22.5, 36.6, 40.2, 54.3, 116.3, 126.1, 128.3, 128.4, 128.8, 130.1, 1302, 133.1, 142. 143.0, 146.7, 149.6; **Analysis** for $C_{23}H_{24}O_4S$ requires C, 69.67; H, 6.10; S, 8.09 found C, 69.43; H, 6.01; S, 7.82%.

General procedure for the preparation of mesylates 79 and 82:

To a stirred solution alcohol **58a** or **81** (1 mmol), triethylamine (0.3 mL, 2 mmol) in dichloromethane (10 mL), was added mesyl chloride (1.1 mL of 1 M solution in CH_2Cl_2) at 0 ºC and allowed to stir for 30 min. After completion of the reaction (monitored by TLC), saturated solution of $NaHCO_3$ (20 mL) was added. The organic layer was separated and aqueous layer extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give crude mesylate. Formation of mesylates **79** and **82** was confirmed by ^{1}H and ^{13}C NMR spectroscopy.

3-(2-(benzyloxy)-5-methylphenyl)-3-phenylpropyl methanesulfonate (79):

Yield: 99%; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.27 (s, 3H), 2.40-2.52 (m, 2H), 2.78 (s, 3H), 3.87 (t, *J* = 4.7 Hz, 1H), 4.46-4.59 (m, 2H), 4.97 (s, 2H), 6.77 (d, *J* = 8.2 Hz, 1H), 6.91-6.99 (m, 2H), 7.14-7.42 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22,4, 33.2, 37.9, 39.2, 67.0, 72.3, 114.7, 125.8, 126.1, 126.3, 127.5, 1279, 128.9, 141.3, 154.3.

2-(3-Methanesulfonoyl-1-phenylpropyl)-4-methylphenyl 4-methylbenzenesulfonate (82):

Yield: 99%; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.26-2.52 (m, 2H), 2.32 (s, 3H), 2.52 (s, 3H), 2.98 (s, 3H), 4.07-4.18 (m, 2H), 4.43 (t, *J* = 8.0 Hz, 1H), 6.89-7.03 (m, 3H), 7.13-7.30 (m, 5H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.83 (d, *J* = 8.1 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.7, 21.2, 31.2, 36.6, 39.1, 67.6, 121.4, 126.4, 127.5, 127.95, 127.99, 128.2, 128.4, 129.6, 132.4, 135.9, 136.7, 141.1, 144.9, 145.3.

General procedure for the preparation of phenol protected tolterodine (59a and 69)

To a stirred solution of mesylate **79** or **82** (4 mmol), NaI (2 mmol), Na_2CO_3 (2 mmol) in DMF (10 mL), was added diisopropylamine (10 mmol) under N_2 atmosphere. It was then stirred at 80 °C for 4 h. After completion of the reaction (monitored by TLC), reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over unhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product. The crude product was purified by column chromatography using flash silica gel (230-400 mesh) and petroleum ether: ethyl acetate: triethyl amine (60:38:2) as eluent afforded protected tolterodine **59a** and **69** in pure form.

3-[2-(Benzyloxy)-5-methylphenyl]-*N,N*-diisopropyl-3-phenylpropan-1-amine (59a):

Yield: 91%, Gum, $[\alpha]^{D}_{25}$ +51 (*c* 1, CH_2Cl_2) Lit.{+52 (*c* 1.04, CH_2Cl_2)}; IR (neat, cm^{-1}) 1025, 1238, 1499, 2868, 2928, 2968, 3030; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.90 (d, J= 6.6 Hz, 12H), 2.30 (m, 2H, and s, 3H), 2.98 (t, *J* = 13.0, 6.8 Hz, 2H), 3.10 (m, 2H), 4.40 (t, *J* = 7.8 Hz, 1H), 5.00 (s, 2H), 6.70-7.50 (m, 13H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.54, 20.62, 20.72, 36.80, 41.45, 43.88, 48.60, 69.98, 111.69, 125.55, 127.11, 127.23, 127.52, 127.91, 128.24, 128.38, 129.57, 133.54, 137.38, 145.04, 153.88; Anal. Calcd for $C_{29}H_{37}NO$: C, 83.81; H, 8.97; N, 3.37; O, 3.85. Found: C, 83.80; H, 8.95; N, 3.35; O, 3.83

2-(3-(diisopropylamino)-1-phenylpropyl)-4-methylphenyl 4-methylbenzenesulfonate (69):

Yield: 92%, Gum, $[\alpha]^{D}_{25}$ +21 (*c* 1, CH_2Cl_2); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.91 (d, *J* = 6.4 Hz, 12H), 1.91-2.07 (m, 2H), 2.24 (t, *J* = 6.9 Hz, 2H), 2.26 (s, 3H), 2.45 (s, 3H), 2.88-3.04 (m, 2H), 4.14 (t, *J* = 6.9Hz, 1H), 6.88 (d, *J* = 1.1Hz, 2H), 7.13-7.29 (m, 8H), 7.76 (d, *J* = 8.3Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.3, 20.6, 21.0, 21.5, 37.1, 41.5, 43.7, 48.7, 121.2, 126.0, 127.4, 128.0, 126.1, 128.2, 128.9, 129.6, 133.4, 136.4, 137.7, 143.1, 144.9, 145.5; **Analysis** for $C_{29}H_{37}NO_3S$ requires C, 72.61; H, 7.77; N, 2.92; S, 6.68; found C, 72.42; H, 7.44; N, 2.99; S, 6.78%.

Preparation of (R)-tolterodine (40a):

To a solution of 3-(2-(benzyloxy)-5-methylphenyl)-*N,N*-diisopropyl-3-phenylpropan-1-amine (**59a**) (0.83 g, 2mmol) in methanol (10 mL), was added 10% Pd/C (50 mg) and allowed to stir for 12 h under H_2 (1 atm). After completion of the reaction, it was passed trough celite and concentrated under reduced pressure to give the crude product. The

crude product was purified by column chromatography using flash silica gel (230-400 mesh) and petroleum ether: ethyl acetate:triethylamine (70:28:2) as eluent afforded 0.58 g of tolterodine **40a** in pure form.

To a stirred solution of tosylate (**69**) (1 mmol) in methanol (5 mL), was added aq. KOH (3 mmol). It was then refluxed for 4 h. After complete hydrolysis, saturated solution of ammonium chloride (20 mL). It was then extracted with ethyl acetate (2 x 20 mL). The combined organic extract was washed with brine (2 x 20 mL), dried over unhyd. Na_2SO_4 concentrated under reduced pressure to give the crude product. The crude product was purified by column chromatography using flash silica gel (230-400 mesh) and petroleum ether: ethyl acetate:triethylamine (70:28:2) as eluent afforded 0.58 g of (*R*)-tolterodine **40a** in pure form.

Yield: 79%; **mp**: 212-216 °C; $[\alpha]^{D}_{25}$ +22.5 (*c* 1, MeOH) Lit.{+23 (*c* 1.0, MeOH)} IR ($CHCl_3$) 754, 968, 3016, 3434 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.08 (d, J = 6.6 Hz, 6H), 6.13 (d, J = 6.7 Hz, 6H), 2.12 (s, 3H), 2.31-2.47 (m, 2H), 2.56-2.78 (m, 2H), 3.23 (m, 2H), 4.48 (dd, J = 3.5, 10.8 Hz, 1H), 6.53 (d, J = 1.3 Hz, 1H), 6.77-6.88 (m, 2H), 7.17-7.34 (m, 5H); **^{13}C NMR** (200 MHz, $CDCl_3$): δ 19.6, 19.9, 20.7, 33.3, 39.3, 42.1, 47.9, 118.0, 126.1, 127.73, 128.2,128.4, 128.6, 129.2, 132.3, 144.7, 153.1; **Analysis** for $C_{22}H_{31}NO$ requires C, 81.18; H, 9.60; N, 4.30; found C, 81.25; H, 9.43; N, 4.11%.

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Chapter IV

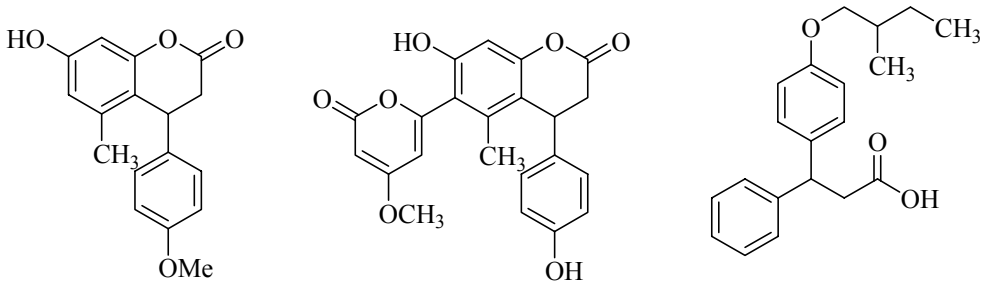
p-Toluenesulfonic acid (p-TSA)-mediated hydroarylation of cinnamic acids with anisoles and phenols under metal- and solvent-free conditions and $Cu(OTf)_2$-catalyzed α-halogenation of ketones

Section I:

p-Toluenesulfonic acid (*p*-TSA) mediated hydroarylation of cinnamic acids with substituted anisoles and phenols under metal- and solvent-free conditions

4.1.1 Introduction

4-aryldihydrocoumarins are widely present in nature and found to be important candidates for treatment of several dieseses.[1] For example, traditional Chinese and Japanese medicines have used tannin-containing plant extracts for the treatment of infections and diseases for centuries.[2] Tannins and other natural products, such as flavonoids, present the skeleton of 4-aryldihydrocoumarins in their structure.[3] The important biological activities that dihydrocoumarin derivatives **1-2** present (inhibition of aldose reductase[3b] and protein kinases,[3c] antiherpetic activity,[4]and selective inhibition of HIV replication[5]) make them attractive candidates for new lead compounds in biological testing. For example, dihydrocoumarin **2** isolated from *Aloe Vera*, exhibits potential antioxidative and immunomodulatory properties.[6] 3-Aryl-3-(4-phenoxy)-propionic Acid (**3**) shows good pharmacokinetic profile as G Protein-coupled receptor 40 agonists and would be beneficial in the treatment of type II diabetes.[7]



1 Neoflavanoid

2

3 GPR-40 Agonist

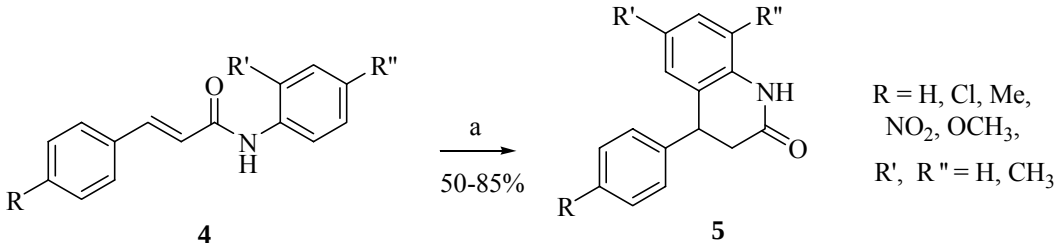
Fig. 1 Examples of dihydrocoumarins and 3-aryl propionic acids

4.1.2 Review of literature

Literature search revealed that hydroarylation reaction was found to be important method in the synthesis of coumarins and dihydrocoumarins.[8] Some of the recent reports are described below.

Johnston's approach (1968)[9]

Johnston's *et al.* reported PPA catalyzed cyclization of *N*-phenylcinnamide (**4**) to the corresponding 4-phenyl-3,4-dihydrocarbostyril (**5**) in good yields. Election-withdrawing substitution on aryl (R = Cl, NO_2) as well as election-donating substitution on aniline nucleus (R', R" = Me) provided good yields of products formed.

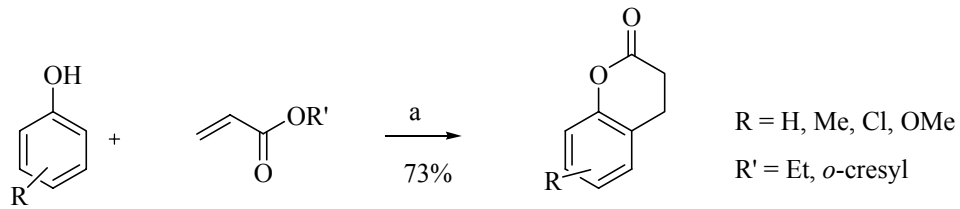


4 **5**

Scheme 1: (a) P_2O_5 : H_3PO_4 (1:1) 130 ºC, 10 min, 1 h.

Pickett's approach (1992)[10]

Pickett *et al*. have used LiH as a base catalyst for hydroarylation of the phenol **6** with acrylate esters **7** to give dihydrocoumarins **8** in high yields

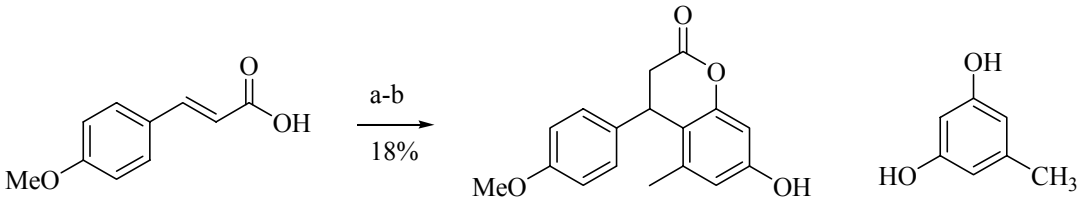


6 **7** **8**

Scheme 2: (a) LiH (0.049 mol), *o*-cresol (2.47 mol), reflux, then added ethyl acrylate

Braz-Pilho's approach (1997)[11]

Braz-Pilho's *et al* reported the two step procedure for the synthesis of neoflavonoids **10**. *p*-Methoxycinnamic acid (**9**) was converted to the acid chloride and its treatment with $AlCl_3$ followed by addition of phenols **11** gave the neoflavonoids **10** in18% yields.

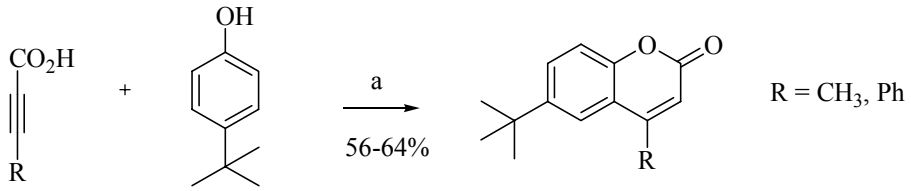


9 **10** **11**

Scheme 3: (a) $(COCl)_2$, CH_2Cl_2, 25 °C; (b) $AlCl_3$, phenol **11**, CS_2, 25 °C, 72 h.

Fujiwara's approach (2000)[12]

Fujiwara *et al* reported the Pd-catalyzed hydroarylation of propionic acids **12** with phenol **13** for the synthesis coumarin **14** in 56-64 %yields.

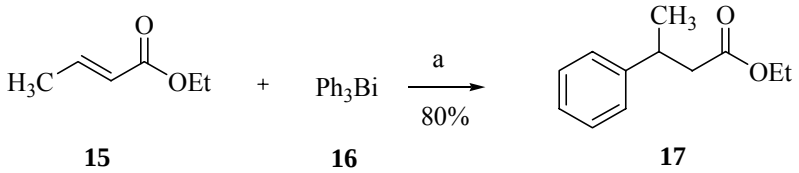


12 **13** **14**

Scheme 4: (a) $Pd(OAc)_2$ or $PtCl_2 \cdot 2AgOAc$ (5mol%), TFA, CH_2Cl_2, 25 °C, 24 h.

Li's approach (2001)[13]

Li *et al.* reported the Rh-catalyzed addition of triphenylbismuth (**16**) onto the α,β-unsaturated esters **15** to give the corresponding conjugated addition products **17** in high yields.

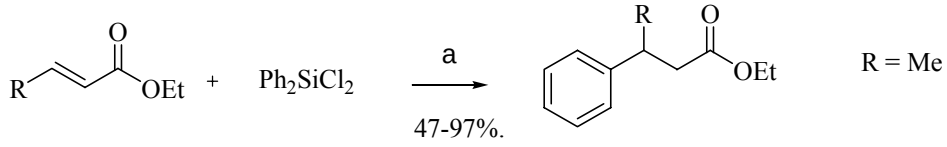


15 **16** **17**

Scheme 5: (a) $Rh_2(COD)_2Cl_2$ (5mol%), THF: H_2O (7:3), 50 °C,12 h.

Li's approach (2001)[14]

Li *et al.* reported the Rh-catalyzed addition of diphenyldichlorosilane **18** onto the *α,β*-unsaturated esters **15** to give the corresponding conjugated addition products **17** in high yields.

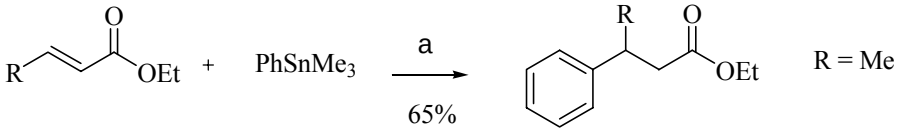


15 **18** **17**

Scheme 6: (a) NaF (5.0 mmol), $(COD)_2RhBF_4$ (0.013 mmol), water (5 mL), 100 °C, 12 h, 47-97%.

