Synopsis

of the thesis entitled

"Development of Novel Methodologies in Asymmetric Synthesis"

to be submitted

as a partial fulfilment for the award of the degree of

DOCTOR OF PHILOSOPHY

in

CHEMISTRY

by

Hiten Bharatbhai Raval

under the supervision of

Prof. Ashutosh V. Bedekar

Professor

Department of Chemistry
Faculty of Science
The Maharaja Sayajirao University of Baroda
Vadodara 390 002,
Gujarat (INDIA)

December 2022

Synopsis of Thesis

to be submitted to

THE MAHARAJA SAYAJIRAO UNIVERSITY OF BARODA

for the award of the degree of

DOCTOR OF PHILOSOPHY

in

CHEMISTRY

Research Student	: **Hiten Bharatbhai Raval**
Title of Thesis	: **Development of Novel Methodologies in Asymmetric Synthesis**
Supervisor	: **Prof. Ashutosh V. Bedekar** **Professor**
Department	: **CHEMISTRY**
Faculty	: **SCIENCE**
Registration No	: **FOS/2069**
Date of Registration	: **September 1, 2017**

The thesis will be presented in the form of following chapters –

Chapter 1

Introduction

Chapter 2

Synthesis and study of fluorine containing Kagan's amides as chiral Solvating agents

Chapter 3 [I]

One-pot preparation of chiral arylalkyl carbinols by Mitsunobu Protocol

Chapter 3 [II]

Silver-Mediated Conversion of Alcohols to Carbonates with Dialkylazodicarboxylate

Chapter 4

Synthesis, Resolution and Application study of Thiourea derivatives

Chapter 1
Introduction

Introduction of chiral chemistry

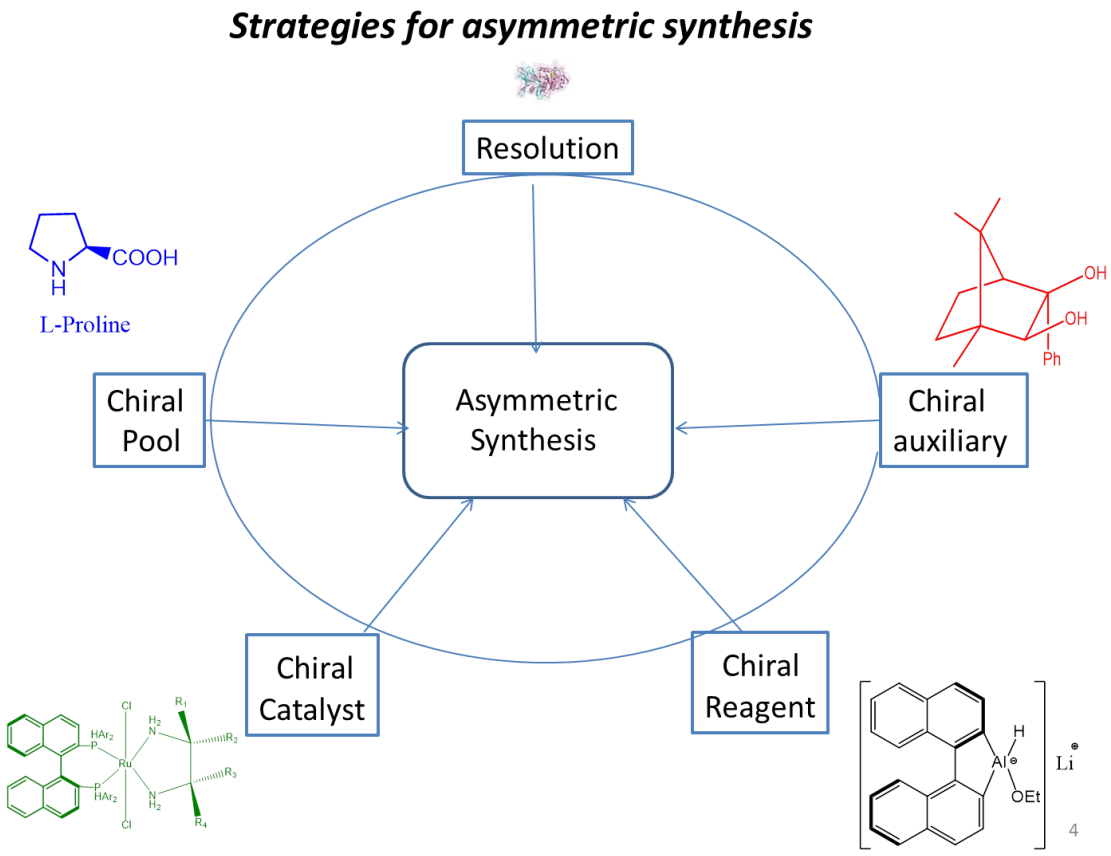
Chirality is an important element in nature. The term chirality introduced by Lord Kelvin in 1873 comes from the Greek word *cheir*, which means handedness and define as a property of an object that is non-super imposable with its mirror image. Carbon with four different groups results in a chiral molecule and is referred to as a chiral or asymmetric or stereogenic center. A familiar example is our left and right hands, which possess mirror-image symmetry, but are non-super imposable on each other

The importance of chirality is well recognised, mainly in connection with the fact that nearly all natural products are chiral and their physiological or pharmacological properties depend upon their recognition by chiral receptors, which will interact only with molecules of the proper absolute configuration. Indeed, the use of chiral drugs in enantiopure form is now a standard requirement for every new chemical entity. Life itself depends on chirality, because living systems interact with enantiomers in a different way. Enantiomers are stereoisomers which are nonsuperimposable mirror images of each other.

The preparation of chiral compounds is an important and challenging area of contemporary synthetic organic chemistry. The broad utility of synthetic chiral molecules as a single enantiomer has been recognised by medicinal chemists for the development of targeted chiral molecules. This has made the chiral synthesis a prominent area of investigation. The search for new and efficient methods for the synthesis and resolution of chirally pure compounds has been an active area of research in organic synthesis. Therefore, synthesis of chiral molecule is a significant and key problem in the design and synthesis of many natural products and pharmaceuticals.

Asymmetric synthesis

- Preparation of optically active product in enriched form, from an achiral starting material is achieved by asymmetric synthesis.
- When a compound containing an asymmetric carbon (CHIRAL) is synthesized by conventional laboratory methods from an achiral compound, the product is obtained in racemic mixture.
- If such a synthesis is carried out under chiral influence, one of optically active isomers will form preferentially over the other.