Li's approach (2001)[15]

Li *et al*. reported the addition trimethylphenylstannanes **19** onto the *α,β*-unsaturated esters **15** to give the corresponding conjugated addition products **17** in high yields.

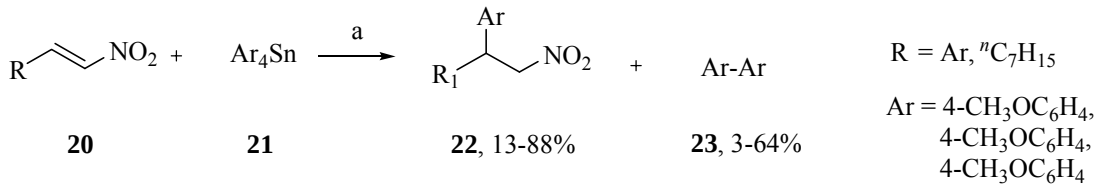


15 **19** **17**

Scheme 7: (a) $[Rh(COD)(CH_3CN)_2]BF_4$ (5 mol%), water (4 mL), 50°C, 12 h, 30-77%.

Uemura's approach (2002)[16]

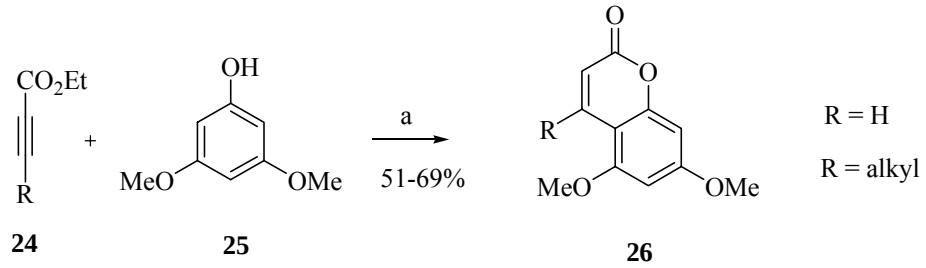
Uemura's approach describes $BiCl_3$ promoted Michel type addition of Ar_4Sn **21** to the *β*-nitrostyrene **20** to provide 1,4-addition diaryl nitro product **22** in moderate yields along with diaryl byproduct **23**.



Scheme 8: (a) **20** (1 mmol), **21** (0.25 mmol), $PdCl_2$ (0.05 mmol), LiCl (2 mmol), AcOH (10 mL) at 25°C for 20 h.

Trost's approach (2003)[17]

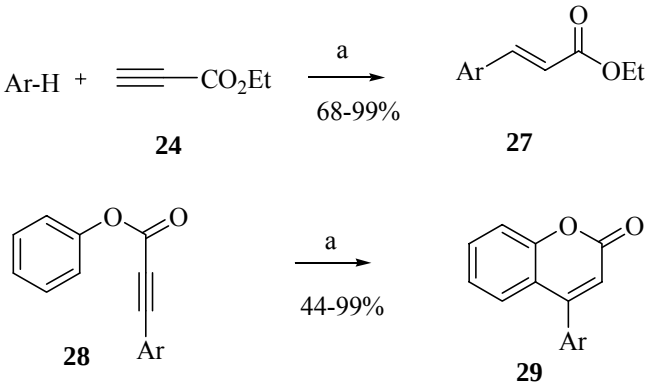
Trost *et al* have used $Pd(OAc)_2$ for the hydroarylation reaction of propionic acid (**24**) with electon rich phenol **25** to afford coumarin derivatives **26** in 51-69% yields.



Scheme 9: (a) $Pd(OAc)_2$ (10 mol%), NaOAc (20 mol%), HCO_2H, 35 °C.

He's approach (2004)[18]

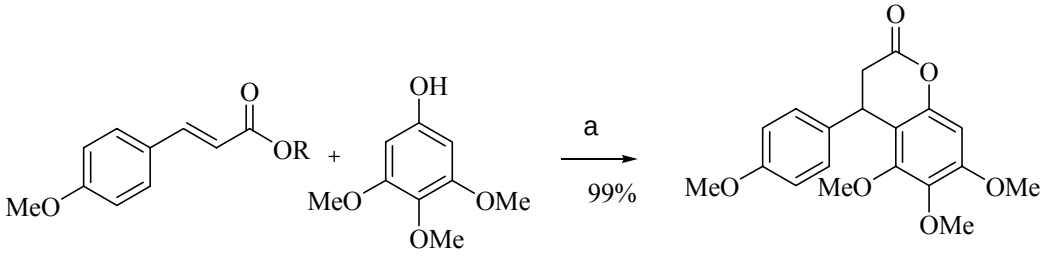
He *et al.* reported Au-catalyzed carbon-carbon bond formation reaction between arenes and electron-deficient alkynes **24** to provide coumarins **29** in 44-99% yields.



Scheme 10: (a) Arene (1 mmol), alkyne (0.5 mmol), $AuCl_3$/3AgOTf (5 mol %), CH_2Cl_2 (2mL), 1-96 h.

Tunge's approach (2005)[19]

Tunge *et al* reported the synthesis of dihydrocoumarin **31** with electron rich phenols **30** and cinnamic acids **9** mediated by TFA in high yields**.**

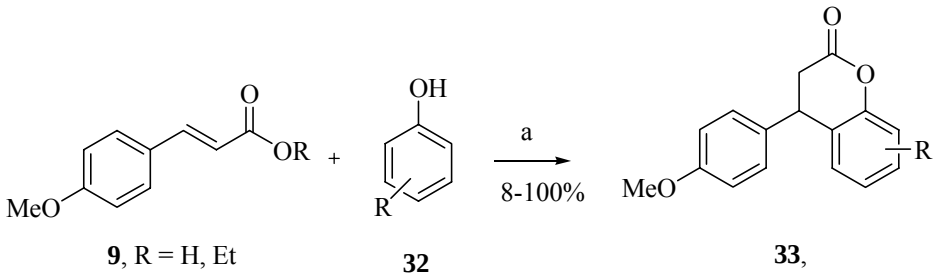


9, R = H, Et **30** **31**

Scheme 11: (a) TFA:CH_2Cl_2 (1:4), 25 °C, 24 h.

Kitamura's approach (2005)[20]

Kitamura *et al.* reported TFA mediated synthesis of 4-aryl-3,4-dihydrocoumarins **33** from activated phenols **32** and electron-rich cinnamic acids and esters **9**.

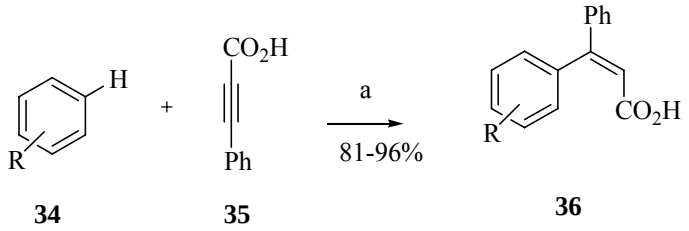


9, R = H, Et **32** **33**,

Scheme 12: (a) Cinnamic acid/ester (1 mmol) and phenol (1 mmol), TFA (1 mL),25 °C , 24 h.

Kitamura's approach (2005)[21]

Kitamura *et al* used K_2PtCl_4 in combination with AgOTf as a Catalyst for hydroarylation of propiolic acids **35** with arenes **34** to provide the 3,3-diarylacrylic acids **36** in 81-96% yields.

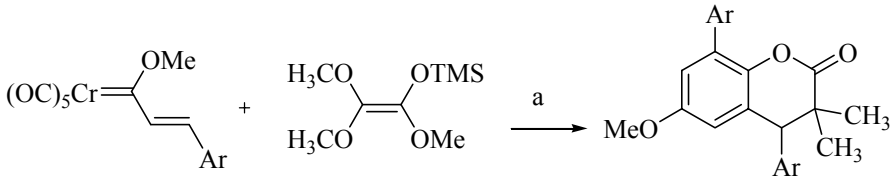


34 **35** **36**

Scheme 13: (a) K_2PtCl_4 (0.05 mmol), AgOTf (0.10 mmol), arene (6 mmol), propiolic acid (2 mmol), TFA (1 mL), 25-40 °C, 15-40 h.

Barluenga's approach (2006)[22]

Barluenga *et al.* reported the reaction of alkenyl carbene chromium(0) complexes **37** with excess ketene acetals **38** to give 4-aryl-3,4-dihydrocoumarins **39** in moderate yield.



37a-c **38**

39a, Ar = Ph, 70%

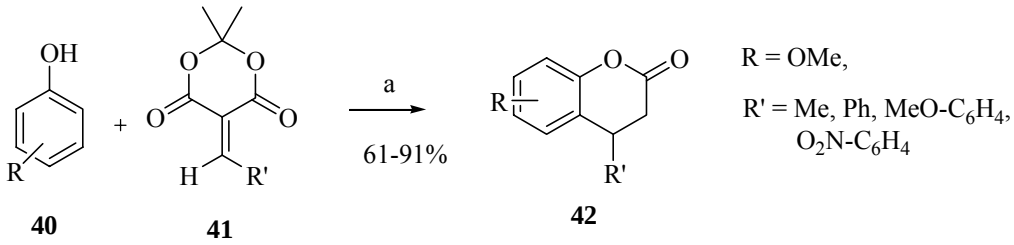
39a, Ar = Fur-2-yl, 65%

39a, Ar = Thiophen-2-yl, 62%,

Scheme 14: (a) Acetal (3 equiv.), THF, 90 °C, sealed tube, 2 h.

Fillion's approach (2006)[23]

Fillion *et al.* have used $Yb(OTf)_3$-catalyzed annulation reactions of activated phenols **40** with 5-alkylidene Meldrum's acids **41** to provide dihydrocoumarin derivatives **42** in 61-91% yields.



40 **41** **42**

Scheme 15: (a) $Yb(OTf)_3$ (10%mol%), CH_3NO_2, 100 °C, 1.5 h

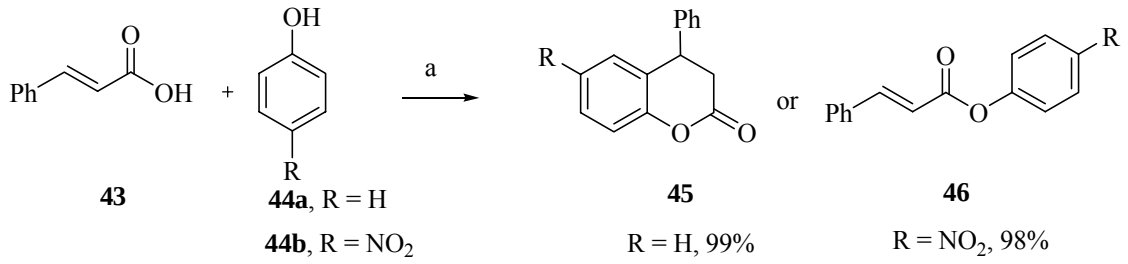
4.1.3 Present work

4.1.3.1 Objective

Literature methods reveal that the preparation of dihydrocoumarins has been accomplished in many ways. However, many of these methods suffer from disadvantages such as lack of substrate generality, the use of large excess of expensive reagents, and the controversy regarding the use of transition metals. For instance, hydroarylation is substrate specific and occurs only with electron-rich phenols and cinnamic acids.[8]

4.1.3.2 Results and Discussion

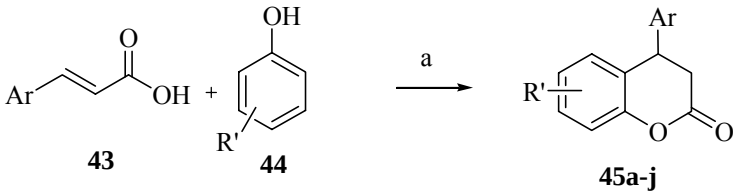
In our study, for the preparation of phenylcinnamate (**46**), we visualized *p*-toluenesulfonic acid-mediated esterification of cinnamic acid (**43**) with simple phenol (**44**) could be achieved. Thus, we subjected *p*-toluenesulfonic acid-mediated esterification of simple cinnamic acid with phenol **44a** (R = H) under solvent-free condition. We have observed that, under the reaction conditions, it took a different course (hydroarylation) to furnish the corresponding dihydrocoumarin **45** in 99% yield (Scheme 1), However, under identical conditions, cinnamic acid was smoothly esterified with 4-nitrophenol **44b** (R = NO_2) to furnish the required ester **46** (R = NO_2) in 98% yield (**Scheme 16**).



43 **44a**, R = H; **44b**, R = NO_2 **45** R = H, 99% **46** R = NO_2, 98%

Scheme 16 : (a) cinnamic acid (5 mmol), phenol (5.5 mmol), *p*-toluenesulfonic acid (5 mmol), 125 ^{o}C, 3 h.

Surprised by this result, we carried out several experiments systematically to optimize the reaction conditions for this transformation. This hydroarylation reaction failed when carried out in organic solvents (CH_2Cl_2, $CHCl_3$, C_6H_6, toluene and DMF, even at reflux temperatures) as well as when using other acid catalysts (camphorsulfonic acid or acetic acid). After several experiments, the combination of *p*-toluenesulfonic acid, phenol and cinnamic acid, all in equimolar amounts and heating at 125 ˚C for 3 h, was found to be the best, which gave dihydrocoumarin in 99% yield. Systematic study of hydroarylation of various cinnamic acids with substituted phenols was carried out subsequently (**Scheme 17**).



43 **44** **45a-j**

Scheme 17 : (a) cinnamic acid (5 mmol), phenol (5.5 mmol), *p*-toluenesulfonic acid (5 mmol), 125 ^{o}C, 3 h.

Phenols with halide, alkyl and O-alkyl substituents underwent hydroarylation smoothly with cinnamic acid to give the corresponding dihydrocoumarins **45 a-j** in 89-99%.

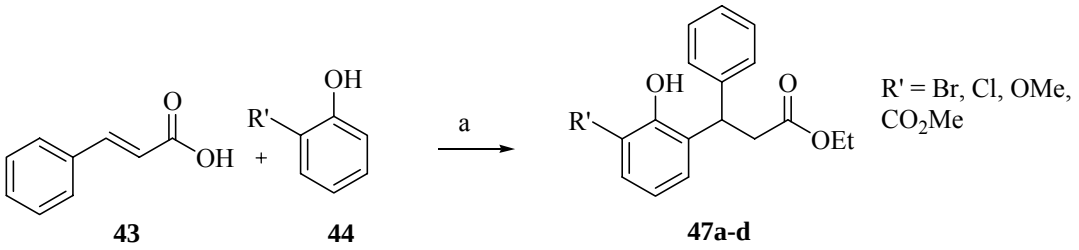
Results are presented in **Table 1**. We observed that, in case of *m*-cresol gave a single *para*-substituted product in 87% yield was obtained.

Table 1: *p*-Toluenesulfonic acid-mediated hydroarylation of cinnamic acids with phenols[a]

Entry	Ar	R'	Yield of **45** (%)
a	Ph	H	99
b	Ph	2-Me	95
c	Ph	3-Me	97
d	Ph	4-Me	99
e	Ph	4-Cl	89
f	Ph	4-Bu^t	89
g	Ph	1-Naphthol	93
h	4-ClC_6H_4	H	87
i	4-ClC_6H_4	4-Me	94
j	4-MeOC_6H_4	H	89

[a] Reaction conditions: cinnamic acid (5 mmol), phenol (5.5 mmol), *p*-toluenesulfonic acid (5 mmol), 125 ^oC, 3 h.
[b] isolated yield after column chromatographic purification.

However, in the case of phenolic substrates with *ortho* substituents such as Cl, Br, OMe and CO_2Me, intramolecular lactonization did not take place; instead the corresponding hydroxy acids were isolated (**Table 2**). In order to make the work-up procedure easier for these substrates, the reaction mixture was quenched with ethyl acetate, followed by addition of water to afford the corresponding hydroxy ethyl esters **47a-d** in excellent yields (**Scheme 18**).



43 **44** **47a-d**

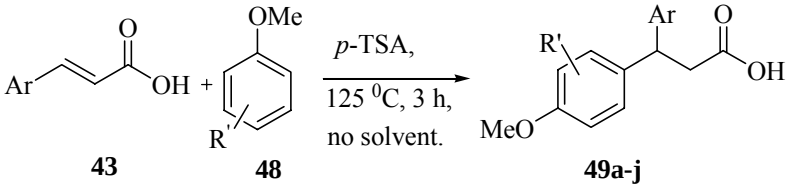
Scheme 18 : (a) cinnamic acid (5 mmol), phenol (5.5 mmol), *p*-toluenesulfonic acid (5 mmol), 125 ^oC, 3 h.

Table 2: *p*-Toluenesulfonic acid mediated hydroarylation of cinnamic acids with phenols[a]

Entry	R'	Yield of **47** (%)
a	2- Br	92
b	2- Cl	87
c	2-OMe	79
d	2-CO_2Me	93

[a] Reaction conditions: cinnamic acid (5 mmol), phenol (5.5 mmol), *p*-toluenesulfonic acid (5 mmol), 125 ^{o}C, 3 h.
[b] isolated yield after column chromatographic purification.
[c] workup: reaction mixture was quenched with ethyl acetate followed by the addition of water.

In contrast, when anisole was subjected to hydroarylation with cinnamic acid **43** under the same reaction conditions, the corresponding 3-(4-methoxyphenyl)-3-phenylpropanoic acid **49a** (*o/p* = 1:1) was obtained in 95% yield (**Scheme 13**).



43 **48** **49a-j**

Scheme 13: cinnamic acid (5 mmol), anisole (5.5 mmol), *p*-toluenesulfonic acid (5 mmol), 125 ^{o}C, 3 h

Subsequently, several anisoles with substituents such as Br, Cl, OMe, etc, were subjected to hydroarylation with cinnamic acids to produce the corresponding carboxylic acids **49a-j** in excellent yields, the results of which are presented in **Table 3**. As can be seen, exclusive *para*-selectivity was observed for all the substrates studied (except **1a**), in accordance with the Friedel-Crafts alkylation mechanism.[24] However, if the *para* position was blocked, alkylation occurred at the *ortho* position (entry g, Table 3). Other less

activated substrates such as toluene failed to undergo hydroarylation. Acetanilide, under the reaction conditions, underwent complete hydrolysis producing aniline. Treatment of chalcone with anisole in the presence of *p*-TSA yielded a mixture of products that was difficult to separate.

Table 3: *p*-Toluenesulfonic acid-mediated hydroarylation of cinnamic acids with anisoles[a]

Entry	Ar	R'	Yield (%)[b]
a	Ph	H	95[c]
b	Ph	2-Br	87
c	Ph	3-Br	88
d	Ph	2-Cl	75
e	Ph	2-Me	91
f	Ph	3-Me	93
g	Ph	4-Me	95[d]
h	Ph	3-OMe	71
i	4-ClC_6H_4	H	82
j	4-$MeOC_6H_4$	H	65

[a]Reaction conditions**:** cinnamic acid (5 mmol), anisole (5.5 mmol), *p*-toluenesulfonic acid (5 mmol), 125 ^oC, 3 h; [b]isolated yield after column chromatographic purification; also ~ 5% of the corresponding demethylated phenolic compounds were formed; [c](*ortho : para* = 1:1); [d]only *ortho* product was formed.

Mechanistically, in the case of phenols, formation of phenolic esters followed by intramolecular Friedel-Crafts type cyclization leads to dihydrocoumarin derivatives **45a-j**.[24] This observation was experimentally proved, substantiated by with the evidence of exclusive formation of *ortho* products. In the case of anisoles, protonation of cinnamic acids leads to a highly electrophilc benzylic carbon such that Friedel-Crafts type alkylation with electron-rich anisole took place producing 3-(4-methoxyphenyl)-3-phenylpropanoic acids **49a-j**.

The formation of all products were confirmed unambiguously from their corresponding spectral analysis. For example, ^1H NMR of the **45a** showed characteristic signals at δ

2.32 (dd) and 4.34 (t) due to methylene (C**H**$_2$) and methine (C**H**) protons respectively. Its ^{13}C NMR spectrum showed typical signals at δ 36.84, 40.43 and 167.4 corresponding to the methylene (**C**H$_2$), methine (**C**H) and ester carbonyl carbon (**C**O$_2$Ar) respectively. Its IR spectrum showed typical absorption band at 1772 cm^{-1} confirming the dihydrocoumarin core (**Fig. 2**).

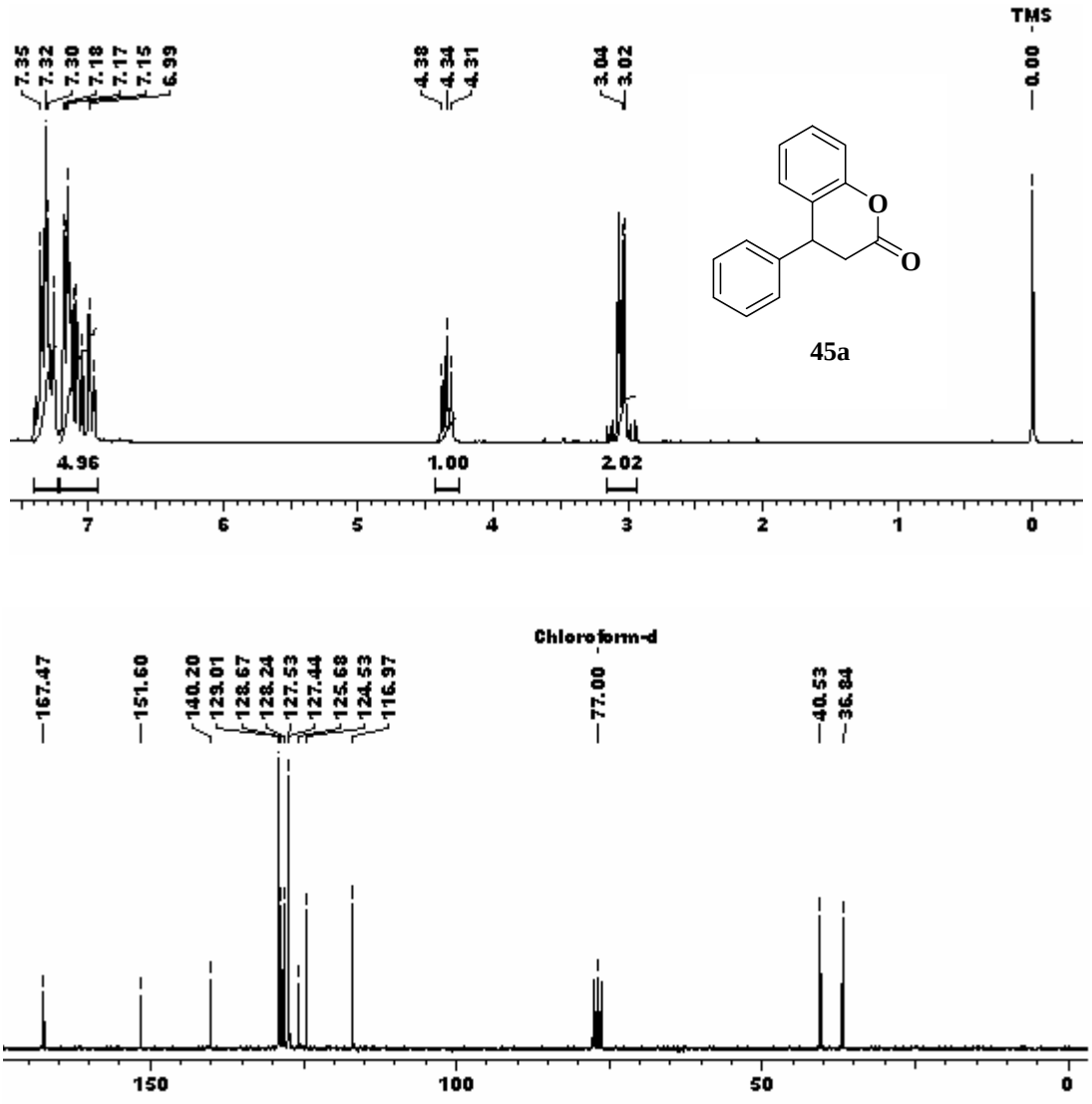


Fig. 2: ^{1}H and ^{13}C-NMR spectra of dihydrocoumarin 45

^{1}H NMR spectrum of **47** showed characteristic signals at δ 1.12 (t) and 4.04 (q) due to protons of ethyl group, Also typical signals at 2.07 (dd), 4.90 (t) and 5.89 (s) corresponding to the methylene (C**H**$_2$) and methine (C**H**) and phenolic hydroxyl (ArOH) protons respectively. Its ^{13}C NMR showed characteristic signals at δ 40.9, 60.4 and 171.8 due to methylene (**C**H$_2$CH) and methine (CH$_2$**C**H) and ester carbonyl carbon respectively. Its IR spectrum showed typical absorption bands at 1733 and 2918 cm^{-1} confirming ester and phenol moieties in **47 (Fig. 3)**.

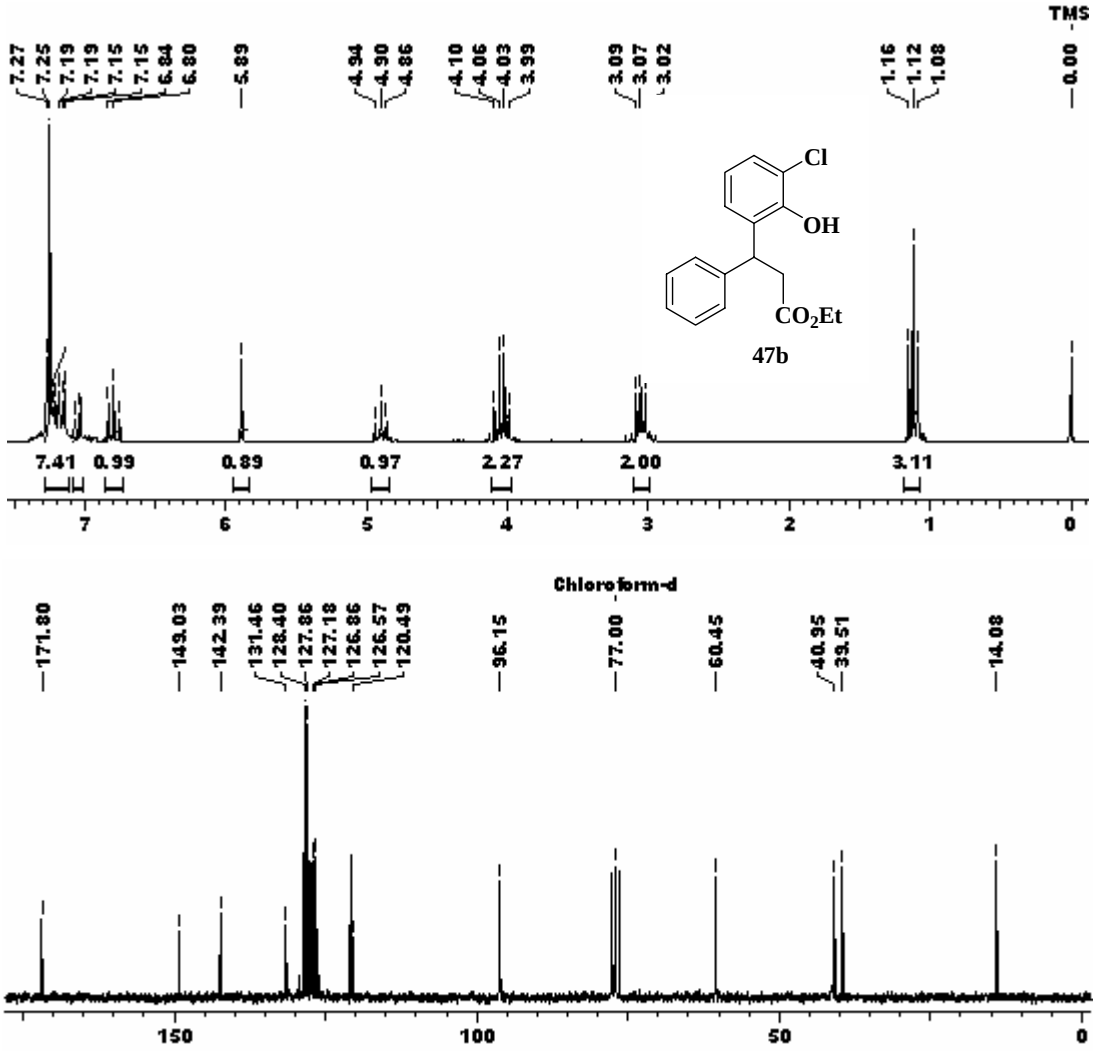


Fig. 3: ^{1}H and ^{13}C NMR spectra of ethyl 3-(3-chloro-2-hydroxyphenyl)-3-phenylpropanoate (47b)

^{1}H NMR spectrum of **49a** showed characteristic signals at δ 3.76 (s), 3.04 (d) and 4.47 (t) due to methyl (OC**H**$_3$), methylene (C**H**$_2$), and methine C**H**) protons respectively. Its ^{13}C NMR showed signals signals at δ 55.08, 40.58 and 45.72 due to methyl, methylene and methine carbon respectively.

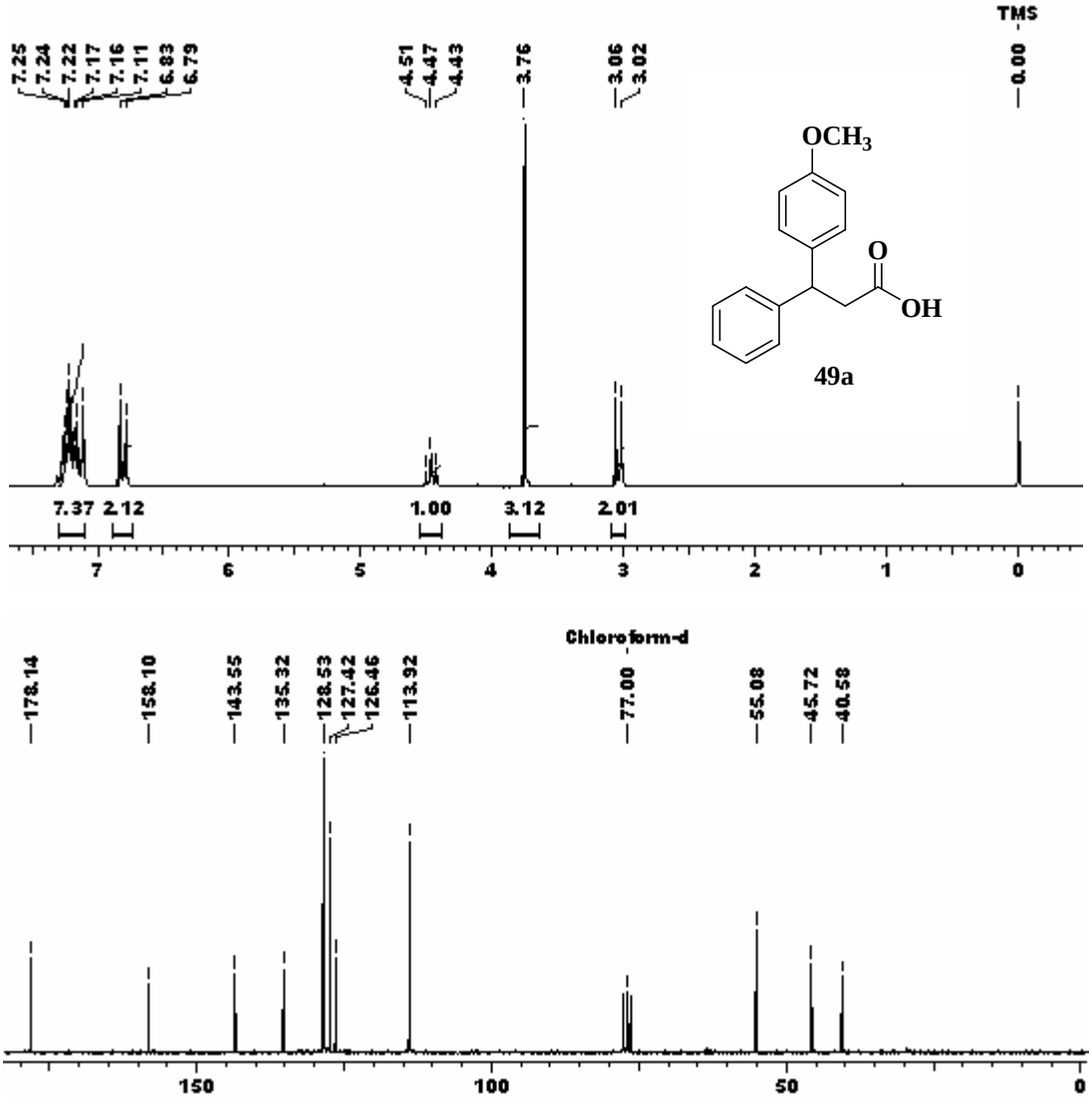


Fig. 4: ^{1}H and ^{13}C NMR spectra of 3-(4-methoxyphenyl)-3-phenylpropanoic acid (49a)

4.1.4 Conclusion

In conclusion, we have developed a convenient, practical, metal and solvent free process for hydroarylation of cinnamic acids with phenols and anisoles mediated by *p*-toluenesulfonic acid affording dihydrocoumarins **3** and 3-(4-methoxyphenyl)-3-phenylpropanoic acids **7a-j**, respectively, in good to high yields. High regioselectivity, easy handling, broad substrate scope and the use of cheap *p*-toluenesulfonic acid as acid mediator are some of the advantages of this methodology.

4.1.5 Experimental section

General experimental procedure for hydroarylation of cinnamic acid with substituted phenols.

To the 25 ml RB flask equipped with reflux condenser, were charged phenol (5 mmol), cinnamic acid (5 mmol) and *p*-TSA (5 mmol). Reaction mixture was heated to 125-130°C under nitrogen atmosphere for 3 h. Reaction mixture was cooled and diluted with ethyl acetate (50 mL). The organic layer was washed with water (2 x 50 mL) and brine (50 mL). The organic layer was dried over anhydrous sodium sulphate, concentrated under reduced pressure. Purified by column chromatography using flash silica gel (230-400 Mesh) using 5%ethyl acetate/petroleum ether as eluent.