Separation of Enantiomers

Enantiomers: Stereoisomers that are non-superimposable mirror images.

- Enantiomers have same physical properties like boiling point,melting point etc. but they have different optical rotation.

Methods for Separating Enantiomers

1. Pasteur Method (Diasteriomeric salt)
2. Conversion to Diastereomers
   - Temporarily convert the enantiomers into a pair of diastereomers (will now have different physical properties).
   - Separate those diastereomers from each other by exploiting their different physical and chemical properties.
   - Regenerate the enantiomers from the separated diastereomers.
3. Enzymes
4. Chiral Chromatography

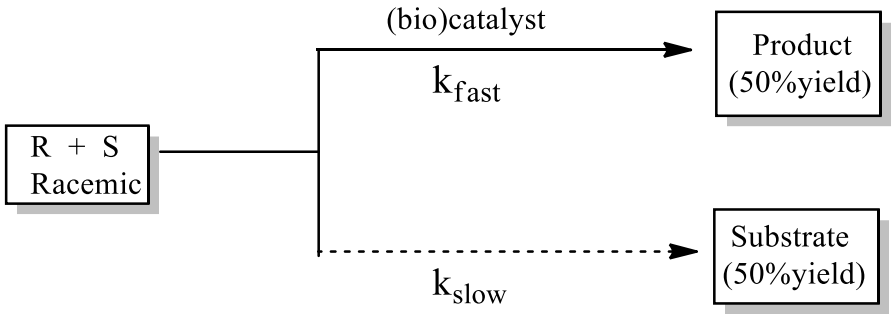
Chapter 2

Synthesis and study of fluorine containing Kagan's amides as chiral solvating agents

Enzymes have been widely used in modern organic synthesis due to their simple processing requirements, high selectivity and mild reaction condition. They possess chemo-selectivity, regeio-selectivity and stereo-selectivity. Research on application of enzymes as catalyst for asymmetric synthetic transformation was mainly driven by growing demand for enantiomerically pure pharmaceuticals. However, the use of enzyme for this purpose was rather limited until the discovery that enzymes can work in organic solvents[9]. Now bio catalytic processes can be carried out in organic solvent as well as aqueous environments, so that polar organic compounds as well as water soluble compounds can be modified selectively and efficiently.

One important approach to obtain enantiomerically pure compounds is kinetic resolution method. The process is based on the difference in reaction rates of the enantiomers. For synthetic purposes the enantioselectivity of the bio catalyst should be as high as possible in order to give the best optical purity and yield. Reactions catalysed by various types of hydrolases are predominant in bio transformation. Among hydrolytic enzymes lipase is frequently used because they accept a broad range of substrate and often exhibit high enantioselectivity. Hence in our study we have used a crude lipase steapsin as bio-catalyst for the resolution of alcohol.

The alcohol was resolved using transesterification and suitable acyl donor under the appropriate condition (Scheme 2).Selection of suitable reaction medium or solvent is critical because some organic solvent can deactivate the enzyme. In literature, generally resolution of various types of alcohol was achieved in ether solvent such as tetrahydrofuran, diisopropyl ether and dioxane..



Best values of enatiomeric excess and yield were achieved by using vinyl acetate (10 eq) as an acetylating agent tetrahydrofuran as solvent and lipase (3 eq) for 8 days in high dilution at room temperature

We also carried outa resolution of **8** 1-(3,5-difluorophenyl)ethan-1-ol with the same reaction conditions using a same amount of steapsin lipase and vinyl acetate as described in table 3 entry 6[a]

But for resolution of **9** 1-(2,6-difluorophenyl)ethan-1-ol using same reaction condition gives a poor enantiomeric excess of acetate as well as alcohol . Hence we used Novozyme 437 in place of steapsin and vinyl acetate as an acyl donor which lead to a better enantiomeric excess for the acetate 99.90% as well as alcohol 90.90% as shown in Table 3 entry 7[b]

The optimisation of condition for efficient separation of enantiomer of various alcohols was developed in the present work and is outlined in the Table 3

SCHEME 3

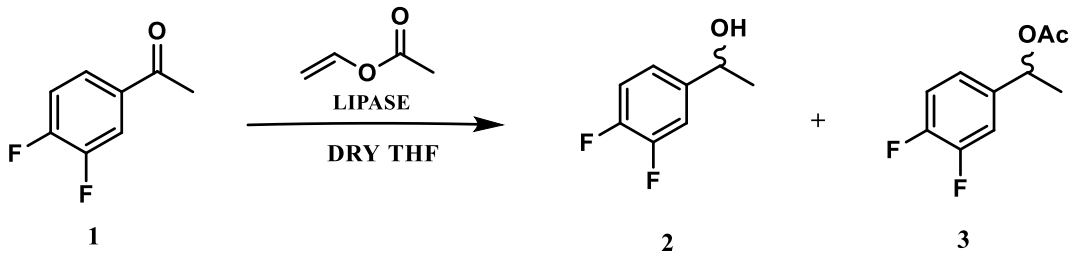
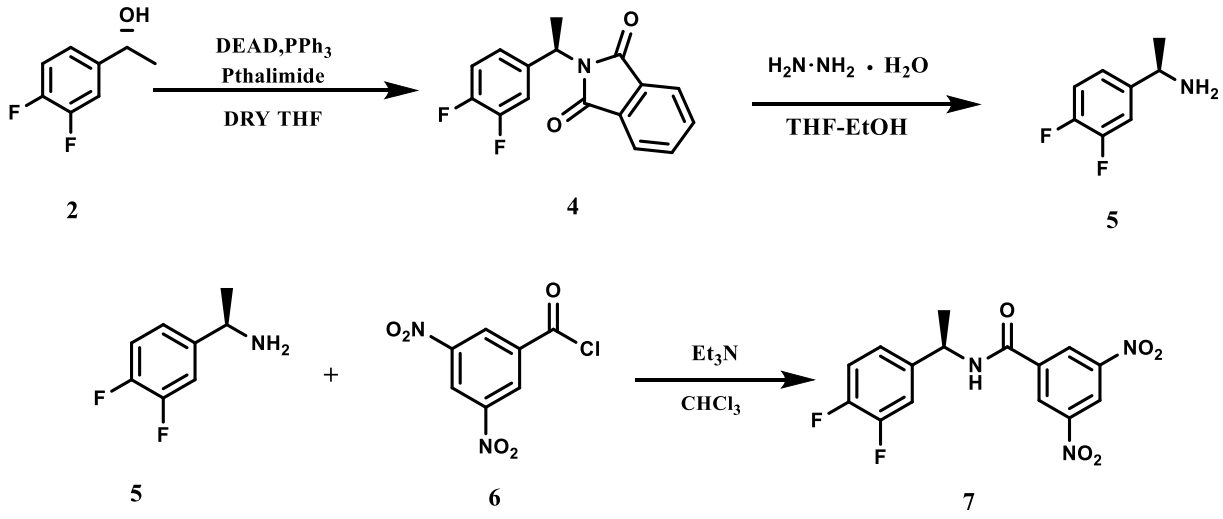


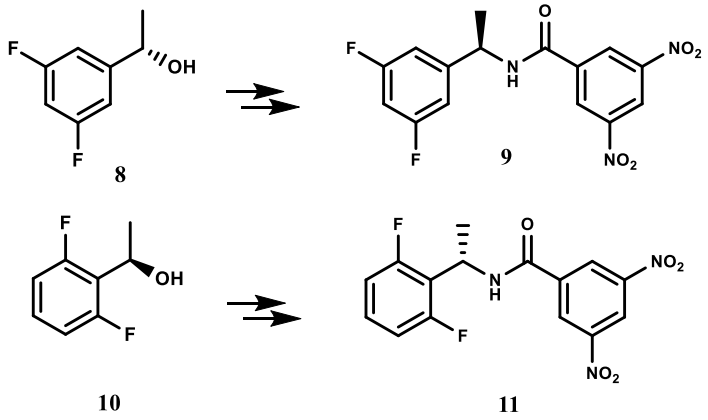
Table 1

No	Lipase Equivalent (Weight/Weight)	Vinyl Acetate Equivalent	Chiral Acetate Yield	Percentage Enantiomeric Excess of chiral Acetate	Chiral Alcohol Yield	Percentage Enantiomeric Excess of chiral Alcohol	Reaction Time (d)
1	1	2	31.76	76.80	58.03	70.02	9
2	2	3	33.33	96.04	54.55	77.52	9
3	3	5	38.09	99.42	45.00	95.84	9
4	**3**	**10**	**42.52**	**99.28**	**45.15**	**99.16**	**8**
5	3	10	46.08	95.04	48.68	99.80	9
6[a]	3	10	45.30	98.97	47.00	99.99	9
7[b]	2(Novozyme)	10	46.60	99.10	48.50	90.90	44 (h)

Where 6[a]is (8) and 7[b] is (10) in below scheme



Enantiomerically pure alcohol **2** was converted to corresponding amine **5** by its reaction with phthalimide using mitsunobu conditions where we get the inversion product which was then deprotected with hydrazine hydrate to give amine **5**. The amine was not isolated but converted directly to the desired amide **7** with 3,5-dinitrobenzoyl chloride **6** in presence of triethyl amine in chloroform[9].



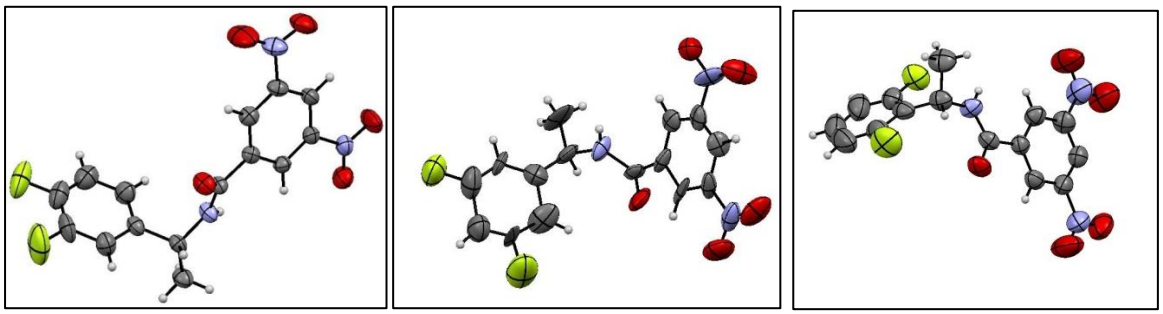
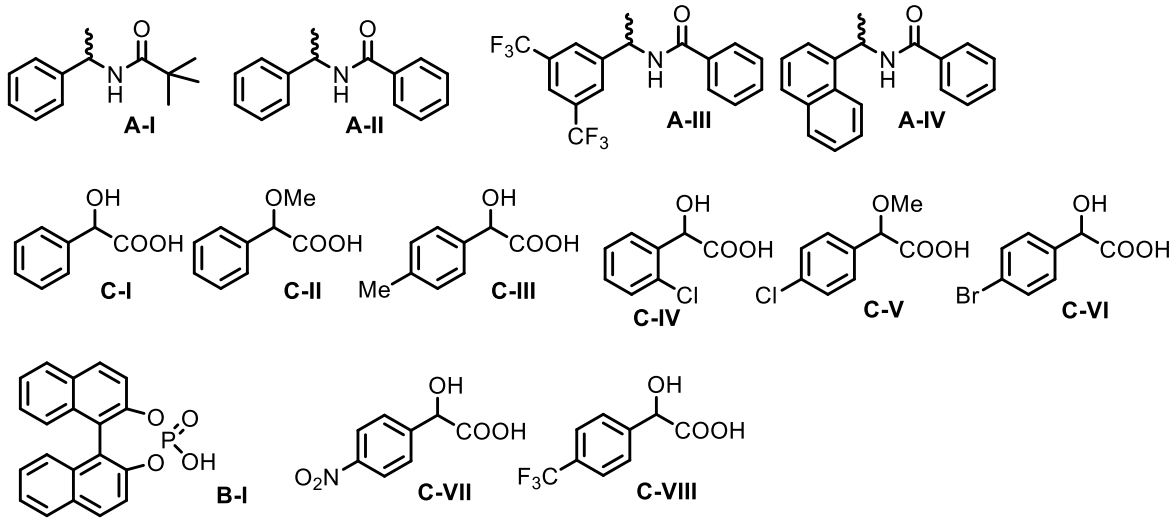


Figure 1: ORTEP Diagram of **7** (CCDC-1835702), **9** (CCDC-1835701) and **11** (CCDC-1835751).

By the same methodology we also synthesised two more kagan's type of ligand 9 and 11 with different positions of two fluorine substituent in aromatic ring. To further understand the supramoleculer interaction of fluorine substituents in ligands with different analytes(A-I to C-VIII) the temporary diasteriomer formation in NMR analysis can be done by mixing an analyte and chiral solvating agent (CSA) .