4-Phenylchroman-2-one (45a):

Yield: 99%, gum, **IR** ($CHCl_3$): 752, 919, 1135, 1218, 1456, 1610, 1772 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.03 (dd, *J* = 2.2, 6.8 Hz ,2H), 4.34 (t, *J* = 6.8, 1H), 6.98 (dd, *J* = 1.8, 7.2 Hz 1H), 7.04-7.18 (m, 4H), 7.25-7.38 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.84, 40.53, 116.97, 124.53, 125.68, 127.44, 127.53, 128.24, 128.67, 129.01, 140.20, 151.60, 167.47; **Analysis** $C_{15}H_{12}O_2$ requires C, 80.34; H, 5.39; found C, 80.35; H, 5.38%.

8-Methyl-4-phenylchroman-2-one (45b):

Yield: 95%**,** gum, **IR** ($CHCl_3$)): 757, 917, 1136, 1225, 1470, 1605, 1775 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.36 (s, 3 H), 3,03 (d, *J* = 6.6 Hz, 2 H), 4.32 (t, *J* = 6.6 Hz, 1 H), 6.80 (d, *J* = 7.5 Hz, 1H), 6.97 (t, *J* = 7.5 Hz, 1H), 7.13-7.17 (m, 3H), 7.25-7.37 (m, 3 H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 15.85, 36.93, 40.83,124.05,125.57, 125.80, 126.38, 127.52, 127.54, 129.05, 130.25, 140.41, 149.99, 167.45; **Analysis** $C_{16}H_{14}O_2$ requires C, 80.65; H, 5.92; found C, 80.64; H, 5.93%.

7-Methyl-4-phenylchroman-2-one (45c):

Yield: 97%**,** gum, **IR** ($CHCl_3$)): 757, 914, 1133, 1232, 1476, 1610, 1775 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.36 (s, 3 H), 3,04 (dd, *J* =1.8, 6.8 Hz, 2H), 4.31 (t, *J* = 6.8Hz, 1H), 6.84-7.06 (m, 3H), 7.14-7.40 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.9, 37.0, 40.2, 117.3, 122.5, 125.2, 127.3, 127.3, 127.9, 128.9, 138.9, 140.4, 151.4, 167.6; **Analysis** $C_{16}H_{14}O_2$ requires C, 80.65; H, 5.92; found C, 80.63; H, 5.94%.

6-Methyl-4-phenylchroman-2-one (45d):

Yield: 99%**,** gum, **IR** ($CHCl_3$): 752, 919, 1135, 1218, 1456, 1610, 1772 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.20 (s, 3 H), 3.01 (dd, *J* = 2.7, 6.8 Hz, 2 H), 4.28 (t, *J* = 6.8 Hz, 1H), 6.76 (d, *J* = 2 Hz, 1H), 6.98-7.16 (m, 4H), 7.25-7.39 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.6, 36.8, 40.5, 116.6, 125.2, 127.3, 127.4, 128.5, 128.9, 129.1, 133.9, 140.4, 149.5, 167.3; **Analysis** $C_{16}H_{14}O_2$ requires C, 80.65; H, 5.92; found C, 80.63; H, 5.94%.

6-Chloro-4-phenylchroman-2-one (45e)

Yield: 89%**,** gum, **IR** ($CHCl_3$): 699, 1217, 759, 880, 925, 1489, 1589, 1602, 1777cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.04 (dd, *J* = 2.8, 3.8 Hz, 2 H), 4.31 (t, *J* = 6.9 Hz, 1H), 6.94 (d, *J* = 2.5 Hz, 1H), 7.07 (d, *J* = 8.7 Hz, 1H), 7.15 (dd, *J* = 2.1, 7.7 Hz, 2H), 7.21-

7.41 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.4, 40.4, 118.3, 127.3, 127.4, 127.8, 128.0, 128.75, 129.2, 129.7, 139.3, 150.0, 167.0; **Analysis** for $C_{19}H_{20}O_2$ requires C, 81.40; H, 7.19; O, 11.41; found C, 81.38; H, 7.20%.

6-*tert*-Butyl-4-phenylchroman-2-one (45f):

Yield: 89%**,** gum, **IR($CHCl_3$)**: 752, 919, 1135, 1218, 1456, 1610, 1772 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.24 (s, 9 H), 3.02 (dd, *J* = 3.6, 6.4 Hz, 2 H), 4.32 (t, *J* = 6.4 Hz, 1H), 6.98 (d, *J* = 2.1 Hz, 1H), 7.05 (d, *J* = 8.6 Hz,1H), 7.13 (dd, *J* = 2.0, 7.9 Hz, 2H), 7.25-7.36 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 31.3, 34.3, 37.2, 40.9, 116.5, 124.7, 125.1, 125.6, 127.4, 127.4, 129.0, 140.6, 147.5, 149.5, 167.4; **Analysis** $C_{19}H_{20}O_2$ requires C, 81.40; H, 7.19; O, 11.41; found C, 81.38; H, 7.20%.

3,4-Dihydro-4-phenylbenzo[*h*]chromen-2-one (45g):

Yield: 93%**,** gum, **IR** ($CHCl_3$): 756, 1134, 1215, 1377, 1506, 1766 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.09-3.17 (dd, *J* = 6.6, 7.3 Hz, 2H), 4.45 (t, *J* = 6.6 Hz, 1H), 7.05-7.18 (m, 3H), 7.27-7.36 (m, 3H), 7.51-7.58 (m, 3H), 7.78-7.83 (m, 1H), 8.23-8.33 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 37.0, 40.9, 119.7, 121.2, 123.6, 124.0, 125.1, 126.5, 126.69, 127.3, 127.4, 127.5, 129.0, 133.5, 140.5, 146.6, 166.8; **Analysis** for $C_{19}H_{14}O_2$ requires C, 83.19; H, 5.14; found C, 83.20; H, 5.13%.

4-(4-Chlorophenyl)chroman-2-one (45h):

Yield: 87%**,** gum, **IR** ($CHCl_3$)): 757, 919, 1134, 1218, 1460, 1614, 1775 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.00-3.07 (dd, *J* = 6.3, 7.7 Hz, 2H), 4.34 (t, *J* = 6.8 Hz, 1H), 6.97 (d, *J* = 7.7 Hz, 1H), 7.06-7.16 (m, 4H), 7.28-7.36 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.7, 39.9, 117.1, 124.6, 125.0, 128.1, 128.8, 128.9, 129.1, 133.3, 138.7, 151.5, 167.1;

Analysis for $C_{15}H_{11}ClO_2$ requires C, 69.64; H, 4.29; Cl, 13.70; found C, 69.62; H, 4.30; Cl, 13.71%.

4-(4-Chlorophenyl)-6-methylchroman-2-one (45i):

Yield: 94%**,** gum, **IR** ($CHCl_3$): 757, 1014, 1147, 1492, 1766 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.27 (s, 3H), 2.97-3.04 (dd, *J* = 6.1, 7.8 Hz, 2H), 4.28 (t, *J* = 6.5 Hz, 1H), 6.77 (d, *J* = 1.8 Hz, 1H), 7.00-7.14 (m, 4H), 7.30-7.34 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ **Analysis** for $C_{16}H_{13}O_2$ requires C, 70.46; H, 4.80; Cl, 13.00; found C, 70.44; H, 4.79; Cl, 12.98%.

4-(4-Methoxyphenyl)chroman-2-one (45j):

Yield: 89%**,** gum, **IR** ($CHCl_3$): 758, 1018, 1147, 14502, 1767 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.99-3.05 (dd, *J* = 6.1, 7.7 Hz, 2H), 3.80 (s, 3H), 4.30 (t, *J* = 6.7 Hz, 1H), 6.87 (d, *J* = 7.7 Hz, 2H), 6.96-7.00 (dd, *J* = 1.5, 7.5 Hz, 1H), 7.06-7.14 (m, 4H), 7.26-7.33 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 37.0, 39.6, 55.1, 114.3, 116.9, 124.5, 126.0, 128.4, 128.5, 132.0, 151.5, 158.8, 167.6; **Analysis** for $C_{16}H_{14}O_2$ requires C, 75.57; H, 5.55; found C, 75.35; H, 5.44%.

Ethyl 3-(3-bromo-2-hydroxyphenyl)-3-phenylpropanoate (46a):

Yield: 92%**,** gum, **IR** ($CHCl_3$): 757, 1215, 1301, 1440, 1490, 1676, 1733, 3153 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.11 (t, *J* = 7.1 Hz, 3H), 3.05-3.12 (dd, *J* = 4.6, 8.3 Hz, 2H), 4.07 (q, *J* = 7.1 Hz, 2H), 4.92 (t, *J* = 8.1 Hz, 1H), 5.40 (s, 1H), 6.70 (t, *J* = 8.1 Hz, 1H), 7.97 (dd, *J* = 1.8, 8.1 Hz, 1H), 7.10-7.27 (m, 6H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.0, 38.5, 40.7, 60.4, 113.4, 122.5, 126.7, 127.1, 127.9, 128.6, 131.47, 142.8, 152.0, 173.8; **Analysis** for $C_{17}H_{17}BrO_3$ requires C, 58.47; H, 4.91; found C, 58.31; H, 4.83%.

Ethyl 3-(3-chloro-2-hydroxyphenyl)-3-phenylpropanoate (46b):

Yield: 84%**,** gum, **IR** ($CHCl_3$): 756, 1020, 1215, 1398, 1454, 1733, 2918 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.12 (t, *J* = 7.1 Hz, 3H), 3.02-3.09 (dd, *J* = 4.4, 8.1 Hz, 2H), 4.05 (q, *J* = 7.1 Hz, 2H), 4.90 (t, *J* = 8.1 Hz, 1H), 5.89 (s, 1H), 6.80 (t, *J* = 7.8 Hz, 1H), 7.03-7.08 (dd, *J* = 1.5, 7.8 Hz, 1H), 7.15-7.27 (m, 6H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.08, 39.51, 40.95, 60.45, 120.49, 126.57, 126.86, 127.18, 127.86, 128.40, 131.46, 142.39, 149.03, 171.80; **Analysis** for $C_{17}H_{17}ClO_3$ requires C, 67.00; H, 5.62; Cl, 11.63; found C, 67.02; H, 5.60; Cl, 11.62%.

Ethyl 3-(2-hydroxy-3-methoxyphenyl)-3-phenylpropanoate (46c):

Yield: 79%**,** gum, **IR** ($CHCl_3$): 757, 1031, 1215, 1265, 1514, 1731, 2939 cm^{-1}; **^{1}H NMR** (200 MHz): δ 1.10 (t, *J* = 7.2 Hz, 3H), 3.08 (dd, *J* = 4.7, 8.0 Hz, 2H), 3.83 (s, 3 H), 4.03 (q, *J* = 7.2 Hz, 2H), 4.92 (t, *J* = 8 Hz, 1H), 5.83 (bs, 1H) 6.58-6.80 (m, 3H), 7.15-7.34 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.9, 39.5, 40.4, 55.9, 61.0, 113.1, 122.1, 122.8, 126.4, 128.8, 129.4, 133.8, 144.0, 151.0, 173.0; **Analysis** $C_{18}H_{20}O_4$ requires C, 71.98; H, 6.71; found C, 71.97; H, 6.69%.

Methyl 3-(2-(ethoxycarbonyl)-1-phenylethyl)-2-hydroxybenzoate (46d):

Yield: 93%**,** gum, **IR** ($CHCl_3$): 757, 1031, 1215, 1265, 1514, 1731, 2939 cm^{-1}; **^{1}H NMR** (200 MHz): δ 1.10 (t, *J* = 7.2 Hz, 3H), 3.02 (d, *J* = 7.9 Hz, 2H), 3.93 (s, 3H), 4.03 (q, *J* = 7.2 Hz, 2H), 4.49 (d, *J* = 7.9 Hz, 1H), 6.89 (d, *J* = 8.6 Hz, 1H), 7.14-7.37 (m, 6H), 7.74 (d, *J* = 2.4 Hz, 1H), 10.62 (br s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.2, 40.4, 45.9, 51.5, 62.2, 112.0, 117.8, 126.6, 127.3, 128.3, 128.5, 129.7, 134.0, 135.1, 143.1, 160.3, 170.2, 171.7; **Analysis** for $C_{19}H_{20}O_5$ requires C, 69.50; H, 6.14; found C, 69.31; H, 6.08%.

General experimental procedure for hydroarylation of cinnamic acid with substituted anisoles.

To the 25 ml RB flask equipped with reflux condenser, were charged anisole (5 mmol), cinnamic acid (5 mmol) and *p*-TSA (5 mmol). Reaction mixture was heated to 125-130°C for 3 h. Reaction mixture was cooled and diluted with ethyl acetate (50 mL). The organic layer was washed with water (2 x 50 mL) and brine (50 mL). The organic layer was dried over anhyd. Na_2SO_4, concentrated under reduced pressure to give the crude product. The crude product was purified by column chromatography using flash silica gel (230-400 Mesh) using 30% ethyl acetate–petroleum ether as eluent gave products **49a-i** in pure form.

3-(4-Methoxyphenyl)-3-phenylpropanoic acid (49a)

Yield: 95%; gum, **IR** ($CHCl_3$): 757, 1031, 1217, 1247, 1512, 1706, 2931 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.04 (d, *J* = 7.9 Hz , 2H), 3.76 (s, 3H), 4.47 (t, *J* = 7.9 Hz, 1H), 6.81 (d, *J* = 8.7 Hz, 2H), 7.11-7.31 (m, 7H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 40.5, 45.7, 55.0, 113.9, 126.4, 127.4, 128.5, 135.3, 143.5, 158.1, 178.1; **Analysis** $C_{16}H_{16}O_3$ requires C, 74.98; H, 6.29; found C, 74.90; H, 6.23%.

3-(3-Bromo-4-methoxyphenyl)-3-phenylpropanoic acid (49b):

Yield: 87%; gum, **IR** ($CHCl_3$, cm^{-1}): 732, 910, 1055, 1282, 1494, 1712, 2925, 3029 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.03 (d, *J* = 7.8 Hz, 2H), 3.83 (s, 3H), 4.43 (t, *J* = 7.8 Hz, 1H), 6.79 (d, *J* = 8.5 Hz, 1H), 7.12 (dd, *J* = 2.0, 8.5 Hz, 1H), 7.17-7.32 (m, 5H), 7.38 (d, *J* = 2.0 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 40.1, 45.2, 55.8, 111.4, 111.7, 126.5, 127.2, 127.3, 128.4, 132.1, 136.7, 142.6, 154.2, 177.5; **Analysis** for $C_{16}H_{15}BrO_3$ requires C, 57.33; H, 4.51; found C, 57.32; H, 4.54%.

3-(2-Bromo-4-methoxyphenyl)-3-phenylpropanoic acid (49c):

Yield: 88%**,** gum, **IR** ($CHCl_3$): 756, 1035, 1217, 1492, 1604, 1712, 2358, 3020, 3274 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.03 (d, *J* = 7.8 Hz, 2H), 3.83 (s, 3H), 4.43 (t, *J* = 7.8 Hz, 1H), 6.79 (d, *J* = 8.5 Hz, 1H), 7.10-7.32 (m, 6H), 7.38 (d, *J* = 2.0 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 39.2, 43.5, 54.1, 112.4, 116.9, 123.4, 125.1, 126.6, 127.1, 127.6, 133.2, 141.5, 157.1, 171.6; **Analysis** for $C_{16}H_{15}BrO_3$ requires C, 57.33; H, 4.51; found C, 57.32; H, 4.54%.

3-(3-Chloro-4-methoxyphenyl)-3-phenylpropanoic acid (49d):

Yield: 75%**,** gum, **IR** ($CHCl_3$): 756, 1056, 1215, 1495, 1714, 2935 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$), 3.04 (d, *J* = 8.0 Hz, 2H), 3.85 (s, 3H), 4.44 (t, *J* = 7.8 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 1H), 7.09 (dd, *J* = 2.0, 8.6 Hz, 1H), 7.15-7.33 (m, 6H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 40.3, 46.2, 55.8, 111.49, 122.2, 126.5, 127.1, 127.4, 128.4, 136.1, 136.7, 143.6, 153.2, 177.6; **Analysis** for $C_{16}H_{15}ClO_3$ requires C, 66.10; H, 5.20; found C, 66.08; H, 5.19%.

3-(4-Methoxy-3-methylphenyl)-3-phenylpropanoic acid (49e):

Yield: 91%, gum, **IR** ($CHCl_3$) 757, 1215, 1253, 1506, 1710, 3020 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.15 (s, 3H), 3.03 (d, *J* = 7.9 Hz , 2H), 3.77 (s, 3H), 4.43 (t *J* = 7.9 Hz, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 6.97 (dd, *J* = 2.4, 8.2 Hz, 1H), 7.04 (d, *J* = 2.4 Hz, 1H), 7.16-7.27 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 16.3, 40.6, 45.7, 55.2, 109.8, 125.4, 126.4, 126.6, 127.4, 128.5, 134.8, 143.7, 156.3, 178.0; **Analysis** $C_{17}H_{18}O_3$ requires C, 75.53; H, 6.71; found C, 75.55; H, 6.73%.