The Kagan's amide is used as chiral solvating agent to discriminate the signals of optically active analytes in NMR spectroscopy. Three fluorinated derivatives of this amide are prepared and studied for their comparison of chiral recognition towards different analytes by NMR analysis. The analysis is accurate to establish a relationship between the theoretical and observed values, suitable for the technique to be extended for determination of ee of samples of unknown purity.

Table 2:

Analyte	**Ligand 7** Δδ (ΔΔδ)	**Ligand 9** Δδ (ΔΔδ)	**Ligand 11** Δδ (ΔΔδ)
A-I	0.073 (0.065)[a] 0.022 (0.020)[b]	0.149 (0.110)[a] 0.044 (0.041)[b]	0.030 (-)[a] 0.017 (0.017)[b]
A-II	-	-	0.214 (0.008)[a] 0.018 (0.017)[b]
A-III	0.139 (0.247)[a]	0.005 (-)[a] 0.001 (0.017)[b]	-
A-IV	0.201 (0.264)[a]	0.392 (0.464)[a]	-

B-I	1.023 (0.033)[c]	1.030 (0.179)[c]	-
C-I	-0.295 (0.006)[a]	-0.321 (0.008)[a]	-
C-II	-0.089 (0.015)[a]	-0.313 (0.017)[a] -0.076 (0.011)[d]	-0.094 (0.013)[a] -0.071 (0.025)[d]
C-III	-0.289 (0.004)[a] -0.034 (0.038)[e]	-0.317 (0.007)[a] -0.140 (0.064)[e]	-0.262 (0.011)[a] -0.078 (0.007)[e]
C-IV	-0.266 (0.004)[a]	-0.272 (0.008)[a]	-0.244 (0.012)[a]
C-V	-0.309 (0.010)[a]	-0.287 (-)[a]	-0.276 (0.011)[a]
C-VI	-0.305 (0.011)[a]	-0.316 (0.009)[a]	-0.270 (0.009)[a]
C-VII	-0.302 (0.002)[a]	-0.308 (0.004)[a]	-0.285 (-)[a]
C-VIII	-0.292 (0.006)[a]	-0.307 (0.008)[a]	-

[a]For C□*H*; [b]For C□C*H3;* (-) = no separation/discrimination;

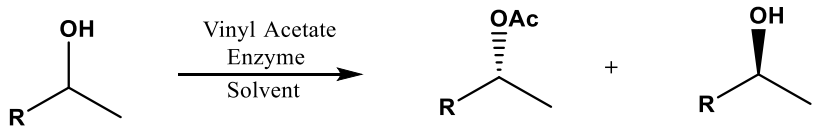
[c]^{31}P NMR; [d]For OCH_3; [e]For ArCH_3. All the spectra were recorded at 400 MHz in $CDCl_3$; at 10 mM concentration. One equivalent of DMAP is added for all **B** and **C** analytes.

Chapter 3

One-pot preparation of chiral arylalkyl carbinols by Mitsunobu protocol

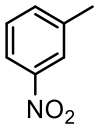
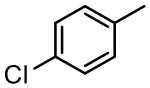
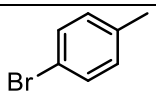
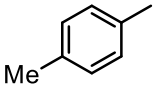
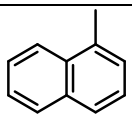
The first step of KR was performed using Novozyme-435 as the immobilized enzyme and vinyl acetate as the acetylating agent. The conditions of using vinyl acetate (10 eq.), diethyl ether as solvent, with the beads of Novozyme-435 (50 % w/w) as biocatalyst and performing the reaction at room temperature was optimized after several experiments. After the KR is achieved, the reaction mixture was filtered to remove the solid matrix of immobilized enzyme and the reaction mixture was treated with metal acetate, DEAD and Ph_3P for the Mitsunobu reaction step (Table 2). As expected the reaction with AgOAc was smooth at room temperature and high conversion to acetate 2 was achieved. The product was isolated and its optical purity measured by HPLC analysis on chiral column. The overall reaction furnished the desired acetate in excellent chemical yield and optical purity.

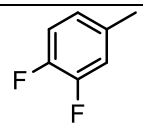
Scheme 1



I II*(R)* I*(S)*

Table 1: Resolution of Alcohol

Sr no.	Substrate (R)	Time(hr)	%Yield of Acetate	%ee of Acetate	%Yield of Alcohol	%ee of alcohol	%Yield of alcohol insitu mitsunobu	%ee of alcohol insitu mitsunobu
1[a]		24	49	98.33	48	99.7	94.2	96.1
2		24	48.31	97.80	46.11	>99.9	85.5	99.0
3		16	48.62	94.73	45.82	>99.9	82.3	96.3
4		48	46.95	98.35	44.48	>99.9	83.6	99.0
5		50	46.30	>99.9	45.54	94.55	79.9	96.03

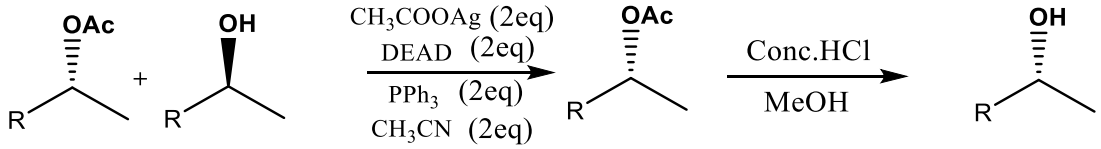
6[b,c]		8 days	42.5	99.3	45.2	99.2	89.3	99.03

[a] Vinyl acetate 3eq

[b] Enzyme –Steapsin Lipase 300%w/w

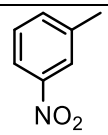
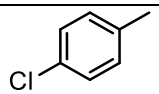
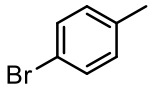
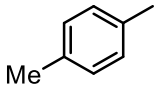
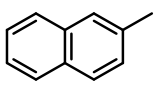
[c] 10ml Dry THF

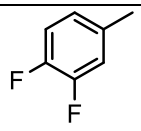
Scheme 2



II*(R)* I*(S)* II*(R)* I*(R)*

Table 2: Insitu Mitsunobu reaction followed by hydrolysis

Substrate (R)	%Yield of Alcohol	%ee of ' alcohol
	94.2	96.1
	85.5	99.0
	82.3	96.3
	83.6	99.0
	79.9	96.03

	89.3	99.03

Conversion of unreactive isomer of alcohol to acetate by inversion of configuration by Mitsunobu reaction is done with acetic acid as the source of acetate ion. The nucleophilicity of acetate ions in the metal salt of AcOH will be appreciably more and will favor the displacement procedure. With this aim we have screened number of metal acetates for the Mitsunobu step in the one-pot sequence of this reaction.

Scheme 3

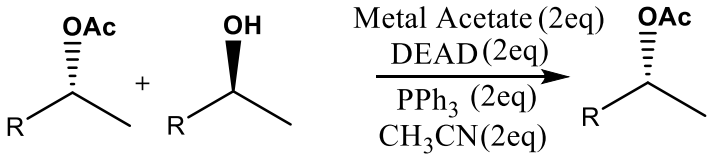


Table 3: Optimisation of mitsunobu reaction with different Metal Acetates

Metal Acetates	Time	Temprature	%Yield of Alcohol	%ee of Alcohol
CH_3COOAg	24	RT	94	96.16
$Pb(OAc)_2$	24	Reflux	70	76.13
$Cu(OAc)_2$	24	Reflux	84	84.88
$Mn(OAc)_2$	24	Reflux	78	86.21
$Mg(OAc)_2$	24	Reflux	82	73.90
$Zn(OAc)_2$	24	Reflux	74	22.48
$Co(OAc)_2$	24	Reflux	76	66.90
$Ni(OAc)_2$	24	Reflux	80	83.30
$Hg(OAc)_2$	24	Reflux	81	91.36

Scheme 4

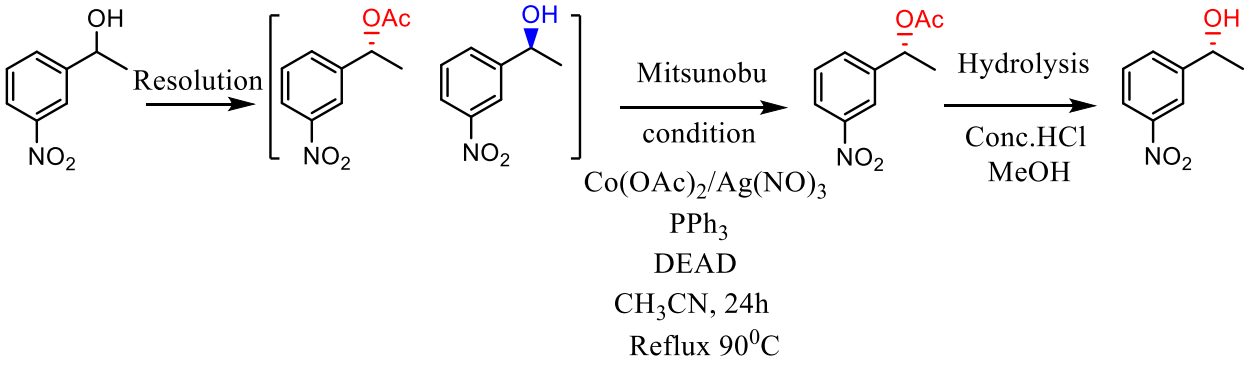


Table 4: Optimisation Table for scheme 4

$AgNO_3$ (eq)	$Co(OAc)_2$ (eq)	Alcohol %Yield	Alcohol %ee
-	2.0	76	66.9
0.25	1.75	81	88
0.50	1.50	88	87.5

The first step of KR was performed using Novozyme-435 After the KR is achieved, the reaction mixture was filtered to remove the solid matrix of immobilized enzyme and the reaction mixture was treated with cobalt acetate and silver nitrate, DEAD and Ph_3P for the Mitsunobu reaction step.

As increase the amount of silver nitrate (Table 4) in a reaction the yield of product is increasing from 76 to 88 percentage while optical purity is comparable The product was isolated and its optical purity measured by HPLC analysis on chiral column. The overall reaction furnished the desired alcohol in excellent chemical yield and optical purity.

Scheme 5

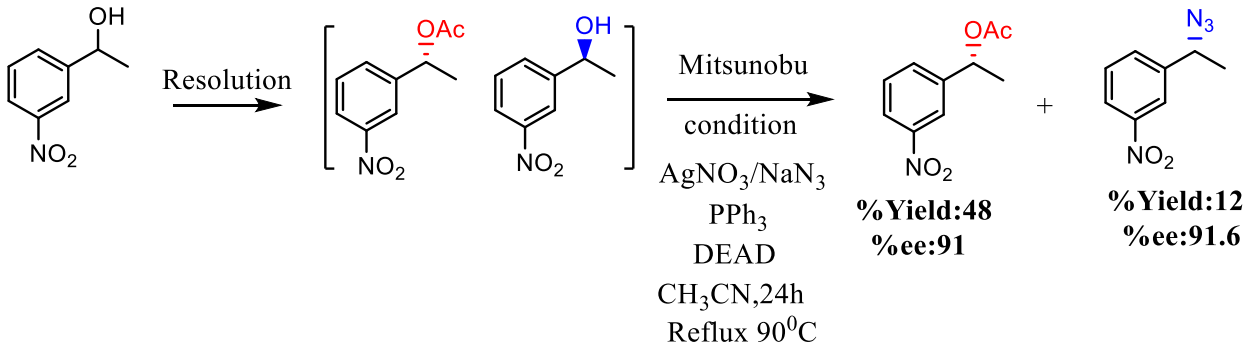


Table 5: Optimisation of scheme 5

$AgNO_3$ (eq)	NaN_3 (eq)	Acetate %Yield	Acetate %ee	Azide %Yield	Azide %ee
-	2.0	44	91	12	91.6
0.25	1.75	45	92	24	90.6
0.50	1.50	46	91.6	36	98.7
0.75	1.25	45	92	39	99.7

The first step of KR was performed using Novozyme-435 After the KR is achieved, the reaction mixture was filtered to remove the solid matrix of immobilized enzyme and the reaction mixture was treated with Sodium azide and silver nitrate, DEAD and Ph_3P for the Mitsunobu reaction step.

As increase the amount of silver nitrate (Table 5) in a reaction the yield of product is increasing from 12 to 39 percentage while optical purity is also increase from 90% to more than 99% The product was isolated and its optical purity measured by HPLC analysis on chiral column. The overall reaction furnished the desired alcohol in excellent chemical yield and optical purity.