3-(4-Methoxy-2-methylphenyl)-3-phenylpropanoic acid (49f):

Yield: 93%, gum, **IR** ($CHCl_3$): 757, 1215, 1238, 1506, 1708, 2345, 3020, 3236 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.30 (s, 3H), 3.4 (dd, *J* =1.8, 8.1 Hz, 2H) 3.73 (s, 3H), 4.85 (t, *J* = 8.1 Hz, 1H), 6.59-6.79 (m, 2H), 6.97 (d, *J* = 8.3 Hz, 1H), 7.15-7.25 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.3, 39.3, 39.8, 55.2, 111.7, 121.0, 126.1, 127.5, 12.7, 128.2, 128.7, 137.5, 143.1, 156.6, 178.1; **Analysis** for $C_{17}H_{18}O_3$ requires C, 75.53; H, 6.71; found C, 75.54; H, 6.74%.

3-(2-Methoxy-5-methylphenyl)-3-phenylpropanoic acid (49g):

Yield: 95%; gum, **IR** ($CHCl_3$): 767, 1027, 1132, 1230, 1502, 1712, 2921 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.23 (s, 3H), 3.04 (d, *J* = 7.6 Hz, 2 H), 3.72 (s, 3H), 4.87 (t, *J* = 7.6 Hz, 1H), 6.71 (d, *J* = 8.5 Hz, 1H), 6.88 (d, *J* = 1.6 Hz, 1H), 6.96 (dd, *J* = 1.6, 8.5 Hz, 1H), 7.14-7.26 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.5, 39.3, 39.9, 55.4, 110.7, 126.1, 127.7, 127.8, 128.2, 128.4, 129.5, 131.4, 142.9, 154.6, 178.6; **Analysis** $C_{17}H_{18}O_3$ requires C, 75.53; H, 6.71; found C, 75.52; H, 6.73%.

3-(2,4-Dimethoxyphenyl)-3-phenylpropanoic acid (49h):

Yield 71%; gum, **IR** ($CHCl_3$): 759, 1031, 1213, 1458, 1610, 1708, 2360, 2925, 3014 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.03 (dd, *J* = 1.8, 7.9 Hz, 2H), 3.72 (s, 3H), 3.76 (s, 3H) 4.81 (t, *J* = 7.9 Hz, 1H), 6.37-6.43 (m, 2H), 6.98 (d, *J* = 9.1 Hz, 1H), 7.13-7.26 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 39.4, 39.6, 55.2, 55.3, 98.7, 103.9, 124.2, 126.1, 127.7, 128.1, 128.2, 143.2, 157.6, 159.4, 178.1; **Analysis** for $C_{17}H_{18}O_4$ requires C, 71.31; H, 6.34; found C, 71.34; H, 6.33%.

3,3-Bis(4-methoxyphenyl)propanoic acid (49j):

Yield: 65%, gum, **IR** ($CHCl_3$): 575, 1033, 1232, 1247, 1510, 1710, 2360, 2927, 3020 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 3.02 (d, *J* = 7.8 Hz, 2H), 3.75 (s, 6H), 4.42 (t, *J* = 7.8

Hz, 1H), 6.80 (d, *J* = 8.7 Hz, 4H), 7.12 (d, *J* = 8.7 Hz, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 40.7, 44.9, 55.1, 113.8, 128.4, 135.7, 158.0, 177.4; **Analysis** for $C_{17}H_{18}O_4$ requires C, 71.31; H, 6.34; O, found C, 71.30; H, 6.31%.

3-(4-Chlorophenyl)-3-(4-methoxyphenyl)propanoic acid (49i):

Yield: 82%, gum, **IR** ($CHCl_3$): 756, 1251, 1512, 1606, 1708, 2360, 2925, 3018, 3139 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.02 (d, *J* = 7.9 Hz, 2H), 3.77 (s, 3H), 4.45 (t, *J* = 7.9 Hz, 1H), 6.82 (d, *J* = 8.8 Hz, 2H), 7.09-7.16 (dd, *J* = 7.0, 8.7 Hz, 4H), 7.25 (d, *J* = 8.8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 40.4, 55.1, 114.0, 128.4, 128.6, 128.8, 132.2, 134.82, 142.0, 158.2, 177.6; **Analysis** for $C_{16}H_{15}ClO_3$ requires C, 66.10; H, 5.20; found C, 66.11; H, 5.17%.

Section II:

$Cu(OTf)_2$-catalyzed *α*-halogenation of ketones with 1,3-dichloro-5,5-dimethylhydantoin and *N*-bromosuccinimide.

4.2.1 Introduction

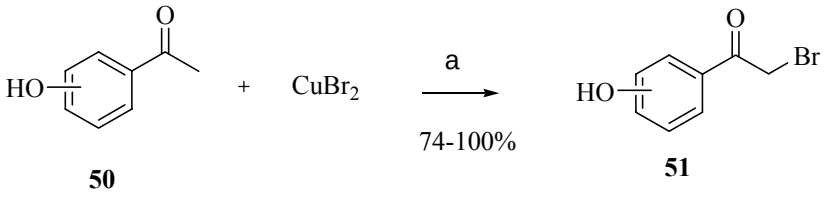
Halogenation of ketones at the *α*-position is a fundamental process in organic chemistry for a wide scope of chemical transformations.[25] The development of new methods for such halogenations of organic compounds has been studied extensively. Carbonyl compounds have been halogenated at the *α*-position by numerous reagents. Generally, direct *α*-halogenation of carbonyl compounds has been achieved in strong acidic and relatively vigorous reaction conditions. A milder route for α-chlorination involves the conversion of ketones to the corresponding enol ethers or enol silanes followed by electrophilic halogenation to give *α*-halo ketones. Metal halides like cupric halide are also used in stoichiometric amounts for halogenation of aldehydes, ketones, enol ethers, enol silanes etc.

4.2.2 Review of literature

Literature search revealed that halogenations of ketones has been achieved by numerous methods.[25] Some of the recent reports are described below.

Ostrum's approach (1964)[26]

Ostrum *et al.* have reported α-bromination of hydroxyacetophenones **50** with stoichiometric amounts of $CuBr_2$ under the heterogeneous conditions to give *α*-bromo acetophenones **51** in high yields. Use of $CuBr_2$ in excess is a limitation of reaction (**Scheme 19**).

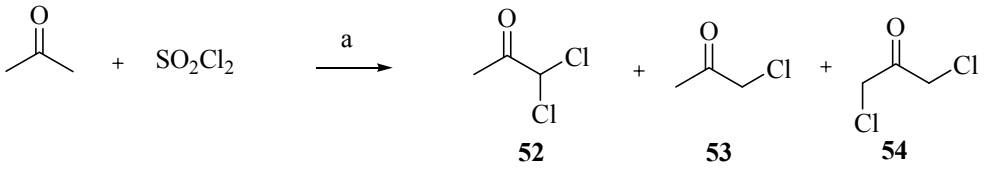


50 **51**

Scheme 19: (a) Hydroxy acetophenone (3 mmol), $CuBr_2$ (5 mmol), EtOAc (25 mL), $CHCl_3$ (25 mL), reflux, 1-5 h.

Kaufman's approach (1964)[27]

Kaufman's *et al.* have described the use of sulfuryl chloride (SO_2Cl_2) for halogenation of various ketones. For example, α-chlorination of acetone resulted in poor selectivity of the chlorinated products (**52-54**) (**Scheme 20**).



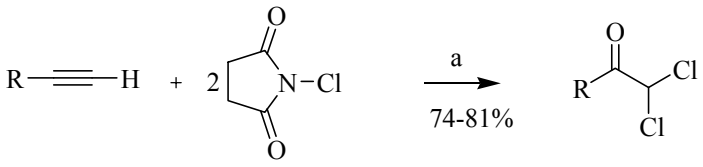
52 **53** **54**

equivalents of SO_2Cl_2	1	58	41	-
	2	72	20	6

Scheme 20: ketone, SO_2Cl_2 (1-2 equiv.), 30-40 ºC, 2-3 h.

Reed's approach (1964)[28]

Reed *et al.* have described the use of *N*-chlorosuccinimide (**56**) in combination with water for oxidative chlorination of acetylenes **55** to give dicloroketones **57** in 74-81% yields (**Scheme 21**).

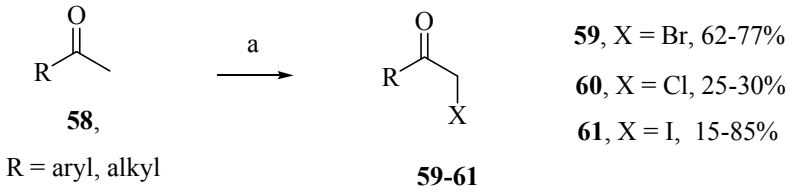


55, R = aryl , alkyl **56** **57**

Scheme 21: (a) MeOH, 25 °C, 3 h, then conc. HCl reflux, 12 h.

Pillai's approach (1989)[29]

Pillai *et al.* have used poly-*N*-haloacrylamide, prepared from commercially available polyacrylamide (PA), a new solid phase polymeric reagents used for the halogenation of ketones **58** to give *α*-haloketones **59-61** (X = Br, Cl and I) (**Scheme 22**).



58,

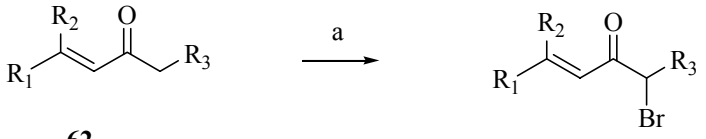
R = aryl, alkyl

59-61

Scheme 22: (a) ketone (5 mmol), $CHCl_3$ (10 mL), polymeric reagent (3-4 molar equiv.), 10 % sulphuric acid, 60 °C, 8-12 h.

Mitani's Approach (1991)[30]

Mitani *et al.* have reported α-bromination of chalcones **62** with $CuBr_2$ to give *α*-bromo chalcones **63** (**Scheme 23**).

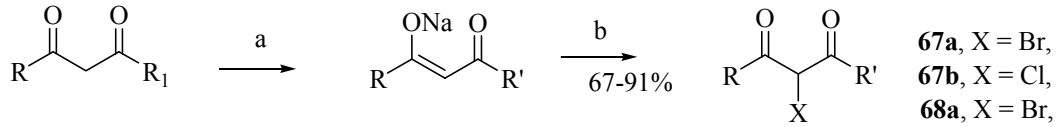


62 **63**

Scheme 23: (a) chalcone (2 mmol), $CuBr_2$ (4 mmol), TFA (8 mmol), Et_4NTs (0.2 mol dm^{-3}) in CH_3CN (10 mL), electrolysis using carbon rod electrodes in an undivided cell.

Dai's approach (1993)[31]

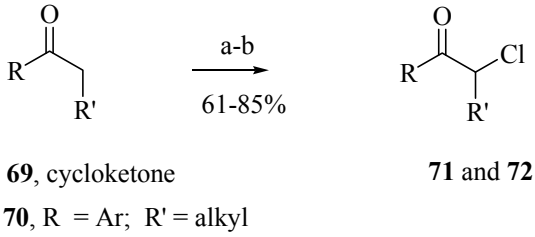
Dai *et al.* have reported a two step procedure for α-halogenation of *β*-dicarbonyl derivatives **64** and **65** to give α-halodicarbonyl derivatives **67a-b** and **68a-b** in high yields (**Scheme 24**).



Scheme 24: (a) keto ester (3 mmol), NaH (3 mmol), DMSO (15 mL), 20 ºC, 2 h, then anhydrous CuX_2 (6-9 mmol), 25- 40 ºC, 7-16 h.

Brummond's approach (1999)[32]

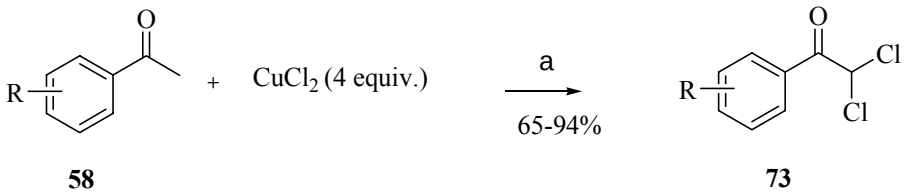
Brummond *et al.* have reported two-step procedures for α-chlorination of ketones **69** and **70**. The procedure involves initial formation of a kinetic enolate of ketones (LDA) and the addition of *p*-toluenesulfonyl chloride as a positive chlorine source to give α-chloro cycloalkanones **71** and α-chloroacetophenones **72** in high yields (**Scheme 25**).



Scheme 25: (a) ketone, LDA (1.0 equiv.), THF, -78 ºC; (b) *p*-toluenesulfonyl chloride (1.0 equiv. 0.1 M solution), THF, -78-0 ºC, 1 h.

Peppe's approach (2002)[33]

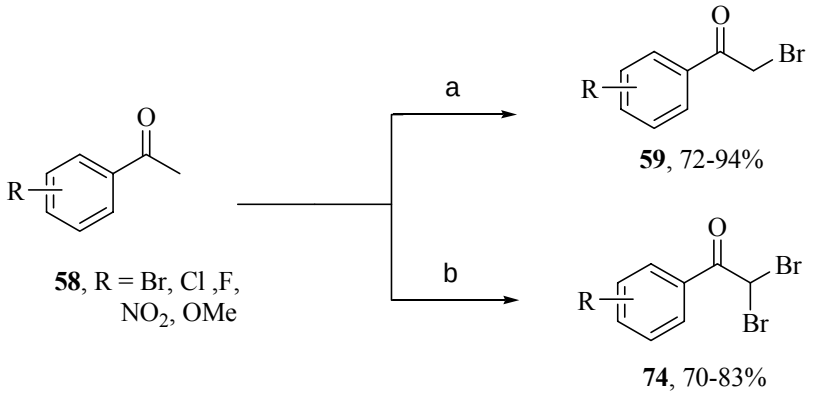
Peppe *et al.* have used execess of $CuCl_2$ for dichlorination of acetophenones **58** in dimethylformamide to produce the corresponding α,α-dichloroacetophenones **73** in high yields (**Scheme 26**).



Scheme 26: (a) $CuCl_2 \cdot 2H_2O$ (11.73 mmol), LiCl (11.73 mmol), DMF (9 mL), then ketone (1.95 mmol), 90 ºC, 2-6 h.

Paul's approach (2003)[34]

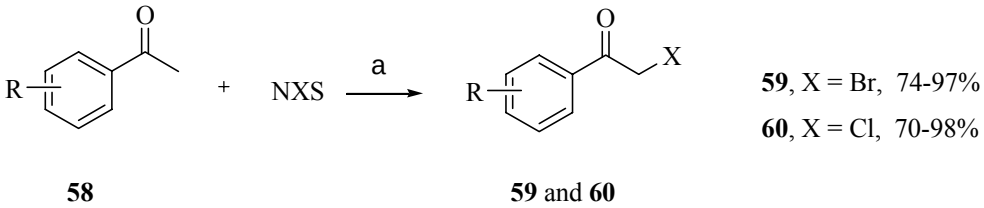
Paul *et al.* have reported the use of dioxane–dibromide complex and silica gel under microwave irradiation for the α-bromination of substituted acetophenones **58.** Acetophenones react with dioxane- dibromide under solvent-free and microwave irradiation condition to give the corresponding conditions α-bromoacetophenones **59** and α,α'-bromoacetophenones **74** in high yields (**Scheme 27**).



Scheme 27: (a) dioxane–dibromide (1.1 equiv.) and silica gel (60–120 mesh, 2 g), microwave , 1-180 min; (b) dioxane–dibromide (2.5 equiv.) and silica gel (60–120 mesh, 5 g), microwave , 1-180 min.

Lee's approach (2003)[35]

Lee *et al.* have used *p*-toluenesulphonic acid-mediated *α*-bromination of ketones **58** to afford the corresponding α-bromoketones **59** in high yields (**Scheme 28)**.

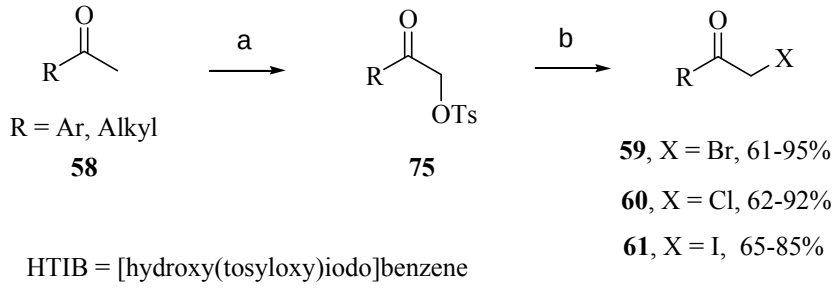


R = H, Cl, NO_2, OMe

Scheme 28: (a) carbonyl compound (1.0 mmol), *p*-toluenesulfonic acid monohydrate (1.5 mmol), CH_3CN (50 mL), NCS or NBS (1.0 mmol), reflux, 1-2 h.

Lee's approach (2004)[36]

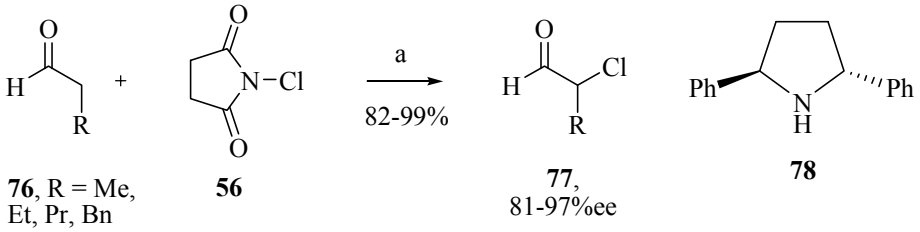
Lee *et al.* have described the α-halogenation of carbonyl compounds using hypervalent iodine(III)sulfonates promoted by microwave irradiation under solvent-free conditions. Halogenation of ketone involves sequential reaction of the carbonyl compounds with [hydroxy(tosyloxy)iodo]benzene (Koser's reagent, HTIB) to produce α-tosyloxycarbonyl intermediate **75** followed by its reaction with MgX_2 (X = Br, Cl, and I) gave α-halo carbonyl derivatives **59**, **60** and **61**(**Scheme 29**).



Scheme 29: (a) carbonyl compound (1.0 mmol), HTIB (1.2 mmol) MWI (700 W), 90 sec, 25 ºC, MgX_2 (2 mmol), MWI (700W), 120 sec, 25 ºC.

Jørgensen's approach (2004)[37]

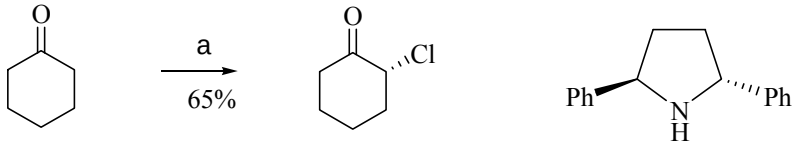
Jørgensen *et al.* have reported an organo-catalytic approach to the asymmetric α-chlorination of aldehydes **76** using NCS as the chlorine source that afforded optically active α-chloroaldehydes **77** in high yields and high optical purity (**Scheme 30**).



Scheme 30: (a) aldehyde, NCS (1.3 equiv.), catalyst **78** (10 mol%), CH_2Cl_2, 0-25 °C, 2-10 h.

Jørgensen's approach (2004)[38]

In another report, Jørgensen *et al.* have described an organo-catalytic asymmetric α-chlorination of ketones **69** using NCS as the chlorine source that afforded optically active *α*-chloroketones **71a** in moderate yields with excellent optical purity (**Scheme 31**).

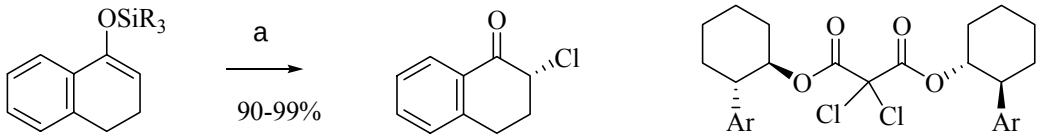


69 **71a**, 97%ee **78**

Scheme 31: ketone (1.25–2.5 mmol), catalyst **78** (10-20 mol%), NCS (0.5 mmol), CH_2Cl_2 , -24 ºC, 24 h.

Yamamoto's approach (2004)[39]

Yamamoto *et al.* have used chiral chlorine sources **81a-c** in combination with $ZrCl_4$ for the chlorination of silyl enol ether **79** to give α-chloro ketones **80** in moderate optical purities with high yields (**Scheme 32**).



79, SiR_3 =TMS, TBDMS, TIPS

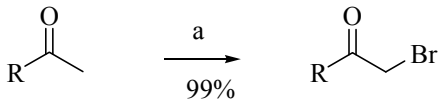
80 42-86%ee

81a-c Ar = Ph, 1-Naphthyl, 9-Naphthyl

Scheme 32: (a) Enolether, $ZrCl_4$ (1 equiv.), CH_2Cl_2, -78 °C, **81** (1 equiv.), 1.5-2 h.

Tanemura's approach (2004)[40]

Tanemura *et al.* have reported NH_4OAc-catalyzed α-bromination of acetophenones **58** to give α-bromoacetophenones **59** in high yields (**Scheme 33**).

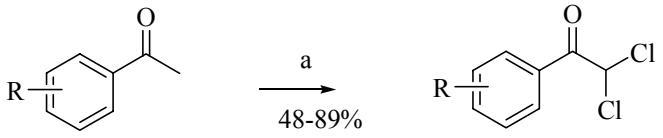


58, R = alkyl, aryl **59**

Scheme 33: substrate (10 mmol), NBS (10.5 mmol), NH_4OAc (1 mmol), Et_2O (10 mL), 25 °C.

Terent'ev's approach[41]

Terent'ev *et al*. have used conc. HCl in combination with H_2O_2 as an effective chlorine source for the dichlorination of acetophenones **58** to give α,α-dichloroacetophenones **73** in good yields (**Scheme 34).**



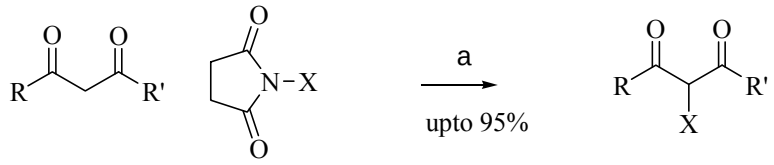
58, **73**

R = Br, Cl ,F, NO_2,

Scheme 34: (a) acetophenones, H_2O_2 (2.7 equiv.) conc. HCl (20 mL), EtOH (20 mL), reflux, 10–15 min.

Yadav's approach (2006)[42]

Yadav *et al.* have described α-halogenation of 1,3-diketones **64** and 1,3-ketoesters **65** in an ionic liquid [Bmim]PF_6 with *N*-halosuccinimide to give the corresponding *α*-halo ketone derivatives **67**, **68** and **82** (**Scheme 35)**.



R = alkyl or aryl

64, R' = alkyl

65, R' =O-alkyl

67, X = Br,

68, X = Cl,

82, X = I

Scheme 35: (a) 1,3-ketoester (1 mmol), *N*-halosuccinimide (1.05 mmol), [Bmim]PF_6 (2 mL), 25 ºC, 10-60 h .

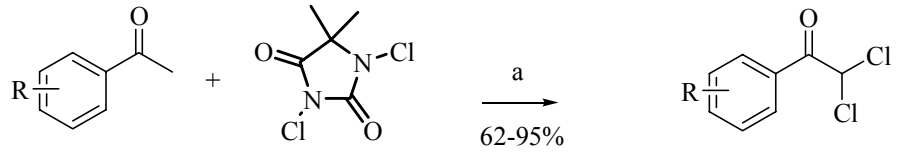
4.2.3 Present work

4.2.3.1 Objective

Although several reagent systems are known in the literature for α-halogenation of carbonyl compounds, these are associated with certain drawbacks such as generality, harsh reaction conditions, stoichiometric amounts of the catalyst, use of toxic gases etc. This provides scope for development of milder conditions for α-halogenation of organic carbonyl compounds. In particular *α*-Halogenation of ketones with metal halides (CuX_2) have been extensively studied to obtain various halo derivatives. Major drawback of this reaction is the use of metal halides in large excess. In this section, we describe $Cu(OTf)_2$-catalyzed *α*-halogenation of ketones using 1,3-dichloro-5,5'-dimethylhydantoin and *N*-bromosuccinimde as halogen sources.

4.2.3.2 Results and Discussion

In continuation of our work[43] on $Cu(OTf)_2$-catalyzed transformations, we became interested in employing $Cu(OTf)_2$, being a mild Lewis acid catalyst, for *α*-halogenation of ketone using 1,3-dichloro-5,5'-dimethylhydantoin as electrophilic chlorine source.[44] Accordingly, we subjected acetophenone **58a** to $Cu(OTf)_2$-catalyzed chlorination of with 1,3-dichloro-5,5'-dimethylhydantoin (**83**, 1 equiv.), which provided 2,2-dichloro-1-phenylethanone **73a** in 92% yield **(Scheme 36).**



58a-l **83** **73a-l**

R = H, halo, OMe, NO_2

Scheme 36: (a) $Cu(OTf)_2$ (1mol%), $CHCl_3$, 80 °C.

Encouraged by this result, we have screened various Lewis acids such as Cu(OTf), $Cu(OAc)_2$, $CuCl_2$, CuCl, CuI, $Co(OAc)_2$ and $CoCl_2$ for the chlorination of acetophenones using 1,3-dichloro-5,5'-dimethylhydantoin **83** as chlorine source, which produced 2,2-dichloro-1-phenylethanone. Results of these studies are presented in **Table 4,** which showed that $Cu(OTf)_2$ was found to be an effective catalyst campared to others for the synthesis of α,α-dichloroacetophenones with very high selectivity and excellent yields.

Table 4: Catalyst screening for dichlorination of acetophenone (**58a**) with 1,3-dichloro 5,5'-dimethylhydration (**83**)

No.	catalyst	Yield of **73a** (%)[a]
1	$Cu(OTf)_2$	92
2	CuOTf	10
3	$Cu(OAc)_2$	23
4	$CuCl_2$	10
5	CuCl	0
6	CuI	0
7	$Co(OAc)_2$	0
8	$CoCl_2$	traces

Reaction conditions: ketone (4 mmol), 1,3-dichloro-5,5'-dimethylhydantion (4.4 mmol), $Cu(OTf)_2$ (5 mol%),$CHCl_3$ (20 ml), reflux.

For $Cu(OTf)_2$-catalyzed chlorination of acetophenone, out of solvents like CH_2Cl_2, CH_3CN, CH_3CO_2H and temperatures ranging from 25 ^oC to reflux, we found that $CHCl_3$ at reflux temperature is the best solvent system for the chlorination. To generalize the scope of reaction, we became interested in subjecting various aromatic ketones to α-chlorination. We found that dichlorination of substituted acetophenones underwent smoothly giving high yields of α,α-dichloroketones with good yield and selectivity, the results of which are summarized in **Table 5**.

Table 5: Dichlorination of substituted acetophenones[a]

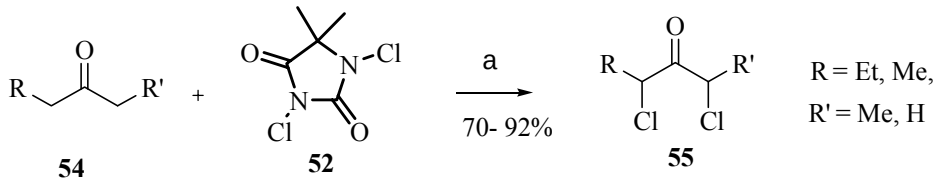
entry	R	time (h)	yield of **73** (%)[b]
a	H	8	92
b	4- O_2N	6	76
c	4-Br	7	77
d	4-Cl	7	71
e	4-F	8	73
f	4-CH_3	5	75
g	4-OCH_3	6	83
h	3,4-$(OCH_3)_2$	6	85
i	3,4,5-$(OCH_3)_3$	5	85[c]
j	Propiophenone	6	87
k	α-Tetralone	7	85
l	2-Acetyl naphthalene	6	86

[a]Reaction conditions: ketone (4 mmol), 1,3-dichloro 5,5'-dimethyl hydration (4.4 mmol), $Cu(OTf)_2$ (5 mol%),$CHCl_3$ (20ml), reflux. [b] [b]Isolated yields after column chromatography,
[c]2-chloro(2-chloro 3,4,5-trimethoxy phenyl)ethanone was obtained.

Remarkably, nuclear chlorination was not at all observed even in the activated aromatic ketones such as methoxyacetophenones (**58g-h**). This can be explained from the fact that $Cu(OTf)_2$ is activating α-position of the ketone by enolization and thus deactivating the aromatic ring for electrophilic chlorination. Only in the case of 3,4,5-trimethoxyacetophenone (**58i**), we observed aromatic chlorination as well as monochlorination at the α-position. As can be seen from **Table 5**, substituted aromatic ketones (nitro, halide, CH_3 and OCH_3) underwent α,α-dichlorination to give the corresponding α,α-dichloroacetophenones **73a-l** in high yields.

We were interested to examine aliphatic ketones as well as chalcones for dichlorination reaction. Thus, $Cu(OTf)_2$-catalyzed α-chlorination of aliphatic ketones **54** were carried

out with 1,3-dichloro-5,5'-dimethylhydantoin which gave α,α'-dichloroketones **55** in good yields (**Scheme 37**).



Scheme 37: (a) $Cu(OTf)_2$ (1 mol%), $CHCl_3$, 80 °C.

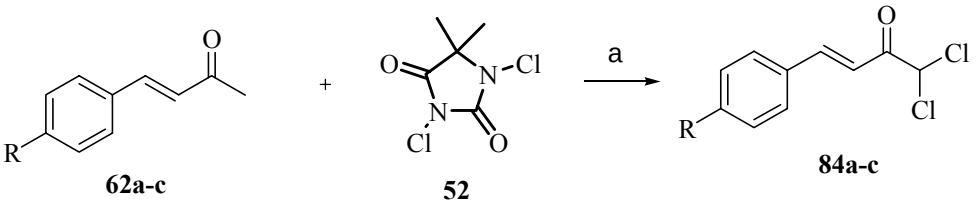
As can be seen from **Table 6,** aliphatic ketones gave α,α'-dichlorination in 61-76% yields. However, 3,3-dimethylbutan-2-one (**54e**) gave 1,1-dichloro-3,3-dimethylbutan-2-one in 71% yield.

Table 6: Dichlorination of aliphatic ketones[a]

entry	ketone (**54a-e**)	time (h)	Yield of **55** (%)[b]
a	cyclohexanone	8	61
b	2-methylcyclohexanone	6	67
c	2-butanone	7	67
d	2 -pentanone	7	76
e	3,3-dimethylbutan-2-one	8	71[c]

[a]Reaction conditions: ketone (4 mmol), 1,3-dichloro 5,5'-dimethyl hydantoin (4.4 mmol), $Cu(OTf)_2$ (5 mol%),$CHCl_3$ (2 0 mL), reflux.
[b]Isolated yields after column chromatography,
[c]1,1-dichloro-3,3-dimethylbutan-2-one was isolated.

In the case of chalcones **62a-c**, α,α-dichlorochalcones **84a-c** were obtained in excellent yields and interestingly the double bond was not affected under the reaction conditions (**Scheme 38**).



62a-c

R = H, Cl, OMe

52

84a-c

Scheme 38: (a) $Cu(OTf)_2$ (1 mol%), $CHCl_3$, 80 °C.

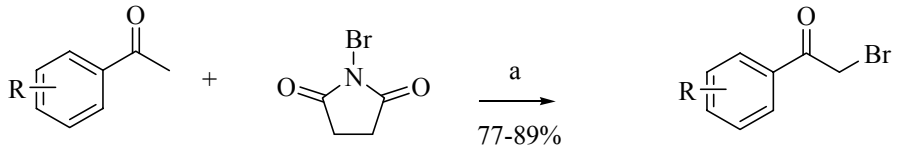
Various chalcones (R = H, Cl, OMe) underwent α,α-dichlorination to give α,α-dichlorochalcones **84a-c** in 83-87% yields (**Table 7**).

Table 7: Dichlorination of chalcones[a]

entry	R (**54a-e**)	time (h)	Yield of **84** (%)[b]
a	H	8	87
b	Cl	6	84
c	OMe	7	83

[a]Reaction conditions: ketone (4 mmol), 1,3-dichloro 5,5'-dimethyl hydantoin (4.4 mmol), $Cu(OTf)_2$ (5 mol%),$CHCl_3$ (20 mL), reflux. [b]Isolated yields after column chromatography,

Next, we have subjected acetophenone to $Cu(OTf)_2$-catalyzed *α*-bromination with *N*-bromosuccinimide. We observed that $Cu(OTf)_2$-catalyzed bromination of acetophenone with NBS (1 equiv.) gave α-bromoacetophenone **59a** in 82% yield (**Scheme 39**).



58a-g

R = H, halo, OMe, NO_2

59a-g

Scheme 39: (a) $Cu(OTf)_2$ (5 mol%), $CHCl_3$, 80 °C

We also observed that α,α-dibromoacetone was formed as a minor product under reaction conditions. The systematic study of various ketones was carried out, the results of which are presented in **Table 8.**

Table 8 : α-Bromination of ketones[a]

Entry	Ketone (R)	time (h)	yield of **59** (%)[b]
a	H	8	82
b	3-NO_2	6	89
c	4-NO_2	6	76
d	3,4-Cl_2	7	77
e	3,4-$(OCH_3)_2$	6	65
f	α-tetralone	7	85
g	2-acetyl-naphthalene	6	86
h	cyclohexanone	6	77
i	2-methyl-cyclohexanone	6	81

[a]Reaction conditions: ketone (4 mmol), *N*BS (4.4 mmol), $Cu(OTf)_2$ (5 mol%),$CHCl_3$ (20 mL), reflux. [b]Isolated yields after column chromatography,
[c]2-chloro(2-chloro 3,4,5-trimethoxy phenyl)ethanone was isolated.