Mitsunobu Reaction of racemic alcohol is carried out with DEAD ,PPh_3 ,$AgNO_3$ and NaN_3 to form the azide and acetate as a product In below EKR-Mitsunobu protocol a very minor spot of ether was observed after completion of reaction

Scheme 6

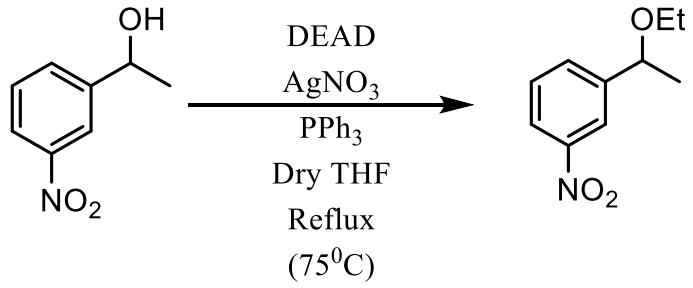
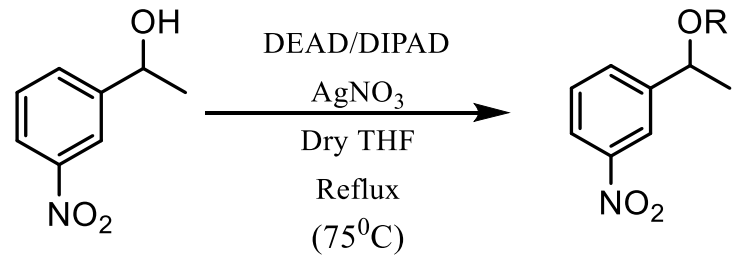


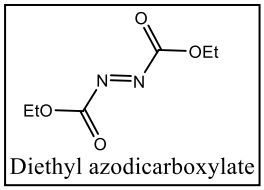
Table 6: Optimisation Table for scheme 6

Sr No.	$AgNO_3$ (Eq)	DEAD (Eq)	PPh_3 (Eq)	Reaction Time(h)	%Yield (Ether)
1	-	2.0	-	72	No Reaction
2	-	-	2.0	72	No Reaction
3	1.0	-	2.0	78	No Reaction
4	-	2.0	2.0	72	<2
5	1.0	2.0	2.0	24	74
6	1.0	2.0	-	48	85

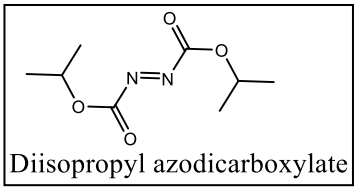
Further investigation for the ether formation during a reaction was done by doing same Mitsunobu protocol .From (Table 6,entry 5) by taking 1eq of silver nitrate,2eq of DEAD and 2eq of PPh_3 74% of ether product observed .and (Table 6,entry 5) by taking 1eq of silver nitrate,2eq of DEAD and 85% of ether product observed.

Scheme 7





Diethyl azodicarboxylate



Diisopropyl azodicarboxylate

Table 7: Optimisation table of scheme 7

Sr No.	$AgNO_3$ (Eq)	Reagent (Eq)	Reaction Time(h)	%Yield (Ether)
1	1.0	DEAD(2.0)	48	85
2	1.0	DIPAD(2.0)	72	63
3	1.0	PhCOOEt(2.0)	78	No Reaction
4	1.0	EtOAc(2.0)	78	No Reaction

Mitsunobu reaction of racemic alcohol with 1eq $AgNO_3$ in a dry THF with different Reagent (DEAD, DIPAD) has been studied in a reflux condition. By talking (Table 7,entry 2)2eq of DIPAD instead of DEAD in a same mitsunobu reaction as discussed in a scheme 7 ,63% yield of product obtained. But with Ethyl benzoate and ethyl acetate (Table 7,entry 4,5) no product formation was observed.

Scheme 8

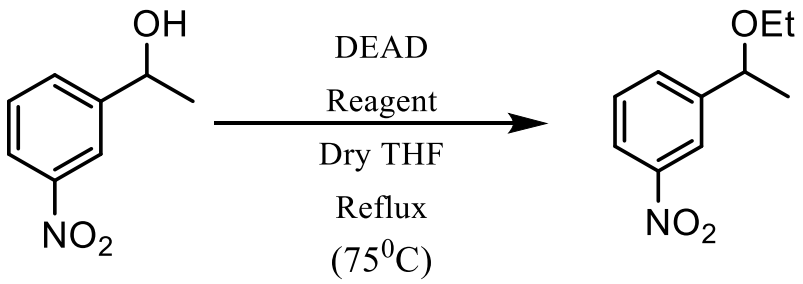


Table 8: optimisation table for scheme 8

Sr No.	Reagent (Eq)	Reaction Time(hr)	%Yield (Ether)
1	AgNO3 (2.0)	48	85
2	AgSO4 (2.0)	72	63
3	Cu(OTf)2 (0.1)	78	29

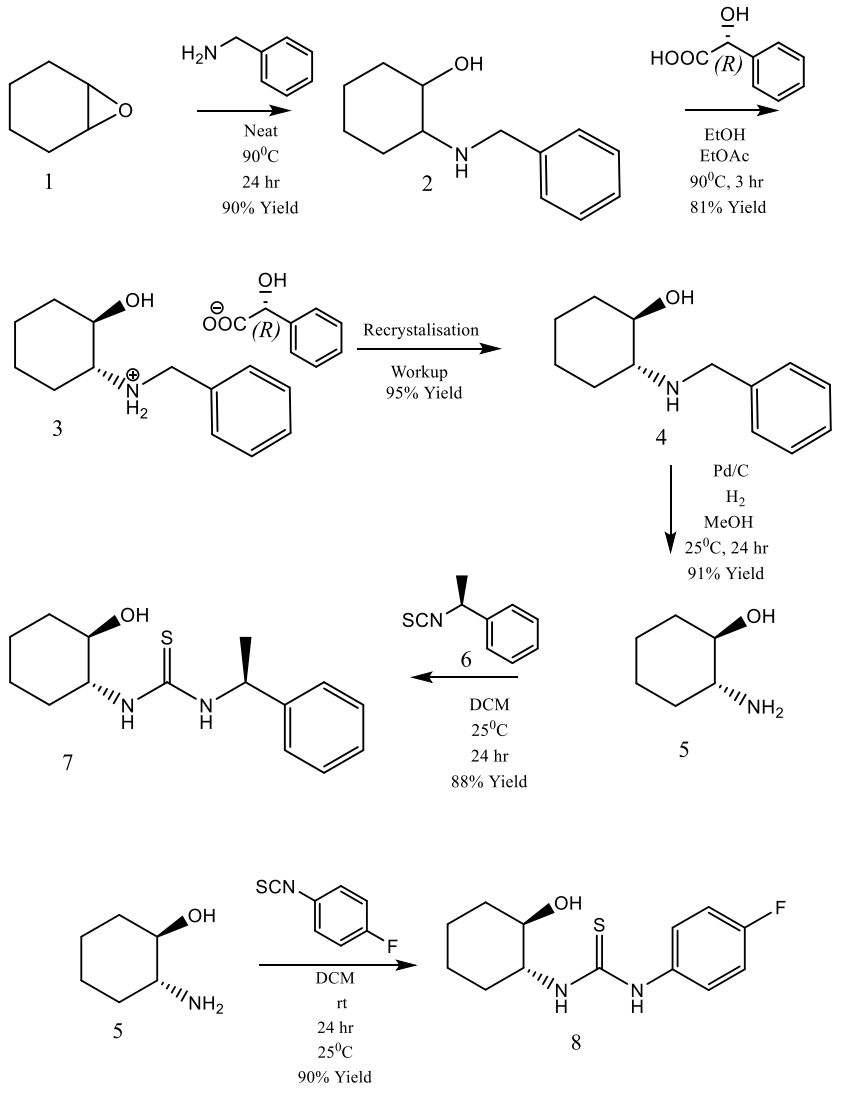
Mitsunobu reaction of racemic alcohol with DEAD in a dry THF with different Reagent has been studied in a reflux condition. By talking (Table 8,entry 2) 1eq of $AgSO_4$instead of $AgNO_3$in a same mitsunobu reaction as discussed in a scheme 8 ,63% yield of product obtained. The same reaction is also carried out with catalytic amount of $Cu(OTf)_2$ instead of $AgNO_3$,29% product was obtained.

Chapter 4

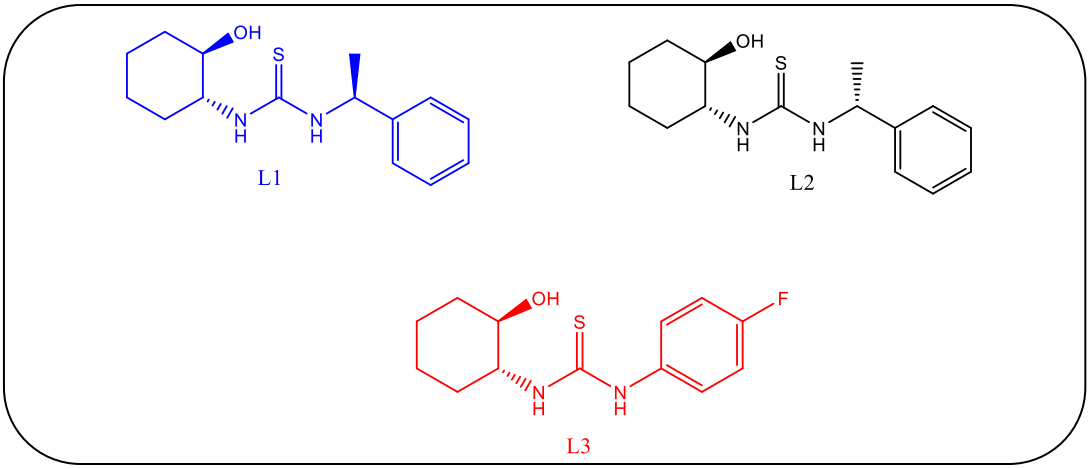
Synthesis, Resolution and Application study of Thiourea derivatives

- The most effective chiral solvating agents have been designed with BINOL, proline, phenylethyl amine, amino naphthol, diamino cyclohexane (DACH) etc as their chiral core.
- The design of CSAs based on cyclohexane have been of prime focus due to their immense success in molecular recognition.
- Some common examples of cyclohexane based CSAs are presented in figure.
- The choice of cyclohexane unit in the design of these compounds may be attributed to the rigid backbone of the ring and the favorable orientation attained by *trans*-1,2-substituents *leading to effective enantiodiscrimination*.

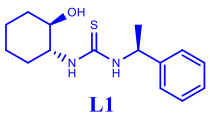
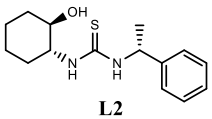
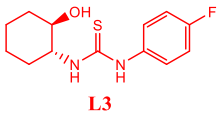
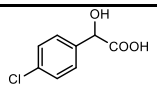
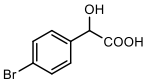
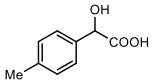
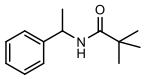
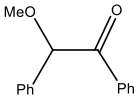
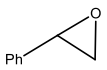
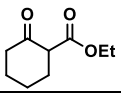
Preparation of Organocatalyst



We have synthesize L1,L2and L3 Ligands for further study its application as organocatalyst as well as in chiral recognition



- *^{1}H NMR induced chemical shift (Δd) and nonequivalence (ΔΔd) of analytes in presence of CSAs* All the spectra were recorded at 400 MHz in $CDCl_3$; at 10 mM concentration

Δδ (ΔΔδ)	 **L1**	 **L2**	 **L3**
	0.050(0.005)	0.047(0.007)	0.017
	0.050(0.005)	0.078(0.007)	0.015
	0.038(0.004)	0.010	0.013
	0.010	0.001	0.008
	0.016	0.015	0.017
	0.012	0.008	0.012
	0.009	0.009	0.018

References

(1) Iwaniuk, D. P.; Wolf, C. *J. Org. Chem.* **2010**, *75*, 6724–6727.

(2) Deshmukh, M.; Dunach, E.; Juge, S.; Kagan, H. B. *Tetrahedron Lett*. **1984**, *25*, 3467–3470; Dunach, E.; Kagan, H. B. *Tetrahedron Lett*. **1985**, *26*, 2649–2652.

(3) Xu, H.; Wolf, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 12249–12252.

(4) Pirkle, W. H.; Hoover, D. J. NMR Chiral Solvating Agents. *Topics in Stereochemistry*, 13, Allinger, N. L., Eliel, E. L., Wilen, S. H., Eds.; John Wiley: Hoboken, NJ, 1982; pp. 263 –331.

(5) Lankhorst, P. P.; Netscher, T.; Duchateau, A. L. L. *Chirality* **2015**, *27*, 850–855.

(6) Williams, T.; Pitcher, R. G.; Bommer, P.; Gutzwiller, J.; Uskokovic, M. *J. Am. Chem. Soc.* **1969**, *91*, 1871–1872.