Mechanism

In the presence of $Cu(OTf)_2$, acetophenone undergoes enolization forming enolate (species **A**), which further undergoes nucleophilic addition onto electrophilic dimethylhydantoin dichloride **83** giving α-chloroacetophenone and dimethylhydantoin chloride (species **B**). α-Chloroacetophenone undergoes second enolization followed by chlorination with dimethylhydantoin chloride to give α,α-dichloro acetophenone **73.**

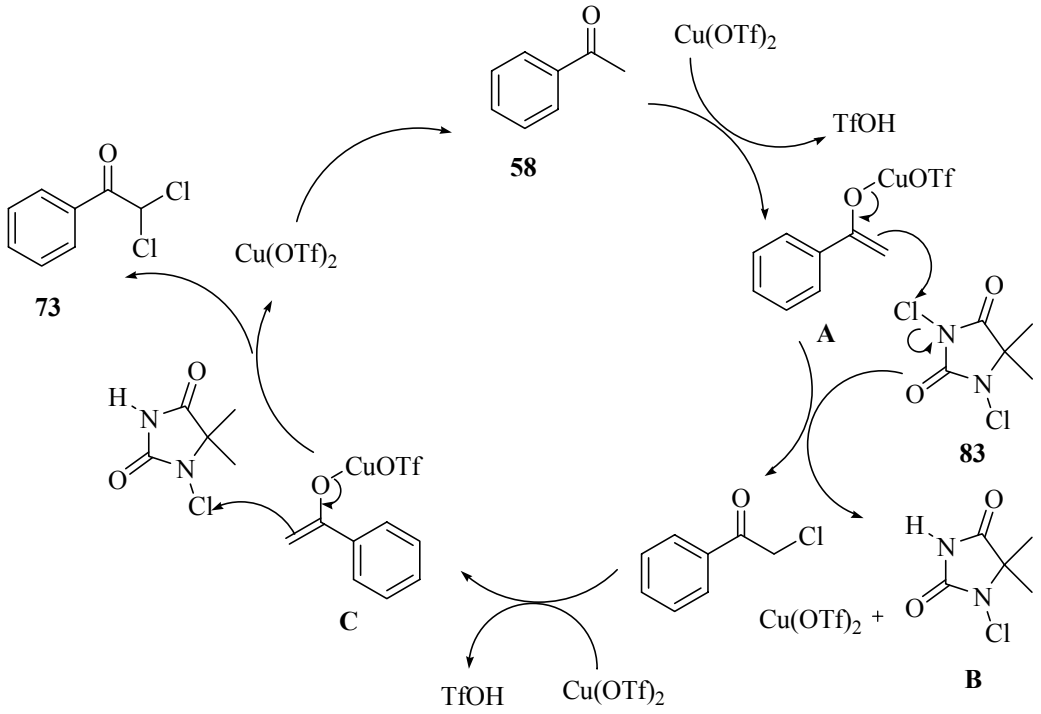


Fig. 6: Mechanism for $Cu(OTf)_2$- catalyzed dichlorination

The characterization of all the products were confirmed unambiguously from their corresponding spectral analysis. For example, ^{1}H NMR of **73f** showed characteristic signals at δ 2.45, 6.65, 7.31 and 7.98 due to methyl (C**H**$_3$), methine (C**H**Cl$_2$) and aromatic protons respectively. Its ^{13}C NMR spectrum showed typical signals at δ 67.7 and 185.2 due to the methine (**C**HCl$_2$) and carbonyl carbons respectively (**Fig. 5).**

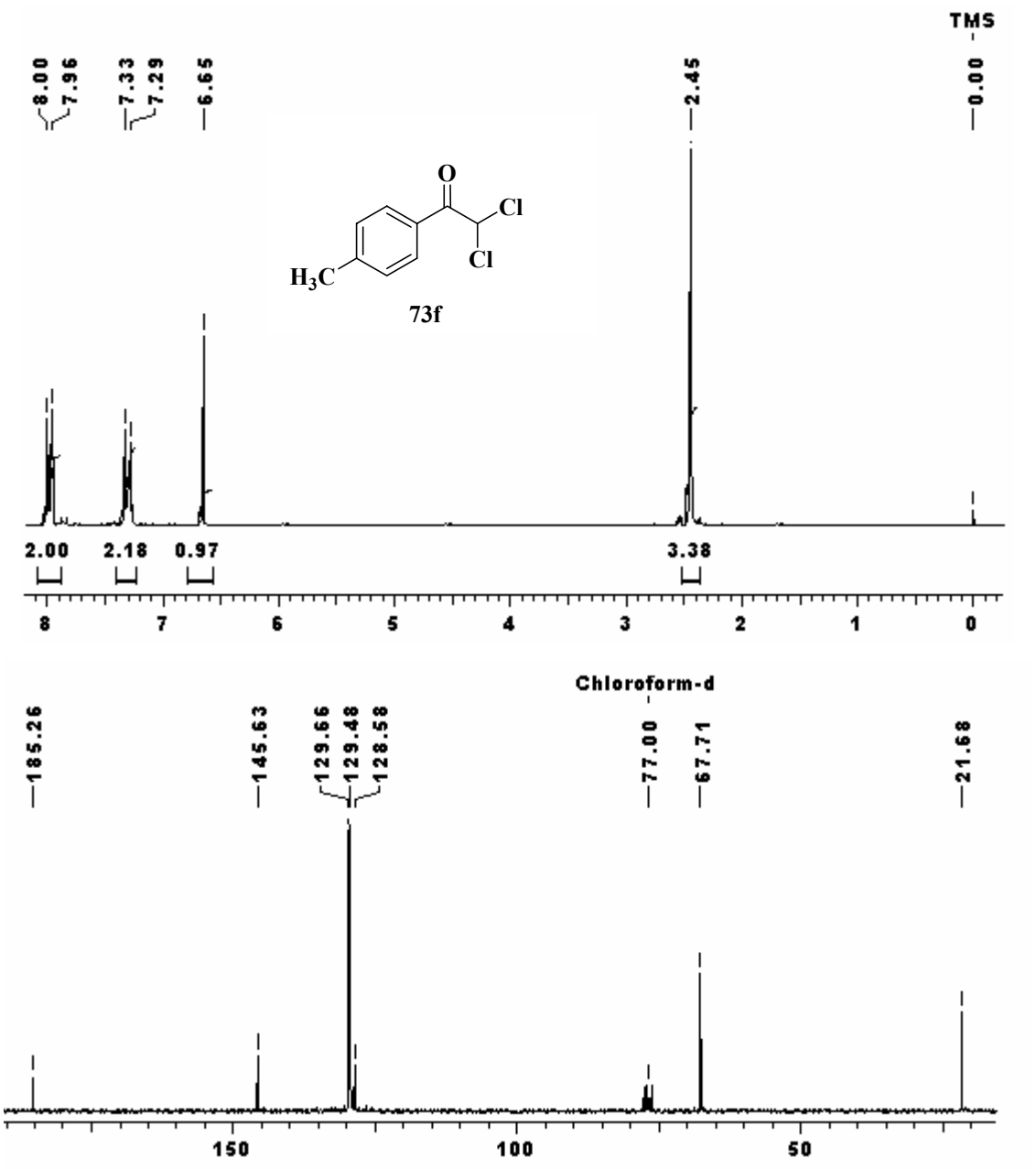


Fig. 5: ^{1}H and ^{13}C NMR spectra of nitrodiol (76a)

As a second example, ^{1}H NMR of **84a** showed characteristic signals at δ 5.95, 7.20 and 7.85 due to the methine (C**H**Cl_2) and olefinic protons respectively. Its ^{13}C NMR spectrum showed typical signals at δ 69.7 and 185.3 due the methine (**C**HCl_2) and carbonyl carbons respectively (**Fig.6).**

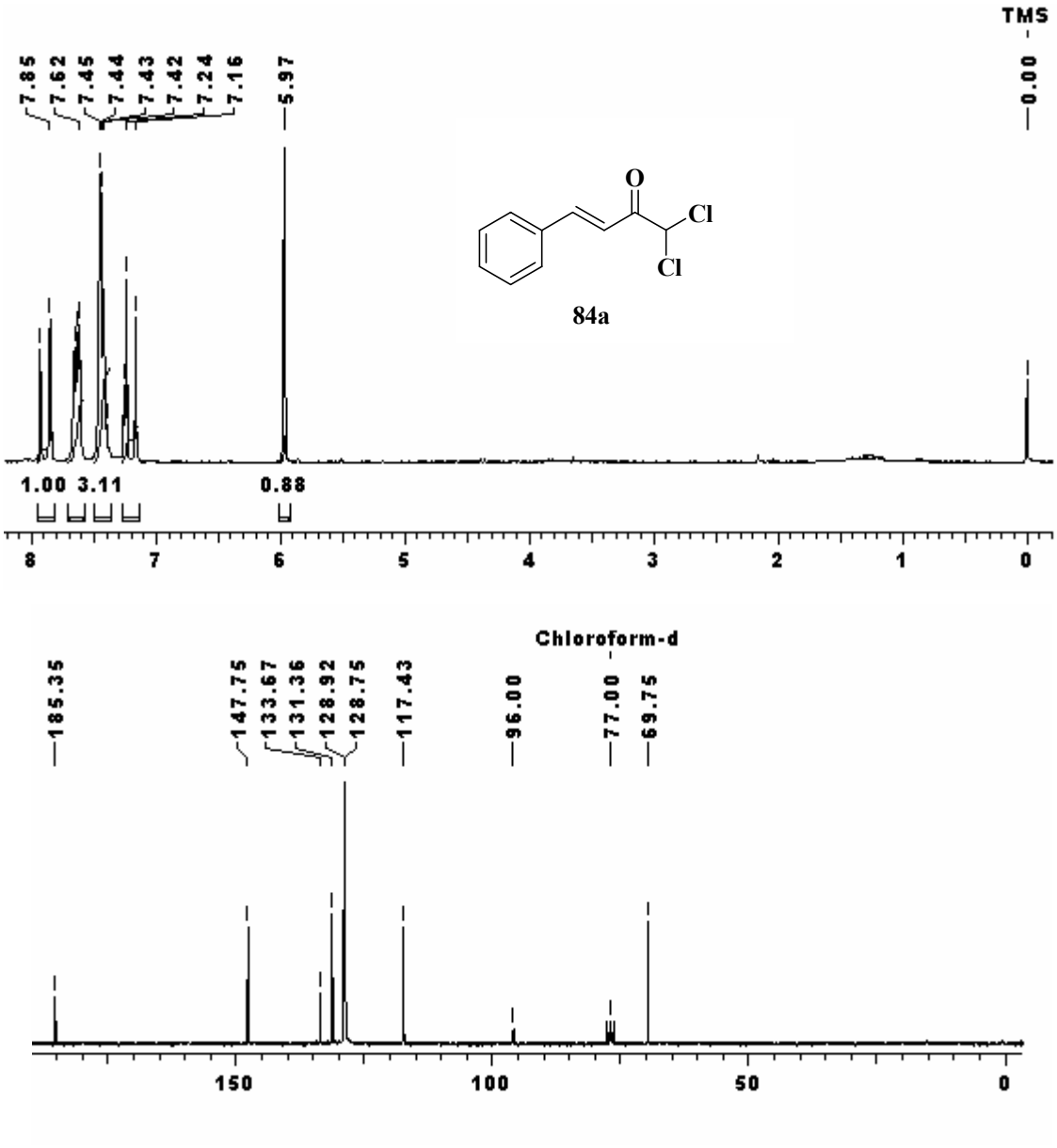


Fig. 6: ^{1}H and ^{13}C NMR spectra of dichlochalcone (84a)

As a third example, ^{1}H NMR of 2-bromo-2-methylcyclohexanone **(59i)** showed a characteristic signal at δ 1.82 (s) for its methyl protons. Its ^{13}C NMR spectrum showed typical signals at δ 27.9, 65.7 and 204.4 due the methyl (CH_3), methine (**C**HCl_2) and carbonyl carbons respectively (**Fig.7)**

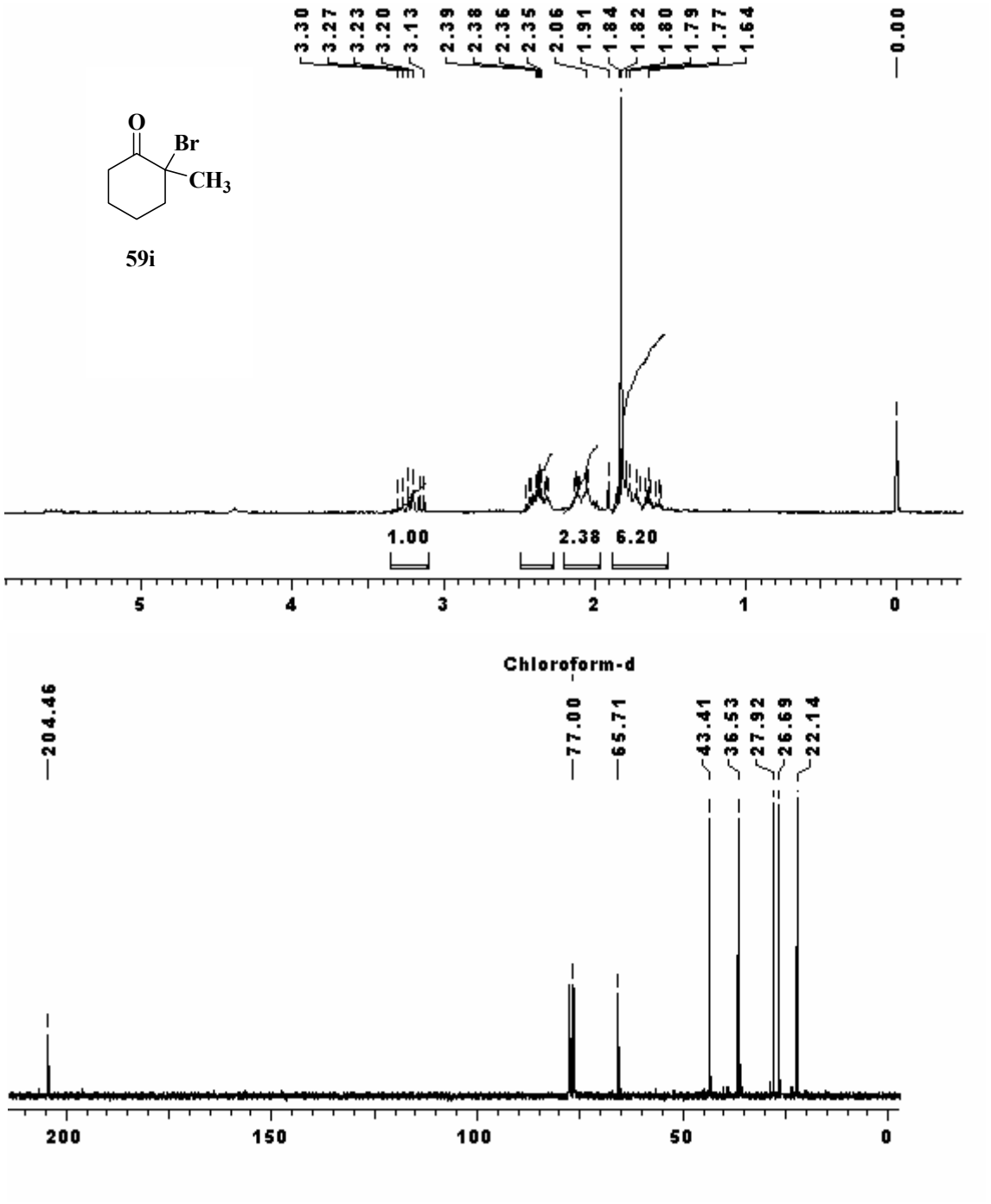


Fig. 7: ^{1}H and ^{13}C NMR spectra 2-bromo-2-methylcyclohexanone (59i)

4.2.4 Conclusion

In conclusion we have developed a simple and efficient catalytic method for dichlorination of ketones. In terms of handling and availability 1,3-dichloro-5,5'-dimethylhydantoin is superior chlorinating agent compared to other chlorine sources known. Our method works very well with variety of ketones and tolerates various functional groups.

4.2.5 Experimental section

A general procedure for α,α-dichlorination of ketones:

To a stirred solution of ketone (4 mmol) and $Cu(OTf)_2$ (2 mol %) in $CHCl_3$ $CHCl_3$ (20 mL), was added 1,3-dichloro-5,5'-dimethyl hydration (4.4 mmol). Then it was refluxed for 8 h under nitrogen atmosphere. After completion of reaction (monitored by TLC), the reaction mixture was diluted with 20 mL chloroform. Organic phase was washed with a saturated sodium thiosulphate solution (20 mL) and brine (20 mL). The organic layer was dried over unhyd. Na_2SO_4, concentrated under reduced pressure to give crude product. Crude product was purified by column chromatography [silica gel (60–120 mesh) and petroleum ether:ethyl acetate as eluent] to give dichloroketone in pure form.

2,2-Dichloro-1-phenylethanone (73a):

Yield: 92%, gum, **IR** ($CHCl_3$): 757, 990, 1093, 1402, 1590, 1712 cm^{-1}; **^{1}H NMR**(200 MHz, $CDCl_3$): δ 6.63 (s, 1H), 7.51 (t, *J* = 7.3 Hz, 2H), 7.64 (t, *J* = 7.3 Hz, 1H), 8.09 (d, *J* = 7.3 Hz, 2H); **^{13}C NMR** (50 MHz $CDCl_3$): δ 67.74, 128.76, 129.62, 131.20, 134.33, 185.45; **Analysis** for $C_8H_6C_{l2}O$ requires C, 50.83; H, 3.20; found C, 50.80; H, 3.21

2,2-Dichloro-1-(4-nitrophenyl)ethanone (73b):

Yield: 76%, gum, **IR** ($CHCl_3$): 757, 990, 1093, 1335, 1402, 1450, 1590, 1711 cm^{-1}; **^{1}H NMR** (200MHz, $CDCl_3$): δ 6.55 (s, 1H), 8.34-8.35 (dd, 4H); **^{13}C NMR** (50 MHz,

$CDCl_3$): δ 67.71, 123.79, 130.85, 135.79, 150.70, 184.35; **Analysis** for $C_8H_5Cl_2NO_3$ requires C, 41.06; H, 2.15; N, 5.98; found C, 40.87; H, 2.07; N, 5.82%.

1-(4-Bromophenyl)-2,2-dichloroethanone (73c):

Yield: 77%, gum, **IR** ($CHCl_3$): 669, 1011, 1075, 1215, 1274, 1400, 1586, 1712 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 6.58 (s, 1H), 7.66 (d, *J* = 8.7 Hz, 2H), 7.97 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 67.63, 129.74, 129.86, 131.05, 133.08, 184.80. **Analysis** for $C_8H_5BrCl_2O$ requires C, 35.86; H, 1.88; found C, 35.71; H, 1.75%.

2,2-Dichloro-1-(4-chlorophenyl)ethanone (73d):

Yield: 71%; gum, **IR** ($CHCl_3$): 669, 850, 1094, 1216, 1274, 1402, 1590, 1712, 2400, 3019 cm^{-1}; **^{1}H-NMR** (200MHz, $CDCl_3$): δ 6.53 (s, 1H), 7.49 (d, *J* = 8.5 Hz, 2H), 8.07 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (50MHz, $CDCl_3$) δ 67.79, 129.17, 129.41, 131.21, 141.09, 184.56; **Analysis** for $C_8H_5Cl_3O$ requires C, 42.99; H, 2.26; found C, 42.76; H, 2.29%.

2,2-Dichloro-1-(4-fluorophenyl)ethanone (73e):

Yield: 73%; **IR** ($CHCl_3$): 767, 849, 1012, 1090, 1410 1592, 1714 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 6.58 (s, 1H), 7.15-7.26 (m, 2H), 8.13-8.21 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 67.75, 116.12 (d, *J* = 22.3 Hz), 127.44 (d, *J* = 2.9 Hz), 132.64 (d, *J* = 9.9 Hz), 166.31 (d, *J* = 258.4 Hz), 184.37; **Analysis** for $C_8H_5Cl_3O$ requires C, 42.99; H, 2.26; found C, 42.81; H, 2.21%.

2,2-Dichloro-1-p-tolylethanone (73f):

Yield: 75%; **IR** ($CHCl_3$): 669, 756, 1216, 1280, 1419, 1607, 1702, 2400, 3091 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.45 (s, 3H), 6.65 (s, 1H), 7.31(d, *J* = 8.3 Hz, 2H), 7.98 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.68, 67.71, 128.58, 129.48, 129.66,

145.63, 185.26; **Analysis** for $C_9H_8OCl_2$ requires C, 53.23; H, 3.97; found C, 53.12; H, 3.82%.

2,2-Dichloro-1-(4-methoxyphenyl)ethanone (73g):

Yield: 83%; **IR** ($CHCl_3$): 857, 1410, 1620, 1711 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.90 (s, 3H), 6.61 (s, 1H), 6.97 (d, *J* = 8.9 Hz, 2H), 8.08 (d, *J* = 8.9 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.40, 67.71, 114.01, 123.67, 131.98, 164.42, 184.24; **Analysis** for $C_9H_8Cl_2O_2$ requires C, 49.34; H, 3.68; found C, 49.21; H, 3.45%.

2,2-Dichloro-1-(3,4-dimethoxyphenyl)ethanone (73h):

Yield: 85%; **IR** ($CHCl_3$): 669, 756, 1092, 1215, 1326, 1491, 1611, 1697, 2399, 3019 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.95 (s, 3H), 3.98 (s, 3H), 6.66 (s, 1H), 6.92 (d, *J* = 8.6 Hz, 2H), 7.60 (d, *J* = 2.0 Hz, 2H), 7.75 (dd, *J* = 2, 8.6 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.56, 55.73, 67.33, 109.82, 111.25, 123.64, 124.11, 148.93, 154,19, 184,16. **Analysis** for $C_{10}H_{10}Cl_2O_3$ requires C, 48.22; H, 4.05; found C, 48.11; H, 4.12%.

2-Chloro-1-(2-chloro-3,4,5-trimethoxyphenyl)ethanone (73i):

Yield: 85%; **IR** ($CHCl_3$): 757, 823, 1410, 1614, 1711 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.89 (s, 3H), 3.91 (s, 3H), 3.95 (s, 3H), 4.75 (s, 2H), 6.96 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 48.68, 55.83, 60.70, 60.76, 108.15, 118.16, 130.83, 146.10, 149.69, 151.99, 192.58; **Analysis** for $C_{11}H_{12}Cl_2O_4$ requires C, 47.33; H, 4.33; found C, 47.21; H, 4.37%.

2,2-Dichloro-1-phenylpropan-1-one (73j):

Yield: 87%; **IR** ($CHCl_3$): 757, 1223, 1410, 1590, 1713 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.35 (s, 3H), 7.41-7.51 (m, 2H), 7.54-7.62 (m 1H), 8.29-8.34 (m, 2H); **^{13}C**

NMR (50 MHz, $CDCl_3$) δ 35.91, 71.10, 127.93, 131.22, 133.38, 187.90; **Analysis** for $C_9H_{10}Cl_2O$ requires C, 52.71; H, 4.91; found C, 52.67; H, 4.83%.

2,2-Dichloro-3,4-dihydronaphthalen-1(2*H*)-one (73k):

Yield: 85%; **IR** ($CHCl_3$): 746, 815, 879, 1123, 1217, 1291, 1425, 1598, 1702 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.96 (t, *J* = 5.9 Hz, 2H), 3.21 (t, *J* = 5.9 Hz, 2H), 7.25 (d, *J* = 7.6Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 8.16 (d, *J* = 7.6 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 27.28, 43.08, 86.22, 127.39, 128.62, 129.68, 134.48, 142.02, 183.65; **Analysis** for $C_{10}H_8Cl_2O$ requires C, 55.84; H, 3.75; found C, 55.65; H, 3.71%.

2,2-Dichloro-1-(naphthalen-4-yl)ethanone(73l):

Yield: 86%; **IR** ($CHCl_3$): 784, 846, 938, 1047, 1373, 1465, 1695, 2941 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 6.79 (s, 1H), 7.47-7.69 (m, 3H), 7.87-8.06 (m, 3H), 8.50 (d, *J* = 8.5 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 69.07, 123.89, 125.17, 126.80, 128.12, 128.54, 129.86, 130.76, 133.71,134.26, 188.08; **Analysis** for $C_{12}H_8Cl_2O$ requires C, 60.28; H, 3.37; found C, 60.11; H, 3.21%.

(*E*)-1,1-Dichloro-4-phenylbut-3-en-2-one (84a):

IR ($CHCl_3$): 746, 981, 1076, 1147, 1216, 1333, 1450, 1613, 1691, 2401, **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.97 (s, 1H), 7.20 (d, *J* = 15.9 Hz, 1H), 7.30-7.45 (m, 3H), 7.62-7.66 (m, 2H), 7.89 (d, *J* = 15.9 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 69.75, 117.43, 128.75, 128.92, 131.36, 133.67, 147.75, 185.35; **Analysis** for $C_{10}H_8Cl_2O$ requires C, 55.84; H, 3.75; found C, 55.67; H, 3.79%.

(*E*)-1,1-Dichloro-4-(4-methoxyphenyl)but-3-en-2-one (84b):

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.86 (s, 3H), 5.96 (s, 1H), 6.93 (d, *J* = 8.9 Hz, 2H), 7.06 (d, *J* = 15.7 Hz, 1H), 7.59 (d, *J* = 8.9 Hz, 2H), 7.85 (d, *J* = 15.7 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.19, 69.85, 114.37, 114.97, 126.42, 130.66, 147.51, 162.30, 185.39; **Analysis** for $C_{11}H_{10}Cl_2O_2$ requires C, 53.90; H, 4.11; found C, 53.79; H, 4.19%.

(*E*)-1,1-Dichloro-4-(4-chlorophenyl)but-3-en-2-one (84c):

^{1}H-NMR (200 MHz, $CDCl_3$): δ 5.96 (s, 1H), 7.18 (d, *J* = 15.9 Hz, 1H), 7.41 (d, *J* = 8.9 Hz, 2H), 7.58 (d, *J* = 8.9 Hz, 2H), 7.84 (d, *J* = 15.9 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 69.70, 117.86, 129.25, 129.89, 132.20, 137.37, 146.21, 185.21; **Analysis** for $C_{10}H_7Cl_3O$ requires C, 48.14; H, 2.83; found C, 48.01; H, 2.89%.

1,3-Dichlorobutan-2-one:

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.67 (d, *J* = 6.9 Hz, 3H), 4.46 (d, *J* = 1.1 Hz, 2H), 4.64 (q, *J* = 6.9, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 19.84, 45.51, 55.57, 196.80; **Analysis** for $C_4H_6Cl_2O$ requires C, 34.07; H, 4.29; found C, 34.23; H, 4.11%.

1,3-Dichloropentan-2-one:

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.06 (t, *J* = 7.3 Hz, 3H), 1.89-2.13 (m, 2H), 4.36-4.56 (q, 1H), 4.44-4.46 (d, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 10.22, 26,79, 45.94, 62.25, 196.47; **Analysis** for C_5H8Cl_2O requires C, 38.74; H, 5.20; found C, 38.66; H, 5.29%.

2,6-Dichloro-2-methylcyclohexanone:

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.71 (s, 3H), 1.78-2.00 (m, 3H), 2.18-2.40 (m, 2H), 2.49-2.64 (m, 1H), 5.23-5.33 (dd, *J* = 6.1, 6.7 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.10, 26.74, 38.39, 42.20, 60.31, 70.69, 196.92; **Analysis** for $C_7H_{10}Cl_2O$ requires C, 46.43; H, 5.57; found C, 46.32; H, 5.51%.

A general procedure for α-bromination of ketones:

To a stirred solution of ketone (4 mmol) and $Cu(OTf)_2$ (2 mol %) in $CHCl_3$ $CHCl_3$ (20 mL), was added N-bromosuccinimide (4 mmol). Then it was refluxed for 8 h under nitrogen atmosphere. After completion of reaction (monitored by TLC), the reaction mixture was diluted with 20 mL chloroform. Organic phase was washed with a saturated sodium thiosulphate solution (20 mL) and brine (20 mL). The organic layer was dried over unhyd. Na_2SO_4, concentrated under reduced pressure to give crude product. Crude product was purified by column chromatography [silica gel (60–120 mesh) and petroleum ether:ethyl acetate as eluent] to give α-bromoketone **57a-i** in pure form.

2-Bromo-1-phenylethanone (57a):

Yield: 82%, gum, **IR** ($CHCl_3$): 759, 1234, 1374, 1462, 1592, 1691 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 4.47 (s, 2H), 7.46-7.62 (m, 3H), 7.99 (dt, *J* = 1.5, 7.0 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 31.15, 128.65, 129.28, 133.57, 134.76, 190.92; **M/S:** 200**,** 198, 105, 91, 77, 65, 51;**Analysis** for C_8H_7BrO requires C, 48.27; H, 3.54; found C, 48.22; H, 3.52%.

2-Bromo-1-(3-nitrophenyl)ethanone (57b):

Yield: 89%, gum**, IR** ($CHCl_3$): 769, 1215, 1265, 1352, 1535, 1614, 1693 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 4.49 (s, 2H), 7.74 (t, *J* = 7.9 Hz, 1H), 8.34 (dd, *J* = 1.1, 7.9 Hz, 1H), 8.48 (dq, *J* = 1.1, 8.2 Hz, 1H), 8.82 (t, *J* = 1.9 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 30.22, 123.48, 127.94, 130.13, 134.35, 134.99, 148.30,189.32; **M/S:** 244, 242, 150, 134, 120, 104, 92, 76, 63, 40; **Analysis** for $C_8H_6BrNO_3$ requires C, 39.37; H, 2.48; N, 5.74; found C, 39.33; H, 2.49; N, 5.77%.

2-Bromo-1-(4-nitrophenyl)ethanone (57c):

Yield: 76%, gum**, IR** ($CHCl_3$): 757, 856, 1190, 1215, 1270, 1346, 1529, 1693 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 4.47 (s, 2H), 8.16 (d, *J* = 9.1 Hz, 2H), 8.35 (d, *J* = 9.1 Hz, 2H), **^{13}C NMR** (50 MHz, $CDCl_3$) δ 30.36. 123.88, 129.92, 138.29, 138.29, 150.51, 189.84; **Analysis** for $C_8H_6BrNO_3$ requires C, 39.37; H, 2.48; N, 5.74; found C, 39.34; H, 2.43; N, 5.73%.

2-Bromo-1-(3,4-dichlorophenyl)ethanone (57d):

Yield: 77%, **IR** ($CHCl_3$): 756, 890, 1192, 1590, 1690 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 4.50 (s, 2H), 7.36 (dd, *J* =1.7, 8.3 Hz, 1H), 7.47 (d, *J* = 1.7 Hz, 1H), 7.56 (d, *J* = 8.3 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 34.15, 127.23, 130.15, 131.07, 132.15, 133.78, 138.11, 192.07; **M/S:** 268, 173, 145, 124, 109, 95, 74, 62, 42; **Analysis** for $C_8H_5BrCl_2O$ rquires C, 35.86; H, 1.88; found C, 35.83; H, 1.85%.

2-Bromo-1-(3,4-dimethoxyphenyl)ethanone (57e):

Yield: 65%, **IR** ($CHCl_3$): 757, 890, 930, 1143, 1590, 1695 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 3.95 (s, 3H), 3.97 (s, 3H), 4.42 (s, 2H), 6.92 (d, *J* = 8.3 Hz, 1H), 7.54 (d, *J* = 2.0 Hz, 1H), 7.63 (dd, *J* =2.0, 8.3 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 32.57, 55.87, 56.01, 110.03, 111.66, 123.20, 124.18, 149.15, 154.29, 184.61; **Analysis** for $C_{10}H_{11}BrO_3$ requires C, 46.36; H, 4.28; found C, 46.32; H, 4.33%.

2-Bromo-3,4-dihydronaphthalen-1(2*H*)-one (57f):

Yield: 85%, gum, **IR** (neat): 796, 887, 1195, 1303, 1598, 1681 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.43-2.54 (m, 2H), 2.86-2.99 (m, 1H), 3.25-3.41 (m, 1H), 4.74 (t, J = 4.1 Hz, 1H), 7.26-7.39 (m, 2H), 7.53 (dt, *J* = 1.5, 7.5Hz, 1H), 8.10(dd, *J* = 1.2, 7.8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 25.79, 31.59, 50.44, 126.70, 128.11, 128.51, 129.52,

133.79, 142.71, 190.07; **Analysis** for $C_{10}H_9BrO$ requires C, 53.36; H, 4.03; found C, 53.31; H, 3.98%.

2-Bromo-1-(naphthalen-5-yl)ethanone (57g):

Yield: 86%, **IR** ($CHCl_3$): 777, 1086, 1168, 1247, 1508, 1685 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.58 (s, 2H), 7.48-7.63 (m, 3H), 7.87-8.07 (m, 3H), 8.63 (d, *J* = 8.2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 33.94, 124.03, 125.43, 126.56, 128.26, 128.36, 128.47, 130.34, 131.91, 133.70, 194.02; **M/S**: 250, 248,155, 141, 127, 115, 95, 77, 63, 42; **Analysis** for $C_{12}H_9BrO$ requires C, 57.86; H, 3.64; found C, 57.82; H, 3.61%.

2-Bromocyclohexanone(57h):

Yield: 77%, gum, **IR** (neat): 1176,1340, 1452, 1717 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.73-2.05 (m, 4H), 2.20-2.41 (m, 3H), 2.91-3.06 (m, 1H), 4.45 (dt, *J* = 1.2, 6.1Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.00, 26.50, 36.61, 37.77, 53.44, 203.05; **M/S**: 180, 176,132, 97, 82, 69, 55, 41; **Analysis** for C_6H_9BrO requires C, 40.71; H, 5.12; found C, 40.74; H, 5.09%.

2-Bromo-2-methylcyclohexanone(57i):

Yield: 81%, colorless liquid, **IR** (neat): 1132, 1340, 1452, 1723 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.56-1.86 (m, 3H), 1.82 (s, 3H), 1.99-2.15 (m, 2H), 2.29-2.45 (m, 2H), 3.13-3.31 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.14, 26.69, 27.92, 56.53, 43.41, 65.71, 204.46; **Analysis** for $C_7H_{11}BrO$ requires C, 44.00; H, 5.80; found C, 44.05; H, 5.82%.

4.3: References

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1 *p*-Toluenesulfonic acid mediated hydroarylation of cinnamic acids with anisoles and phenols under metal and solvent-free conditions

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4 A new methodology for the asymmetric synthesis of tetrahydroquinolin-3-ol *via* asymmetric dihydroxylation and $CoCl_2$-catalyzed reduction of cyclic sulphite with $NaBH_4$: Application in the synthesis of Sumanirole maleate (PNU95666-E).

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6 $Cu(OTf)_2$-catalyzed α-halogenation of ketones with 1,3-dichloro-5,5-dimethylhydantoin and *N*-bromosuccinimide

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