(7) Storch, G.; Haas, M.; Trapp, O. *Chem. Eur. J.* **2017**, *23*, 5414–5418.

(8) Garcia-Rodriguez, R.; Hanf, S.; Bond, A. D.; Wright, D. S. *Chem. Commun.* **2017**, *53*, 1225–1228.

(9) Wagger, J.; Grdadolnik, S. G.; Groselj, U.; Meden, A.; Stanovnik, B.; Svete, J. *Tetrahedron: Asymmetry* **2007**, *18*, 464–475.

(10) Wagger, J.; Svete, J.; Stanovnik, B. *Synthesis* **2008**, 1436–1442.

(11) Malavasic, C.; Wagger, J.; Stanovnik, B.; Svete, J. *Tetrahedron: Asymmetry* **2008**, *19*, 1557 –1567.

(12) (a)Ward T. J. , Ward K. D. , *Anal.Chem*, **2010,** *82*, 4712 (b) Pirkle W. H. , Liu Y. , *J. Chromatogr. A* **1996**, *736*, 31 (c) Gao X. , Kagan H. B. , *Chirality* **1998**, *10*, 120 (d) Gennary C., Ceccarelli S., Piarulli U., Montalbetti C., Jackson R. F. W., *J. Org. Chem*. **1998**, *63*, 5312 (e) Yashima E., *J. Chromatogr. A* **2001**, *906*, 105 (f) Wolf C., Hawes P. A. *J. Org. Chem*. **2002**, *67*, 2727

(13) Polavarapu L., Prasad L., *Chirality* **2002,** *14*, 768.

(14) Ding K., Shii A., Mikami K.,. *Angew. Chem. Int. Ed.* **1999**, *38*, 497. (

(15) Ding K., Shii A., Mikami K., *Angew. Chem.. Int. Ed.,* **1999**, *38*, 497.

(16) Minick D. J., Copley R. C. B., Szewczyk J. R., Rutkowske R. D., L.Miller L. A., *Chirality*, **2007,** *19*, 731. (b) Stephens P. J., Pan J. J., Krohn K., *J. Org. Chem.,* **2007**, *72*, 7641. (c) Flack H. D., *Acta Chim. Slov.* **2008**, *55*, 689.

(17) Abato P., Seto C. T., *J. Am. Chem. Soc.* **2001**, ***123***, 9206. (b) Matsushita M., Yoshida K., Yamamoto N., Wirsching P., Lerner R. A., Janda K. D., *Angew. Chem., Int. Ed.,* **2003,** *42*, 5984.

(18) Wenzel T. J., Chisholm C. D., *Prog. Nucl. Magn. Reson. Spectrosc.* **2011**, *59*, 1.

(19) Dale J. A., Mosher H. S., *J. Am. Chem. Soc.* **1973**, *95*, 512.

(20) Parker D., *Chem. Rev.* **1991**, *91*, 1441. (b) Wenzel T. J., Wilcox J. D., *Chirality* **2003**, *15*, 256.

(21) Whitesides G. M., Lewis D. W., *J. Am. Chem. Soc*. **1970**, *92*, 6969.

(22) Klingenberg J. J. *Organic Syntheses, Coll.* Vol.4, **1963**, 110

(23) Gaoswami S., Ghosh K., Dasgupta S., *Tetrahedron* **1996**, *52*, 12223.

(53)Pitchen P., Duñach E., Deshmukh M.,Kagan H. B., *J. Am. Chem. Soc*. **1984**, *106*, 8188-8193.

(24) Deshmukh M., Duñach E., Juge S., Kagan H. B., *Tetrahedron Lett*. **1984**, *25*, 3467-3470.

(25) Duñach E.,Kagan H. B., *Tetrahedron Lett*. **1985**, *26*, 2649-2652.

(26) Chaprin P., Duñach E., Kagan H. B., Theobald F.R., *Tetrahedron Lett*. **1986**, *27*, 2989-2992.

(27) Jain N.,Patel R. B., Bedekar A. V., *RSC Adv.* **2015**, *5*, 45943-45955.

(28) Jain N., Khanvilkar A. N.,Sahoo S., Bedekar A. V., *Tetrahedron* **2018**, *74*, 68-76.

(29) Bilz A.,Stork T., Helmchen G., *Tetrahedron*: *Asymmetry* **1997**, *8*, 3999.

(30) Iwaniuk D. P.,Wolf C., *J. Org. Chem.* **2010**, *75*, 6724-6727.

(31) Kannappan J., Jain N., Bedekar A. V., *Tetrahedron*: *Asymmetry* **2015**, *26*, 1102-1107.

(32) Khanvilkar A. N.,Bedekar A. V., *Org. Biomol. Chem*. **2016**, *14*, 2742

(33) Gupta R., Gonnade R. G., Bedekar A. V., *J. Org. Chem*. **2016**, *81*, 7384-7392.

(34) Kannappan J., Khanvilkar A. N., Upadhyay G. M.,Bedekar A. V., *Tetrahedron: Asymmetry* **2017**, *28*, 1297-1303.

(35) Chaudhary A. R.,Yadav P., Bedekar A. V., *Tetrahedron*: *Asymmetry* **2014**, *25*, 767-774.

(36) Howard J. A. K., Hoy V. J., O'Hagan D.,Smith G. T., *Tetrahedron* **1996**, *52*, 12613-12622.

(37) O'Hagan D., *Chem. Soc*. *Rev*. **2008**, *37*, 308-319.

(38) Uneyama K., (Ed.) *Hydrogen bonding in organofluorine compounds*, Wiley, 2007.

(39) Dalvit C., Vulpetti A., *Chem. Eur. J.* **2016**, *22*, 7592-7601.

(40) Swamy K. C., Kumar N. N., Balaraman E., Kumar K. V., *Chem*. *Rev*. **2009**, *109*, 2551-2651.

(41) Faber K., *Biotransformations in organic chemistry*, Springer-Verlag, Berlin, Heidelberg, 6th edn, 2011.

(42) Wolf C., Cook A. M., Dannatt J. E., *Tetrahedron*: *Asymmetry* **2014**, *25*, 163-169.

(43) Parmar D., Sugiono E., Raja S., Rueping M., *Chem. Rev.* **2014**, *114*, 9047-9153.

(44) Xiao J., Wong Z. Z., Lu Y. P., Loh T. P., *Adv. Synth. Catal*. **2010**, *352*, 1107-1112.

(45) Martínez-Montero L., Gotor V., Gotor-Fernández V., Lavandera I., *Green Chem*. **2017**, *19*, 474-480.